

# **Predictors of Relapse in Polymyalgia Rheumatica Patients Treated with Low-Dose Glucocorticoid Therapy**

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## I. Abstract

Polymyalgia rheumatica (PMR) is a chronic inflammatory condition characterised by subacute-onset shoulder and pelvic girdle pain, and early morning stiffness. Oral glucocorticoids represent the treatment mainstay and whilst cessation of therapy is the goal, a subset of patients with relapsing disease remains poorly delineated.

This thesis aimed to characterise the demographic, clinical, laboratory and imaging phenotype of patients that relapse by undertaking a prospective longitudinal cohort study of newly diagnosed, steroid naïve PMR cases (2012 EULAR/ACR classification criteria) treated with a weaning schedule of prednisolone (BSR guideline). Disease relapse, as defined by the PMR-activity score (PMR-AS), represented the primary outcome measure and was observed in 25/32 participants (78.1%) during the 46-week follow-up period. Older age at diagnosis (HR 1.07) and female sex (HR 2.38) were subsequently associated with an increased risk of relapse, whilst a volar pattern of  $^{18}\text{F}$ -FDG uptake on whole body PET/CT conferred a distinct prognostic advantage (HR 0.25). Half of the study participants also met criteria for the secondary endpoint of glucocorticoid-resistant disease. Baseline predictors for this outcome again included older age and female sex, along with high BMI and high neutrophil to lymphocyte ratio (NLR).

Results from this work additionally informed a proof-of-concept PET/MRI fusion study identifying hamstring peritendonitis as the anatomic correlate of abnormalities observed adjacent to the ischial tuberosities. A nested case-control subsequently achieved a sensitivity of 90.9% and specificity of 92.4% for diagnosing PMR on whole body PET/CT based upon a novel scoring algorithm that combined this finding with other key sites of extra-capsular pathology. Finally, data was utilised for preliminary validation of candidate instruments being considered for inclusion in a PMR core outcome measurement set to be endorsed by the international body, OMERACT.

Overall, the findings presented in this thesis confirm the hypothesis that discrete phenotypic differences exist among PMR patients with relapsing disease and make a substantive novel contribution to the literature concerning the pathology, diagnosis, monitoring and management of this rheumatic disease. The low incidence of sustained clinical remission observed in this study following a standardised wean of glucocorticoid therapy should however serve as a timely reminder of the ongoing need for an alternate treatment paradigm in PMR.

## II. Declaration

This is to certify that:

- The thesis comprises only my original work towards the Doctor of Philosophy degree except where indicated in the Preface;
- Due acknowledgement has been made in the text to all other material used;
- The thesis is fewer than 100,000 words in length, exclusive of tables, figures, references and appendices.

Claire Elizabeth Owen

July 10<sup>th</sup>, 2020.

### III. Preface

- This thesis includes a literature review, original research articles and an editorial to which other authors contributed as follows:

|                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Owen CE, Buchanan RRC & Hoi A. Recent Advances in Polymyalgia Rheumatica. <i>Internal Medicine Journal</i> ; 45(11):1102-8.                                                                                                                                                                                                                                                                | Author CO prepared and revised the manuscript (75%); Authors AH and RB reviewed and edited the manuscript.                                                                                                                                                                 |
| Owen CE, Poon AMT, Lee ST, Yap LP, Zwar RB, McMenamin CM, Lam SKL, Liew DFL, Pathmaraj K, Kemp A, Scott AM & Buchanan RRC. Fusion of PET/CT with MRI Demonstrates Hamstring Peritendonitis in Untreated Patients with Polymyalgia Rheumatica. <i>Rheumatology Oxford</i> ; 57(2):345-53.                                                                                                   | Author CO designed the study, prepared and revised the manuscript (70%); Authors AP, STL, LY and RZ analysed imaging findings; Authors CM, KP and AK assisted with data collection and image acquisition; Authors SKL, DL, AS and RB reviewed and edited the manuscript.   |
| Owen CE, Poon AMT, Yang V, McMaster C, Lee ST, Liew DFL, Leung JL, Scott AM & Buchanan RRC. Abnormalities at Three Musculoskeletal Sites on Whole Body Positron Emission Tomography/Computed Tomography Can Diagnose Polymyalgia Rheumatica with High Sensitivity and Specificity. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> ; 2020 Feb 23, online ahead of print. | Author CO designed the study, prepared and revised the manuscript (70%); Authors AP and SL analysed imaging findings; Author VY assisted with data collection; Author CM performed the statistical analysis; Authors DL, JL, AS and RB reviewed and edited the manuscript. |
| Owen CE, McMaster C, Liew DFL, Leung JL, Scott AM & Buchanan RRC. Neutrophil to Lymphocyte Ratio Predicts Glucocorticoid Resistance in Polymyalgia Rheumatica. <i>International Journal of Rheumatic Diseases</i> ; submitted on 23/6/20.                                                                                                                                                  | Author CO designed the study, prepared and revised the manuscript (80%); Author CM performed the statistical analysis; Authors DL, JL, AS and RB reviewed and edited the manuscript                                                                                        |

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Owen CE, Yates M, Twohig H, Muller S, Neill LM, Harrison E, Shea B, Simon LS, Hill CL & Mackie SL. Toward a Core Outcome Measurement Set for Polymyalgia Rheumatica: Report from the OMERACT 2018 Special Interest Group. <i>Journal of Rheumatology</i> ; 01:01. | Author CO assisted with the systematic literature review and online respondent survey, led the raw data analysis, prepared and revised the manuscript (60%); Author MY led the online respondent survey; Author HT led the systematic literature review; Author SM contributed patient data and assisted with the raw data analysis; Authors LN, EH, BS, LS, CH and SM reviewed and edited the manuscript. |
| Owen CE, Liew DFL & Buchanan RRC. Musculotendinous Inflammation: The Defining Pathology of Polymyalgia Rheumatica? <i>The Journal of Rheumatology</i> ; 46(12):1552-5.                                                                                            | Author CO prepared and revised the manuscript (80%); Authors DL and RB reviewed and edited the manuscript.                                                                                                                                                                                                                                                                                                 |

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## VII. List of Abbreviations

|                           |                                                  |
|---------------------------|--------------------------------------------------|
| <b>ACPA</b>               | Anti-citrullinated peptide antibodies            |
| <b>ACR</b>                | American College of Rheumatology                 |
| <b>ANCA</b>               | Anti-neutrophil cytoplasmic antibodies           |
| <b>BMI</b>                | Body mass index                                  |
| <b>BSR</b>                | British Society of Rheumatology                  |
| <b>CRP</b>                | C-reactive protein                               |
| <b>DAS-28</b>             | Disease activity score-28                        |
| <b>DMARD</b>              | Disease modifying anti-rheumatic drug            |
| <b>EMS</b>                | Early morning stiffness                          |
| <b>ESR</b>                | Erythrocyte sedimentation rate                   |
| <b>EUL</b>                | Elevation of upper limbs                         |
| <b>EULAR</b>              | European League Against Rheumatism               |
| <b>FBE</b>                | Full blood examination                           |
| <b><sup>18</sup>F-FDG</b> | <sup>18</sup> F-Fluorodeoxyglucose               |
| <b>FSE</b>                | Fast spin-echo                                   |
| <b>GCA</b>                | Giant cell arteritis                             |
| <b>GM-CSF</b>             | Granulocyte-macrophage colony-stimulating-factor |
| <b>HAQ-DI</b>             | Health assessment questionnaire-disability index |
| <b>HLA</b>                | Human leucocyte antigen                          |
| <b>HREC</b>               | Human research ethics committee                  |
| <b>IFN</b>                | Interferon                                       |
| <b>IL</b>                 | Interleukin                                      |
| <b>LV-GCA</b>             | Large vessel-giant cell arteritis                |
| <b>m-HAQ</b>              | Modified health assessment questionnaire         |
| <b>MPR-PMR</b>            | Melbourne predictors of relapse in PMR           |
| <b>MRI</b>                | Magnetic resonance imaging                       |
| <b>MST</b>                | Early morning stiffness                          |
| <b>NLR</b>                | Neutrophil to lymphocyte ratio                   |
| <b>NRS</b>                | Numeric rating scale                             |

|                          |                                                                           |
|--------------------------|---------------------------------------------------------------------------|
| <b>OMERACT</b>           | Outcome measures in rheumatology                                          |
| <b>PET/CT</b>            | Positron emission tomography/computed tomography                          |
| <b>PGA</b>               | Physician global assessment                                               |
| <b>PICF</b>              | Patient information consent form                                          |
| <b>PLR</b>               | Platelet to lymphocyte ratio                                              |
| <b>PMR</b>               | Polymyalgia rheumatica                                                    |
| <b>PMR-AS</b>            | Polymyalgia rheumatica-activity score                                     |
| <b>RA</b>                | Rheumatoid arthritis                                                      |
| <b>RS3PE</b>             | Remitting seronegative symmetrical synovitis with pitting oedema syndrome |
| <b>STIR</b>              | Short T1 inversion recovery                                               |
| <b>SUV<sub>max</sub></b> | Maximum standardised uptake value                                         |
| <b>TLRs</b>              | Toll-like receptors                                                       |
| <b>TNF</b>               | Tumour necrosis factor                                                    |
| <b>TSS</b>               | Total skeletal score                                                      |
| <b>TVS</b>               | Total vascular score                                                      |
| <b>VAS</b>               | Visual analogue scale                                                     |
| <b>WCC</b>               | White cell count                                                          |

# Chapter 1: Introduction and Literature Review

## 1.1 Preface

In the first chapter, the existing medical literature pertaining to polymyalgia rheumatica (PMR) will be critically appraised. Areas of focus include the role played by imaging in diagnosis and the contribution these modalities have made to uncovering the distinctive pathology of this condition. The few recognised adverse prognostic indicators in PMR will also be examined. This will lead to a summation of existing deficiencies in PMR research, followed by an outline of the aims for this thesis.

This literature review served as the basis for an article published in 2015 –

Owen CE, Buchanan RRC & Hoi A. Recent Advances in Polymyalgia Rheumatica. *Internal Medicine Journal*; 45(11):1102-8. The full text version of this publication is included in appendix 1.

## 1.2 Introduction

PMR is a chronic inflammatory condition characterised by the subacute-onset of shoulder and pelvic girdle pain, and early morning stiffness in men and women over the age of 50 years.(1) Despite ranking second only to rheumatoid arthritis (RA) in terms of its lifetime incidence risk, PMR remains poorly understood relative to other rheumatic conditions.(2)

In the absence of a gold standard test, diagnosis is based upon a clinical construct and laboratory evidence of systemic inflammation. Controversy has therefore existed as to whether PMR represents a disease in its own right or an umbrella term that encapsulates a clinical presentation common to a range of related conditions. For example, an initial “polymyalgic” presentation may evolve to an alternate diagnosis such as late-onset RA or spondyloarthritis. Similarly, concomitant giant cell arteritis (GCA) is recognised in 16-21% of PMR cases.(3)

In 2012, collaboration between the European League Against Rheumatism and American College of Rheumatology (EULAR/ACR) resulted in standardised classification criteria being released in order to improve the homogeneity of this population for future study.(4) Increasing use of imaging modalities such as ultrasound, magnetic resonance imaging (MRI) and whole body positron emission tomography/computed tomography (PET/CT) in PMR has also shed new light on the extra-capsular, rather than intra-articular, pathology that predominates in this condition.

Despite certain advances, glucocorticoids still represent the treatment mainstay for PMR.(5) Historically characterised as a self-limiting, exquisitely steroid-responsive entity, current evidence indicates that up to 50% of patients still require prednisolone 2-3 years after diagnosis.(6) The role of disease modifying anti-rheumatic drugs (DMARDs) has been examined, but there is a lack of evidence to support their use from the outset in all comers.(7) Sadly, the morbidity associated with low-dose glucocorticoid therapy is not insignificant either, with studies indicating adverse event rates in PMR double that encountered in comparable rheumatic conditions.(8)

Ultimately, the subset of patients with relapsing PMR who are likely to benefit from early initiation of a steroid-sparing agent requires better characterisation. Were this to be achieved, an alternate treatment paradigm could then be studied in this population.

### 1.3 History

Dr William Bruce first described PMR in 1888 when he documented a series of five elderly patients presenting with disabling proximal joint and muscle pain, which he called “senile rheumatic gout”.(9) Peripheral synovitis was noted in two of the cases. After a period of approximately two years, complete resolution of symptoms was observed.

No further reports of PMR are recognised in the literature until over 50 years later, when independent authors described similar clinical presentations as “periarthrosis humeroscapularis” and “peri-extraarticular rheumatism”.(1) As in Bruce’s work, the natural history was reported to be that of a self-limiting illness. A possible relationship between PMR and RA was postulated by Bagratuni in 1956 when it was suggested that the syndrome represented a prodrome to established inflammatory arthritis called “anarthric rheumatoid disease”.(10) However, none of Bagratuni’s patients actually developed RA during follow-up, thereby discrediting this hypothesis. An overlap between PMR and GCA was similarly reflected around this time by the term “polymyalgia arteritica”, although Hamrin et al. incorrectly believed that the two conditions always existed concurrently.(11)

By 1960, the term PMR became commonplace following Barber’s realisation that peripheral arthritis like that seen in RA was not a cardinal clinical feature.(12) Subsequent work focussed upon therapeutics, with glucocorticoids recognised early for their effectiveness in symptom relief.(1) Higher doses than that in current use were initially advocated, primarily based upon concerns regarding the coexistence of GCA in PMR patients. In 1961, Boyle and Beatty

reported treatment success with a starting prednisolone dose of 15mg/day or less.(13) This approach is still favoured to this day.

## 1.4 Epidemiology and Pathophysiology

When compared with other inflammatory conditions, PMR ranks second only to RA in terms of its lifetime incidence risk (estimated at 2.43% for women and 1.66% for men).(2) The incidence is highest in individuals of Northern European descent, with a prevalence of approximately 6/1000 people.(14) Women are significantly more likely to be diagnosed with the condition, whilst rates increase steadily with age until the eighth decade of life. Hoganson et al. investigated the relationship between body mass index (BMI) and PMR in their study, however no association was found.(15) Aside from age, sex and ethnicity, few risk factors for the development of PMR have been identified.

### 1.4.1 Genetics and Environmental Factors

The aetiology of PMR is poorly understood. Like most autoimmune conditions, it is postulated to result from the interaction of susceptible genetics with as yet unidentified environmental factors.

In the Scandinavian population, a clear association with human leucocyte antigen (HLA) class II genes, specifically HLA-DRB1\*04, has been established.(16) This finding highlights the genetic relationship between PMR and both GCA and RA, in that all of these conditions exhibit an over-representation of this allele when compared with healthy controls.(17) Furthermore, PMR associated with HLA-DRB1\*04 is more likely to occur in the context of GCA and express a disease phenotype characterised by relapse.(18)

The genetic susceptibility to PMR in other ethnic groups is distinct though, with HLA-DRB1\*04 being infrequently identified in Southern European patients.(19) Such evidence supports the argument that PMR is in fact a polygenic condition where genes other than HLA-class II, particularly those involved in the inflammatory cascade, contribute to disease pathogenesis.

In North-Western Spain, a microsatellite polymorphism encoding tumour necrosis factor (TNF), TNF-b3, is strongly linked with PMR and this association has been proven to be independent of HLA class II.(20) Similarly, genes responsible for endothelial-cell adhesion molecules have been proposed as susceptibility factors following a study of Italian PMR patients that demonstrated a high frequency of an intercellular adhesion molecule 1 polymorphism.(19) This

result however, could not be replicated in a Spanish population.(21) Conversely, an association between the interleukin (IL) 6-174 allele C has been identified among GCA patients from Spain presenting with polymyalgia.(22) Yet again though, the same genetic predisposition has failed to be appreciated in an Italian cohort.(23)

More recent efforts have focussed on the role of the innate inflammatory pathway. Research examining the expression and function of nine human toll-like receptors (TLRs) in PMR and GCA found increased expression of TLR-7 and TLR-9 in patients compared with healthy controls.(24) Unfortunately, subsequent work assessing TLR-9 polymorphisms failed to demonstrate a significant difference in allele frequencies.(25)

Various infectious agents (e.g. *Mycoplasma pneumonia*, parvovirus B19) have been implicated as possible triggers of PMR, however no microorganism has been consistently linked to the pathogenesis of the condition.(16) Other studies have reported seasonal variations or cycles of incidence, but the cause of these findings remains unclear.(26)

#### 1.4.2 Immunology and Inflammatory Cytokines

In GCA, dendritic cells at the vessel's adventitia-media border are hypothesised to interact with an unknown antigen resulting in a switch from antigen-processing to antigen-presenting cells.(27) Following CD4+ T cell activation, T helper 1 cells generate the critical cytokine interferon-  $\gamma$  (IFN- $\gamma$ ) and modulate macrophage activation, whilst T helper 2 cells produce IL-17 thereby promoting cytokine production by macrophages and fibroblasts (including IL-1, IL-6 and TNF- $\alpha$ ).(28) The end result is a granulomatous vasculitis that leads to concentric hyperplasia of the intima and luminal occlusion.

PMR has been previously suggested to represent a “forme fruste” of GCA whereby systemic inflammation predominates and vasculitis remains subclinical.(28) Indeed, the profile of T-cell and macrophage-derived cytokines in temporal artery biopsy specimens from patients with PMR resemble those of GCA, with the exception of INF- $\gamma$  production and thus the presence of granulomatous vasculitis.(29) Consequently, INF- $\gamma$  is thought key in determining the clinical phenotype of GCA and PMR.

The precise location of the inflammatory process in PMR is still debated based upon available histologic studies. A mild synovitis with CD4+ T cell and macrophage infiltration characterises the pathology of PMR within the glenohumeral joint, although extra-capsular structures are also known to be affected.(30) Some of the very first biopsy reports in this condition documented

oedema and perivascular chronic inflammatory cell infiltration of the deltoid muscular fascia and its tendinous septum.(31) Similar inflammatory changes were identified at the shoulder joint capsule and bursa, whilst many arterioles exhibited active intimal endothelial cell proliferation raising a possible patho-aetiological link between PMR and GCA.

More recently, the cytokine profile from muscle in PMR patients has been studied.(32) A micro dialysis technique was utilised to measure pro-inflammatory and anti-inflammatory mediators before and after 14 days of prednisolone treatment. In symptomatic trapezius and vastus lateralis muscles, concentrations of IL-1 $\beta$  and IL-6, but not TNF- $\alpha$  were significantly higher among patients with PMR than controls at baseline. These levels were subsequently normalized by glucocorticoid therapy and correlated clinically with complete symptom resolution.

In the peripheral blood, PMR is characterised by hyperproduction of IL-6, however serum levels of IL-1 $\beta$  and TNF- $\alpha$  are not raised compared with controls.(33) The source of IL-6 is therefore unclear, with a similar percentage of circulating monocytes seen and no significant difference observed in cytokine production following ex-vivo stimulation. Similarly, CD3+ T lymphocytes from patients with PMR express similar amounts of intracellular cytokines to controls.

## 1.5 Clinical Phenotype and Diagnosis

Sudden-onset bilateral shoulder girdle pain is the presenting complaint in 70-95% of PMR patients and is typically accompanied by prolonged early morning stiffness (>45 minutes duration).(34) Involvement of the hip region is less common (50-70%), although its presence together with a limited range of movement on examination is more characteristic of PMR than other forms of inflammatory arthritis including RA.(4) One third of patients will exhibit constitutional features including low-grade fever, fatigue and loss of weight.(35) These symptoms in combination with raised laboratory markers of inflammation form the basis for a diagnosis of PMR.

Despite this textbook description, non-classical features occur in a substantial proportion of PMR cases. In particular, distal manifestations are seen in almost one-half of patients including peripheral arthritis and remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome.(4) Distinguishing this group from late-onset RA at presentation is especially difficult, although the combination of wrist and metacarpophalangeal or proximal interphalangeal synovitis is significantly more common in RA than PMR.(36) Furthermore, the peripheral arthritis of PMR is typically a short-lived phenomenon that exhibits a rapid response to treatment with prednisolone. Detection of rheumatoid factor and/or anti-citrullinated peptide

antibodies (ACPA) is also consistent with late-onset RA, however up to 35% of subjects are seronegative in this population.(37)

With concomitant GCA recognised in 16-21% of PMR cases, another challenge for diagnosticians is differentiating between a “polymyalgic” presentation of large vessel vasculitis and isolated PMR.(3) GCA can develop before, during or after PMR. Whilst symptoms such as headache, scalp tenderness, jaw claudication and sudden visual change should be screened for at diagnosis and follow-up in all patients, such typical features are not always present in GCA-associated PMR. Persistent systemic manifestations such as fever and inflammatory markers that fail to respond to treatment can reflect an underlying untreated vasculitic process.

Despite best efforts, a shift in diagnosis is observed in 5-23% of PMR patients after long-term follow-up.(38, 39) A range of mimics including infection, malignancy and other inflammatory conditions such as spondyloarthritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis have been reported.(20) The consensus-based 2012 EULAR/ACR classification criteria were developed to standardize the definition of PMR and thereby address the uncertainty that commonly surrounds its diagnosis.(4) One-hundred-and-twenty-five patients with new-onset PMR and 169 controls with conditions mimicking PMR (including late-onset RA) were prospectively evaluated in this study for a range of clinical, laboratory and ultrasound features. Hip involvement, early morning stiffness, the modified health assessment questionnaire (m-HAQ), weight loss and raised C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) were subsequently identified on univariate logistic regression as key discriminators between patients with PMR and comparison subjects. Following further in-depth analyses, age at onset  $\geq 50$  years, bilateral shoulder aching and, abnormal ESR and/or CRP were established as required criteria with an additional scoring algorithm developed as outlined in Table 1.1. A score of  $\geq 4$  points on the clinical algorithm is consistent with a diagnosis of PMR.

Macchioni and colleagues have since compared the performance of these with six other classification/diagnostic criteria, concluding that the 2012 EULAR/ACR criteria were the most sensitive (92.6%) and exhibited comparable specificity (81.5%).(40) When utilised to distinguish PMR from late-onset RA, the 2012 EULAR/ACR classification criteria similarly performed well (sensitivity 86%, specificity 91%). Although higher specificities were observed with both the Jones and Nobunaga criteria (96.7% and 97.8% respectively), mostly due to their emphasis on the absence of peripheral arthritis, this occurred at the expense of their sensitivity values (63.1% and 58.2%).

**Table 1.1:** The 2012 EULAR/ACR classification criteria scoring algorithm without and including ultrasound.(4)

| Features                                                                                                                                                     | Clinical Criteria<br>(without Ultrasound) | Criteria including<br>Ultrasound |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------------|
| <b>Morning stiffness &gt;45 minutes</b>                                                                                                                      | 2 points                                  | 2 points                         |
| <b>Hip pain or limited range of movement</b>                                                                                                                 | 1 point                                   | 1 point                          |
| <b>Normal Rh factor or ACPA</b>                                                                                                                              | 2 points                                  | 2 points                         |
| <b>Absence of other joint pain</b>                                                                                                                           | 1 point                                   | 1 point                          |
| <b>Ultrasound:</b>                                                                                                                                           |                                           |                                  |
| At least 1 shoulder with subdeltoid bursitis +/- biceps tenosynovitis +/- glenohumeral synovitis AND at least 1 hip with synovitis +/- trochanteric bursitis | N/A                                       | 1 point                          |
| Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis                                                                      | N/A                                       | 1 point                          |

Abbreviations: Rh factor – rheumatoid factor; ACPA – anti-citrullinated peptide antibodies.

## 1.6 Laboratory Investigations

The inflammatory markers, CRP and ESR, are typically elevated by two to ten times the upper limit in patients with PMR, however 7-20% of cases have been reported to have normal results.(41) In two separate studies by the same authors, the role of these acute phase reactants in assessing disease activity and predicting relapse have been evaluated.(41, 42) Whilst it is generally accepted that CRP and ESR levels should respond and eventually normalise following treatment with prednisolone in PMR, with symptom recurrence expected to coincide with rising inflammation, the findings presented by Salvarani et al. and Cantini et al. point to discrete functions for each marker.

In consecutive untreated patients with PMR, an elevated ESR (but not CRP) at diagnosis was correlated with a relative risk of 6.7 (95% CI 0.9-51.6,  $p=0.07$ ) for  $\geq 1$  disease relapse.(42) On the other hand, persistently elevated CRP (rather than ESR) levels during follow-up were significantly associated with symptom recurrence (RR 4.0 [95% CI 1.3-12.2],  $p=0.02$ ). ESR is thus considered superior for predicting relapse at baseline but CRP performs better as a monitor of subsequent disease activity.

That said, a number of issues inevitably arise when interpreting CRP and ESR results. In particular, both markers are non-specific for measuring disease activity in PMR; ESR increases with age, smoking and renal failure, whilst a significant percentage of patients without concomitant morbidity exhibit abnormal CRP levels.(43, 44) Furthermore, normal CRP and ESR results have been documented in up to 14 and 27% of relapses respectively.(45) There is consequently a compelling argument for a novel biomarker that can be monitored in PMR.

Given CRP is a surrogate for IL-6, it is not surprising that ongoing elevation of this acute phase reactant has similarly been associated with symptom recurrence and disease relapse.(42) An early study of disease activity in PMR and GCA established that glucocorticoid therapy merely suppressed the production of IL-6 for a period of hours before levels rebounded to the pathologic range.(46) Short-term treatment withdrawal also correlated with rising IL-6 plasma concentrations and symptom recurrence. The authors therefore concluded that IL-6 represented a sensitive marker of treatment response that could be utilised for decisions regarding prednisolone dose adjustment. Unfortunately, this practice has not become commonplace due to the absence of a readily available and inexpensive IL-6 laboratory assay.

More recently, fibrinogen has been investigated as a biomarker for disease activity in PMR following recognition of its close relationship with IL-6 production. McCarthy et al. studied

fibrinogen, CRP and ESR levels at baseline and 6 weeks in 60 patients with PMR (25 with active and 35 with inactive disease).(45) As a measure of treatment response, fibrinogen was found to be significantly superior with a sensitivity of 92% and specificity of 96%. Its specificity for clinical remission was also higher than that calculated for CRP and ESR. Though these findings are promising, further validation of this biomarker in a large, multi-centre trial is now necessary.

Additional laboratory tests carried out as part of the work-up for PMR are primarily aimed at excluding common differential diagnoses including other inflammatory conditions (eg. myositis, ANCA-associated vasculitis), metabolic disorders (eg. hypothyroidism), infection and malignancy. Simple investigations like a full blood examination, creatine kinase levels and thyroid function testing are recommended.

## **1.7 Imaging**

### **1.7.1 Ultrasound**

From the very beginning, ultrasound has been an appealing imaging modality with which to further investigate the pathogenesis, diagnosis and prognosis of PMR. Both B mode and Power Doppler ultrasound have been studied to date, the latter permitting assessment of hyperaemia within the synovial membrane which is known to strongly correlate with histological synovitis.(47)

Bilateral subacromial-subdeltoid bursitis is considered the hallmark lesion of PMR, being associated with 92.9% sensitivity and 99.1% specificity.(48) Findings of biceps tenosynovitis and glenohumeral synovitis of the shoulders, and trochanteric bursitis of the hips are similarly recognised as consistent with the diagnosis.(49) When compared with MRI as the gold standard, ultrasound exhibits high sensitivity and specificity for the detection of PMR inflammatory findings.(48) It also has the added potential of being performed by the patient's rheumatologist at the bedside, as an extension of the clinical examination.

Ultrasound's ability to differentiate between PMR and late-onset RA has been evaluated in several studies. Lange et al. first examined the glenohumeral joints of 22 patients with typical PMR symptoms (2 of whom had histological GCA on temporal artery biopsy) and contrasted these results with 29 individuals diagnosed with seronegative late-onset RA.(50) In this instance, intra-articular effusion or synovitis was seen in the shoulder of only one PMR case compared with six instances among the RA group. Interestingly, subacromial-subdeltoid bursitis

and biceps tenosynovitis were also found to be more frequent and severe in late-onset RA patients, however no formal statistical analysis comparing the groups was undertaken.

Falsetti et al. have subsequently evaluated the ability of ultrasound to predict the diagnostic outcome in patients presenting with polymyalgic symptoms.(51) In their study, 61 consecutive individuals underwent B mode and Power Doppler ultrasound examination of both proximal (shoulder, hip) and distal (elbow, wrist, metacarpophalangeal) joints. Contrasting with Lange's results, a significant difference existed between those patients diagnosed with late-onset RA as compared with PMR; subacromial-subdeltoid bursitis was more frequent in PMR (79% cf. late-onset RA 33%,  $p<0.01$ ), whilst intra-articular effusion/synovitis of the wrist ( $p<0.001$ ) and metacarpophalangeal joints ( $p<0.001$ ) was typical of late-onset RA. The presence of Power Doppler signal at the glenohumeral and wrists joints was similarly associated with late-onset RA, rather than PMR.

Following on from these initial studies, ultrasound was assessed as a feasible investigation for inclusion in the 2012 EULAR/ACR classification criteria for PMR.(4) In the comparison of cases with controls, the PMR cohort was found to exhibit more abnormal ultrasound findings at the shoulders (particularly subacromial-subdeltoid bursitis and biceps tenosynovitis) and hips. These results alone however did not permit PMR to be distinguished from RA. Factor analysis did reveal however that bilateral shoulder abnormalities or abnormalities in one shoulder and hip improved the specificity of the classification criteria from 78 to 81%. Whilst the specificity figure for discriminating RA from PMR was lower (70%) than that for all comparison subjects, an optional scoring algorithm including ultrasound has been subsequently incorporated in the criteria (Table 1.1). A score of  $\geq 5$  points on the ultrasound algorithm is consistent with a diagnosis of PMR.

In RA, ultrasound has been found to have comparable repeatability and reproducibility to surrogate clinical scores of disease activity such as the disease activity score-28 (DAS-28).(52) Furthermore, the presence of Power Doppler signal is recognised to predict clinical relapse and radiographic progression.(53, 54) Two studies to date have similarly evaluated the role of ultrasound in assessing disease activity and predicting relapse in PMR.

Macchioni et al. performed B mode and Power Doppler shoulder ultrasound on 57 consecutive PMR patients at diagnosis and following initiation of a standardised prednisolone weaning schedule.(55) An inflammatory abnormality in at least one shoulder was detected in 56 patients (98.2%) at baseline. This number fell, but only to 37 patients (64.9%) at the time of the second examination. Relapse was defined as the recurrence of clinical features in association with

raised inflammatory markers, however most individuals (60%) with persistent ultrasound abnormalities were adjudged to be in clinical remission or a state of low disease activity. Unfortunately, the relationship between these subclinical findings and long-term treatment outcomes could not be established in this study during the 12-month follow-up period. The presence of Power Doppler signal in articular and extra-capsular synovial structures at baseline did however predict subsequent clinical relapse ( $p=0.03$ ).

In a similar study, Jimenez-Palop et al. evaluated the resolution of abnormalities on B mode ultrasound in PMR following treatment with glucocorticoid therapy.(56) Scanning was performed at baseline, 4 and 12 weeks. Thirty-four patients (69%) in this instance had evidence of inflammation in at least one bilateral site at diagnosis, with 50% found to exhibit persistent abnormalities at weeks 4 and 12. In addition, ultrasound findings showed equal or superior responsiveness to change than conventional disease activity parameters including CRP and ESR, suggesting it may have particular utility in patients with low or normal inflammatory markers.

### 1.7.2 Magnetic Resonance Imaging

MRI has been an especially useful adjunct to ultrasound in delineating the pathology that is typical of PMR and distinct from that of late-onset RA. McGonagle et al. first demonstrated a significant difference in the anatomic distribution of inflammation in their MRI study contrasting the shoulders of 14 patients with PMR with 14 RA patients.(57) Whilst both groups exhibited a similar incidence of joint effusion, bursitis and tenosynovitis, extra-capsular soft tissue oedema was seen in 9/14 PMR cases (10/20 joints) as opposed to 2/14 patients with RA (2/20 joints) ( $p=0.02$ ).

A subsequent study by the same authors investigated the distribution of hand involvement by performing MRI of the metacarpophalangeal joints.(58) In this instance, far greater Gadolinium-enhancement in the extra-capsular soft tissues of patients with PMR was also noted (8/10 patients) as compared to that seen in early RA (2/10 patients) ( $p=0.025$ ). Interestingly, the amount of synovitis, tenosynovitis and even bone erosions quantified were found to be comparable in both groups. A more recent study by Cimmino et al. similarly confirmed no difference in synovitis, erosion or bone oedema scores when MRI of the hand was performed in 15 PMR patients and 13 healthy controls.(59) In this instance however, there were higher rates of tenosynovitis (particularly in the extensor compartment) recorded – 8/15 patients (53.3%) versus 1/13 controls (7.7%) ( $p=0.02$ ).

Taken together, these results support the hypothesis that extra-capsular, not intra-articular, inflammation is the prevailing pathology in PMR.(59) Oedema of the tendon sheath rather than synovial cellular proliferation also seems characteristic, thereby explaining the rapid resolution of joint symptoms that typically accompanies glucocorticoid treatment.(51)

Extra-capsular inflammation has since been correlated with long-term treatment outcomes in PMR. In their prospective whole body MRI study comparing 22 PMR cases with 16 RA controls, Mackie et al. documented a complete patient-reported response to glucocorticoid therapy at first follow-up in 11/13 PMR patients (84.6%) exhibiting this imaging pattern. This subset of participants was however less likely than their non-extra-capsular peers to be able to discontinue prednisolone within 1 year of diagnosis (1/14 extra-capsular cf. 4/7 non-extra-capsular patients,  $p=0.03$ ). The authors rightfully concluded that categorisation of patients based upon this pathoanatomical difference might significantly improve the homogeneity of PMR populations being studied in clinical trial settings.

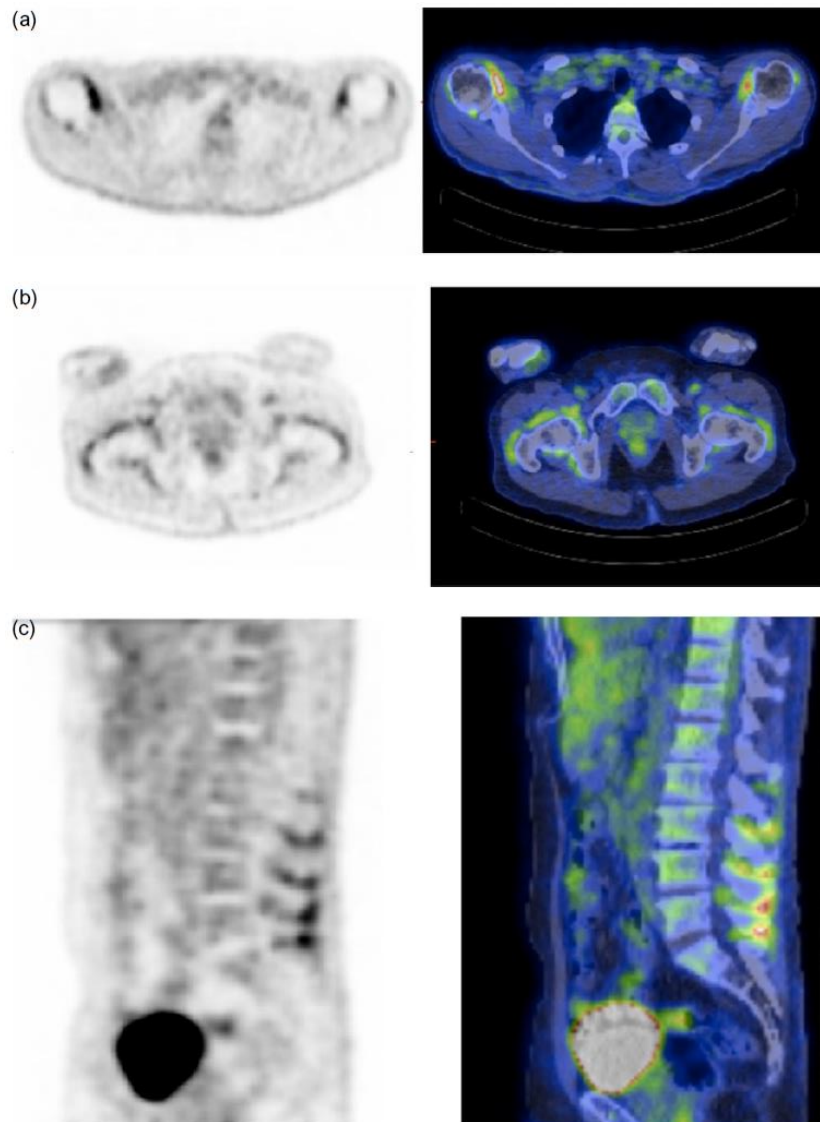
### 1.7.3 Whole Body Positron Emission Tomography/Computed Tomography

Historically, PET has been predominantly used in oncology to stage malignancy. In 1999 however, Blockmans et al. documented the ability of whole body PET to detect large vessel involvement in both GCA and PMR.(60) Since then, numerous studies have examined the utility of this investigation for the detection of large vessel vasculitis, although relatively few until recently have focussed upon PET as a diagnostic test for PMR.

Initial studies of PET in PMR primarily focussed on its overlap with GCA by investigating the incidence of subclinical large vessel vasculitis. In the largest prospective study of its kind, the extent of  $^{18}\text{F}$ -Fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake in seven vascular regions was assessed in 35 patients with isolated PMR.(61) A negative temporal artery biopsy was notably necessary for inclusion. In this context, large vessel involvement was detected in 11/35 PMR patients (31%), although its extent was insufficient for a diagnosis of vasculitis in all but two cases. It is thus acknowledged that a minority of PMR patients will possess vascular FDG uptake in keeping with concomitant GCA, however a larger proportion may exhibit milder changes. Whether this lesser degree of uptake impacts upon long-term treatment outcomes is however unknown.

The ability of PET to detect articular inflammation in PMR also became apparent from this work, with abnormalities in a shoulder and hip distribution documented in 94% and 89% of cases respectively (Figure 1.1).(61) In addition, a novel finding involving the processi spinosi of the vertebrae was first reported (51%). This has since been localised to the interspinous bursae

**Figure 1.1:** Whole body PET/CT demonstrating characteristic  $^{18}\text{F}$ -FDG uptake in the shoulders (a), hips (b) and interspinous bursae (c) of a patient with PMR.(62)



Abbreviations: PET/CT – positron emission tomography/computed tomography;  $^{18}\text{F}$ -FDG –  $^{18}\text{F}$ -Fluorodeoxyglucose.

on MRI and sheds light on the aetiology of pain in the cervical and lumbar spine that is commonly reported by affected patients.(63, 64) Repetitive PET has also been evaluated as a means to predict disease relapse in PMR, however no difference was identified in articular or vascular FDG uptake at baseline, 3 or 6 months in the group who relapsed compared with those who did not.(61) Naturally, the relatively short duration of follow-up in this study may have had some bearing upon these results.

Whilst the low resolution of PET images previously presented a barrier to the study of PMR's distinct anatomic distribution of inflammation, the advent of hybrid PET/CT technology has helped to overcome this issue. Yamashita et al. explored the similarities and differences on whole body PET/CT among patients with PMR, RA and spondyloarthritis.(65) Detection of inflammation adjacent to the ischial tuberosities, trochanteric and interspinous bursa was found to discriminate between PMR and RA, but not between PMR and spondyloarthritis (the prototype of enthesal disease). Higher FDG uptake intensity was however detected in PMR patients compared with both RA and spondyloarthritis. Similarly, a higher frequency of capsular as opposed to intra-articular knee  $^{18}\text{F}$ -FDG uptake on whole body PET/CT has been reported in PMR.(66) Again, these findings reinforce distinct pathological differences between PMR and other rheumatic conditions, and hence the focus of more recent PET/CT research has been upon delineating those anatomical structures that are commonly involved.

A Japanese group first attributed  $^{18}\text{F}$ -FDG uptake at the pelvic girdle in PMR to the entheses of the pectineus and rectus femoris muscles in their study comparing 15 PMR with 7 late-onset RA patients. None of the RA patients exhibited these abnormalities.(67) Subsequent to this, Rehak et al. explored their previous documentation of praepubic  $^{18}\text{F}$ -FDG accumulation by retrospectively reviewing the PET/CT scans of 23 PMR patients, 15 of whom had undergone a repeat scan following treatment with prednisolone.(68) Improvement in the degree of  $^{18}\text{F}$ -FDG uptake was noted in all treated patients, with the authors concluding that the observed PET findings represented "another type of extra-articular inflammation" in PMR, namely enthesitis and tenosynovitis of the pectineus and adductor longus muscles.

An inherent advantage of whole body PET/CT over ultrasound or MRI is its ability to detect recognised mimics such as infection and malignancy. Consequently, this modality has been proposed as a "one stop shop" for diagnosing PMR, although limitations include radiation exposure, availability and cost.(69) The performance of PET as a diagnostic tool has been evaluated in two major studies to date. In the first, whole body PET/CT scans from 50 patients with a PMR diagnosis (2012 EULAR/ACR classification criteria) were retrospectively analysed and compared to 53 malignancy controls. Differences between the two groups were found for

<sup>18</sup>F-FDG uptake scores and the number of musculoskeletal regions involved, with  $\geq 3$  sites of significant uptake being associated with a sensitivity of 74% and specificity of 79% for a diagnosis of PMR. Of note, the PMR group in this instance included 7 patients with “PMR syndrome associated with other diseases”, likely adversely affecting the authenticity of the results presented. By contrast, Henckaerts et al. have recently published a prospective PET study of 99 patients, sixty-seven of whom had a final diagnosis of PMR based on expert opinion. PMR patients were similarly reported to exhibit more intense <sup>18</sup>F-FDG uptake than their non-PMR peers, although none of the individual musculoskeletal regions evaluated were associated with adequate sensitivity and specificity for diagnostic purposes. Instead, the authors generated a total skeletal score to aid PMR diagnosis based upon qualitative <sup>18</sup>F-FDG scores at 12 articular sites, with a value of  $>16$  achieving a sensitivity of 85.1% and specificity of 87.5%. Whilst the composite nature of this system may be feasible in research settings, a more simplified approach would likely prove advantageous for use in everyday clinical practice.

## 1.8 Treatment

To this day, glucocorticoids constitute the mainstay of treatment for PMR.(5) The ideal approach for prednisolone therapy remains controversial though, as high level evidence to support a particular starting dose and weaning schedule is lacking.

In a prospective observational study of patients with PMR, Myklebust and Gran found that an initial prednisolone dose of  $\leq 15$ mg/day (as compared with  $>15$ mg/day) resulted in a lower maintenance glucocorticoid requirement at 2 years follow-up (5.2mg/day cf. 6.7mg/day,  $p = <0.001$ ).<sup>(70)</sup> The initial dose did not affect disease relapse or treatment discontinuation in this instance. However, in a randomised trial whereby PMR patients initially received either 10 or 20mg/day of prednisolone, those receiving the higher dose at baseline were observed to experience a lesser likelihood of symptom recurrence.<sup>(71)</sup> Similarly, Gonzalez-Gay et al. demonstrated in their study that a tapering rate of  $\leq 1$ mg/month (as compared with  $>1$ mg/month) after initial prednisolone doses of 10-20mg/day was associated with fewer relapses.<sup>(18)</sup>

The utility of methylprednisolone injections as an alternative to oral glucocorticoids has also been examined. In a study contrasting intramuscular depot with oral prednisolone therapy in newly diagnosed PMR patients, both regimens successfully induced clinical remission however a lower rate of treatment discontinuation was achieved at follow-up with the injection.<sup>(72)</sup> That said, a higher cumulative dose and therefore an increased risk of glucocorticoid-induced side effects was observed with oral treatment.

On the basis of available evidence and consensus opinion, the British Society for Rheumatology (BSR) has developed a regimen for low-dose glucocorticoid treatment.(73) Prednisolone 15mg daily is initiated for three weeks, reduced to 12.5mg for an additional three weeks, then 10mg for 4-6 weeks, and finally dropped by 1mg every 4-8 weeks thereafter. In the event of disease relapse (arbitrarily defined by the recurrence of symptoms and elevated inflammatory markers), the dose should be increased to the previous higher level for four weeks before the weaning schedule is reinstated.

However, even patients with a classic presentation of PMR may vary in their response to therapy with three distinct groups previously identified in one study: 1) those that responded rapidly and required prednisolone for less than 1 year duration; 2) those that responded well initially but did not tolerate prednisolone weaning and; 3) those that had only a partial response to the initial prednisolone dose.(74) Treatment dilemmas therefore arise from non-response, inability to dose-reduce and the need for therapy beyond 2 years. In other inflammatory conditions, a steroid-sparing drug or DMARD would typically be introduced in these situations. The role of these agents in the management of PMR however is somewhat unclear.

Three randomised controlled trials have assessed the efficacy of methotrexate for initial treatment of PMR with mixed results (two positive, one negative).(75-77) Low doses of methotrexate ( $\leq 10$ mg weekly) were utilised though and patients with GCA were also included in the trial population. In the most methodologically sound study, Caporali et al. randomised patients to prednisolone (initial dose 25mg/day) plus oral methotrexate (10mg/week) or prednisolone plus placebo.(75) A steroid-sparing effect was observed in the methotrexate group with a significantly higher number of patients off glucocorticoid therapy at 76 weeks (28/32 cf. 16/30 for placebo), together with a lower incidence of disease relapse and lower median prednisolone dose. In the BSR guideline, commencement of methotrexate is suggested in the event that a patient has relapsed on more than two occasions.(73)

Other DMARDs have been tried in PMR, including leflunomide which is a small molecule inhibiting pyrimidine synthesis with immunomodulatory and anti-inflammatory effects, and proven efficacy in RA. Interest in the use of leflunomide in PMR however arises from its lesser-known effect on inhibition of aberrant dendritic cell activation and down-stream modulation of cytokine production including IL-6.(78) Two recent case series have supported its efficacy as a steroid-sparing agent in patients with difficult to treat disease.(79, 80) In their study, Adizie et al. introduced leflunomide (initial dose 10mg/day) after a minimum three months of glucocorticoid therapy and reported a complete or partial response (determined by percentage patient global improvement, normal CRP and reduction in prednisolone dose) in 13/14

patients.(79) This finding is further supported by work from Norway which demonstrated a statistically significant reduction in prednisolone dose and CRP following three months of leflunomide treatment.(80) A randomised controlled trial examining the role of leflunomide in achieving sustained clinical remission in PMR is now underway.(81)

Due to the unprecedented success of TNF-blockade in RA, TNF inhibitors have also been trialled in refractory PMR. In a recent review of 99 cases with persistent disease activity or glucocorticoid-induced complications, a moderate steroid-sparing effect was reported.(82) The evidence is less compelling though when the two largest randomised controlled studies to date involving infliximab and etanercept are further scrutinised. In the former, no difference in relapse rate was observed with the addition of infliximab to standardised low-dose glucocorticoid therapy at 52 weeks follow-up (30% cf. 37% in the placebo group,  $p=0.80$ ). That said, the prednisolone dose was rapidly weaned and a low dosage of infliximab was utilised, which may have influenced the outcome. However, the results from a randomised placebo-controlled study of 20 newly diagnosed, steroid naïve patients treated with etanercept alone appear to counter the argument for TNF-blockade as a therapeutic approach in PMR; only a 24% improvement in disease activity parameters was seen in the treatment group compared with the controls. Such a change is likely to amount to a modest clinical benefit at best and further supports the available evidence that TNF- $\alpha$  is not central to the pathogenesis of PMR.

Based on biologic plausibility and its recent success in GCA(83), there is growing interest in the use of tocilizumab, a humanized monoclonal IgG antibody that binds directly to the IL-6 receptor. In 2016, Devauchelle-Pensec et al. reported the results of their open-label, prospective longitudinal study evaluating the effect of tocilizumab on disease activity in 20 newly diagnosed PMR patients.(84) Impressively, every patient achieved the primary endpoint of low disease activity and no flares occurred in the initial treatment phase or during the aggressive wean of glucocorticoid therapy that followed. This difference in practice amounted to a 70.2% reduction in steroid exposure compared with the standard BSR guideline. Further evaluation of IL-6 blockade as a therapy for PMR is accordingly underway in a randomised placebo-controlled trial of sarilumab.(85)

## 1.9 Prognosis and Complications

As outlined, the disease course of patients with PMR typically exhibits heterogeneity. Despite early studies reporting a self-limiting natural history, up to 50% of cases require prednisolone beyond two years and approximately 25% receive more than 4 years of continuous glucocorticoid therapy.(6) In a five year prospective study of treatment duration in 176 PMR

patients, Mackie et al. identified high plasma viscosity (HR 0.43 [95% CI 0.26-0.71],  $p=0.001$ ) and initial prednisolone dose  $>15\text{mg/day}$  (HR 0.57 [95% CI 0.37-0.87],  $p=0.010$ ) as statistically significant predictors of prolonged treatment.(86) In this cohort, 83 patients (49.1%) experienced relapse, suggesting the disease course in a significant proportion of PMR cases is in fact refractory. Other prognostic indicators previously associated with an increased risk of relapse in the literature include female sex, high ESR at diagnosis and the presence of peripheral arthritis.(87)

Indeed, these findings further support the hypothesis that two types of patients with PMR exist: those with a self-limiting illness that remits completely with standardised low-dose glucocorticoid therapy; and those with a relapsing course that requires protracted treatment. There is much controversy as to whether a safe long-term glucocorticoid dose exists. In RA which has been better studied to date, prednisolone  $<7.5\text{mg/day}$  has not been found to cause significant toxicity in the first 24 months of treatment besides weight gain and glaucoma.(88) That said, definite conclusions cannot be drawn in the absence of high quality evidence such as randomised controlled trials. Furthermore, it is known that a single prednisolone dose of only 2.5mg has near immediate effects on bone biology.(89) Accordingly, minimising the dose and duration of glucocorticoid therapy exposure in PMR must be a management priority.

Hutchings et al. reported 81% of patients with newly diagnosed PMR experienced at least one adverse event of prednisolone within the first 12 months of treatment in a prospective study of 129 cases.(90) Weight gain (43.5%), dyspepsia (39.3%), Cushingoid appearance (28.7%) and hypertension (24.6%) represented the most common complications. Whilst this rate is higher than others reported in the literature (65% by Gabriel et al. and 36% by Kyle et al.), it is clear that glucocorticoid-induced side effects are common among patients with PMR and typically occur more frequently when compared with other rheumatic conditions.(71, 91) In particular, a systematic review of the incidence of adverse events with low- to medium-doses ( $\leq 30\text{mg/day}$ ) of prednisolone found PMR was associated with a risk of 80/100 patient-years as compared with 43/100 patient-years in RA.(8) A RA treatment paradigm characterised by early and aggressive DMARD initiation is likely to account for this disparity.

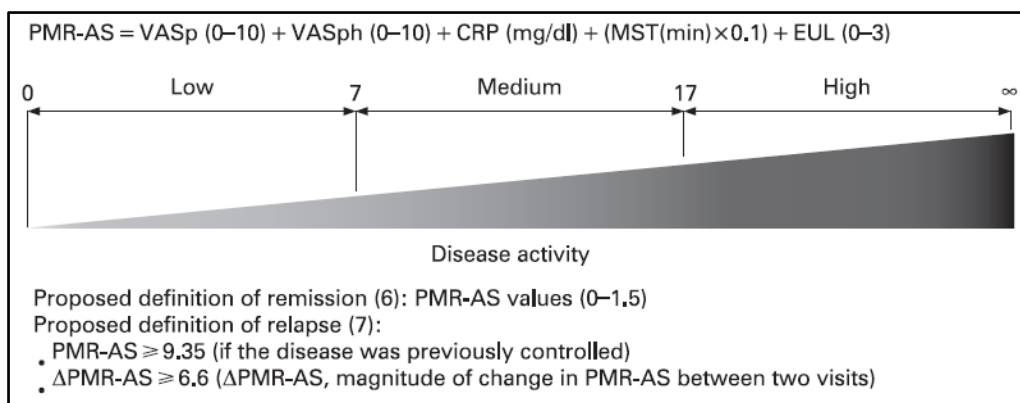
In Gabriel et al., the long-term side effects of low-dose glucocorticoid therapy were prospectively studied in 232 patients with PMR (30 of whom had concomitant GCA) for a mean follow-up period of 8.0 years.(91) One-hundred-and-sixty patients (65%) experienced an adverse event, an average of 1.6 years after the commencement of therapy, whilst the mean duration of treatment in this group was 3.5 years (cf. 2.4 years in all cases). Older age ( $p=0.0001$ ), a cumulative prednisolone dose  $\geq 1800\text{mg}$  ( $p=0.0092$ ) and female sex ( $p=0.04$ )

independently increased the side effect risk, with the incidence of diabetes mellitus, vertebral and hip fractures found to be 2-5 times greater in the PMR cohort as compared with age- and sex-matched controls. Significant morbidity was therefore observed to result from low-dose glucocorticoid therapy, particularly in those PMR patients with a protracted treatment course. More recently, these results have been replicated, albeit in a retrospective study.(92) Duration of therapy >2 years and cumulative glucocorticoid dose were similarly significantly associated with osteoporosis, fragility fractures and hypertension in this instance.

An increased risk of cardiovascular disease is reported in numerous inflammatory conditions including RA and systemic lupus erythematosus. In PMR, several studies have explored the incidence of vascular events and mortality. Kremers et al. reported patients with PMR were much more likely to experience myocardial infarct (OR 1.78 [95% CI 1.13-1.82), stroke (OR 1.60 [95% CI 1.08-2.39]) or peripheral vascular disease (OR 2.21 [95% CI 1.37-3.60]) compared with controls; however, the timing of these events relative to diagnosis was unclear.(93) Another study has since supported the association identified between PMR and peripheral vascular disease.(94) As for mortality, two large scale studies have found conflicting results: one reported an excess of vascular fatalities among PMR patients compared with the general population; whilst another failed to demonstrate an increased risk of death from ischaemic heart disease or stroke.(95, 96)

In GCA, overall survival is similar to that of the general population.(97) Among the subset of GCA patients with large vessel involvement however, an increased mortality is observed from aortic aneurysm/dissection (HR 3.4, 95% CI 2.2-5.4).(97) In PMR, overall mortality does not appear to be increased. Rather, a large prospective study of 274 patients found improved survival in cases when compared with age- and sex-matched controls (RR 0.70, 95% 0.52-0.95).(98) Despite further efforts to delineate the cause for this finding, the authors eventually concluded that regular medical surveillance following a diagnosis of PMR was the most likely explanation.(95)

The assessment of disease activity in PMR is central to balancing the risks posed by both disease-related and glucocorticoid-induced complications. In 2003, the European Collaborating PMR Group generated a core set of treatment response criteria including CRP or ESR, pain visual analogue scale (VASp), physician global assessment (VASph), early morning stiffness (EMS or MST) and elevation of upper limbs (EUL).(99) Leeb and Bird subsequently created a PMR-activity score (PMR-AS) incorporating these 5 variables (Figure 1.2).(100) A PMR-AS value <7 indicates low disease activity, whilst values  $\geq 7$  and  $\leq 17$ , and >17 correlate with moderate and high disease activity respectively.

**Figure 1.2:** Calculation of the PMR-AS and interpretation of results.(101)

Abbreviations: PMR-AS – polymyalgia rheumatica-activity score; VASp – patient pain visual analogue scale; VASph – physician global assessment; CRP – C-reactive protein; MST – morning stiffness; EUL – elevation of upper limb score.

A number of studies have since validated the PMR-AS as a measure of disease activity. DeJaco et al. confirmed that CRP, ESR, VASp, VASph, EMS/MST, EUL and current glucocorticoid dose were the priority items for defining relapse and remission in their Delphi-based expert consensus study.(101) In a prospective study of 89 patients with newly diagnosed PMR, the effectiveness of the PMR-AS in diagnosing disease flares was also evaluated.(102) A PMR-AS value  $\geq 9.35$  was found to be 96.6% sensitive and 90.7% specific, whilst a change in PMR-AS  $\geq 6.6$  between two visits demonstrated even better performance for flare diagnosis (sensitivity 100%, specificity 97.1%). Finally, a definition for clinical remission using the PMR-AS has been proposed by Leeb et al..(103) In this instance, a threshold of 0-1.5 was generated following analysis of median PMR-AS values in patients satisfying predetermined criteria for remission.

## 1.10 Conclusion

From a syndrome characterised by subacute onset bilateral shoulder and pelvic girdle pain together with raised inflammatory markers, our understanding of PMR is progressively evolving. There is now adequate evidence to support the ideology that this condition represents a distinct disease entity rather than an umbrella term which encapsulates a common clinical presentation. Despite shared genetic origins (HLA-DRB1\*04), key differences in the inflammatory cytokine profiles of patients with PMR compared with both GCA and RA are now appreciated. In particular, IFN- $\gamma$  and TNF- $\alpha$  are seen to be of diminishing importance relative to IL-6. The distribution of inflammation characteristic of PMR similarly appears different to RA, with extra-capsular, rather than intra-articular, involvement seen on ultrasound, MRI and whole body PET/CT.

Despite these advances, making a diagnosis of PMR can still be exceedingly difficult for the average clinician. With the introduction of the 2012 EULAR/ACR classification criteria, it is hoped that the homogeneity of PMR populations under study will be improved and the chances of wrongly diagnosing patients with other rheumatic conditions such as late-onset RA lessened. Indeed, these criteria have already been proven to outperform many that have come before them. However, the inherent disadvantage of basing a diagnosis upon clinical features combined with raised inflammatory markers will always be the misclassification of patients. There remains an unmet need for a definitive diagnostic test in PMR that is both cost-effective and readily available.

Although ultrasound has proven insufficient as the sole tool with which to differentiate between PMR and late-onset RA among patients presenting with polymyalgic symptoms, its utility as an aid to diagnosis has been established. In addition, the presence of Power Doppler signal at baseline is recognised to predict subsequent clinical relapse in PMR. As yet though, the prognostic implications of frequently identified subclinical inflammatory findings and the potential role of ultrasound in monitoring disease activity are unknown. Longitudinal study of low-grade large vessel uptake on whole body PET/CT in patients with clinically isolated PMR is similarly needed.

PMR is one of very few remaining rheumatic conditions whereby treatment with prednisolone alone is still advocated. In most other instances, glucocorticoid exposure is minimised and early DMARD initiation occurs to prevent steroid-related side effects. Although a percentage of patients with PMR do possess a self-limiting illness that remits completely with standardised low-dose glucocorticoid therapy, another larger group is characterised by a relapsing-remitting course. The evidence clearly indicates that significant morbidity arises from glucocorticoid-induced complications in the event that protracted treatment with prednisolone is necessary.

Unfortunately, studies exploring the role of DMARDs in PMR have been disappointing to date. In most instances though, these medications have been trialled in all comers rather than the subset of PMR patients with refractory disease. This represents a certain limitation when interpreting the results of this research. In the event that the baseline demographic, laboratory and imaging characteristics of patients with a relapsing-remitting course of PMR could be delineated, the effectiveness of DMARDs in this cohort could be better evaluated. That said, targeted therapeutic approaches which obviate the need for all PMR patients to be treated with glucocorticoids should remain the ultimate goal.

### **1.11 Aims of this Thesis**

Considering the available literature, it is hypothesised that PMR which relapses with standardised, low-dose glucocorticoid therapy represents a distinct, but as yet undefined, disease subset.

The primary aim of this thesis is therefore:

- 1) To characterise the demographic, clinical, laboratory and imaging phenotype of patients with PMR that relapses with standardised, low-dose glucocorticoid therapy.

- This aim will be addressed in Chapter 3, *Characterisation of an Untreated PMR Population on Whole Body PET/CT* and Chapter 5, *Results of the Melbourne Predictors of Relapse in PMR (MPR-PMR) Study*.

Secondary aims of this work are as follows:

- 1) To investigate the pathologic basis of PMR by determining precise anatomic correlates of abnormal  $^{18}\text{F}$ FDG uptake on whole body PET/CT:
  - Also addressed in Chapter 3;
- 2) To determine the sensitivity and specificity of novel  $^{18}\text{F}$ -FDG whole body PET/CT findings for the diagnosis of PMR:
  - This aim will be addressed in Chapter 4, *Sensitivity and Specificity of Novel Whole Body PET/CT Findings for a Diagnosis of PMR*;
- 3) To ascertain the role of musculoskeletal ultrasound in evaluating treatment response and clinical remission in PMR:
  - Also addressed in Chapter 5;
- 4) To evaluate the efficacy of a standardised low-dose glucocorticoid weaning schedule for the treatment of PMR:
  - Also addressed in Chapter 5;
- 5) To identify a novel biomarker that accurately measures PMR disease activity:
  - This aim will be addressed in Chapter 6, *Neutrophil to Lymphocyte Ratio as a Predictor of Glucocorticoid Resistance in PMR*;
- 6) To utilise collected data for the preliminary validation of instruments used to measure outcomes in clinical trials and observational research involving patients with PMR:
  - This aim will be addressed in Chapter 7, *Developing an OMERACT Endorsed Core Outcome Measurement Set for PMR*.

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## **Chapter 2: Methodology**

### **2.1 Preface**

In the previous chapter, it was established that the phenotype of PMR refractory to standardised, low-dose glucocorticoid therapy is poorly delineated. It concluded with the aims of this thesis, primarily to characterise the demographic, clinical, laboratory and imaging features of patients with relapsing PMR. This chapter will therefore outline the methods pertaining to the body of work that is subsequently presented.

### **2.2 Methods**

#### **2.2.1 Setting**

In a prospective, single-centre, cohort study (known as the Melbourne Predictors of Relapse in PMR [MPR-PMR] study), patients with suspected PMR were consecutively recruited to an early referral clinic located in the Rheumatology Department at Austin Health, Heidelberg Repatriation Campus, Heidelberg, Victoria, Australia. Referral sources included the Austin Hospital Emergency Department and acute inpatient units, along with primary care providers and rheumatologists in the Hospital's catchment area (north-eastern suburbs of Melbourne, Australia). Recruitment commenced on 14/7/2014, with the final participant enrolled on 9/5/2017. Prior ethics approval was received from the Austin Health Research Ethics Committee (HREC/14/Austin/158) and the trial prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000696695). A full copy of the MPR-PMR study protocol is included in appendix 2.

#### **2.2.2 Participants**

Prospective participants attended a screening visit to ensure key inclusion criteria had been satisfied, specifically a new diagnosis of PMR as defined by the 2012 EULAR/ACR classification criteria (utilising the clinical scoring algorithm).(1) Patients with symptoms suggestive of GCA (headache, jaw claudication, scalp tenderness or visual disturbance) were excluded, along with cases of cancer within the past 5 years, neuromuscular disease, active infection, other inflammatory conditions (eg. RA), chronic pain syndromes and uncontrolled psychiatric conditions, hypertension or diabetes. Initiation of glucocorticoid therapy or concomitant DMARDs prior to screening were also not permitted.

Information outlining the research project's purpose and participant involvement was provided to eligible patients prior to obtaining written consent. A full copy of the patient information consent form (PICF) is included in appendix 3.

### 2.2.3 Initial Visit

At the first study visit after enrolment (week 0), baseline demographic data was collected including date of birth, gender, race, co-morbidities and smoking status (Table 2.1). Disease onset, distribution of joint/muscle involvement (indicated by the patient on a human mannequin), duration of early morning stiffness and presence of constitutional symptoms (loss of weight, fever and fatigue) were also recorded. A standard physical examination including vital signs and BMI was carried out, with specific focus upon the presence of active synovitis or effusions of the peripheral joints and range of motion at the shoulders bilaterally (EUL score). In order to generate a PMR-AS, participants marked a visual analogue scale (VAS) scoring the severity of their current joint/muscle pain and the investigator (qualified rheumatologists including the PhD candidate) completed a physician global assessment. To gauge physical disability, the health assessment questionnaire-disability index (HAQ-DI) was also administered. A full copy of the participant questionnaire undertaken at initial and subsequent study visits is included in appendix 4.

Baseline laboratory investigations comprised FBE, CRP, ESR, creatine kinase, thyroid function testing, vitamin D, rheumatoid factor, ACPA, ANCA and HbA1C.

#### *X-Ray*

Bilateral wrist and hand x-rays (anteroposterior, lateral and “ball catcher’s” views) to assess for erosive change were performed using an x-ray unit with DR retrofit (Shimadzu Corporation, Kyoto, Japan). All images were interpreted by a qualified radiologist.

#### *Ultrasound*

B mode ultrasound scanning was undertaken at both shoulders (to assess for subacromial bursitis, biceps tenosynovitis and glenohumeral joint effusion) and hips (to assess for trochanteric bursitis and hip joint effusion) by the PhD candidate (qualified in musculoskeletal ultrasound) using a LOGIQ e machine (GE Healthcare, Chicago, IL, USA) with a linear 5-13 MHz transducer. The following parameters from a prior study(2) were used to clearly define abnormal findings:

- Subacromial bursitis - a thickness of hypoechoic material within the bursa of >1.1mm;

**Table 2.1:** Visit schedule and relevant assessments undertaken for the MPR-PMR study.

| Assessment                                                                                                                                                | Week 0                                                      | Week 4          | Week 8          | Week 16         | Week 24         | Week 32         | Week 46         | Unscheduled     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>Demographic Information</b>                                                                                                                            | ✓                                                           |                 |                 |                 |                 |                 |                 |                 |
| <b>Symptom Questionnaire:</b>                                                                                                                             | ✓                                                           | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               |
| <ul style="list-style-type: none"> <li>• Distribution of joint/muscle pain</li> <li>• Duration of EMS</li> <li>• Patient VAS</li> <li>• HAQ-DI</li> </ul> |                                                             |                 |                 |                 |                 |                 |                 |                 |
| <b>Glucocorticoid-Related Side Effects</b>                                                                                                                |                                                             | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               |
| <b>Physical Examination</b>                                                                                                                               | ✓                                                           | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               |
| <b>Laboratory Testing</b>                                                                                                                                 | ✓                                                           | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               | ✓               |
|                                                                                                                                                           | (FBE, CRP, ESR, CK, TSH, Vitamin D, RhF, ACPA, ANCA, HbA1C) | (FBE, CRP, ESR) | (FBE, CRP, ESR) | (FBE, CRP, ESR) | (FBE, CRP, ESR) | (FBE, CRP, ESR) | (FBE, CRP, ESR) | (FBE, CRP, ESR) |
| <b>Bilateral Wrist and Hand X-rays</b>                                                                                                                    | ✓                                                           |                 |                 |                 |                 |                 |                 |                 |
| <b>Musculoskeletal Ultrasound</b>                                                                                                                         | ✓                                                           | ✓               |                 | ✓               |                 |                 | ✓               |                 |
| <b>Whole body PET/CT Scan</b>                                                                                                                             | ✓                                                           |                 |                 |                 |                 |                 |                 |                 |
| <b>Targeted MRI</b>                                                                                                                                       | ✓                                                           |                 |                 |                 |                 |                 |                 |                 |
|                                                                                                                                                           | (in representative patients)                                |                 |                 |                 |                 |                 |                 |                 |

Abbreviations: EMS – early morning stiffness; VAS – visual analogue scale; HAQ-DI – health assessment questionnaire-disability index; FBE – full blood examination; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; CK – creatinine kinase; TSH – thyroid stimulating hormone; RhF- rheumatoid factor; ACPA – anti-citrullinated peptide antibodies; ANCA – anti-neutrophil cytoplasmic antibodies; PET/CT – positron emission tomography/computed tomography; MRI – magnetic resonance imaging.

- Effusion in the bicipital groove - a distance between the tendon and bicipital groove >2.5mm;
- Glenohumeral joint effusion - a distance between the humeral neck convexity and joint capsule at the axillary recess of >3.5mm;
- Hip joint effusion – a distance between the femoral neck convexity and joint capsule >8mm.

At the bilateral wrists and metacarpophalangeal joints of the hands, ultrasound was similarly utilised to assess for greyscale synovitis and Power Doppler signal.

#### *Whole Body PET/CT*

A whole body  $^{18}\text{F}$ -FDG PET/CT scan (Gemini-TF64 or Ingenuity-TF128 PET/CT system; Phillips, Cleveland, OH, USA) from skull vertex to toes (including dedicated hand views) was performed within 7 days of the screening visit and prior to the commencement of glucocorticoid therapy.

Following a minimum 6-hour fast, participants received a weight-based intravenous injection of  $^{18}\text{F}$ -FDG. The emission study and low-dose CT was acquired after a 1-hour rest period, with CT attenuation correction performed on all images prior to independent qualitative and semi-quantitative analysis of abnormal  $^{18}\text{F}$ -FDG uptake by two experienced nuclear medicine physicians. Any significant differences in results were resolved by consensus.

Qualitative analysis involved visual evaluation of  $^{18}\text{F}$ -FDG uptake using the following scoring system: 0 – no uptake; 1 – lower than normal liver uptake; 2 – similar to normal liver uptake; 3 – higher than normal liver uptake. A score of  $\geq 1$  was considered a positive result. For semi-quantitative analysis, a region of interest was drawn around each site and the maximum standardised uptake value ( $\text{SUV}_{\text{max}}$ ) calculated. The following musculoskeletal sites were specifically assessed: two peri-articular shoulder regions; two glenohumeral joints; two acromioclavicular joints; two sternoclavicular joints; two peri-articular hip regions; two hip joints; two trochanteric regions; regions adjacent to the two ischial tuberosities; two knee joints; two posteromedial knee regions; two wrist joints; two hands; and most PET avid interspinous bursa. A total skeletal score (TSS) out of a maximum of 18 points was accordingly generated based upon the sum of qualitative scores from six key areas (peri-articular shoulder, peri-articular hip, trochanteric, adjacent to ischial tuberosities, interspinous and posteromedial knee).

Scoring of  $^{18}\text{F}$ -FDG uptake in the following large vessels was also performed: carotid arteries; subclavian arteries; axillary arteries; thoracic aorta; abdominal aorta; iliac arteries; and femoral arteries. A total vascular score (TVS) was similarly calculated using the qualitative analysis scores.

#### *MRI correlation and fusion of PET/CT with MRI*

To precisely identify anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake, MRI was performed in representative patients at the pelvis, knee and, wrist and hand using a 1.5 Tesla magnet (Siemens Avanto, Erlangen, Germany) with a Siemens i-PAT compatible 6-element design phased array body matrix, Siemens 12 channel transmit/receive configuration knee coil and Invivo 8 channel wrist coil respectively.

For imaging of the pelvis, non-contrast T1-weighted fast spin-echo (FSE) sequences in the axial plane, proton density-weighted FSE sequences in the axial, sagittal and coronal planes with fat saturation in the coronal plane, and T2-weighted FSE sequences with fat saturation in the axial plane centred on the ischial tuberosities were obtained.

For imaging of the knee, proton density-weighted FSE and T2-weighted FSE sequences with fat saturation in the coronal plane, proton density-weighted FSE and with fat saturation in the sagittal plane and, proton density-weighted FSE and T2-weighted FSE images with fat saturation in the axial plane were obtained.

For imaging of the wrist and hand, the following sequences were performed before intravenous injection: proton density-weighted FSE in the axial, coronal and sagittal planes with fat saturation in the coronal plane; T2-weighted FSE in the axial plane with fat suppression; and 3D T2\*-weighted GRE in the coronal plane. Following intravenous injection of 10mls of gadolinium-based contrast agent (Dotarem, gadoterate meglumine, Guerbet USA), T1-weighted FSE fat suppression images in the axial and coronal planes were obtained.

Interpretation of MRI images was performed by two experienced musculoskeletal radiologists. Medview fusion software (Ann Arbor, Michigan, USA) was utilised to align and superimpose PET and MRI image datasets, and to anatomically correlate sites of abnormal  $^{18}\text{F}$ -FDG uptake.

### *Treatment*

Following the completion of all initial visit assessments, participants commenced a standardised schedule of low-dose glucocorticoid therapy as outlined in the BSR guideline for the management of PMR(3):

- Prednisolone 15mg oral daily for 3 weeks;
- Prednisolone 12.5mg oral daily for 3 weeks;
- Prednisolone 10mg oral daily for 4 weeks, weaning by 1mg every 4 weeks until cessation (total course 46 weeks).

### 2.2.4 Follow-Up

Subsequent study visits for data collection occurred at weeks 4, 8, 16, 24, 32 and 46 post enrolment and comprised the same standardised format. Distribution of joint/muscle involvement (indicated by the patient on a human mannequin), duration of early morning stiffness, presence of constitutional symptoms (loss of weight, fever, fatigue), development of symptoms suggestive of GCA (headache, jaw claudication, scalp tenderness or visual disturbance) and current dose of prednisolone were recorded. Participants were also specifically questioned about whether they had developed any side effects that they attributed to glucocorticoid therapy. Physical examination of the peripheral joints was undertaken and the range of motion at the shoulders bilaterally assessed (EUL score). A PMR-AS was re-calculated following completion of a participant pain VAS and physician global assessment. The HAQ-DI was also re-administered. Laboratory testing comprised FBE, CRP and ESR, whilst musculoskeletal ultrasound of bilateral shoulders, hips, wrists and metacarpophalangeal joints was repeated at weeks 4, 16 and 46.

A PMR-AS score of  $\geq 9.35$  in a patient who had achieved clinical remission (PMR-AS  $< 9.35$ ) or increase in PMR-AS by  $\geq 6.6$  if the participant had been previously responding to treatment (PMR-AS  $\geq 9.35$  but falling between successive visits) constituted the definition of disease relapse during follow-up. When this occurred, the patient's prednisolone dose was increased to the previous higher dose for 4 weeks and an additional study visit undertaken to determine if the weaning schedule could be reinstated. If a relapse occurred on more than two occasions, methotrexate was introduced in line with the BSR guideline(3) and the participant was withdrawn from the study.

If the participant experienced a suspected relapse between scheduled reviews, an unscheduled visit was arranged upon request. This visit comprised the same format outlined above.

If the patient developed symptoms suggestive of GCA (headache, jaw claudication, scalp tenderness or visual disturbance), their prednisolone dose was immediately increased to 50mg oral daily and a temporal artery biopsy urgently arranged. Participants with biopsy-confirmed GCA were withdrawn from the study to permit ongoing treatment with high-dose glucocorticoid therapy; those with negative results returned to their previous PMR prednisolone dose and continued with study visits. Large vessel  $^{18}\text{F}$ -FDG uptake consistent with vasculitis on whole body PET/CT at the initial visit was treated as per biopsy-confirmed GCA.

### 2.2.5 Outcome Measures

Disease relapse as defined by a PMR-AS score of  $\geq 9.35$  in a patient who had achieved clinical remission (PMR-AS  $< 9.35$ ) or increase in PMR-AS by  $\geq 6.6$  if the participant had been previously responding to treatment (PMR-AS  $\geq 9.35$  but falling between successive visits) constituted the primary outcome measure.

Glucocorticoid resistance, which has been previously defined by Mori et al. in PMR as non-response to an initial prednisolone dose of 15mg/day or initial response followed by disease relapse upon weaning prednisolone to 5mg/day(4), represented the secondary outcome of interest.

### 2.2.6 Sample Size

In the absence of substantive literature indicating anticipated effect size in a pilot study such as this, sample size calculations proved difficult. Accordingly, a cut-off of 35 patients was selected to be commensurate with the largest prospective study of whole body PET in PMR when recruitment commenced in 2014.(5)

### 2.2.7 Controls

To ascertain the diagnostic performance of whole body PET/CT in PMR, four historic age- and sex-matched controls were consecutively identified from the electronic medical record for each case. Clinical data pertaining to indication for PET/CT, underlying diagnosis and history of rheumatic conditions was extracted. Potential controls with a diagnosis of PMR or GCA were excluded, along with those being evaluated for large vessel vasculitis. Audit level ethical approval was received from Austin Health HREC prior to commencement (LNR/16/Austin/356).

Qualitative and semi-quantitative analysis of the same musculoskeletal sites on whole body PET/CT was replicated in the controls.

### 2.2.8 Statistical Analysis

All statistical analyses were conducted using Stata 13.0(6) and R version 3.5.2.(7) Continuous variables are reported as mean ( $\pm$  standard deviation) or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages).

#### *Chapter 4 – Sensitivity and Specificity of Novel PET/CT Findings for a Diagnosis of PMR*

Whole body PET/CT scores for PMR cases and controls were compared using the Mann-Whitney U test. Receiver operating characteristics (ROC) curves were generated for qualitative scoring results at each musculoskeletal site, along with the area under the curve (AUC), sensitivity and specificity values for a diagnosis of PMR. Results informed the development of a novel diagnostic algorithm using a classification and regression trees (CART) method.

#### *Chapter 5 – Results of the MPR-PMR Study*

Univariable linear regression analysis was performed to detect variables affecting disease activity (PMR-AS). The Cox proportional-hazards model investigated the relationship between time to first relapse and baseline characteristics. Predictors of glucocorticoid resistance were subsequently identified using generalised linear modelling.

#### *Chapter 6 – Neutrophil to Lymphocyte Ratio as a Predictor of Glucocorticoid Resistance in PMR*

Univariable Bayesian linear regression established the relationship between neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), and PMR-AS (baseline and mean). Several multivariable, Bayesian logistic regression models were compared using leave-one-out cross-validation to select predictors of resistance to low-dose glucocorticoid therapy.

#### *Chapter 7 – Developing an OMERACT Endorsed Core Outcome Measurement Set for PMR*

For the raw data analysis component, pain VAS, EMS and HAQ-DI results were first scrutinised for a completion rate  $>80\%$ . A frequency distribution histogram was generated for each candidate instrument. The proportion of participants with the lowest (“floor”) and highest (“ceiling”) values were recorded, and the normality of each distribution assessed (based upon the coefficient of skewness where 0 = normal and -0.5 to 0.5 is approximately symmetric).

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## Chapter 3: Characterisation of an Untreated Polymyalgia Rheumatica Population on Whole Body PET/CT

### 3.1 Preface

In chapter 3, results from a preliminary study characterising the initial 22 patients enrolled in the MPR-PMR study will be presented. The predominant focus of this work related to documenting the distribution and extent of abnormalities on whole body PET/CT observed in a steroid naïve, newly diagnosed PMR population. PET/MRI fusion was subsequently utilised to determine precise anatomic correlates of sites of abnormal  $^{18}\text{F}$ -FDG uptake. This novel technology, whose typical application concerns the localisation of metastatic deposits in oncology settings(1, 2), permits co-registration of metabolic activity and structural information.(3) It was hoped this endeavour would delineate the inflamed structures corresponding to abnormalities observed on PET/CT in PMR and thereby advance our understanding of its underlying pathology, which has proved somewhat elusive to date.

The following journal article was published in 2018 – Owen CE, Poon AMT, Lee ST, Yap LP, Zwar RB, McMenamin CM, Lam SKL, Liew DFL, Pathmaraj K, Kemp A, Scott AM & Buchanan RRC. Fusion of PET/CT with MRI Demonstrates Hamstring Peritendonitis in Untreated Patients with Polymyalgia Rheumatica. *Rheumatology Oxford*; 57(2):345-53.

### 3.2 Summary of Main Findings

- On whole body PET/CT, PMR is associated with a distinctive pattern of abnormal  $^{18}\text{F}$ -FDG uptake around the shoulder and hip joints, in the trochanteric regions, interspinous bursae and adjacent to the ischial tuberosities.
- In addition, peripheral joint involvement is frequently observed at the knee and, wrist and/or hand, reinforcing the fact that this condition is not limited to the shoulder and hip girdle.
- $^{18}\text{F}$ -FDG uptake detected adjacent to the ischial tuberosities recorded the highest mean  $\text{SUV}_{\text{max}}$  value throughout the body.
- At the posteromedial knee, a novel pattern of  $^{18}\text{F}$ -FDG uptake was also documented.
- Using PET/MRI fusion, peritendonitis of the proximal hamstring tendon origins was identified as the anatomical correlate of abnormalities detected adjacent to the ischial tuberosities, whilst abnormal  $^{18}\text{F}$ -FDG uptake of posteromedial knee structures correlated with peritendonitis of the distal semimembranosus tendon.

- A distinctive volar pattern of  $^{18}\text{F}$ -FDG uptake on whole body PET/CT at the hand was found to correspond with flexor tenosynovitis on MRI, however the same fusion technique could not be utilised due to discrepancies in positioning.

### 3.3 Interpretation

This is the first study to utilise PET/MRI fusion technology to ascertain precise anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake on whole body PET/CT in PMR. By doing so, the condition's predilection for tendinous structures within the pelvis and at peripheral joints including the knee and, wrist and/or hand was established, and our knowledge of its true nature and extent advanced.

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# Fusion of positron emission tomography/computed tomography with magnetic resonance imaging reveals hamstring peritendinitis in polymyalgia rheumatica

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## Abstract

**Objectives.** To characterize <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) uptake on whole-body PET/CT in PMR, and identify its precise anatomic correlate using MRI.

**Methods.** Patients with newly diagnosed PMR according to the 2012 EULAR/ACR classification criteria were prospectively recruited. Participants with GCA were excluded. A whole-body <sup>18</sup>F-FDG PET/CT scan was performed in all untreated patients. Qualitative and semiquantitative [standardized uptake value maximum (SUV<sub>max</sub>)] scoring of abnormal <sup>18</sup>F-FDG uptake was undertaken. MRI of the pelvis, knee and wrist and hand was performed in three representative patients with anatomical correlation of FDG-avid sites carried out using Medview fusion software.

**Results.** Twenty-two patients with PMR were recruited. Their mean age was 68.3 years (s.d. 6.3) and 13/22 were male. On whole-body PET/CT, <sup>18</sup>F-FDG uptake adjacent to the ischial tuberosities was observed in 21 participants (95.4%) and recorded the highest mean SUV<sub>max</sub> value [3.6 (s.d. 1.7)]. A high frequency of posteromedial knee (61.9%) and wrist and/or hand involvement (66.7%) was also appreciated. MRI of the pelvis revealed high T2 signal surrounding the proximal hamstring tendon origins of both semimembranosus and the conjoint tendon of the semitendinosus and biceps femoris. At the knee, peritendinitis at the distal insertion of the semimembranosus was observed. PET/MRI fusion at the pelvis and knee confirmed semimembranosus peritendinitis as the anatomical correlate of <sup>18</sup>F-FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures.

**Conclusion.** Hamstring peritendinitis is a common and distinctive manifestation of PMR on whole-body PET/CT.

**Trial registration:** Australian New Zealand Clinical Trials Registry, <http://www.anzctr.org.au>, ACTRN1261400696695.

**Key words:** polymyalgia rheumatica, whole-body positron emission tomography/computed tomography, magnetic resonance imaging, hamstring, peritendinitis

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### Rheumatology key messages

- PMR exhibits a distinctive pattern of abnormal  $^{18}\text{F}$ -FDG uptake on whole-body PET/CT.
- Hamstring peritendonitis correlates with  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures.
- Frequent wrist and/or hand involvement is observed on whole-body PET/CT in PMR patients.

## Introduction

PMR is an inflammatory condition predominantly characterized by subacute-onset shoulder and hip pain and stiffness in patients  $\geq 50$  years of age. Some controversy has existed as to whether PMR represents a distinct disease entity due to its close relationship with both GCA and late-onset RA, however, imaging modalities such as PET have recently uncovered its distinctive pathology [1–3].

Blockmans *et al.* [4] first reported the ability of PET to detect articular inflammation in PMR, finding abnormal  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake in the shoulders and hips in 94 and 89% of patients, respectively. They additionally described a novel finding involving the processus spinosi of the vertebrae, which has since been localized to the interspinous bursa on MRI [5, 6].

The pairing of whole-body PET with low-dose CT has facilitated further study of the anatomic distribution of PMR.  $^{18}\text{F}$ -FDG uptake in the trochanteric region and adjacent to the ischial tuberosities has been attributed to trochanteric and ischiogluteal bursitis, respectively [7]. A high frequency of knee involvement due to capsulitis has similarly been reported [8]. However, the low resolution of whole-body PET/CT images remains a limitation to precise identification of anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake.

Peripheral joint involvement is appreciated clinically in almost half of PMR patients [9]. Distinguishing this group from late-onset RA at presentation is especially difficult. However, it is increasingly apparent from imaging studies that the prevailing pathology in PMR is extra-articular rather than intra-articular [10]. Unlike RA, a predilection for tendinous and bursal structures combined with capsular joint involvement is typically observed.

In this study we sought to further characterize the pattern of  $^{18}\text{F}$ -FDG uptake on whole-body PET/CT in untreated patients with newly diagnosed PMR. Utilizing dedicated hand views, additional emphasis was also placed upon the distribution and frequency of peripheral joint involvement. MRI was subsequently performed in representative patients before fusion technology was employed to precisely identify anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake.

## Methods

### Patients

Patients with newly diagnosed PMR according to the 2012 EULAR/ACR classification criteria (utilizing the clinical scoring algorithm) [9] were prospectively recruited from primary care, community and hospital rheumatology practices. Participants who had received prior prednisolone

treatment and those with symptoms suggestive of GCA (headache, scalp tenderness, jaw claudication or visual disturbance) were excluded, as were patients with a history of cancer within the past 5 years, neuromuscular disease, active infection, other inflammatory conditions and chronic pain syndromes. The study was approved by the Austin Health Human Research Ethics Committee prior to commencement and registered with the Australian New Zealand Clinical Trials Registry (trial identification ACTRN1261400696695).

### Clinical and laboratory variables

Following appropriate written consent, demographic and clinical data were collected. Participants also completed the HAQ disability index (HAQ-DI). A standard physical examination was carried out with specific focus on the presence of peripheral synovitis. Baseline laboratory testing comprised full blood count, CRP, ESR, creatinine kinase, thyroid function testing, RF and ACPAs. Bilateral wrist and hand X-rays were performed to assess for erosive change. B-mode and power Doppler US was undertaken at both wrists by a rheumatologist experienced in US (C.E.O.) using a LOGIQ e machine (GE Healthcare, Chicago, IL, USA) with linear 5–13 MHz transducer.

### Whole-body PET/CT

A whole body  $^{18}\text{F}$ -FDG PET/CT scan (Gemini-TF64 or Ingenuity-TF128 PET/CT system; Phillips, Cleveland, OH, USA) from skull vertex to toes (including dedicated hand views) was performed within 7 days of the screening visit and prior to the commencement of prednisolone treatment.

Following a minimum 6 h fast, participants received a weight-based i.v. injection of  $^{18}\text{F}$ -FDG. The emission study and low-dose CT was acquired after a 1 h rest period, with CT attenuation correction performed on all whole-body and dedicated hand images prior to independent qualitative and semiquantitative analysis of abnormal  $^{18}\text{F}$ -FDG uptake by two experienced nuclear medicine physicians (A.P. and S.T.L.). Any significant differences in results were resolved by consensus.

Qualitative analysis involved visual evaluation of  $^{18}\text{F}$ -FDG uptake using the following scoring system: 0, no uptake; 1, lower than normal liver uptake; 2, similar to normal liver uptake; 3, higher than normal liver uptake. A score  $\geq 1$  was considered a positive result. For semiquantitative analysis, a region of interest was drawn around each site and the maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) calculated. The following sites were specifically assessed: two shoulder joints, two hip joints, two trochanteric regions, regions adjacent to the two ischial

tuberosities, most FDG-avid interspinous bursa, two knee joints, two wrist joints and two hands.

### MRI correlation and fusion of PET/CT with MRI

To precisely identify anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake, MRI was performed in three representative patients at the pelvis, knee and wrist and hand using a 1.5 T magnet (Siemens Avanto, Erlangen, Germany) with a Siemens i-PAT compatible six-element design phased array body matrix, Siemens 12 channel transmit/receive configuration knee coil and Invivo 8 channel wrist coil, respectively.

For imaging of the pelvis, non-contrast T1-weighted fast spin-echo (FSE) sequences in the axial plane, proton density-weighted FSE sequences in the axial, sagittal and coronal planes with fat saturation in the coronal plane and T2-weighted FSE sequences with fat saturation in the axial plane centred on the ischial tuberosities were obtained.

For imaging of the knee, proton density-weighted FSE and T2-weighted FSE sequences with fat saturation in the coronal plane, proton density-weighted FSE with fat saturation in the sagittal plane and proton density-weighted FSE and T2-weighted FSE images with fat saturation in the axial plane were obtained.

For imaging of the wrist and hand, the following sequences were performed before i.v. injection: proton density-weighted FSE in the axial, coronal and sagittal planes with fat saturation in the coronal plane; T2-weighted FSE in the axial plane with fat suppression and 3D T2\*-weighted GRE in the coronal plane. Following i.v. injection of 10 ml of gadolinium-based contrast agent (Dotarem, gadoterate meglumine, Guerbet USA, Princeton, NJ, USA), T1-weighted FSE fat suppression images in the axial and coronal planes were obtained.

Interpretation of MRIs was performed by two experienced musculoskeletal radiologists (L.Y., R.Z.). Medview fusion software (Ann Arbor, MI, USA) was utilized to align and superimpose PET and MRI datasets and to anatomically correlate sites of abnormal  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures.

### Statistical analysis

Results for continuous variables are reported as mean (s.d.) or median [interquartile range (IQR)]. Categorical variables are represented as proportions (percentages). All statistical analyses were undertaken using Stata 13.0 (StataCorp, College Station, TX, USA).

## Results

### Patient demographics, clinical and laboratory features

Twenty-two patients met the inclusion criteria for a diagnosis of PMR [mean clinical algorithm score 5.1 (s.d. 0.7)]. Their demographic data are summarized in Table 1. The mean age at diagnosis was 68.3 years (s.d. 6.3). Thirteen patients (59.1%) were male and all participants were Caucasian.

**TABLE 1** Baseline demographic data and clinical features

| Demographic or clinical features        | Value            |
|-----------------------------------------|------------------|
| Age, mean (s.d.), years                 | 68.3 (6.3)       |
| Male, <i>n</i> (%)                      | 13 (59.1)        |
| Caucasian, <i>n</i> (%)                 | 22 (100)         |
| BMI, mean (s.d.), kg/m <sup>2</sup>     | 28.6 (5.1)       |
| Ever smoked, <i>n</i> (%)               | 10 (45.4)        |
| Shoulder pain, <i>n</i> (%)             | 22 (100)         |
| Hip pain, <i>n</i> (%)                  | 18 (81.8)        |
| Back pain, <i>n</i> (%)                 | 13 (59.1)        |
| Knee pain, <i>n</i> (%)                 | 14 (63.6)        |
| Wrist/hand pain, <i>n</i> (%)           | 12 (54.5)        |
| Morning stiffness >45 min, <i>n</i> (%) | 18 (81.8)        |
| Median CRP, median (IQR), mg/l          | 40.8 (24.6–67.1) |
| Median ESR, median (IQR), mm            | 45.5 (29–64)     |
| PMR-activity score, mean (s.d.)         | 71.3 (38.8)      |
| Median HAQ-DI score, median (IQR)       | 2 (1.4–2.2)      |

Consistent with the 2012 EULAR/ACR classification criteria, all patients possessed bilateral shoulder pain, with 18/22 (81.8%) also reporting concomitant hip pain. Fourteen participants (63.6%) indicated involvement of their knees, while 12 (54.5%) reported wrist and/or hand symptoms. The median duration of early morning stiffness was 120 min (IQR 60–120). On clinical examination, synovitis at the wrist and/or hand was detected in nine patients (40.9%) and six (27.3%) exhibited swelling and/or tenderness of the knee.

All participants were negative for ACPAs. Three patients returned a low positive RF result [14 IU/ml in two participants and 17 IU/ml in the third (*n* < 14 IU/ml)]. A single patient was found to possess a subtle marginal erosion of the right fourth metacarpal head on bilateral wrist and hand X-rays. Using US, greyscale synovitis was detected at the wrist in eight patients (36.4%), five (22.7%) of whom had associated power Doppler signal.

Using the PMR activity score, disease activity was judged to be high [mean 71.3 (s.d. 38.8)]. Participants reported a severe level of disability because of their symptoms on the HAQ-DI [median 2 (IQR 1.4–2.2)].

### Whole-body PET/CT

A mean dose of 288.6 MBq (s.d. 29.6) of  $^{18}\text{F}$ -FDG was administered intravenously prior to whole-body PET/CT. The average time from injection to scan acquisition was 66.6 min (s.d. 9.3). In one patient, imaging of the knees could not be undertaken because the study was abandoned due to severe pain. Hand views obtained in another individual were deemed insufficient upon consensus review.

Abnormal  $^{18}\text{F}$ -FDG uptake in a peri-articular distribution was observed at the shoulder and hip joints in 22 (100%) and 19 patients (86.4%), respectively (Table 2). FDG avidity was present in all cases in the trochanteric regions.

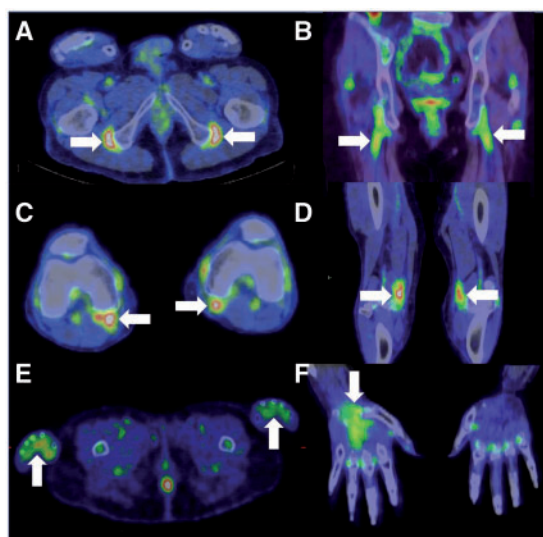
Adjacent to the ischial tuberosities (Fig. 1A and B) represented another site of frequent  $^{18}\text{F}$ -FDG uptake (95.4%) and recorded the highest value for mean reference score

**TABLE 2** Analysis of  $^{18}\text{F}$ -FDG uptake on whole-body PET/CT

| Site                        | Frequency of $^{18}\text{F}$ -FDG uptake $\geq 1$ , <i>n</i> (%) | Frequency of $^{18}\text{F}$ -FDG uptake $\geq 2$ , <i>n</i> (%) | Mean reference score | Mean SUV <sub>max</sub> |
|-----------------------------|------------------------------------------------------------------|------------------------------------------------------------------|----------------------|-------------------------|
| Shoulder                    | 22 (100)                                                         | 17 (77.3)                                                        | 2.4 (0.9)            | 3.4 (1.4)               |
| Hip                         | 19 (86.4)                                                        | 17 (77.3)                                                        | 2 (1.1)              | 3.0 (2.0)               |
| Trochanteric                | 22 (100)                                                         | 13 (59.1)                                                        | 1.9 (0.8)            | 2.5 (1.1)               |
| Ischial                     | 21 (95.4)                                                        | 20 (90.9)                                                        | 2.4 (0.6)            | 3.6 (1.7)               |
| Interspinous                | 18 (81.8)                                                        | 12 (54.5)                                                        | 1.8 (1.2)            | 2.9 (1.9)               |
| Knee ( <i>n</i> = 21)       | 16 (76.2)                                                        |                                                                  |                      |                         |
| Posteromedial               | 13 (61.9)                                                        | 11 (52.4)                                                        | 1.5 (1.3)            | 3.2 (1.0)               |
| Capsule                     | 10 (47.6)                                                        | 6 (28.6)                                                         | 1.0 (1.2)            | 2.9 (0.9)               |
| Wrist/hand ( <i>n</i> = 21) | 14 (66.7)                                                        |                                                                  |                      |                         |
| Wrist joint                 | 12 (57.1)                                                        | 6 (28.6)                                                         | 1.0 (1.1)            | 2.8 (1.1)               |
| Volar hand                  | 7 (33.3)                                                         | 3 (14.3)                                                         | 0.6 (1.0)            | 2.4 (0.9)               |

mean reference score: mean reference to normal liver score.

**Fig. 1** Whole-body PET/CT findings



(A and B) Characteristic intense  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities (white arrows). (C and D) FDG avidity of posteromedial knee structures. (E and F)  $^{18}\text{F}$ -FDG uptake in the hands in a volar distribution.

compared with normal liver [2.4 (s.d. 0.6)] and highest mean SUV<sub>max</sub> [3.6 (s.d. 1.7)].

At the knees, abnormal  $^{18}\text{F}$ -FDG uptake was observed in 16 patients (76.2%). In the majority of these, focal areas of intense FDG avidity in a posteromedial distribution were appreciated (Fig. 1C and D).

A high frequency of wrist and/or hand involvement was also detected (66.7%). At the hand, a volar distribution of abnormal  $^{18}\text{F}$ -FDG uptake was typically observed (Fig. 1E and F). Vascular  $^{18}\text{F}$ -FDG uptake in the large vessels consistent with a diagnosis of GCA (qualitative score  $\geq 2$ ) was not present in any participant.

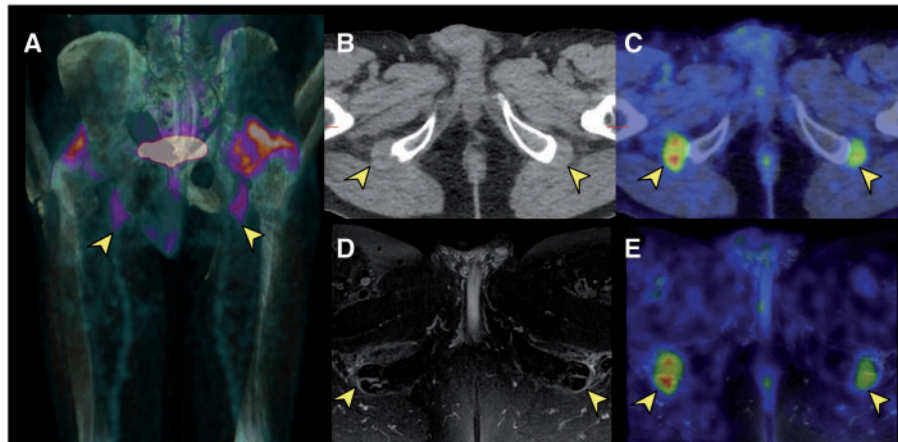
### MRI correlation and fusion of PET/CT with MRI

MRI of the pelvis in a patient with characteristic, intense  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities revealed bilateral and symmetric high T2 signal surrounding the proximal hamstring tendon origins of the semimembranosus and the conjoint tendon of the semitendinosus and biceps femoris (Fig. 2D). These changes were confined to the paratenon, with only minimally increased signal noted for the tendons themselves. There was similarly no abnormality observed at the musculotendinous junctions, nor any evidence of bone oedema adjacent to the tendon entheses.

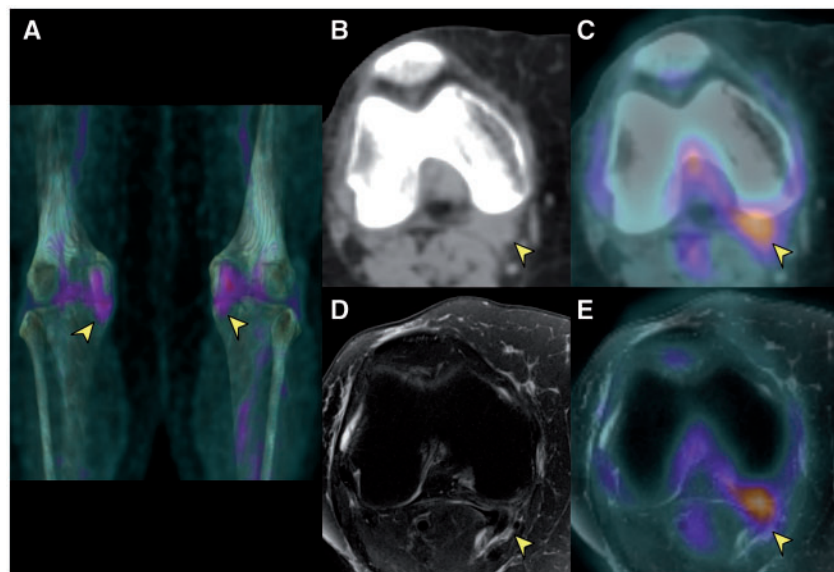
At the knee, MRI in a representative patient with posteromedial  $^{18}\text{F}$ -FDG uptake on whole-body PET/CT revealed peritendinitis of the semimembranosus and to a lesser extent the gracilis tendons at their distal insertion (Fig. 3D). No bone oedema was appreciated at the medial tibial plateau. The distal semitendinosus tendon was normal in this instance.

MRI of the wrist and hand in a patient with a volar distribution of  $^{18}\text{F}$ -FDG uptake revealed extensive synovial thickening and enhancement within the carpal tunnel with extension to involve the common flexor tendon sheaths of the digits, in keeping with tenosynovitis (Fig. 4B). Mild extensor tenosynovitis was also appreciated, along with moderate mid-carpal joint synovitis (Fig. 4D).

PET/MRI fusion at the pelvis subsequently confirmed peritendinitis of the proximal hamstring tendon origins as the anatomical correlate of abnormal  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities on whole-body PET/CT (Fig. 2E), while abnormal  $^{18}\text{F}$ -FDG uptake of posteromedial knee structures correlated with peritendinitis of the distal semimembranosus tendon (Fig. 3E). The same technique could not be utilized at the wrist and hand due to discrepancies in positioning between the two imaging modalities at this site.

**Fig. 2** Fusion of PET/CT with MRI adjacent to the ischial tuberosities

(A) 3D fused  $^{18}\text{F}$ -FDG PET/CT. (B) Low-dose CT. (C) Fused  $^{18}\text{F}$ -FDG PET/CT. (D) T2-weighted FS MRI reveals high signal surrounding the proximal hamstring tendon origins of the semimembranosus and biceps femoris (yellow arrows). (E) Fused  $^{18}\text{F}$ -FDG PET/MRI confirms peritendinitis of the proximal hamstring tendon origins as the anatomical correlate of  $^{18}\text{F}$ -FDG uptake at this site. FS: fat suppressed.

**Fig. 3** Fusion of PET/CT with MRI of posteromedial knee structures

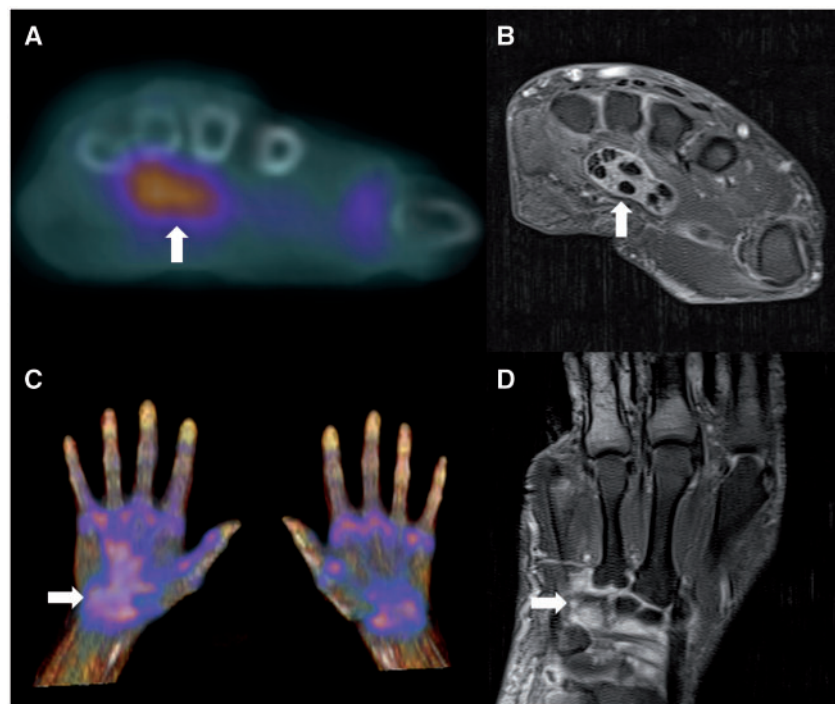
(A) 3D fused  $^{18}\text{F}$ -FDG PET/CT. (B) Low-dose CT. (C) Fused  $^{18}\text{F}$ -FDG PET/CT. (D) T2-weighted FS MRI reveals high signal surrounding the distal hamstring tendon insertions of the semimembranosus and gracilis (yellow arrows). (E) Fused  $^{18}\text{F}$ -FDG PET/MRI confirms peritendinitis of the distal semimembranosus tendon as the anatomical correlate of  $^{18}\text{F}$ -FDG uptake at this site. FS: fat suppressed.

## Discussion

On whole-body PET/CT, 22 untreated patients with newly diagnosed PMR exhibited a distinctive pattern of abnormal  $^{18}\text{F}$ -FDG uptake around the shoulder and hip joints, in the trochanteric regions and interspinous bursae and

adjacent to the ischial tuberosities. In addition, a high frequency of knee and wrist and/or hand involvement was appreciated. Using PET/MRI fusion, hamstring peritendinitis was identified as the anatomical correlate of  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures.

**Fig. 4** MRI findings of the wrist and hand



**(A)** Volar <sup>18</sup>F-FDG uptake on whole-body PET/CT in a representative patient (white arrow). **(B)** T2-weighted FS MRI of the wrist and hand reveals corresponding flexor tenosynovitis. **(C)** Fused <sup>18</sup>F-FDG PET/CT volume rendered at the hands in the same patient. **(D)** Mid-carpal joint synovitis seen on T1-weighted FS MRI. FS: fat suppressed.

Uptake adjacent to the ischial tuberosities has been previously reported in whole-body PET/CT studies of PMR patients at rates ranging from 52 to 94% [1–3, 7, 11–14]. Our results reinforce a high incidence of involvement at this site, with abnormal uptake present in all but one patient. Furthermore, these focal areas of FDG avidity within the pelvis recorded the highest value for mean reference score compared with normal liver and highest mean SUV<sub>max</sub>. Intense <sup>18</sup>F-FDG uptake adjacent to the ischial tuberosities should therefore be considered an imaging hallmark of PMR on whole-body PET/CT.

The ischiogluteal bursa is situated over the ischial tuberosity, hence abnormal <sup>18</sup>F-FDG uptake in this region on whole-body PET/CT has been previously attributed to ischiogluteal bursitis [15]. Cantini *et al.* [16] studied hip inflammatory changes on US and MRI in 20 consecutive PMR patients but found no significant difference in the incidence of ischiogluteal bursitis compared with a group of controls (20% vs 25%). Conversely, a recent retrospective study of whole-body PET/CT proposed that praepubic <sup>18</sup>F-FDG uptake in PMR represented a correlate of pectineus and adductor longus enthesitis and tenosynovitis [13]. The superior ramus of the ischium is also the tendinous origin for several hamstring muscles [17]. Given that our MRI correlation at the pelvis revealed high T2 signal confined to the paratenon of semimembranosus and the conjoint tendon of semitendinosus and

biceps femoris without corresponding abnormality of the ischiogluteal bursa, we conclude that hamstring peritendonitis (as opposed to ischiogluteal bursitis) represents the anatomical correlate of <sup>18</sup>F-FDG uptake adjacent to the ischial tuberosities in PMR.

Cimmino *et al.* [8] first reported a high frequency of knee involvement in PMR on whole-body PET/CT. In their study, 24/25 patients (96%) exhibited <sup>18</sup>F-FDG uptake in a distribution that highlighted the contour of the fibrous joint capsule. Focal areas of FDG avidity were also appreciated in 13 participants (52%), predominantly in a posteromedial distribution. We have similarly detected <sup>18</sup>F-FDG uptake at the knee capsule in 10/21 patients (47.6%) and of posteromedial knee structures in 13/21 patients (61.9%). Based on results from the MRI correlation undertaken at the knee, this pattern of posteromedial knee involvement on whole-body PET/CT is also attributable to peritendonitis of the semimembranosus tendon at its insertion on the medial condyle of the tibia.

Pelvic girdle symptoms are said to occur in ~60% of PMR cases, although a higher incidence of hip pain was recorded in this study (81.8%). Patients with PMR commonly report gluteal and posterior thigh pain and stiffness that are aggravated by prolonged sitting. It has been previously acknowledged that hip joint synovitis provides an inadequate explanation for this distribution of symptoms, given such pathology is typically felt in the groin [16].

Our documentation of hamstring peritendonitis on PET/MRI fusion would therefore appear to provide a better explanation for this symptomatology.

To our knowledge, this is the first study to evaluate the distribution and frequency of peripheral joint involvement on whole-body PET/CT in PMR. Dedicated hand views were utilized for this purpose, detecting abnormal  $^{18}\text{F}$ -FDG uptake at the wrist and/or hand in 14 patients (66.7%). Twelve participants (54.5%) reported wrist and/or hand pain at study enrolment, with nine of these individuals (75.0%) possessing corresponding findings on whole-body PET/CT. Upon further analysis of this subgroup, reasonable concordance [7/8 patients (87.5%)] was seen between the presence of abnormal  $^{18}\text{F}$ -FDG uptake at the wrist and/or hand and greyscale synovitis on US. None of the participants with wrist and/or hand involvement on whole-body PET/CT possessed erosive changes on plain X-ray. There were similar frequencies of abnormal  $^{18}\text{F}$ -FDG uptake observed at the shoulder (100% vs 100%), hip (92.9% vs 71.4%), trochanteric regions (100% vs 100%) and adjacent to the ischial tuberosities (100% vs 85.7%) between patients with wrist and/or hand involvement and those without.

Values for the mean reference score and  $\text{SUV}_{\text{max}}$  at the wrist/hand were lower than most other sites throughout the body, with only six (28.6%) and three (14.3%) patients exhibiting  $^{18}\text{F}$ -FDG uptake  $\geq 2$  at the wrist joint and volar hand, respectively. While this may infer an overestimate of abnormal findings at the wrist and/or hand in this study, significant FDG avidity was consistently appreciated at the knee. It therefore seems clear that both clinical and subclinical peripheral joint involvement occurs frequently in PMR, firmly contradicting the notion that PMR is a condition limited to the shoulder and hip girdle but also clouding its relationship with late-onset RA. In the 2012 EULAR/ACR classification criteria, peripheral synovitis, presence of RF and/or ACPAs and hip pain/limited range of motion best discriminated RA from PMR, yet distal swelling, tenosynovitis or arthritis was appreciated in 39% of the PMR cohort studied and 51% reported other joint pain [9]. This, together with our findings, demonstrates the difficulty of using peripheral joint involvement as a means of distinguishing PMR from late-onset RA. Further studies of abnormal  $^{18}\text{F}$ -FDG uptake in the peripheries on whole-body PET/CT and the longitudinal outcomes of PMR patients with this pattern of involvement are needed.

Correlation of volar  $^{18}\text{F}$ -FDG uptake at the hand with flexor tenosynovitis on MRI is also noteworthy. A previous study of 13 consecutive patients with PMR (who were not selected on the basis of peripheral arthritis) and 13 controls who underwent MRI of the wrist and hand demonstrated an increased occurrence of tenosynovitis but not synovitis [18]. Extensor tendon tenosynovitis was seen in 9/26 PMR hands (34.6%) compared with 1/26 controls (3.8%) ( $P=0.002$ ), with flexor tenosynovitis appreciated in 12/26 PMR hands (46.1%) compared with 4/26 (15.4%) controls ( $P=0.03$ ). Since seven patients (33.3%) in our study exhibited a volar distribution of abnormal

$^{18}\text{F}$ -FDG uptake at the hand, the incidence of flexor tenosynovitis appears to be similar in this cohort.

Together, these results highlight a predilection for tendon involvement in PMR and further substantiate the hypothesis that intra-articular inflammation is not the prevailing pathology in this condition. McGonagle *et al.* [19] initially proposed that a capsular and extracapsular pattern of joint involvement predominated following their MRI study comparing the shoulders of PMR patients with those affected by RA. More recently, this distribution of inflammation on whole-body MRI has been associated with complete patient-reported glucocorticoid response [20]. Recognition of a distinct imaging phenotype on both MRI and whole-body PET/CT has significant implications for ongoing research in the PMR field. Utilization of these modalities in future studies will be vital to ensure population homogeneity beyond that which can be achieved with conventional classification criteria.

There are several limitations to our study. First, small numbers may have resulted in an overrepresentation of participants with peripheral joint involvement by chance alone. Furthermore, the 2012 EULAR/ACR classification criteria have been utilized to determine a diagnosis of PMR in this instance. While these criteria have been established as highly sensitive, their ability to discriminate PMR from other inflammatory conditions with shoulder pain has been questioned [21, 22]. Misclassification therefore remains an inherent difficulty when researching PMR, with ~8% of patients according to the 2012 criteria having a change in diagnosis after long-term follow-up [9, 22].

Three patients returned low positive RF results that were deemed clinically insignificant. All three of these were notably ACPA negative. Only one of these individuals [RF 14 IU/l (normal <14 IU/ml)] reported wrist and/or hand pain, however, synovitis could not be appreciated on physical examination. Importantly, the exclusion of these three patients from the statistical analyses does not significantly alter the study results. In particular, knee and wrist and/or hand involvement is still appreciated in the remaining 13/18 participants (72.2%) and 11/18 participants (61.1%), respectively.

Finally, neither healthy controls nor controls with other rheumatic conditions (e.g. late-onset RA, OA) were enrolled as comparator groups in this study. In the former case, this was due to ethical concerns regarding the radiation exposure associated with whole-body PET/CT. It is well established, however, that  $^{18}\text{F}$ -FDG uptake in a distribution like that observed in our patients does not routinely occur in the absence of underlying pathology. Furthermore, a recent retrospective study comparing PET/CT findings in patients with PMR and cancer controls without rheumatologic disease demonstrated highly statistically significant differences in  $^{18}\text{F}$ -FDG uptake at multiple sites including the shoulders, interspinous bursae and adjacent to the ischial tuberosities ( $P < 0.00001$  for FDG uptake score) [11]. Whether the involvement of posteromedial knee structures that we have documented is highly specific to PMR remains unknown and will, in the

future, need to be compared with patterns of peripheral joint  $^{18}\text{F}$ -FDG uptake in other rheumatic conditions.

## Conclusion

Intense  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures is common among untreated patients with PMR on whole-body PET/CT. Using fusion technology, we have provided the first documentation of a hamstring peritendonitis as the anatomical correlate of abnormalities detected at both of these sites. In doing so, an alternate explanation for the aetiology of the gluteal and posterior thigh pain that typically characterizes PMR is proposed. A high frequency of wrist and/or hand involvement has also been observed for the first time in this study by performing dedicated views on whole-body PET/CT. Abnormal  $^{18}\text{F}$ -FDG uptake in a volar distribution at the hand was found to correlate with flexor tenosynovitis on MRI. These findings add to our growing understanding of the imaging phenotype of PMR and further highlight its distinctive pathology, including a predilection for extra-articular structures distal to the shoulder and pelvic girdles. Further studies are now needed to determine the relationship between peripheral abnormalities detected on whole-body PET/CT and the longitudinal outcomes in this subset of PMR patients.

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## Chapter 4: Sensitivity and Specificity of Novel PET/CT Findings for the Diagnosis of Polymyalgia Rheumatica

### 4.1 Preface

In the previous chapter, novel  $^{18}\text{F}$ -FDG whole body PET/CT findings were documented at the posteromedial knee and in a volar pattern at the hand in a steroid naïve, newly diagnosed PMR population. Accordingly, this chapter will be dedicated to ascertaining the performance of this imaging modality in diagnosing PMR, with a focus upon those abnormalities now known to represent hamstring peritendonitis. In order to achieve this, a nested case-control study was undertaken comparing 33 included cases from the MPR-PMR cohort to 132 historic age- and sex-matched controls who had previously undergone whole body PET/CT from skull vertex to toes. Unfortunately, sensitivity and specificity values could not be established for volar  $^{18}\text{F}$ -FDG uptake at the hand using this methodology as the imaging protocol utilised in the MPR-PMR study included dedicated hand views, which are not otherwise routinely performed.

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### 4.2 Summary of Main Findings

- On whole body PET/CT, abnormalities detected at individual musculoskeletal sites generally proved inadequate for diagnosing PMR, with higher than anticipated rates of low-grade  $^{18}\text{F}$ -FDG uptake observed in controls at the shoulder and pelvic girdle likely attributable to age-related degeneration of musculotendinous structures.
- Novel posteromedial  $^{18}\text{F}$ -FDG uptake was validated as a PET/CT finding with high specificity for PMR.
- When a combination of distinctive extra-capsular pathology adjacent to the ischial tuberosities, at the interspinous bursa and in a peri-articular distribution at the shoulders was present, whole body PET/CT was associated with a sensitivity of 93.9% and specificity of 97% for a diagnosis of PMR.
- Based upon these results, a scoring algorithm was generated comprising  $^{18}\text{F}$ -FDG uptake  $\geq 2$  adjacent to the ischial tuberosities in combination with either abnormalities at the

peri-articular shoulder or interspinous bursa, and found to possess a sensitivity of 90.9% and specificity of 92.4% for diagnosing PMR.

### **4.3 Interpretation**

This is the largest prospective study to evaluate the diagnostic performance of whole body PET/CT in the PMR literature to date, achieving sensitivity and specificity values surpassing those previously reported by employing a combination of musculoskeletal sites known to correspond with distinctive extra-capsular pathology. Whole body PET/CT can consequently be considered a viable diagnostic test for PMR.



# Abnormalities at three musculoskeletal sites on whole-body positron emission tomography/computed tomography can diagnose polymyalgia rheumatica with high sensitivity and specificity

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## Abstract

**Purpose** To evaluate the sensitivity and specificity of PET/CT findings in PMR and generate a diagnostic algorithm utilizing a minimum number of musculoskeletal sites.

**Methods** Steroid-naïve patients with newly diagnosed PMR (2012 EULAR/ACR classification criteria) were prospectively recruited to undergo whole-body <sup>18</sup>F-FDG PET/CT. Each PMR case was age- and sex-matched to four PET/CT controls. Control scan indication, diagnosis and medical history were extracted from the clinical record. Qualitative and semi-quantitative scoring (maximum standardized uptake value [SUV<sub>max</sub>]) of abnormal <sup>18</sup>F-FDG uptake at 21 musculoskeletal sites was undertaken for cases and controls. Results informed the development of a novel PET/CT diagnostic algorithm using a classification and regression trees (CART) method.

**Results** Thirty-three cases met the inclusion criteria and were matched to 132 controls. Mean age was 68.6 ± 7.4 years for cases compared with 68.2 ± 7.3 for controls, and 54.5% were male. Median CRP was 49 mg/L (32–65) and ESR 41.5 mm/h (24.6–64.4) in the PMR group. The predominant control indication for PET/CT was malignancy (63.6%). Individual musculoskeletal sites proved insufficient for diagnostic purposes. A novel algorithm comprising <sup>18</sup>F-FDG uptake ≥ 2 adjacent to the ischial tuberosities in combination with either abnormalities at the peri-articular shoulder or interspinous bursa achieved a sensitivity of 90.9% and specificity of 92.4% for diagnosing PMR.

**Conclusions** The presence of abnormal <sup>18</sup>F-FDG uptake adjacent to the ischial tuberosities together with findings at the peri-articular shoulder or interspinous bursa on whole-body PET/CT is highly sensitive and specific for a diagnosis of PMR.

**Trial registration** Clinical Trial Registration: Australian New Zealand Clinical Trials Registry, <http://www.anzctr.org.au>, ACTRN1261400696695

**Keywords** Polymyalgia rheumatica · Whole-body positron emission tomography/computed tomography · Diagnosis · Sensitivity · Specificity

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## Introduction

Polymyalgia rheumatica (PMR) is an inflammatory condition that predominantly affects musculotendinous structures of the shoulder and hip girdle. In the absence of a gold standard test, diagnosis is based upon clinical symptoms and laboratory evidence of systemic inflammation. Ultrasound findings improve the overall sensitivity and specificity of classification criteria to 66% and 81% respectively; however, their ability to distinguish PMR from the more relevant differential diagnosis of rheumatoid arthritis (RA) yields a specificity of only 70% [1].

On whole-body positron emission tomography/computed tomography (PET/CT), PMR is associated with a distinct anatomic distribution of  $^{18}\text{F}$ -Fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake around the shoulder and hip joints, trochanteric bursa, interspinous bursa and adjacent to the ischial tuberosities [2]. Whilst this pattern of inflammation is known to discriminate between PMR and RA [3], abnormalities at individual musculoskeletal sites do not possess sufficient sensitivity and specificity for diagnostic purposes [4]. Composite scoring systems have accordingly been proposed; however, a more simplified approach would likely be advantageous in everyday clinical practice.

Having frequently observed PET avidity adjacent to the ischial tuberosities and of posteromedial knee structures among PMR patients, we recently reported hamstring peritendonitis as the anatomic correlate of abnormal  $^{18}\text{F}$ -FDG uptake at these sites [2]. These findings have since been replicated in an MRI study, which found peritendinous enhancement of the pelvic tendons to be the imaging hallmark of PMR [5]. The diagnostic accuracy of this pattern at the pelvis and knees on whole-body PET/CT is, however, yet to be established.

In this study, we sought to determine the sensitivity and specificity of  $^{18}\text{F}$ -FDG uptake on whole-body PET/CT, with a focus upon abnormalities known to represent hamstring involvement. These results were then utilized to generate a novel PET/CT scoring algorithm for the diagnosis of PMR.

## Methods

### PMR cases

Patients with newly diagnosed PMR (2012 EULAR/ACR classification criteria) [1] were prospectively recruited from primary care, community and hospital rheumatology practices. Participants who had received prednisolone treatment and those with symptoms suggestive of giant cell arteritis (GCA) were excluded. The study was approved by the Austin Health Human Research Ethics Committee (HREC/14/Austin/158) prior to commencement and registered with the Australian New Zealand Clinical Trials Registry (trial identification ACTRN1261400696695).

Following appropriate written consent, case demographic and clinical data were collected. Baseline laboratory testing comprised full blood examination, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatine kinase, thyroid function testing, rheumatoid factor, anti-citrullinated peptide antibodies (ACPA) and anti-neutrophil cytoplasmic antibodies. In order to measure disease activity using the PMR-activity score (PMR-AS) [6], participants marked a visual analogue scale indicating pain severity and the investigator provided a physician global assessment.

Whole-body  $^{18}\text{F}$ -FDG PET/CT scanning (Gemini-TF64 or Ingenuity-TF128 PET/CT system; Phillips, Cleveland, OH, USA) from skull vertex to toes was undertaken prior to the commencement of glucocorticoid therapy. This involved PMR cases receiving a weight-based intravenous injection of  $^{18}\text{F}$ -FDG after a minimum 6-h fast. The emission study and low-dose CT were acquired after a 1-h rest period, with CT attenuation correction performed on all images prior to independent qualitative and semi-quantitative analysis of abnormal  $^{18}\text{F}$ -FDG uptake by two experienced nuclear medicine physicians (AP and STL).

Qualitative analysis comprised visual evaluation of  $^{18}\text{F}$ -FDG uptake using the following scoring system: 0—no uptake, 1—lower than normal liver uptake, 2—similar to normal liver uptake and 3—higher than normal liver uptake [7]. A score of  $\geq 1$  was considered a positive result, given no consensus presently exists for the degree of  $^{18}\text{F}$ -FDG uptake on whole body PET/CT that constitutes an abnormal musculoskeletal finding. For semi-quantitative analysis, a region of interest was drawn around each site and the maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) calculated. The following musculoskeletal sites were specifically assessed: two peri-articular shoulder regions, two glenohumeral joints, two acromioclavicular joints, two sternoclavicular joints, two peri-articular hip regions, two hip joints, two trochanteric regions, regions adjacent to the two ischial tuberosities, two knee joints, two posteromedial knee regions and most PET avid interspinous bursa. An atlas with pictorial examples is provided in the supplementary information (Online Resource 1). The large vessels were also evaluated for abnormal  $^{18}\text{F}$ -FDG uptake  $\geq 2$  consistent with concomitant GCA.

All PMR cases were subsequently treated with a standardized schedule of low-dose glucocorticoid therapy as outlined in the British Society of Rheumatology (BSR) guideline [8]. Follow-up visits were scheduled at weeks 4, 8, 16, 24, 32 and 46 (the minimum duration of this treatment protocol), and disease activity was re-calculated. Clinical remission was defined as a PMR-AS score  $< 9.35$ .

### Controls

Age- and sex-matched controls who had undergone whole-body PET/CT from skull vertex to toes were identified from

the hospital's electronic medical record. The first four consecutive controls matched to each PMR case were utilized, in keeping with best practice study design [9]. Clinical data pertaining to the indication for PET/CT, underlying diagnosis and history of rheumatic conditions was extracted. Potential controls with a diagnosis of PMR or GCA were excluded, along with those being evaluated for large vessel vasculitis. Audit level ethical approval was received from Austin Health HREC prior to commencement (LNR/16/Austin/356).

Qualitative and semi-quantitative analysis of the same musculoskeletal sites on whole-body PET/CT was replicated in the controls.

## Statistical analysis

Statistical analyses were conducted using Stata 13.0 [10] and R version 3.5.2. [11]. Continuous variables are reported as mean ( $\pm$  standard deviation) or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages). Whole-body PET/CT scores for PMR cases and controls were compared using the Mann-Whitney *U* test, with a *p* value  $< 0.05$  considered statistically significant. Receiver operating characteristics (ROC) curves were generated for qualitative scoring results at each musculoskeletal site, along with the area under the curve (AUC), sensitivity and specificity values for a diagnosis of PMR. Results informed the development of a novel diagnostic algorithm using a classification and regression trees (CART) method from the *rpart* package [12]. A more detailed description of the statistical analysis is provided in the supplementary information (Online Resource 2).

## Results

### Demographics, clinical and laboratory features

Thirty-three cases met the inclusion criteria for a diagnosis of PMR. Their demographic and clinical data compared with 132 age- and sex-matched controls is summarized in Table 1.

All PMR cases were negative for ACPA, although three participants returned low-positive rheumatoid factor (RF) results (14 IU/L in two and 17 IU/L in the third [ $n < 14$  IU/mL]), which were not deemed clinically significant. Using the PMR-activity score (PMR-AS), case disease activity was high at diagnosis (mean  $73.5 \pm 35.4$ ).

The predominant indication for controls to undergo whole-body PET/CT was malignancy (63.6%). Forty-three controls (32.6%) had a documented rheumatic condition including nine with inflammatory arthritis (seven with RA, one with psoriatic arthritis and one with an immune-related adverse event from cancer immunotherapy).

Longitudinal data relating to treatment response was available for 32/33 PMR cases as one participant required a modified schedule of glucocorticoid therapy due to a history of prednisolone-induced central serous retinopathy. By week 4, 13/32 (40.6%) patients met the PMR-AS definition of clinical remission, with 21/30 (70%) achieving this endpoint at week 16.

### Whole-body PET/CT

Mean scan acquisition times were comparable between the cases and controls. In one PMR patient, knee imaging could not be undertaken as the study was abandoned due to severe

**Table 1** Baseline demographic data and clinical features for cases compared with controls. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages)

| Demographic                        | PMR Cases ( <i>n</i> = 33) | Controls ( <i>n</i> = 132) |
|------------------------------------|----------------------------|----------------------------|
| Age (years)                        | 68.6 $\pm$ 7.4             | 68.2 $\pm$ 7.3             |
| Male                               | 18 (54.5%)                 | 72 (54.5%)                 |
| <sup>18</sup> F-FDG dose (MBq)     | 284.5 $\pm$ 32.0           | 276.2 $\pm$ 35.8           |
| Scan acquisition (mins)            | 66.4 $\pm$ 11.7            | 71.2 $\pm$ 11.7            |
| Median CRP (mg/L)                  | 49 (32–65)                 | –                          |
| Median ESR (mm/h)                  | 41.5 (24.6–64.4)           | –                          |
| EULAR/ACR clinical algorithm score | 5.2 $\pm$ 0.6              | –                          |
| EMS (mins)                         | 120 (60–180)               | –                          |
| PMR-AS                             | 73.5 $\pm$ 35.4            | –                          |
| Median HAQ-DI                      | 1.75 (1.125–2.125)         | –                          |
| Malignancy                         | –                          | 84 (63.6%)                 |
| PUO                                | –                          | 26 (19.7%)                 |
| Rheumatic disease:                 | –                          | 43 (32.6%)                 |
| Osteoarthritis                     | –                          | 19 (14.4%)                 |
| Inflammatory arthritis             | –                          | 9 (6.8%)                   |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EMS, early morning stiffness; PMR-AS, polymyalgia rheumatica-activity score; HAQ-DI, health assessment questionnaire-disability index; PUO, pyrexia of unknown origin

pain. In several controls, scoring of hip and knee structures was not possible due to bilateral joint replacement. The acromioclavicular joints of an additional control were also not assessed due to interference from an adjacent PET-avid lesion. None of the PMR cases exhibited abnormal vascular  $^{18}\text{F}$ -FDG uptake in keeping with large vessel-GCA.

$^{18}\text{F}$ -FDG uptake in a peri-articular distribution at the shoulder and hip was seen in 32/33 (97%) cases, with 103/132 (78%) and 81/132 (61.4%) of controls similarly exhibiting changes at these sites (Table 2). The degree of  $^{18}\text{F}$ -FDG uptake as measured by mean reference score compared with normal liver and  $\text{SUV}_{\text{max}}$  was, however, significantly higher in cases than controls at the peri-articular shoulder ( $p = 0.0001$ ), interspinous bursa ( $p = 0.0001$ ), peri-articular hip ( $p = 0.0001$ ), adjacent to the ischial tuberosities and posteromedial knee ( $p = 0.0001$ ).

Involvement of the glenohumeral and hip joints was much more common in PMR cases (72.7% and 60.6%) than controls (4.5% and 20.0%). At the knee joint, however, no difference was observed between the groups.

Posteromedial knee  $^{18}\text{F}$ -FDG uptake did discriminate between cases and controls, being present in 24/33 (72.7%) PMR patients as compared with only 25/132 (19.8%) controls. Other musculoskeletal sites with similar differentiating capacity included the interspinous bursa and, to a lesser extent, adjacent to the ischial tuberosities.

Based on these findings whereby  $^{18}\text{F}$ -FDG uptake  $\geq 1$  was considered a positive result, no individual musculoskeletal site proved adequate for diagnostic purposes (Table 2). This was primarily due to sites with high sensitivity values exhibiting poor specificity. Abnormalities at the glenohumeral joint (sensitivity 72.7%, specificity 95.4%), interspinous bursa (sensitivity 90.1%, specificity 82.6%) and posteromedial knee (sensitivity 75%, specificity 80.1%) were associated with the highest combined values. Further analysis of the control subgroup with documented inflammatory arthritis found specificity results were relatively well maintained for  $^{18}\text{F}$ -FDG uptake at the glenohumeral joint (88.9%) and posteromedial knee (75%).

Results for the best performed musculoskeletal sites based upon the ROC analysis are presented in Table 3. Similar issues in achieving a balance between sensitivity and specificity occurred at most of the individual sites with this approach, although the diagnostic performance of  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities improved vastly (sensitivity 93.9%, specificity 96.2%). Peri-articular shoulder  $^{18}\text{F}$ -FDG uptake combined with abnormalities at the interspinous bursa and adjacent to the ischial tuberosities subsequently achieved the highest sensitivity (93.9%) and specificity (97%) values for diagnosing PMR. Similar results were achieved by substituting posteromedial knee involvement for either the peri-articular shoulder (sensitivity 93.9%, specificity 92.4%) or interspinous bursa (sensitivity 93.9%, specificity 91.7%) (Table 4).

**Table 2** Incidence of abnormal findings, qualitative score (mean reference score compared to normal liver) [7] and mean  $\text{SUV}_{\text{max}}$  for cases compared with controls at each musculoskeletal site. Results for continuous variables are reported as mean  $\pm$  standard deviation

| Musculoskeletal site    | $^{18}\text{F}$ -FDG uptake $\geq 1$ cases<br>( $n = 33$ ) | $^{18}\text{F}$ -FDG uptake $\geq 1$ controls<br>( $n = 132$ ) | Mean ref.<br>score cases | Mean ref.<br>score controls | $p$ value<br>(mean ref. score) | Mean $\text{SUV}_{\text{max}}$<br>cases | Mean $\text{SUV}_{\text{max}}$<br>controls | $p$ value<br>( $\text{SUV}_{\text{max}}$ ) |
|-------------------------|------------------------------------------------------------|----------------------------------------------------------------|--------------------------|-----------------------------|--------------------------------|-----------------------------------------|--------------------------------------------|--------------------------------------------|
| Peri-articular shoulder | 32 (97.0%)                                                 | 103 (78.0%)                                                    | 2.5 $\pm$ 0.8            | 1.1 $\pm$ 0.9               | 0.0001                         | 3.4 $\pm$ 1.3                           | 2.2 $\pm$ 0.9                              | 0.0001                                     |
| GH joint                | 24 (72.7%)                                                 | 6 (4.5%)                                                       | 1.0 $\pm$ 1.0            | 0.1 $\pm$ 0.3               | 0.0001                         | 1.9 $\pm$ 1.0                           | 1.3 $\pm$ 0.4                              | 0.002                                      |
| AC joint                | 33 (100%)                                                  | 87 (66.4%) ( $n = 131$ )                                       | 1.5 $\pm$ 0.9            | 0.8 $\pm$ 0.7               | 0.0001                         | 1.9 $\pm$ 0.7                           | 1.8 $\pm$ 0.6                              | 0.54                                       |
| SC joint                | 29 (87.9%)                                                 | 75 (56.8%)                                                     | 1.3 $\pm$ 0.9            | 0.6 $\pm$ 0.6               | 0.0001                         | 1.9 $\pm$ 0.7                           | 2.0 $\pm$ 0.5                              | 0.34                                       |
| Interspinous bursa      | 30 (90.9%)                                                 | 23 (17.4%)                                                     | 2.1 $\pm$ 1.0            | 0.3 $\pm$ 0.6               | 0.0001                         | 2.9 $\pm$ 1.5                           | 1.7 $\pm$ 1.1                              | 0.0001                                     |
| Peri-articular hip      | 32 (97.0%)                                                 | 81 (61.4%)                                                     | 2.3 $\pm$ 0.9            | 0.9 $\pm$ 0.8               | 0.0001                         | 3.4 $\pm$ 1.8                           | 2.0 $\pm$ 0.7                              | 0.0001                                     |
| Hip joint               | 20 (60.6%)                                                 | 26 (20.0%) ( $n = 130$ )                                       | 0.9 $\pm$ 1.0            | 0.3 $\pm$ 0.6               | 0.0001                         | 1.8 $\pm$ 1.2                           | 1.5 $\pm$ 0.5                              | 0.57                                       |
| Trochanteric bursa      | 33 (100%)                                                  | 98 (75.4%) ( $n = 130$ )                                       | 2.1 $\pm$ 0.8            | 1.0 $\pm$ 0.7               | 0.0001                         | 2.5 $\pm$ 0.9                           | 2.1 $\pm$ 0.8                              | 0.005                                      |
| Ischial tuberosities    | 33 (100%)                                                  | 77 (58.3%)                                                     | 2.7 $\pm$ 0.5            | 0.8 $\pm$ 0.8               | 0.0001                         | 3.6 $\pm$ 1.4                           | 2.0 $\pm$ 0.7                              | 0.0001                                     |
| Knee joint              | 17 (53.1%) ( $n = 32$ )                                    | 68 (54.0%) ( $n = 126$ )                                       | 1.1 $\pm$ 1.3            | 0.8 $\pm$ 0.9               | 0.48                           | 2.8 $\pm$ 1.0                           | 2.1 $\pm$ 1.1                              | 0.02                                       |
| Posteromedial knee      | 24 (72.7%) ( $n = 32$ )                                    | 25 (19.8%) ( $n = 126$ )                                       | 1.7 $\pm$ 1.1            | 0.3 $\pm$ 0.6               | 0.0001                         | 2.7 $\pm$ 1.0                           | 1.4 $\pm$ 0.7                              | 0.0001                                     |

$^{18}\text{F}$ -FDG,  $^{18}\text{F}$  Fluorodeoxyglucose; mean ref. score, mean reference to normal liver score;  $\text{SUV}_{\text{max}}$  maximum standardized uptake value; GH, glenohumeral; AC, acromioclavicular; SC, sternoclavicular

**Table 3** Sensitivity and specificity values for PMR diagnosis based upon  $^{18}\text{F}$ -FDG uptake  $\geq 1$  at each musculoskeletal site. Specificity results are presented using the whole control cohort ( $n = 132$ ) and an inflammatory arthritis control subgroup ( $n = 9$ )

| Musculoskeletal site    | Sensitivity (overall) | Specificity (overall) | Specificity (inflammatory arthritis subgroup) |
|-------------------------|-----------------------|-----------------------|-----------------------------------------------|
| Peri-articular shoulder | 97.0%                 | 18.2%                 | 0%                                            |
| Glenohumeral joint      | 72.7%                 | 95.4%                 | 88.9%                                         |
| Acromioclavicular joint | 100%                  | 33.6%                 | 22%                                           |
| Sternoclavicular joint  | 87.9%                 | 43.2%                 | 50%                                           |
| Interspinous bursa      | 90.1%                 | 82.6%                 | 66.7%                                         |
| Peri-articular hip      | 97.0%                 | 37.7%                 | 22.2%                                         |
| Hip joint               | 60.6%                 | 80.0%                 | 55.5%                                         |
| Trochanteric bursa      | 100%                  | 24.6%                 | 0%                                            |
| Ischial tuberosities    | 100%                  | 41.6%                 | 11.1%                                         |
| Knee joint              | 53.1%                 | 46.0%                 | 25%                                           |
| Posteromedial knee      | 75%                   | 80.1%                 | 75%                                           |

 $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -Fluorodeoxyglucose

Using CART models, abnormalities on whole-body PET/CT adjacent to the ischial tuberosities in association with either the peri-articular shoulder or interspinous bursa were found to be superior to any alternate combination for inclusion in the novel diagnostic algorithm. Pre-specified qualitative scores at these musculoskeletal sites as outlined in Fig. 1 yielded a sensitivity of 90.9% and specificity of 92.4% for the diagnosis of PMR. A significant difference in the algorithm's performance was not identified when controls with a documented rheumatic disease were excluded (sensitivity 93.1% and specificity 93.3%). Furthermore, when patients with osteoarthritis were used as a non-inflammatory arthritis control group, sensitivity and specificity results were maintained at 93.9% and 95% respectively.

**Table 4** AUC, sensitivity and specificity for PMR diagnosis based upon qualitative scoring results at each musculoskeletal site and their various combinations

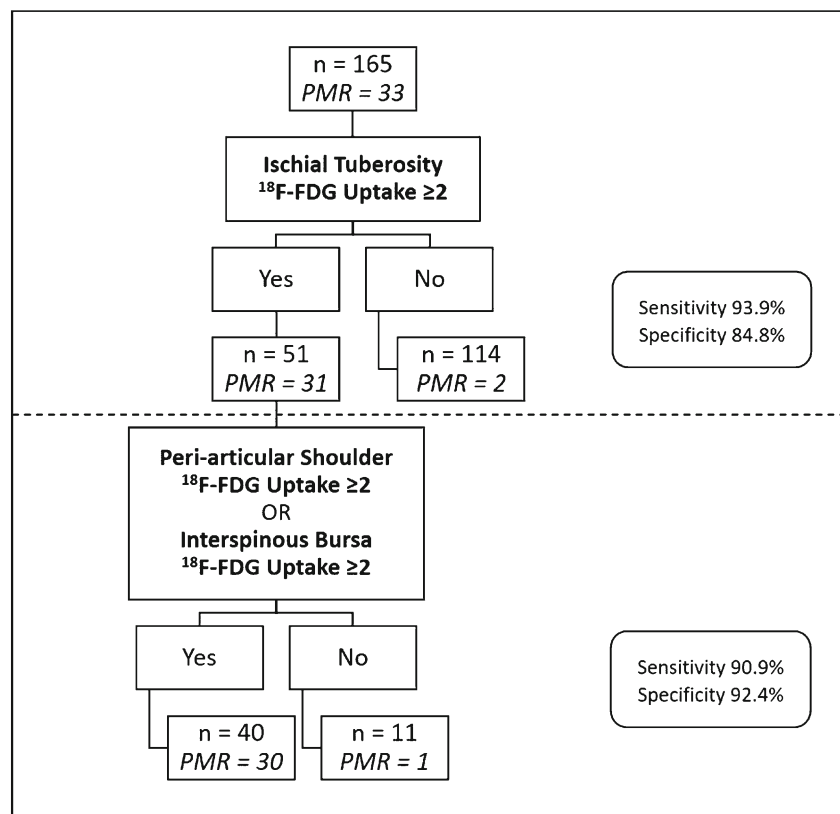
| Musculoskeletal site                                                | AUC   | Sensitivity | Specificity |
|---------------------------------------------------------------------|-------|-------------|-------------|
| Peri-articular shoulder                                             | 0.898 | 81.8%       | 90.9%       |
| Glenohumeral joint                                                  | 0.974 | 100.00%     | 94.70%      |
| Interspinous bursa                                                  | 0.959 | 100.0%      | 82.6%       |
| Peri-articular hip                                                  | 0.888 | 75.8%       | 95.4%       |
| Hip joint                                                           | 0.869 | 100.00%     | 79.55%      |
| Trochanteric bursa                                                  | 0.901 | 97.0%       | 79.5%       |
| Ischial tuberosities                                                | 0.980 | 93.9%       | 96.2%       |
| Posteromedial knee                                                  | 0.940 | 100.0%      | 80.3%       |
| Peri-articular shoulder + interspinous bursa                        | 0.941 | 84.8%       | 96.2%       |
| Peri-articular shoulder + ischial tuberosity                        | 0.962 | 93.9%       | 91.7%       |
| Peri-articular shoulder + posteromedial knee                        | 0.930 | 93.9%       | 83.3%       |
| Interspinous bursa + ischial tuberosity                             | 0.971 | 93.9%       | 93.9%       |
| Interspinous bursa + posteromedial knee                             | 0.959 | 93.9%       | 85.6%       |
| Ischial tuberosity + posteromedial knee                             | 0.976 | 93.9%       | 92.4%       |
| Peri-articular shoulder + interspinous bursa + ischial tuberosities | 0.964 | 93.9%       | 97.0%       |
| Peri-articular shoulder + ischial tuberosities + posteromedial knee | 0.965 | 93.9%       | 91.7%       |
| Interspinous bursa + ischial tuberosities + posteromedial knee      | 0.971 | 93.9%       | 92.4%       |

AUC, area under the curve

## Discussion

In our study of 33 prospectively recruited, steroid-naïve cases matched to 132 historic age- and sex-matched controls, whole-body PET/CT proved a highly sensitive and specific test for the diagnosis of PMR. Whilst abnormalities at individual musculoskeletal sites were generally inadequate for diagnostic purposes, the combination of abnormal  $^{18}\text{F}$ -FDG uptake at the peri-articular shoulder, interspinous bursa and adjacent to the ischial tuberosities sufficiently discriminated between the two groups. We accordingly propose a simple algorithm for diagnosing PMR on whole-body PET/CT using pre-specified qualitative scores at these musculoskeletal sites.

**Fig. 1** A novel algorithm for diagnosing PMR on whole-body PET/CT utilizing pre-specified qualitative scores at three musculoskeletal sites. PET/CT, positron emission tomography/computed tomography;  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -Fluorodeoxyglucose



The absence of a gold standard diagnostic test has often raised questions as to the legitimacy of PMR as a distinct disease entity. Despite best efforts, a shift in diagnosis is observed in 5–23% of PMR patients during follow-up [13, 14]. A range of mimics, including infection, malignancy and other rheumatic conditions, has been reported [13]. Distinguishing PMR from late-onset seronegative RA at presentation is especially problematic, although recent MRI and whole-body PET/CT studies have borne out distinctive differences in their respective imaging phenotypes. An extra-capsular pattern of inflammation is now recognized as characteristic of PMR, whereas in RA intra-articular pathology predominates [15–18].

Peri-articular abnormalities at the shoulders and hips were observed in almost every PMR patient in our study. By comparison, a lesser frequency and lower intensity of intra-articular  $^{18}\text{F}$ -FDG uptake was noted at the glenohumeral and hip joints. Involvement of musculoskeletal sites recognized as typical of PMR including the trochanteric bursa and adjacent to the ischial tuberosities was also universal among this group. The location and extent of abnormalities detected on whole-body PET/CT in the PMR cases can therefore be considered homogenous; however, a higher than anticipated incidence of  $^{18}\text{F}$ -FDG uptake at the peri-articular shoulder and hip, along with the trochanteric bursa and ischial tuberosities, was identified in the controls.

The demographic of the population under study likely provides an explanation for these findings, in that the incidence of

degenerative tendinopathy increases substantially with advancing age [19]. In an ultrasound study of 90 asymptomatic adults, partial or full thickness tears of the rotator cuff were present in 50% of dominant shoulders by the seventh decade and 80% of subjects over 80 years of age [20]. Similarly at the hip on MRI, findings of peri-trochanteric oedema and tendinosis are frequently observed in the absence of greater trochanteric pain syndrome [21]. We therefore hypothesise that the high frequency of low-grade peri-articular changes in this study's control group represents age-related degeneration of shoulder and pelvic girdle musculotendinous structures.

Sensitivity and specificity values for a diagnosis of PMR were higher for abnormal  $^{18}\text{F}$ -FDG uptake at certain musculoskeletal sites including adjacent to the ischial tuberosities and of posteromedial knee structures. Using PET/MRI fusion, these findings have been established to correlate anatomically with peritendinitis of the hamstring tendons at their proximal origin and distal insertion points [2]. The diagnostic performance of these regions is consequently particularly noteworthy. Firstly,  $^{18}\text{F}$ -FDG uptake at the posteromedial knee can now be added to the list of extra-capsular sites possessing high specificity for a diagnosis of PMR. Imaging of the knees should therefore be routine when PET/CT is undertaken for this indication. Secondly, peritendinitis is further substantiated as an imaging hallmark of PMR and the condition's unique predilection for musculotendinous structures is once again confirmed. This provides yet more evidence for this

distribution of pathology representing a point of difference between PMR and other rheumatic diseases, and ultimately validates it as a distinct disease entity.

The presence of  $^{18}\text{F}$ -FDG uptake at the glenohumeral and, to a lesser degree, hip joint still proved both sensitive and specific for a diagnosis of PMR. As outlined, the incidence and PET avidity of abnormalities at these sites was lower than that detected in a peri-articular distribution; however, the specificity figure at the glenohumeral joint was unexpectedly maintained when a subgroup analysis of controls with documented inflammatory arthritis was undertaken. Of course, the distribution and state of disease activity in these individuals at the time of whole-body PET/CT is not known; hence, it remains to be seen whether these results would be reproduced if the comparator group consisted solely of newly diagnosed, late-onset RA patients with proximal joint involvement.

Two other studies have recently evaluated the performance of PET as a diagnostic tool in PMR. In the first, whole-body PET/CT scans from 50 patients with a PMR diagnosis (2012 EULAR/ACR classification criteria) were retrospectively analysed and compared to 53 malignancy controls [22]. As in our study, best results were achieved when basing the diagnosis of PMR upon the presence of abnormal  $^{18}\text{F}$ -FDG uptake at  $\geq 3$  musculoskeletal sites. The sensitivity and specificity figures achieved, however, were much lower (74% and 79% respectively). Possible explanations for this differential include the retrospective nature of this study, the smaller number of controls examined and the fact that cases were not necessarily new diagnoses or treatment naïve. Furthermore, the PMR group included seven patients with “PMR syndrome associated with other diseases” like haematological disorders and malignancy, the addition of whom seems likely to have compromised case homogeneity.

In the largest study to date, Henckaerts et al. evaluated the PET appearance of 99 prospectively recruited patients, sixty-seven of whom had a final diagnosis of PMR based on expert opinion [4]. PMR patients were similarly found to exhibit more intense  $^{18}\text{F}$ -FDG uptake than their non-PMR peers, and once again none of the individual musculoskeletal regions evaluated exhibited adequate sensitivity and specificity for diagnostic purposes. Instead, the authors generated a total skeletal score to aid PMR diagnosis based upon qualitative scores at 12 articular sites, with a value of  $> 16$  achieving a sensitivity of 85.1% and specificity of 87.5%. Whilst these results were also lower than ours, the methodology employed arguably provides a superior comparator subject in that each of the controls was being evaluated for a possible PMR diagnosis. The major limitation of the study, however, pertains to the use of PET rather than PET/CT hybrid technology. It therefore seems probable that higher values might be achieved with PET/CT courtesy of its ability to accurately correlate findings anatomically.

Taken together, these findings clearly endorse whole-body PET/CT as a viable diagnostic test for PMR. Its performance is dependent though upon detecting abnormalities at multiple musculoskeletal sites. Whilst composite scoring systems may be feasible in research settings, their application in everyday clinical practice would prove cumbersome. We have consequently developed a diagnostic algorithm to overcome this issue using pre-specified qualitative scores at just three musculoskeletal sites. The presence of distinctive extra-capsular pathology adjacent to the ischial tuberosities, in combination with the peri-articular shoulder or interspinous bursa, achieved a sensitivity of 90.9% and specificity of 92.4%. Such values surpass those reported by other studies using far more complex methods. Clinicians can now be highly confident of a PMR diagnosis when these features alone are present on whole-body PET/CT.

There are some limitations to our study. Firstly, PMR patients were recruited as part of a small, investigator-initiated pilot and this may have resulted in selection bias. In particular, a larger proportion of male participants were included than would usually be anticipated and it is unclear whether this occurred due to chance alone. All cases had newly diagnosed steroid-naïve PMR; hence, it is possible that the results obtained might be less applicable to patients with established disease who are already taking prednisolone. The controls were also identified from historic data rather than being prospectively recruited. This approach enabled timely identification of four age- and sex-matched controls for every PMR case and avoided any ethical concerns related to radiation exposure in healthy individuals; however, most of the control patients identified were consequently undergoing whole-body PET/CT for established or suspected malignancy and thus do not represent a real-world comparator group for a potential diagnosis of PMR. A prospective study evaluating the accuracy of whole-body PET/CT in distinguishing PMR from other rheumatic diseases like late-onset RA and spondyloarthritis is now needed. Finally, PET/CT scoring was not undertaken in a blinded fashion owing to the study design employed. Whilst the nuclear medicine physicians involved were not privy to clinical assessments or responsible for the extraction of information from the medical record, the designation of patients as cases or controls was nonetheless readily apparent to them.

Moving forward, we propose that imaging modalities like whole-body PET/CT are utilized to select participants for inclusion in clinical trials of PMR. This will ensure much greater population homogeneity than that which can be achieved with current clinical classification criteria. In truth, whole-body PET/CT possesses very real potential as a gold standard diagnostic test for PMR. Cost, radiation exposure and access remain major drawbacks to this approach, but these should be balanced against the risk of making an incorrect diagnosis and unnecessarily exposing a patient to the perils of glucocorticoid therapy. Added advantages include whole-body PET/CT's ability to detect concomitant large vessel-GCA and rule out other relevant differentials like infection and malignancy.

## Conclusion

Using pre-specified qualitative scores at three musculoskeletal sites recognized for their distinctive extra-capsular pathology, whole-body PET/CT was found to be a sensitive and specific test for diagnosing PMR. Novel  $^{18}\text{F}$ -FDG uptake of posteromedial knee structures was also validated as an additional imaging finding exhibiting high specificity in this study. Whole-body PET/CT possesses real potential as the gold standard investigation for PMR; however, further prospective evaluation of this imaging modality's ability to differentiate this diagnosis from other relevant rheumatic conditions is now necessary.

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## Compliance with ethical standards

**Conflict of interest** Author CO has received speaking honoraria from Roche, Janssen and Pfizer and meeting sponsorship from Roche. Author AP declares no conflict of interest. Author VY declares no conflict of interest. Author CM declares no conflict of interest. Author SL declares no conflict of interest. Author DL declares no conflict of interest. Author JL has received a speaking honorarium from Abbvie and meeting sponsorship from Gilead. Author AS declares no conflict of interest. Author RB declares no conflict of interest.

**Ethical approval** All procedures performed in this study were carried out in accordance with the ethical standards of the Austin Health Human Research Ethics Committee (HREC/14/Austin/158).

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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# Chapter 5: Results of the Melbourne Predictors of Relapse in Polymyalgia Rheumatica Study

## 5.1 Preface

In this chapter, the main results of the Melbourne predictors of relapse in PMR (MPR-PMR) study are presented. This work aimed to delineate the demographic, clinical, laboratory and imaging features of relapsing PMR by enrolling newly diagnosed patients according to the 2012 EULAR/ACR classification criteria in a single-centre, prospective, longitudinal cohort study. Following baseline characterisation, participants commenced a weaning schedule of prednisolone as outlined in the BSR guideline(1), with assessments of disease activity subsequently undertaken at weeks 4, 8, 16, 24, 32 and 46. Relapse according to PMR-AS(2) represented the study's primary outcome measure, with glucocorticoid resistance defined as non-response to an initial prednisolone dose of 15mg/day or initial response followed by disease relapse upon weaning prednisolone to 5mg/day.(3)

Characteristics of the MPR-PMR study population at baseline will first be described here, prior to exploring the correlation between these factors and disease activity. Further in-depth analysis of predictors of relapsing PMR and glucocorticoid-resistant disease will ensue.

## 5.2 Baseline Characterisation

### 5.2.1 Demographics

Thirty-five patients met the study inclusion criteria for a new diagnosis of PMR (mean EULAR/ACR clinical algorithm score(4)  $(5.2 \pm 0.6)$ ). Their demographic data are summarised in Table 5.1. Mean age was  $69.5 \pm 7.1$  years. Nineteen participants (54.3%) were male and 34/35 patients (97.1%) were Caucasian. Mean body mass index (BMI) was in the overweight range ( $28.0 \pm 5.0 \text{ kg/m}^2$ ). Most patients were lifelong non-smokers, but other cardiovascular risk factors including hypertension (57.1%) and hypercholesterolaemia (54.3%) were commonplace.

### 5.2.2 Clinical Features

As dictated by the 2012 EULAR/ACR classification criteria, all participants reported bilateral shoulder pain, with 31/35 (88.6%) indicating concomitant hip symptoms when asked to mark areas of pain on a human mannequin (Table 5.2). Twenty-three patients (65.7%) reported knee involvement, whilst wrist and/or hand pain was present in 17/35 participants (48.6%). Based on VAS scoring, pain intensity was moderately severe at baseline. EMS was extended, with a

**Table 5.1:** Baseline demographic data for participants in the MPR-PMR study. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages).

| <b>Demographic</b>                                     | <b>Patients (n=35)</b> |
|--------------------------------------------------------|------------------------|
| <b>Age (years)</b>                                     | 69.5 $\pm$ 7.1         |
| <b>Male</b>                                            | 19 (54.3%)             |
| <b>Caucasian</b>                                       | 34 (97.1%)             |
| <b>Smoking Status:</b>                                 |                        |
| Current Smoker                                         | 3 (8.6%)               |
| Ex-Smoker                                              | 14 (40%)               |
| Never Smoked                                           | 18 (51.4%)             |
| <b>BMI (kg/m<sup>2</sup>)</b>                          | 28.0 $\pm$ 5.0         |
| <b>Obese (BMI <math>\geq</math>30kg/m<sup>2</sup>)</b> | 13 (37.1%)             |
| <b>Past Medical History:</b>                           |                        |
| Hypertension                                           | 20 (57.1%)             |
| Hypercholesterolaemia                                  | 19 (54.3%)             |
| Impaired Fasting Glucose                               | 3 (8.6%)               |
| Diabetes Mellitus                                      | 6 (17.1%)              |
| Ischaemic Heart Disease                                | 3 (8.6%)               |

Abbreviations: BMI – body mass index.

**Table 5.2:** Baseline clinical features for participants in the MPR-PMR Study. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages).

| <b>Clinical Feature</b>               | <b>Patients (n=35)</b> |
|---------------------------------------|------------------------|
| <b>Median Symptom Duration (days)</b> | 84 (42 – 150)          |
| <b>Distribution of Pain:</b>          |                        |
| Shoulder Pain                         | 35 (100%)              |
| Hip Pain                              | 31 (88.6%)             |
| Neck Pain                             | 18 (51.4%)             |
| Back Pain                             | 20 (57.1%)             |
| Hand Pain                             | 17 (48.6%)             |
| Knee Pain                             | 23 (65.7%)             |
| <b>Patient Pain VAS (mm)</b>          | 7.0 $\pm$ 2.2          |
| <b>Median Duration of EMS (mins)</b>  | 120 (60 – 180)         |
| <b>Fatigue</b>                        | 33 (94.3%)             |
| <b>Loss of Weight</b>                 | 18 (51.4%)             |
| <b>Loss of Weight (kg)</b>            | 1.5 $\pm$ 0.5          |
| <b>Fevers</b>                         | 7 (20%)                |
| <b>EUL Score:</b>                     |                        |
| 0 – Above Shoulder Girdle             | 17 (48.6%)             |
| 1 – Up to Shoulder Girdle             | 7 (20%)                |
| 2 – Below Shoulder Girdle             | 11 (31.4)              |
| <b>Wrist and/or Hand Synovitis</b>    | 14 (40%)               |
| <b>Physician Global (mm)</b>          | 5.9 $\pm$ 2.0          |
| <b>PMR-AS</b>                         | 71.6 $\pm$ 35.5        |
| <b>Median HAQ-DI</b>                  | 1.75 (1.125 – 2.25)    |

Abbreviations: VAS – visual analogue scale; EMS – early morning stiffness; EUL – elevation of upper limb; PMR-AS – polymyalgia rheumatica-activity score; HAQ-DI – Health Assessment Questionnaire-Disability Index.

median duration of 2 hours. Fatigue was almost universally reported as a constitutional symptom (94.3%). The median symptom duration preceding PMR diagnosis was 12 weeks.

On clinical examination, more than half of the cohort were unable to raise their upper limbs above the shoulder girdle. Wrist and/or hand synovitis was present in fourteen patients (40%), with three participants (8.6%) exhibiting concurrent pitting oedema in keeping with RS3PE syndrome.

Using the PMR-AS, disease activity was judged to be high at baseline (mean  $71.6 \pm 35.5$ ). Participants reported a moderate to severe level of disability because of their symptoms on the HAQ-DI.

### 5.2.3 Laboratory Features

Baseline laboratory features for the MPR-PMR study cohort are summarised in Table 5.3. All participants were negative for ACPAs. Three patients returned a low positive rheumatoid factor result (14IU/L in two participants and 17IU/L in the third [ $n < 14$  IU/mL]). Other relevant differential diagnoses were excluded based on normal creatine kinase levels and thyroid function, and negative ANCA testing.

As anticipated, median CRP and ESR values were significantly elevated. A subset of patients had abnormalities on their baseline FBE including anaemia (40%) and thrombocytosis (28.6%).

### 5.2.4 Imaging Features

#### *X-Ray*

Two participants possessed erosive change on their baseline bilateral wrist and hand x-rays. The first had a subtle marginal erosion of the right fourth metacarpal head, whilst the second exhibited possible changes at the base of the 5<sup>th</sup> metacarpals bilaterally. No pathognomonic features of an alternate differential diagnosis were reported in either case and both participants had normal rheumatoid factor results.

#### *Ultrasound*

Thirty patients (85.7%) had evidence of subacromial bursitis affecting at least one shoulder on B-mode ultrasound scanning, with 18 (51.4%) meeting the criteria for this finding bilaterally (Table 5.4). Biceps tenosynovitis was also frequently observed (65.7%). A single participant exhibited bilateral glenohumeral effusions at baseline, although a further 12 patients (34.2%) possessed unilateral or bilateral findings of effusion in the bicipital groove.

**Table 5.3:** Baseline laboratory features for participants in the MPR-PMR study. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages).

| Laboratory Test                                  | Patients (n=35)   |
|--------------------------------------------------|-------------------|
| Median CRP (mg/L)                                | 40.2 (19 – 64.4)  |
| Median ESR (mm)                                  | 46 (21 – 65)      |
| ACPA (IU/mL)                                     | 0 (0%)            |
| Rheumatoid Factor (IU/mL)                        | 3 (8.6%)          |
| Haemoglobin (g/L)                                | 120.6 $\pm$ 17.1  |
| Anaemic (Hb <110 g/L)                            | 14 (40%)          |
| Platelets ( $\times 10^9$ /L)                    | 345.6 $\pm$ 100.0 |
| Thrombocytosis (Platelets >400 $\times 10^9$ /L) | 10 (28.6%)        |
| HbA1C (%)                                        | 6.0 $\pm$ 0.7     |
| HbA1C >6.49%                                     | 7 (20%)           |
| Vitamin D Level (nmol/L)                         | 79.4 $\pm$ 29.9   |
| Vitamin D Deficient (<50 nmol/L)                 | 6 (17.1%)         |

Abbreviations: CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; ACPA – anti-citrullinated peptide antibodies.

**Table 5.4:** Baseline B-mode and Power Doppler ultrasound findings for participants in the MPR-PMR study. Categorical variables are represented as proportions (percentages).

| Ultrasound Finding                              | Patients (n=35) |
|-------------------------------------------------|-----------------|
| <b>Subacromial Bursitis<sup>#</sup>:</b>        | 30 (85.7%)      |
| Bilateral                                       | 18 (51.4%)      |
| Left                                            | 21 (60%)        |
| Right                                           | 24 (68.6%)      |
| <b>Biceps Tenosynovitis:</b>                    | 23 (65.7%)      |
| Bilateral                                       | 15 (42.8%)      |
| Left                                            | 18 (51.4%)      |
| Right                                           | 18 (51.4%)      |
| <b>Effusion in the Bicipital Groove*:</b>       | 12 (34.3%)      |
| Bilateral                                       | 5 (14.3%)       |
| Left                                            | 6 (17.1%)       |
| Right                                           | 11 (31.4%)      |
| <b>Glenohumeral Joint Effusion<sup>^</sup>:</b> | 1 (2.8%)        |
| Bilateral                                       | 1 (2.8%)        |
| Left                                            | 1 (2.8%)        |
| Right                                           | 1 (2.8%)        |
| <b>Wrist and/or Hand:</b>                       |                 |
| Greyscale Synovitis                             | 19 (54.3%)      |
| Power Doppler Signal                            | 14 (40%)        |

<sup>#</sup>Defined as a thickness of hypoechoic material within the bursa of >1.1mm.

\*Defined as a distance between the tendon and bicipital groove >2.5mm.

<sup>^</sup>Defined as a distance between the humeral neck convexity and joint capsule at the axillary recess of >3.5mm.

At the wrists and/or hands, greyscale synovitis was documented in 19 participants (54.3%), 14 (73.7%) of whom possessed associated Power Doppler signal. Of these individuals, only 11 (57.9%) had indicated pain at the wrist and/or hand on their human mannequin.

B mode scanning at the hip for trochanteric bursitis and joint effusion proved difficult using the available ultrasound equipment, which was not well suited to evaluating deeper musculoskeletal structures. Results were consequently considered unreliable and scanning of this region was abandoned early in the study.

#### *Whole Body PET/CT*

The incidence of abnormal findings by musculoskeletal site on whole body PET/CT for the MPR-PMR cohort are summarised in Table 5.5. A peri-articular pattern of  $^{18}\text{F}$ -FDG uptake was observed at the shoulders and hips in 34/35 (97.1%) and 33/35 (94.3%) patients respectively. FDG avidity of the acromioclavicular joint was noted in all cases.

$^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities was also observed in 34/35 participants, with corresponding posteromedial knee involvement (representing the distal anatomical correlate of hamstring peritendonitis) in 25/35 (73.5%). The highest mean  $\text{SUV}_{\text{max}}$  was recorded adjacent to the ischial tuberosities ( $3.5 \pm 1.4$ ), followed by the peri-articular shoulder ( $3.3 \pm 1.3$ ) and hip ( $3.3 \pm 1.8$ ).

The incidence of intra-articular  $^{18}\text{F}$ -FDG uptake at the glenohumeral and hip joints was less frequent (68.6% and 57.1% respectively), with lower recorded mean  $\text{SUV}_{\text{max}}$  scores. Peripheral joint involvement was observed at the wrist and/or knee in half the cohort. A volar pattern of hand  $^{18}\text{F}$ -FDG uptake was present in 12/35 patients (35.3%), including all three of the participants with clinical evidence of RS3PE syndrome.

Mean total skeletal score (TSS) was  $11.94 \pm 4.54$ , whilst mean total vascular score (TVS) was  $1.67 \pm 2.19$ . A single participant exhibited abnormal  $^{18}\text{F}$ -FDG uptake in multiple vascular territories and was consequently diagnosed with concomitant large vessel-GCA based on this imaging appearance. A further patient had uptake in the iliac vessels that was similar to normal liver levels, however this finding in isolation was considered insufficient for a diagnosis of large vessel vasculitis.

**Table 5.5:** Analysis of  $^{18}\text{F}$ -FDG uptake by musculoskeletal site on whole body PET/CT for participants in the MPR-PMR study. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]). Categorical variables are represented as proportions (percentages).

| Musculoskeletal Site           | Frequency of $^{18}\text{F}$ -FDG Uptake $\geq 1$ | Frequency of $^{18}\text{F}$ -FDG Uptake $\geq 2$ | Mean Ref. Score | Mean $\text{SUV}_{\text{max}}$ |
|--------------------------------|---------------------------------------------------|---------------------------------------------------|-----------------|--------------------------------|
| <b>Shoulder:</b>               |                                                   |                                                   |                 |                                |
| • Peri-articular               | 34 (97.1%)                                        | 27 (79.4%)                                        | 2.4 $\pm$ 0.9   | 3.3 $\pm$ 1.3                  |
| • Glenohumeral Joint           | 24 (68.6%)                                        | 8 (22.8%)                                         | 1.0 $\pm$ 1.0   | 1.9 $\pm$ 1.0                  |
| <b>Acromioclavicular Joint</b> | 35 (100%)                                         | 12 (34.3%)                                        | 1.5 $\pm$ 0.9   | 1.9 $\pm$ 0.7                  |
| <b>Sternoclavicular Joint</b>  | 30 (85.7%)                                        | 16 (45.7%)                                        | 1.2 $\pm$ 0.9   | 1.9 $\pm$ 0.7                  |
| <b>Hip:</b>                    |                                                   |                                                   |                 |                                |
| • Peri-articular               | 33 (94.3%)                                        | 25 (71.4%)                                        | 2.2 $\pm$ 1.0   | 3.3 $\pm$ 1.8                  |
| • Hip Joint                    | 20 (57.1%)                                        | 8 (22.8%)                                         | 0.9 $\pm$ 1.0   | 1.8 $\pm$ 1.1                  |
| <b>Trochanteric</b>            | 34 (97.1%)                                        | 23 (65.7%)                                        | 2.0 $\pm$ 0.8   | 2.4 $\pm$ 0.9                  |
| <b>Ischial</b>                 | 34 (97.1%)                                        | 32 (91.4%)                                        | 2.6 $\pm$ 0.7   | 3.5 $\pm$ 1.4                  |
| <b>Interspinous</b>            | 31 (88.6%)                                        | 22 (62.8%)                                        | 2.0 $\pm$ 1.1   | 2.8 $\pm$ 1.6                  |
| <b>Knee: (n=34)</b>            | 27 (79.4%)                                        |                                                   |                 |                                |
| • Posteromedial                | 25 (73.5%)                                        | 19 (55.9%)                                        | 1.6 $\pm$ 1.1   | 2.7 $\pm$ 1.0                  |
| • Joint                        | 18 (52.9%)                                        | 12 (35.3%)                                        | 1.0 $\pm$ 1.3   | 2.7 $\pm$ 1.0                  |
| <b>Wrist/Hand: (n=34)</b>      | 24 (68.6%)                                        |                                                   |                 |                                |
| • Wrist Joint                  | 17 (50.0%)                                        | 10 (29.4%)                                        | 0.8 $\pm$ 1.1   | 1.8 $\pm$ 1.1                  |
| • Volar Hand                   | 12 (35.3%)                                        | 9 (25.7%)                                         | 0.7 $\pm$ 1.1   | 2.4 $\pm$ 1.0                  |

Abbreviations:  $^{18}\text{F}$ -FDG –  $^{18}\text{F}$ -Fluorodeoxyglucose; mean ref. score – mean reference to normal liver score;  $\text{SUV}_{\text{max}}$  – standardised uptake value maximum.

### 5.3 Analysis of Baseline Factors

#### 5.3.1 Disease Activity Correlates

Linear regression was undertaken to establish the relationship between PMR-AS and a range of independent variables at baseline. The results of this analysis are presented in Table 5.6.

A statistically significant relationship (0.76 [95% CI 0.43 – 1.09]) existed between baseline PMR-AS and ESR. The association between CRP and PMR-AS was not evaluated as this marker of systemic inflammation is incorporated in the disease activity score. Haematologic parameters including haemoglobin and platelet counts, whose levels undergo change in the presence of systemic inflammation, were similarly found to correlate with disease activity. Scatter-plots illustrating the linear relationship between these variables and PMR-AS are detailed in Figure 5.1.

Loss of weight as a constitutional symptom was also associated with significantly higher baseline disease activity (31.14 [95% CI 4.70 – 57.57]).

#### 5.3.2 Whole Body PET/CT Correlates

The performance of whole body PET/CT TSS was next evaluated as a measure of PMR severity by analysing its relationship with conventional disease activity parameters (Table 5.7).

Statistically significant associations were found between TSS and baseline patient pain VAS, physician global assessment, CRP and PMR-AS. A trend towards significance existed between TSS and ESR. Scatter-plots depicting the linear relationship between these variables and TSS are detailed in Figure 5.2.

### 5.4 Longitudinal Outcomes

#### 5.4.1 Disease Relapse

Thirty-two of the 35 patients (91.4%) recruited at baseline were suitable for inclusion in the final analysis: one patient was excluded due to aforementioned large vessel vasculitis on whole body PET/CT consistent with concomitant GCA; another patient's final diagnosis was revised to Parkinson's disease following a negative whole body PET/CT scan and the development of neurological signs; and the third patient required a modified schedule of glucocorticoid therapy and early initiation of a steroid-sparing agent due to a history of prednisolone-induced central serous retinopathy.

**Table 5.6:** Linear regression analysis of the relationship between PMR-AS and a range of independent variables at baseline in the MPR-PMR study.

| <b>Independent Variable</b>          | <b>Coefficient</b> | <b>Standard Error</b> | <b>p-value</b> | <b>95% CI</b>  |
|--------------------------------------|--------------------|-----------------------|----------------|----------------|
| <b>Age (years)</b>                   | 1.28               | 0.81                  | 0.12           | -0.36 – 2.92   |
| <b>Male</b>                          | -4.82              | 12.20                 | 0.69           | -29.64 – 20.00 |
| <b>Never smoked</b>                  | -1.96              | 22.62                 | 0.55           | -48.09 – 44.17 |
| <b>BMI (kg/m<sup>2</sup>)</b>        | 0.77               | 1.36                  | 0.58           | -2.03 – 3.57   |
| <b>Duration of EMS (mins)</b>        | 0.10               | 0.07                  | 0.17           | -0.04 – 0.25   |
| <b>Symptom Duration (days)</b>       | -0.02              | 0.01                  | 0.06           | -0.05 – 0.00   |
| <b>Loss of Weight</b>                | 31.14              | 12.98                 | <b>0.02</b>    | 4.70 – 57.57   |
| <b>Fever</b>                         | -27.48             | 16.21                 | 0.10           | -60.51 – 5.55  |
| <b>Peripheral Synovitis</b>          | -0.34              | 12.43                 | 0.98           | -25.64 – 24.96 |
| <b>EULAR/ACR Score</b>               | 8.90               | 9.65                  | 0.36           | -10.73 – 28.54 |
| <b>ESR (mm)</b>                      | 0.76               | 0.16                  | <b>0.02</b>    | 0.43 – 1.09    |
| <b>Haemoglobin (g/L)</b>             | -1.15              | 0.30                  | <b>0.0004</b>  | -1.77 – -0.55  |
| <b>Platelets (x10<sup>9</sup>/L)</b> | 0.18               | 0.05                  | <b>0.001</b>   | 0.07 – 0.29    |
| <b>HbA1C (%)</b>                     | 3.95               | 8.88                  | 0.66           | -14.12 – 22.02 |
| <b>Vitamin D (nmol/L)</b>            | -0.07              | 0.21                  | 0.72           | -0.49 – 0.34   |
| <b>HAQ-DI</b>                        | 13.51              | 9.56                  | 0.17           | -5.93 – 32.95  |

Abbreviations: PMR-AS – polymyalgia rheumatica-activity score; CI – confidence interval; BMI – body mass index; EMS – early morning stiffness; ESR – erythrocyte sedimentation rate; HAQ-DI – health assessment questionnaire-disability index.

**Figure 5.1:** Scatter plots illustrating the linear relationships between baseline PMR-AS and haemoglobin levels (A), platelet levels (B) and ESR (C).



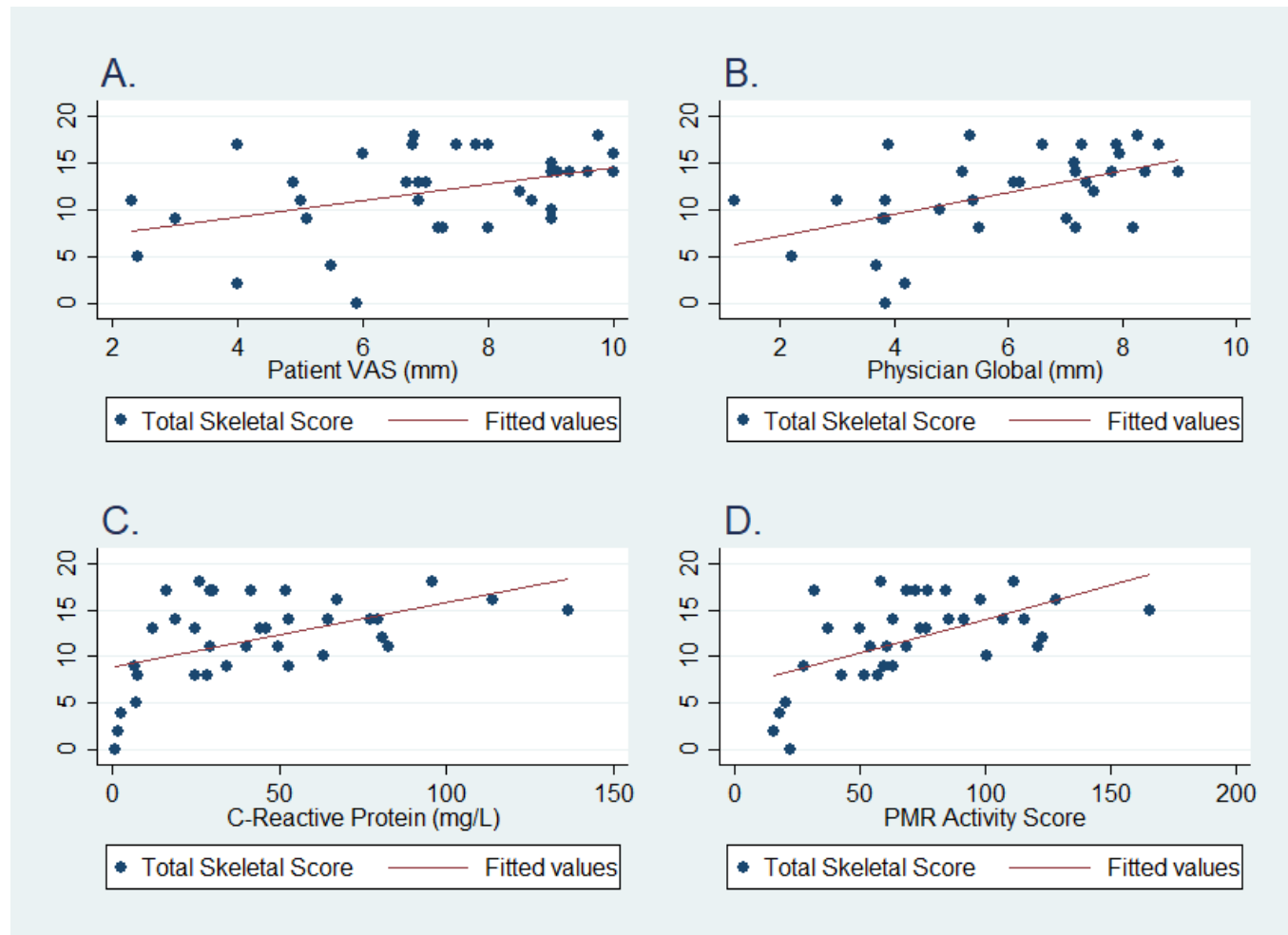
Abbreviations: PMR-AS – polymyalgia rheumatica-activity score; ESR – erythrocyte sedimentation rate.

**Table 5.7:** Linear regression analysis of the relationship between TSS on whole body PET/CT and conventional disease activity parameters at baseline in the MPR-PMR study.

| <b>Independent Variable</b>   | <b>Coefficient</b> | <b>Standard Error</b> | <b>p-value</b> | <b>95% CI</b> |
|-------------------------------|--------------------|-----------------------|----------------|---------------|
| <b>Patient Pain VAS (mm)</b>  | 0.88               | 0.33                  | <b>0.01</b>    | 0.20 – 1.55   |
| <b>Physician Global (mm)</b>  | 1.18               | 0.34                  | <b>0.001</b>   | 0.49 – 1.87   |
| <b>Duration of EMS (mins)</b> | 0.01               | 0.009                 | 0.23           | -0.008 – 0.03 |
| <b>CRP (mg/L)</b>             | 0.07               | 0.02                  | <b>0.002</b>   | 0.03 – 0.11   |
| <b>ESR (mm)</b>               | 0.05               | 0.02                  | 0.07           | -0.005 – 0.10 |
| <b>PMR-AS</b>                 | 0.07               | 0.02                  | <b>0.0004</b>  | 0.03 – 0.11   |

Abbreviations: TSS – total skeletal score; CI – confidence interval; VAS – visual analogue scale; EMS – early morning stiffness; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PMR-AS – polymyalgia rheumatica-activity score.

**Figure 5.2:** Scatter plots illustrating the relationships between TSS on whole body PET/CT and conventional disease activity parameters including patient pain VAS (A), physician global assessment (B), CRP (C) and PMR-AS.



Abbreviations: TSS – total skeletal score; VAS – visual analogue scale; CRP – C-reactive protein; PMR-AS – polymyalgia rheumatica-activity score.

A total of 258 study visits were completed. In Figure 5.3, each participant's disease activity as measured by PMR-AS is charted throughout the course of the MPR-PMR study. A further seven patient withdrawals occurred during the 46 weeks of follow-up:

- Two additional patients were diagnosed with concomitant GCA, one at week 20 and the other at week 30. In both instances, the participants did not develop classic cranial symptoms but exhibited unexplained rises in their systemic inflammatory markers that warranted further investigation. Temporal artery biopsy proved positive in both cases;
- Three participants required the initiation of a DMARD to aid symptom control. In the first patient, this occurred following complete non-response to the initial prednisolone dose of 15mg daily. By contrast, methotrexate was commenced as dictated by the study protocol in the other two cases following more than two successive disease relapses (one participant was withdrawn at week 24, the other at week 39);
- One patient elected to withdraw from the study at week 10 due to intolerable glucocorticoid-induced side effects;
- One participant chose not to attend for their week 46 follow-up visit.

Twenty-five patients (78.1%) met the primary study endpoint of disease relapse, with the average relapse rate per participant being 1.2 events. The median time to remission (PMR-AS  $\leq 9.35$ ) following the commencement of low-dose glucocorticoid therapy was 6.1 weeks. Relapse (PMR-AS  $\geq 9.35$  or  $\Delta$  in PMR-AS  $\geq 6.6$ ) most commonly occurred at week 24, at which point in time participants were taking a median prednisolone dose of 7mg (Table 5.8 and Figure 5.4). Eleven participants (31.4%) relapsed at least twice throughout the study.

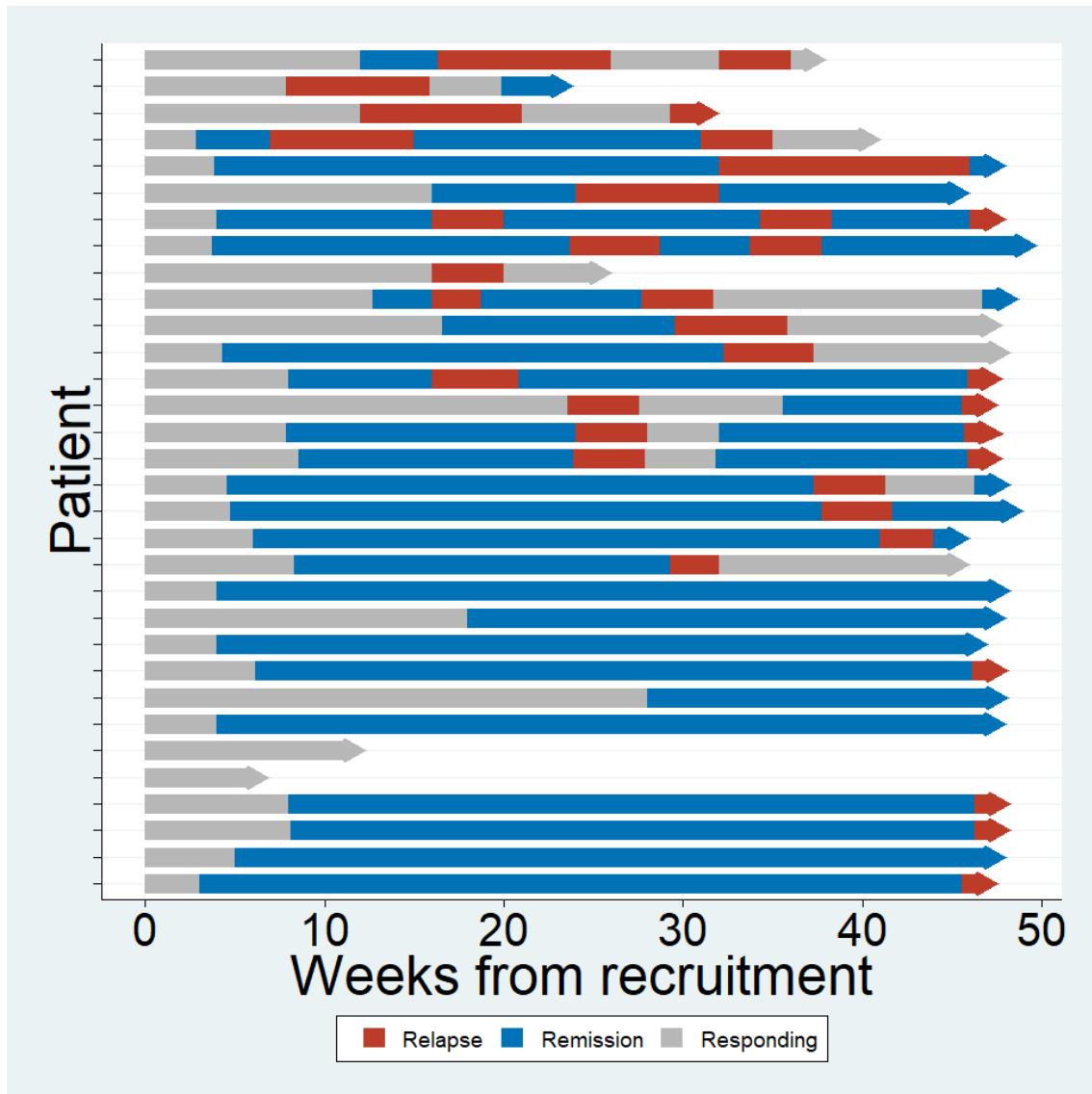
Despite this, the majority of patients (21/32 [65.6%]) still managed to achieve a prednisolone dose of  $\leq 5$ mg by week 46. However, at this point in time, mean PMR-AS had trended up to  $14.0 \pm 12.0$  consistent with moderate disease activity. Figure 5.5 illustrates mean PMR-AS and median prednisolone dose throughout the MPR-PMR study.

#### 5.4.2 Glucocorticoid Resistance

Sixteen of the remaining 32 participants (50%) fulfilled the secondary outcome measure of glucocorticoid resistance during follow-up; their demographic details compared with those patients with glucocorticoid-responsive PMR are presented in Table 5.9.

Glucocorticoid-resistant patients were older and typically female compared with their glucocorticoid-responsive counterparts. Baseline CRP, but not ESR, and disease activity (PMR-AS) were also higher. Comparison of haematologic parameters between the groups revealed

**Figure 5.3:** Disease activity, as measured by PMR-AS, is charted throughout the course of the MPR-PMR study for each participant.



Abbreviations: PMR-AS – polymyalgia rheumatica-activity score.

**Table 5.8:** Median prednisolone dose, mean PMR-AS and incidence of relapse by week in the MPR-PMR study. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]).

| <b>Week</b> | <b>Median PNL Dose<br/>(mg)</b> | <b>Mean<br/>PMR-AS</b> | <b>First<br/>Relapse (n)</b> | <b>Second<br/>Relapse (n)</b> |
|-------------|---------------------------------|------------------------|------------------------------|-------------------------------|
| <b>0</b>    | 15 (15 – 15)                    | 74.2 $\pm$ 35.7        | 0                            | 0                             |
| <b>4</b>    | 12.5 (12.5 – 12.5)              | 14.8 $\pm$ 11.49       | 0                            | 0                             |
| <b>8</b>    | 10 (10 – 10)                    | 10.2 $\pm$ 8.5         | 3                            | 1                             |
| <b>16</b>   | 8 (8 – 9)                       | 10.4 $\pm$ 10.9        | 5                            | 1                             |
| <b>24</b>   | 7 (6 – 8)                       | 8.9 $\pm$ 8.7          | 8                            | 2                             |
| <b>32</b>   | 6 (5 – 7)                       | 18.8 $\pm$ 36.7        | 5                            | 3                             |
| <b>46</b>   | 4 (2 – 5)                       | 14.0 $\pm$ 12.0        | 4                            | 4                             |

Abbreviations: PNL – prednisolone; PMR-AS – polymyalgia rheumatica-activity score.

**Figure 5.4:** Median prednisolone dose plotted against the incidence of relapse by week in the MPR-PMR study.

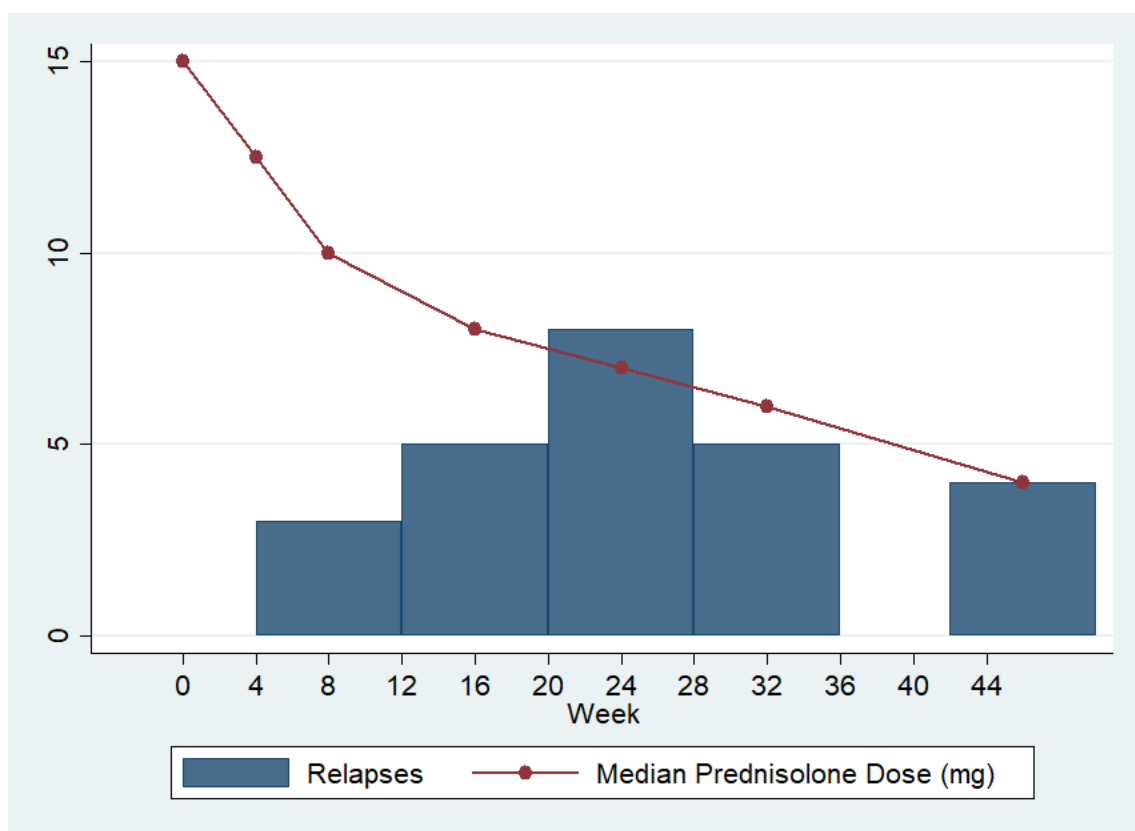
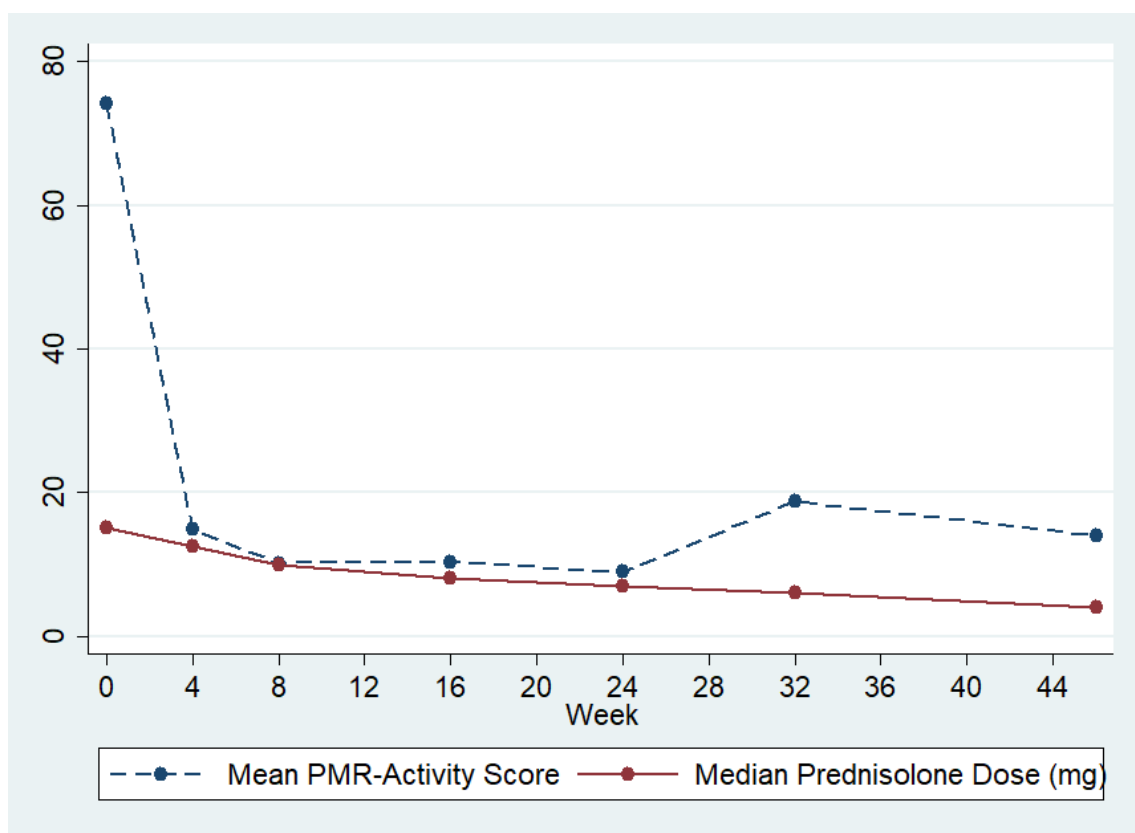


**Figure 5.5:** Mean PMR-AS and median prednisolone dose by week throughout the MPR-PMR study.



Abbreviations: PMR-AS – polymyalgia rheumatica-activity score.

**Table 5.9:** Baseline demographic information for glucocorticoid-resistant and glucocorticoid-responsive patients in the MPR-PMR study. Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range [IQR]).

| <b>Demographic</b>                            | <b>Glucocorticoid-Resistant</b><br>(n=16) | <b>Glucocorticoid-Responsive</b><br>(n=16) |
|-----------------------------------------------|-------------------------------------------|--------------------------------------------|
| <b>Age (years)</b>                            | 71.9 $\pm$ 7.0                            | 66.1 $\pm$ 6.4                             |
| <b>Gender:</b>                                |                                           |                                            |
| - Female                                      | 10 (62.5%)                                | 5 (31.25%)                                 |
| - Male                                        | 6 (37.50%)                                | 11 (68.75%)                                |
| <b>CRP (mg/L)</b>                             | 59.3 $\pm$ 46.0                           | 36.4 $\pm$ 27.6                            |
| <b>ESR (mm)</b>                               | 50.7 $\pm$ 28.6                           | 49.4 $\pm$ 30.1                            |
| <b>PMR-AS</b>                                 | 85.3 $\pm$ 35.3                           | 63.0 $\pm$ 33.7                            |
| <b>Median WCC (x10<sup>9</sup>/L)</b>         | 8.55 (7.4 – 9.25)                         | 7.95 (7.0 – 9.23)                          |
| <b>Median neutrophils (x10<sup>9</sup>/L)</b> | 5.5 (4.9 – 6.73)                          | 5.1 (3.8 – 5.9)                            |
| <b>Median lymphocyte (x10<sup>9</sup>/L)</b>  | 1.7 (1.6 – 1.8)                           | 2.1 (1.9 – 2.3)                            |
| <b>Median platelets (x10<sup>9</sup>/L)</b>   | 362 (297 – 409)                           | 332 (264 – 448)                            |

Abbreviations: CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PMR-AS – polymyalgia rheumatica-activity score; WCC – white cell count.

similarities in white cell (WCC), neutrophil and platelet counts, but lymphocyte levels were lower in glucocorticoid-resistant patients (1.7 [1.6 – 1.8] cf. 2.1 [1.9 – 2.3]).

### 5.4.3 Ultrasound Correlates

For the most part, ultrasound findings were observed to respond to the commencement of glucocorticoid therapy (Table 5.10). A subgroup of participants did however maintain persistent abnormalities.

By week 4, the percentage of patients with subacromial bursitis affecting at least one shoulder had reduced from 85.7% to 53.1%, with only six participants (13.3%) possessing residual changes at week 46. A lesser rate of improvement was seen in association with the finding of biceps tenosynovitis, which may be accounted for by a physiological amount of fluid commonly existing around this tendon. By comparison, all but one of the patients with effusion in the bicipital groove at baseline resolved this abnormality by week 46, however three of these cases represented early study withdrawals. Interestingly, both of the participants who commenced methotrexate following more than two successive disease relapses exhibited this finding.

A reduction in the frequency of abnormal findings on B-mode and Power Doppler ultrasound scanning was similarly noted at the wrist and hand throughout the study, with the percentage of patients exhibiting peripheral changes reducing from 54.3% at baseline to 30% by week 16. Further improvement by week 46 was not observed though, in that 7/25 participants (28%) exhibited evidence of wrist and/or metacarpophalangeal synovitis at this study visit. Only two of these individuals (28.6%) had a PMR-AS  $\geq 9.35$  consistent with disease relapse.

The relationship between complete resolution of shoulder findings on ultrasound and clinical remission as measured by PMR-AS is explored in Table 5.11. Few participants possessed no residual imaging abnormalities at weeks 4 and 16, although a slightly higher proportion was noted by week 46 (7/25 [28%]). The correlation between normal ultrasound and clinical remission was also poor in the early stages of the study. Despite 21/30 patients (70%) having a PMR AS  $< 9.35$  by week 16, only three participants in total had resolved their shoulder findings from baseline. At week 46 however, whilst a lower percentage of participants met the definition of clinical remission (52%), greater concordance was observed between low disease activity and normal ultrasound with overlap in 6/7 cases (85.7%).

Of the three participants that met clinical and ultrasound remission criteria through week 16, two subsequently relapsed suggesting no protective benefit from achieving this combination of

**Table 5.10:** B-mode and Power Doppler ultrasound findings for participants throughout the MPR-PMR study. Categorical variables are represented as proportions (percentages).

| Ultrasound Finding                       | Week 4 (n= 32) | Week 16 (n=30) | Week 46 (n=25) |
|------------------------------------------|----------------|----------------|----------------|
| <b>Subacromial Bursitis<sup>#</sup>:</b> | 17 (53.1%)     | 14 (46.7%)     | 6 (24%)        |
| Bilateral                                | 11 (34.4%)     | 6 (20%)        | 4 (13.3%)      |
| Left                                     | 14 (43.7%)     | 8 (26.7%)      | 6 (24%)        |
| Right                                    | 14 (43.7%)     | 12 (40%)       | 4 (16%)        |
| <b>Biceps Tenosynovitis:</b>             | 18 (56.2%)     | 12 (40%)       | 17 (68%)       |
| Bilateral                                | 10 (31.2%)     | 7 (23.3%)      | 6 (24%)        |
| Left                                     | 11 (34.4%)     | 10 (33.3%)     | 11 (44%)       |
| Right                                    | 17 (53.1%)     | 9 (30%)        | 12 (48%)       |
| <b>Wrist and/or Hand:</b>                |                |                |                |
| Greyscale Synovitis                      | 12 (37.5%)     | 9 (30%)        | 7 (28%)        |
| Power Doppler Signal                     | 10 (31.2%)     | 7 (23.3%)      | 7 (28%)        |

<sup>#</sup>Defined as a thickness of hypoechoic material within the bursa of >1.1mm.

**Table 5.11:** Relationship between normal shoulder findings on ultrasound and clinical remission as measured by PMR-AS in the MPR-PMR study.

| <b>Week</b> | <b>Clinical Remission<br/>(PMR-AS &lt;9.35)</b> | <b>Normal<br/>Shoulder US</b> | <b>Remission + Normal<br/>Shoulder US</b> |
|-------------|-------------------------------------------------|-------------------------------|-------------------------------------------|
| <b>4</b>    | 13/32 (40.6%)                                   | 5/32 (15.6%)                  | 2/5 (40%)                                 |
| <b>16</b>   | 21/30 (70%)                                     | 5/30 (16.7%)                  | 1/5 (20%)                                 |
| <b>46</b>   | 13/25 (52%)                                     | 7/25 (28%)                    | 6/7 (85.7%)                               |

Abbreviations: PMR-AS – polymyalgia rheumatica-activity score; US – ultrasound.

factors. Given the MPR-PMR study concluded at 46 weeks, it remains unclear whether a similar trajectory existed in the additional six patients with simultaneous low disease activity and normal shoulder ultrasound findings.

#### 5.4.4 Glucocorticoid-Related Side Effects

Participants frequently reported side effects that they attributed to glucocorticoid therapy. A total of 102 adverse events were recorded, with the average number per participant being 3.2 complications.

Weight gain was the commonest reported side effect overall (20.7%), a finding supported by BMI data which increased from an average of  $27.7 \pm 5.1$  to  $28.1 \pm 5.6$  throughout the study. In Figure 5.6, a pie chart depicts the incidence of various glucocorticoid-induced complications. Other common adverse events included cosmetic changes (eg. Cushingoid facies, thin skin, bruising, hirsutism [18%]), insomnia (12.6%) and gastrointestinal upset (eg. gastro-oesophageal reflux, nausea, constipation [9.9%]). Fortunately, more serious side effects like fracture and infection were very rare (0.9% and 1.8% respectively).

A dose-related complication rate was observed, with a higher incidence of adverse events occurring when more moderate doses of prednisolone were being taken (Table 5.12). At earlier visits, weight gain, gastrointestinal upset and insomnia were more common, whereas cosmetic changes became the greatest concern by weeks 24, 32 and 46.

### 5.5 Analysis of Predictors

#### 5.5.1 Predictors of Disease Relapse

The Cox proportional-hazards model investigated the relationship between baseline characteristics and time to first relapse. The results of this analysis are presented in Table 5.13.

Female patients were more likely to experience disease relapse than their male counterparts (HR 2.38 [1.03 – 5.47]), as were older participants (HR 1.07 [1.00 – 1.15]). Peripheral joint manifestations did not however portend an adverse prognosis in this instance. Rather, the presence of a volar pattern of  $^{18}\text{F}$ -FDG uptake on whole body PET/CT was strongly associated with later time to first relapse/no relapse (Figure 5.7).

**Figure 5.6:** Pie chart illustrating the incidence of different glucocorticoid-related side effects throughout the MPR-PMR study.

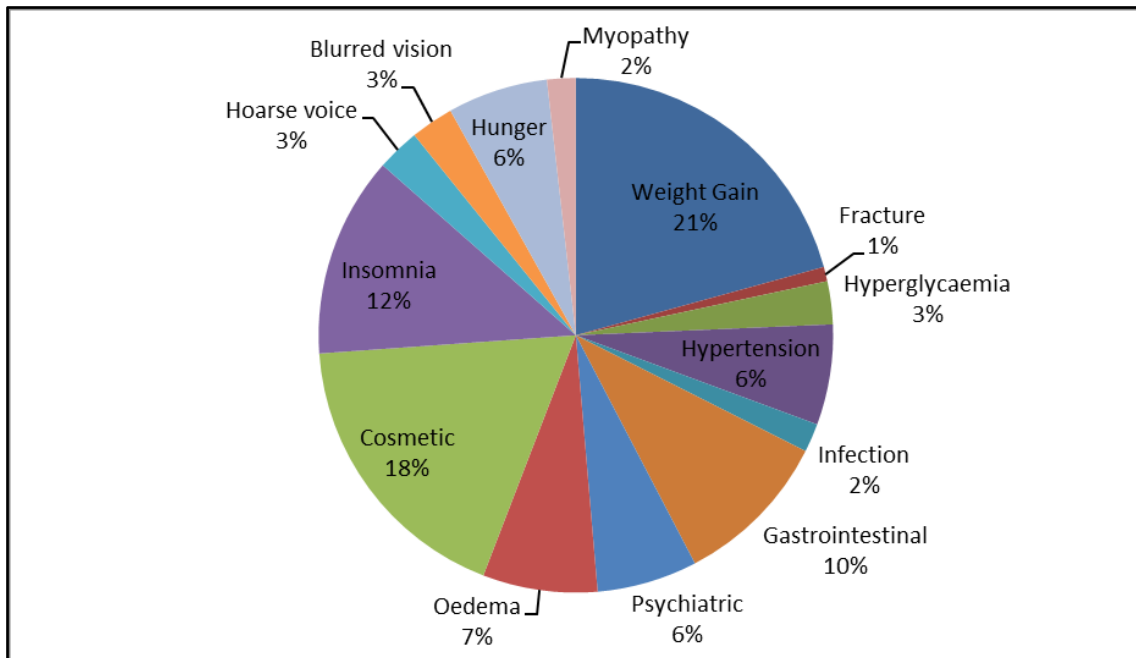


**Table 5.12 – 1:** The incidence of glucocorticoid-related complications by week in the MPR-PMR study.

| Week                | Median PNL dose<br>(mg) | Glucocorticoid-Related<br>Complications | Type                                                                                                                                                                                              |
|---------------------|-------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>4</b><br>(n= 32) | 12.5 (12.5 – 12.5)      | 20 (62.5%)                              | Weight gain – 6<br>Gastrointestinal – 5<br>HTN – 4<br>Hunger – 4<br>Psychiatric – 3<br>Insomnia – 3<br>Oedema – 3<br>Hoarse voice – 2<br>Hyperglycaemia – 2<br>Cosmetic – 2<br>Blurred vision – 1 |
| <b>8</b><br>(n=30)  | 10 (10 – 10)            | 16 (53.3%)                              | Insomnia – 6<br>HTN – 3<br>Gastrointestinal – 2<br>Psychiatric – 2<br>Oedema – 2<br>Weight gain – 2<br>Blurred vision – 1<br>Cosmetic – 1<br>Hyperglycaemia – 1<br>Hunger – 1<br>Infection – 1    |
| <b>16</b><br>(n=30) | 8 (8 – 9)               | 15 (50%)                                | Weight gain – 8<br>Cosmetic – 3<br>Gastrointestinal – 2<br>Myopathy – 2<br>Blurred vision – 1<br>Fracture – 1<br>Infection – 1<br>Psychiatric – 1                                                 |

Abbreviations: PNL – prednisolone.

**Table 5.12 – 2:** The incidence of glucocorticoid-related complications by week in the MPR-PMR study.

| Week                | Median PNL dose<br>(mg) | Glucocorticoid-Related<br>Complications | Type                                                                                                                                  |
|---------------------|-------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| <b>24</b><br>(n=28) | 7 (6 – 8)               | 14 (50%)                                | Cosmetic – 5<br>Weight gain – 3<br>Insomnia – 2<br>Blurred vision – 1<br>Hunger – 1<br>Infection – 1<br>Oedema – 1<br>Psychiatric – 1 |
| <b>32</b><br>(n=27) | 6 (5 – 7)               | 8 (29.6%)                               | Cosmetic – 4<br>Weight gain – 4<br>Gastrointestinal – 2                                                                               |
| <b>46</b><br>(n=25) | 4 (2 – 5)               | 7 (28%)                                 | Cosmetic – 5<br>Insomnia – 3<br>Oedema – 2<br>Hoarse voice – 1                                                                        |

Abbreviations: PNL – prednisolone.

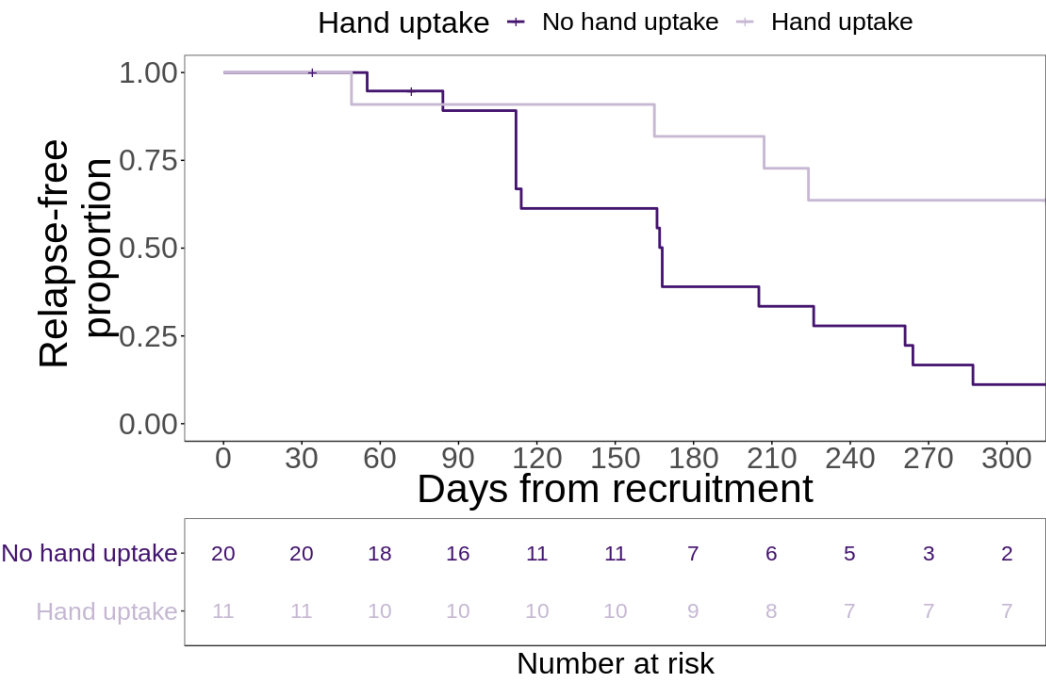
**Table 5.13:** Cox proportional-hazards model of the relationship between disease relapse and a range of independent variables in the MPR-PMR study.

Abbreviations: CI – confidence interval; BMI – body mass index; ESR – erythrocyte

| <b>Independent Variable</b>            | <b>Hazard Ratio</b> | <b>95% CI</b> | <b>p-value</b> |
|----------------------------------------|---------------------|---------------|----------------|
| <b>Age</b> (years)                     | 1.07                | 1.00 – 1.15   | <b>0.04</b>    |
| <b>Female</b>                          | 2.38                | 1.03 – 5.47   | <b>0.04</b>    |
| <b>BMI</b> (kg/m <sup>2</sup> )        | 1.03                | 0.97 – 1.10   | 0.30           |
| <b>Hand Pain</b>                       | 0.40                | 0.17 – 0.93   | <b>0.03</b>    |
| <b>Peripheral Synovitis</b>            | 0.31                | 0.11 – 0.86   | <b>0.01</b>    |
| <b>EULAR/ACR Score</b>                 | 1.55                | 0.72 – 3.33   | 0.25           |
| <b>ESR</b> (mm)                        | 1.00                | 0.99 – 1.02   | 0.51           |
| <b>Haemoglobin</b> (g/L)               | 0.99                | 0.97 – 1.01   | 0.40           |
| <b>Platelets</b> (x10 <sup>9</sup> /L) | 1.00                | 1.00 – 1.00   | 0.48           |
| <b>HAQ-DI</b>                          | 1.36                | 0.71 – 2.57   | 0.35           |
| <b>Ultrasound:</b>                     |                     |               |                |
| Greyscale Synovitis                    | 1.21                | 0.54 – 2.70   | 0.64           |
| Power Doppler Signal                   | 0.95                | 0.41 – 2.17   | 0.90           |
| <b>Whole Body PET/CT:</b>              |                     |               |                |
| Volar <sup>18</sup> F-FDG Uptake       | 0.25                | 0.09 – 0.70   | <b>0.004</b>   |

sedimentation rate; HAQ-DI – health assessment questionnaire-disability index; PET/CT – positron emission tomography/computed tomography.

**Figure 5.7:** The relationship between the presence or absence of volar hand <sup>18</sup>F-FDG uptake and time to first relapse/no relapse in the MPR-PMR study.



Abbreviations: <sup>18</sup>F-FDG - <sup>18</sup>F-Fluorodeoxyglucose.

### 5.5.2 Predictors of Glucocorticoid Resistance

Generalised linear models were created to establish the relationship between glucocorticoid resistance and a range of independent variables (Table 5.14). Statistically significant associations existed between glucocorticoid-resistant PMR and older age ( $p=0.001$ ), female sex ( $p=0.005$ ) and higher BMI ( $p=0.0001$ ). Lower haemoglobin and higher platelet levels were similarly found to predict this treatment outcome. Results from further in-depth analysis of FBE correlates in the MPR-PMR study will be presented in chapter 6.

## 5.6 Discussion

In a prospective longitudinal study of 35 steroid-naïve patients with newly diagnosed PMR, predictors of relapsing disease were examined. Older age and female sex were subsequently identified as adverse prognostic factors, whilst higher baseline BMI was associated with glucocorticoid-resistance. A volar pattern of abnormal  $^{18}\text{F}$ -FDG uptake at the hands, known to correlate anatomically with flexor tenosynovitis based upon results presented in chapter 3, conferred a prognostic advantage with later time to relapse/no relapse in patients exhibiting this abnormality on whole body PET/CT.

Except for a majority of male participants, the MPR-PMR study population appears representative of a typical PMR cohort. Patients were on average in their seventh decade of life and almost exclusively of Caucasian ethnicity. Pain in the shoulder and hip girdle was unanimous, with wrist and/or hand pain recorded in the expected one-half of participants. Knee involvement was additionally present in twenty-three cases (65.7%) at diagnosis; a significant proportion given this manifestation is not commonly reported in the existing PMR literature. That said, such a finding is entirely consistent with a prior PET/CT study and results from this thesis documenting frequent abnormal  $^{18}\text{F}$ -FDG uptake at the knees in this condition.(5) Clinicians' certainty of a PMR diagnosis should only be bolstered by the presence of knee symptoms in a patient presenting with polymyalgia.

As treatment was yet to be initiated, pain scores were high at baseline and the duration of morning stiffness extended. Average disease activity, as measured by the PMR-AS, easily exceeded the "high" cut-off, and disability, according to the HAQ-DI, was moderate to severe. Such significant functional impairment does surpass figures reported by other authors using the same instrument, although a qualitative study did find it was common for PMR patients to describe a sudden, life-changing reduction in their ability to carry out activities of daily living.(6-8) A median time of 12 weeks between symptom onset and diagnosis in the MPR-PMR cohort is also noteworthy, particularly in light of the severity of their symptomatology.

**Table 5.14:** Generalised linear modelling of the relationship between glucocorticoid resistance and a range of independent variables in the MPR-PMR study.

| <b>Independent Variable</b>          | <b>Coefficient</b> | <b>Standard Error</b> | <b>p-value</b> | <b>95% CI</b>    |
|--------------------------------------|--------------------|-----------------------|----------------|------------------|
| <b>Age (years)</b>                   | 0.02               | 0.004                 | <b>0.001</b>   | 0.02 – 0.03      |
| <b>Female</b>                        | 0.43               | 0.14                  | <b>0.005</b>   | 0.14 – 0.71      |
| <b>BMI (kg/m<sup>2</sup>)</b>        | 0.02               | 0.007                 | <b>0.0001</b>  | 0.01 – 0.04      |
| <b>Peripheral Synovitis</b>          | 0.12               | 0.09                  | 0.17           | -0.05 – 0.30     |
| <b>EULAR/ACR Score</b>               | 0.23               | 0.14                  | 0.13           | -0.06 – 0.52     |
| <b>ESR (mm)</b>                      | 0.002              | 0.002                 | 0.20           | -0.00 – 0.005    |
| <b>Haemoglobin (g/L)</b>             | -0.005             | 0.002                 | <b>0.03</b>    | -0.009 – -0.0005 |
| <b>Platelets (x10<sup>9</sup>/L)</b> | 0.001              | 0.0004                | <b>0.0009</b>  | 0.0005 – 0.002   |
| <b>HAQ-DI</b>                        | 0.06               | 0.04                  | 0.15           | -0.02 – 0.15     |

Abbreviations: CI – confidence interval; BMI – body mass index; ESR – erythrocyte sedimentation rate; HAQ-DI – health assessment questionnaire-disability index.

Given participants were prioritised for rheumatology review in this study, it would seem likely that earlier delays occurred in recognising a possible PMR diagnosis. Again, this appears consistent with the patient-reported experience in the literature and suggests care might be improved by raising awareness of PMR among referring medical practitioners.(8)

Imaging results further substantiated suspected clinical diagnoses of PMR in the MPR-PMR study. The vast majority of patients had evidence of unilateral subacromial bursitis on ultrasound, with over half exhibiting abnormalities bilaterally. On whole body PET/CT, a homogeneous pattern of  $^{18}\text{F}$ -FDG uptake was observed around the shoulder and hip joints, in the trochanteric regions, interspinous bursae, adjacent to the ischial tuberosities and at the posteromedial knee. One participant however only exhibited mild shoulder abnormalities with a TSS that was substantially lower (6) than the study mean (11.94). This patient subsequently had their final diagnosis revised to Parkinson's disease following the development of neurological signs, thereby reaffirming the fallacy of a PMR diagnosis based upon findings at a single musculoskeletal site. That said, the potential of whole body PET/CT as a gold standard diagnostic test remains clear because of this case, with irrefutable evidence of its ability to outperform conventional classification criteria.

Only one participant (2.8%) had abnormal  $^{18}\text{F}$ -FDG uptake in multiple vascular territories consistent with a diagnosis of concomitant LV-GCA. Given an earlier study by Blockmans et al. documented vascular findings in 11/35 PMR patients (31%), the MPR-PMR rate seemed comparatively low.(9) It would appear however that such a discrepancy can be adequately explained by the definition utilised, with the authors more recently stating that only two cases (5.7%) exhibited intense change consistent with GCA.(10) A further two patients in the MPR-PMR study were diagnosed with biopsy positive GCA following persistent elevation of their systemic inflammatory markers despite treatment for PMR. Notably, both participants had low TVS at baseline (1 and 2), meaning there was no suggestion on whole body PET/CT of large vessel involvement. Interestingly, Prieto-Pena et al. recently investigated predictive factors for a positive LV-GCA PET/CT scan among patients with unresolved PMR. Results identified atypical features including bilateral diffuse lower limb pain and inflammatory low back pain as suggestive symptomatology.(11) Certainly, it seems clear based on these observations that a low threshold should remain for undertaking investigations like temporal artery biopsy and whole body PET/CT among PMR patients that do not exhibit a standard clinical and biochemical response to low-dose glucocorticoid therapy. It would however appear unlikely that PET/CT at PMR diagnosis possesses the ability to predict the later development of GCA in patients with cranial disease.

Results for correlates of PMR disease activity were additionally presented in this chapter. In particular, haemoglobin and platelet levels were found to have a statistically significant relationship with PMR-AS at baseline. These haematologic parameters similarly predicted a disease course characterised by glucocorticoid resistance, whilst glucocorticoid-resistant patients were noted to have lower lymphocyte levels than their glucocorticoid-responsive peers. Taken together, these findings suggest that a simple FBE might prove useful for measuring disease activity and predicting long-term treatment outcomes in PMR. The MPR-PMR study is not however the first to find such potential. A recent hierarchical cluster analysis of 61 Japanese patients similarly identified a platelet count of  $>450 \times 10^9/L$  as a predictor of incomplete treatment response at one month and refractory disease at two years.(12) Furthermore, NLR, calculated from dividing the neutrophil count by the lymphocyte count on a FBE, has been documented to correlate with conventional disease activity measures like CRP in a retrospective study of PMR patients.(13) Dedicated investigation into clinical and prognostic applications of haematologic parameters in PMR is accordingly warranted on the basis of this emerging research trend.

The relationship between disease activity and imaging was also explored in the MPR-PMR study. TSS, a numeric representation of PET avidity across key musculoskeletal sites, was found to correlate strongly with variables including patient VAS, physician global, CRP and PMR-AS. To the author's knowledge, this represents first documentation of whole body PET/CT findings mirroring patient-reported outcomes in PMR. Similarly, such associations provide sound evidence for the ability of this imaging modality to accurately assess disease activity. By contrast, the performance of ultrasound in evaluating treatment response and clinical remission in PMR was underwhelming. Whilst findings were noted to improve with glucocorticoid therapy, complete normalisation of involved shoulder structures was rare. Significant concordance was also not observed between low disease activity and resolution of ultrasound abnormalities, nor was the combination of clinical remission and a normal ultrasound scan protective against later disease relapse.

Three other studies have previously investigated the role of longitudinal ultrasound examination in PMR. Jimenez-Palop et al. performed ultrasound at baseline, weeks 4 and 12 in 53 patients with active disease finding substantial improvement in the rates of inflammatory findings at the shoulders and hips post the initiation of glucocorticoid therapy.(14) Like the MPR-PMR study however, half the participants with bilateral abnormalities failed to resolve these by the study's conclusion. Such results are further substantiated by two separate Italian groups who documented the persistence of shoulder inflammation in 64.9% of patients at  $24 \pm 3$  weeks and 28% at 12 months respectively.(15, 16) In the former study, the relationship between persistent

abnormalities and disease activity was additionally evaluated, with 26/44 participants (59%) in clinical remission or a low disease activity state still exhibiting abnormal findings on imaging. It would therefore seem apparent that shoulder structures do not necessarily return to normal following prednisolone treatment in PMR and normalisation of these structures is not a prerequisite for clinical remission. Furthermore, Macchioni et al. has previously established the absence of an association between persistent inflammation and subsequent disease relapse, whilst the MPR-PMR study found a normal scan result did not prevent this eventuality.(15) Overall, the body of evidence now weighs heavily against the utility of serial ultrasound for monitoring disease activity and predicting treatment outcomes in PMR.

The predominant aim of the MPR-PMR study was to identify those demographic, clinical, laboratory and imaging factors that characterise a relapsing disease phenotype in PMR. It was hoped that this information might serve to delineate a distinct subgroup of patients who would benefit from early initiation of a steroid-sparing agent. Indeed, older age and female sex proved to be predictors of this outcome. By contrast, a volar pattern of  $^{18}\text{F}$ -FDG uptake at the hand on whole body PET/CT was associated with a statistically significant reduction in time to first relapse/no relapse. Previously, De Jaco et al. identified female sex, high ESR and peripheral arthritis as prognostic factors associated with higher rates of relapse in PMR.(17) Improved outcomes among participants with hand involvement in the MPR-PMR study should consequently be considered a notable result. Other authors have suggested however that disparate prognostic outcomes may accompany peripheral manifestations of PMR. In particular, patients with “distal extremity swelling with pitting oedema”, also known as RS3PE syndrome, have been identified as a subset more likely to follow a glucocorticoid-responsive disease course.(18) With the knowledge that flexor tenosynovitis correlates anatomically with volar  $^{18}\text{F}$ -FDG uptake on whole body PET/CT and tenosynovial sheath inflammation represents the imaging hallmark of RS3PE syndrome, it would seem likely that this seemingly incongruent observation is in fact explained by established differences in treatment outcomes among PMR patients with peripheral joint involvement.

Finally, the glaring need for an alternate treatment paradigm in PMR has been highlighted once more by the findings presented in this chapter. In truth, very few studies have evaluated the incidence of relapse among PMR patients being treated with a dedicated weaning schedule of low-dose glucocorticoid therapy. Results from the MPR-PMR study are therefore unique in that they additionally reflect the BSR management guideline’s efficacy. Unfortunately, with relapse documented in 78.1% of participants during follow-up, it is apparent this regimen falls short of achieving sustained clinical remission in most instances. Furthermore, an obvious trend towards increasing disease activity as prednisolone was weaned occurred, with a peak in relapse rates by

week 24 coinciding with a median dose of 7mg daily. Without doubt, such poor outcomes would be more bearable for patients and clinicians alike if the treatment concerned came without the added disadvantage of a substantial side effect profile. This too though cannot be said of glucocorticoid therapy, as evidenced by an average of 3.2 steroid-related complications per patient in the MPR-PMR study. The sheer inadequacy of the current standard of care in PMR is hence readily apparent. Finding an efficacious and well tolerated treatment remains one of the greatest research priorities in this rheumatic condition.

## 5.7 Summary of Main Findings

- Disease relapse occurred commonly and typically coincided with weaning prednisolone as outlined in the BSR guideline to the 7mg daily mark in this prospective longitudinal cohort study of patients with newly diagnosed PMR.
- Whilst most participants were able to achieve a prednisolone dose of  $\leq 5$ mg daily by week 46, their average disease activity as measured by PMR-AS had risen to a moderate level.
- Morbidity from glucocorticoid-related side effects was found to be significant, with an average of 3.2 complications reported per patient.
- Statistically significant predictors of disease relapse included older age (HR 1.07) and female sex (HR 2.38). Conversely, a volar pattern of  $^{18}\text{F}$ -FDG uptake at the hand on whole body PET/CT was strongly associated with later time to first relapse/no relapse (HR 0.23).
- Glucocorticoid-resistant PMR was similarly associated with older age ( $p=0.001$ ) and female sex ( $p=0.005$ ), however high BMI ( $p=0.0001$ ) also predicted this treatment outcome.

## 5.8 Interpretation

Relapse is frequent among PMR patients treated with a weaning schedule of low-dose glucocorticoid therapy. Discrete phenotypic differences do however influence the likelihood of this treatment outcome.

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# **Chapter 6: Neutrophil to Lymphocyte Ratio as a Predictor of Glucocorticoid Resistance in Polymyalgia Rheumatica**

## **6.1 Preface**

In chapter 5, results from the MPR-PMR and other recent studies revealed an emerging association between haematologic parameters and disease activity in PMR. More specifically, haemoglobin and platelet levels were found to correlate strongly with baseline PMR-AS. Furthermore, low haemoglobin and high platelets levels predicted a subsequent disease course characterised by glucocorticoid resistance, whilst lower lymphocyte levels were noted in glucocorticoid-resistant patients. Given the absence of a reliable and readily accessible biomarker for measuring disease activity and predicting treatment outcomes in PMR, such observations prompted further in-depth analysis of FBE correlates in the MPR-PMR study. As part of this work, preliminary evaluation of haematologic indices including NLR and PLR, and their potential clinical and prognostic applications in PMR was undertaken.

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## **6.2 Summary of Main Findings**

- In a prospective observational cohort study of 32 newly diagnosed, steroid-naïve patients, baseline NLR was identified as a distinct predictor of glucocorticoid-resistant PMR (OR 14.01) and outperformed conventional inflammatory markers including ESR and CRP.
- A statistically significant relationship was additionally established between disease activity (PMR-AS) and both NLR (OR 28.1) and PLR (OR 40.6) at baseline.
- During the 46-week follow-up period, PLR correlated with mean PMR-AS (OR 15.6), whilst a trend towards significance was observed between NLR and PMR-AS.

### 6.3 Interpretation

This is the first study to prospectively evaluate the relationship between the haematologic indices, NLR and PLR, and treatment outcomes in PMR. Baseline NLR was identified as a predictor of glucocorticoid-resistant disease, thereby delineating a distinct subset of patients who may benefit from early DMARD initiation. In addition, results confirm NLR and PLR as novel biomarkers of PMR disease activity.

## Neutrophil to Lymphocyte Ratio Predicts Glucocorticoid Resistance in Polymyalgia Rheumatica

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### **Author Contributions**

Author CO designed the study, collected the patient data and was chiefly responsible for writing the manuscript. Author CM analyzed and interpreted all data presented. Author DL proposed further study of NLR and PLR in PMR and together with authors JL, AS and RB improved several iterations of the manuscript. All authors read and approved the final product.

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### **Conflict of Interest Statement**

Author CO has received speaking honoraria from Roche, Janssen, Novartis and Pfizer, and meeting sponsorship from Roche. Author CM declares no conflict of interest. Author DL declares no conflict of interest. Author JL has received a speaking honorarium from Abbvie and meeting sponsorship from Gilead. Author AS declares no conflict of interest. Author RB declares no conflict of interest.

**ABSTRACT**

**Aim:** Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) correlate with disease activity in several rheumatic diseases, however their utility in polymyalgia rheumatica (PMR) remains unclear. This study evaluated their relationship with disease activity and glucocorticoid resistance in PMR.

**Method:** Data for disease activity (PMR-AS) and full blood examination was obtained from a prospective observational cohort comprising newly diagnosed, steroid-naïve PMR patients treated with low-dose glucocorticoid therapy. Glucocorticoid resistance was defined as non-response to prednisolone 15mg/day or initial response followed by flare (PMR-AS  $\geq 9.35$  or  $\Delta \geq 6.6$ ) upon weaning to 5mg/day. Univariable Bayesian linear regression analysis of the relationship between PMR-AS (baseline and mean) and NLR and PLR was performed. Predictors of glucocorticoid resistance were identified using a multivariable outcome model, with variables derived from Bayesian model selection.

**Results:** Of the 32 included patients, 16 (50%) fulfilled the primary outcome measure of glucocorticoid resistance. These participants were older, typically female, and had higher baseline CRP than their glucocorticoid-responsive counterparts. A statistically significant relationship was identified between PMR-AS and both NLR (OR 28.1 [95% CI 1.6 – 54.7]) and PLR (OR 40.6 [95% CI 10.1 – 71.4]) at baseline, with PLR also found to correlate with disease activity during follow-up (OR 15.6 [95% CI 2.7 – 28.2]). Baseline NLR proved a statistically significant predictor of glucocorticoid-resistant PMR (OR 14.01 [95% CI 1.49 – 278.06]).

**Conclusion:** Baseline NLR can predict glucocorticoid resistance in newly diagnosed PMR patients. Both NLR and PLR may be reliable biomarkers of disease activity in PMR.

**Key Words:** polymyalgia rheumatica; neutrophils; lymphocytes; glucocorticoids; prognosis.

**Trial registration:** Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>) – trial identification ACTRN1261400696695, registered 2/7/2014.

Polymyalgia rheumatica (PMR) is an inflammatory condition characterised by subacute-onset shoulder and hip pain, and stiffness. Oral glucocorticoids represent the treatment mainstay and whilst cessation of therapy is the ultimate goal, up to 50% of patients still require prednisolone 2-3 years after diagnosis.<sup>1</sup> A higher baseline erythrocyte sedimentation rate (ESR) has been associated with disease relapse and lower probability of glucocorticoid discontinuation, however these findings have not been consistently reproduced.<sup>2</sup> To date, a reliable and readily accessible biomarker to measure disease activity and predict resistance to standardised low-dose glucocorticoid therapy has not been identified in PMR.

Neutrophil, platelet and lymphocyte counts undergo temporary changes in an active inflammatory state. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can be calculated from a routine full blood examination (FBE) using the neutrophil count or platelet count divided by the lymphocyte count. In oncology, high NLR and PLR are associated with poor prognostic outcomes across a range of solid organ malignancies.<sup>3,4</sup> These indices have similarly been found to correlate with disease activity in several rheumatic diseases including most recently PMR, but their role in predicting treatment response in this condition is less well-defined.<sup>5-8</sup>

In this study, we sought to prospectively characterize the relationship between NLR and PLR, and disease activity in patients with newly diagnosed PMR. The ability of NLR and PLR to predict resistance to standardised low-dose glucocorticoid therapy was also evaluated.

## **METHOD**

### **Patients**

Patients with newly diagnosed, steroid-naïve PMR according to the 2012 EULAR/ACR classification criteria<sup>9</sup> were prospectively recruited from primary care, community and hospital rheumatology practices. Participants with symptoms suggestive of giant cell arteritis (GCA)

including headache, jaw claudication, scalp tenderness or visual disturbance were excluded, along with cases of cancer within the past 5 years, neuromuscular disease, active infection, other inflammatory conditions (eg. rheumatoid arthritis [RA]) and chronic pain syndromes. The study was approved by the Austin Health Human Research Ethics Committee (HREC/14/Austin/158) prior to commencement and registered with the Australian New Zealand Clinical Trials Registry (trial identification ACTRN1261400696695).

Following written consent, demographic and clinical data were collected and the health assessment questionnaire–disability index (HAQ-DI) completed. A standard physical examination was undertaken including measurement of the shoulder range of motion (elevation of upper limb score). In order to measure disease activity using the PMR-activity score (PMR-AS)<sup>10</sup>, participants marked a visual analogue scale indicating pain severity and the investigator provided a physician global assessment. Relevant differential diagnoses were excluded by testing creatine kinase, thyroid function, rheumatoid factor, anti-citrullinated peptide antibodies (ACPA) and anti-neutrophil cytoplasmic antibodies. FBE, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were performed at baseline and each subsequent visit. A whole body <sup>18</sup>F-Fluorodeoxyglucose (<sup>18</sup>F-FDG) positron emission tomography/computed tomography (PET/CT) scan (Gemini-TF64 or Ingenuity-TF128 PET/CT system; Phillips, Cleveland, OH, USA) from skull vertex to toes was also undertaken in all participants within 7 days of study enrolment.

### **Treatment Protocol**

Participants were treated with a standardised schedule of low-dose glucocorticoid therapy as outlined in the British Society of Rheumatology (BSR) guideline.<sup>11</sup> Follow-up visits were scheduled at weeks 4, 8, 16, 24, 32 and 46 (the minimum duration of this treatment protocol) and disease activity was re-calculated. A PMR-AS score of  $\geq 9.35$  in a patient who had achieved clinical remission (PMR-AS  $< 9.35$ ) or increase in PMR-AS by  $\geq 6.6$  if the participant had been previously responding to treatment (PMR-AS  $\geq 9.35$  but falling between successive visits)

constituted the definition of disease relapse. When this occurred, the patient's prednisolone dose was increased to the previous higher dose for 4 weeks and an additional study visit performed to determine if the weaning schedule could be reinstated. If relapse occurred on more than two occasions, methotrexate was commenced as a steroid-sparing agent, and the participant was withdrawn from the study.

### Glucocorticoid Resistance

Glucocorticoid resistance has been previously defined by Mori et al. in PMR as non-response to an initial prednisolone dose of 15mg/day or initial response followed by disease relapse upon weaning prednisolone to 5mg/day.<sup>12</sup> This definition was accordingly utilised as the primary outcome measure for glucocorticoid-resistant disease in our study.

### Statistical Analyses

All statistical analyses were conducted using R version 3.5.2 and the package *rstanarm*.<sup>13</sup>  
<sup>14</sup> Results for continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range). NLR and PLR, both right-skewed distributions, were log-transformed prior to analysis. Univariable Bayesian linear regression was used to analyse the relationship between NLR and PLR, and PMR-AS (baseline and mean). Several multivariable, Bayesian logistic regression models were compared using leave-one-out cross-validation – from the *loo* package<sup>15</sup> – to select predictors of resistance to low-dose glucocorticoid therapy. All outcomes are reported as odds ratios (OR) with 95% credible intervals (CI).<sup>16</sup> Weakly-informative prior distributions were applied using student t-distribution with 7 degrees of freedom.<sup>17</sup>

## RESULTS

Thirty-two of the 35 patients (91.4%) recruited at baseline were suitable for inclusion in the final analysis (Table 1): one patient was excluded due to large vessel vasculitis on whole body PET/CT consistent with concomitant GCA; another patient's final diagnosis was revised to

Parkinson's disease; and the third patient required a modified schedule of glucocorticoid therapy due to a history of prednisolone-induced central serous retinopathy.

Twenty-five/32 participants (78.1%) relapsed during the 46-week follow-up period. Relapse most commonly occurred at week 24, at which point in time patients were taking a median prednisolone dose of 7mg. Three participants required the initiation of methotrexate as dictated by the study protocol.

Sixteen patients (50%) fulfilled the primary outcome measure of resistance to low-dose glucocorticoid therapy; their demographic details compared with those participants with glucocorticoid-responsive PMR are presented in Table 2.

Glucocorticoid-resistant patients were older and typically female compared with their glucocorticoid-responsive counterparts. Baseline CRP, but not ESR, and disease activity (PMR-AS) were also higher. In terms of haematologic parameters, median white cell count (WCC), neutrophil and platelet counts were similar between the two groups, but the median lymphocyte count was lower in glucocorticoid-resistant patients (1.7 [1.6 – 1.8] cf. 2.1 [1.9 – 2.3]). Consequently, values for mean log-transformed NLR ( $1.20 \pm 0.48$ ) and PLR ( $5.37 \pm 0.37$ ) were higher in this group than the glucocorticoid-responsive cohort (NLR  $0.87 \pm 0.38$ ; PLR  $5.12 \pm 0.38$ ).

A statistically significant relationship was identified between disease activity (PMR-AS) and both NLR (OR 28.1 [95% CI 1.6 – 54.7]) and PLR (OR 40.6 [95% CI 10.1 – 71.4]) at baseline. During follow-up, PLR correlated with mean PMR-AS (OR 15.6 [95% CI 2.7 – 28.2]), with a trend towards significance observed between NLR and mean PMR-AS (OR 10.1 [95% CI -0.9 – 21.3]).

Using Bayesian outcome modelling, baseline NLR was found to be a statistically significant predictor of glucocorticoid-resistant PMR during follow-up (OR 14.01 [95% CI 1.49

– 278.06]). A trend towards significance was also noted for baseline PLR (OR 5.02 [0.49 – 71.54]), along with age (OR 1.14 [95% CI 1.00 – 1.34]) and female sex (OR 2.98 [0.54 – 18.39]). There was no correlation between baseline CRP and glucocorticoid resistance after adjusting for demographic factors (OR 1.02 [95% CI 0.99 – 1.05]). Figure 1 illustrates the relationship between baseline laboratory values for CRP, ESR and NLR, and glucocorticoid-resistant PMR.

## DISCUSSION

In a cohort of 32 patients with newly diagnosed PMR, 16 (50%) had a disease course characterized by resistance to low-dose glucocorticoid therapy, with baseline NLR proving a distinct predictor of this outcome. A trend towards significance was also observed between NLR and disease activity, with a statistically significant correlation found between PLR and PMR-AS both at baseline and during follow-up. All participants were steroid-naïve at study enrolment, glucocorticoid therapy thus having no bearing upon baseline haematologic parameters.

An increasing body of evidence now refutes historical opinion that PMR is a self-limiting, perpetually steroid-responsive entity. In a recent population-based study, around 25% of patients required more than 4 years of continuous prednisolone.<sup>18</sup> Significant morbidity is known to arise from this treatment paradigm whereby glucocorticoid monotherapy is advocated in the first instance and steroid-sparing agents are only initiated following recurrent relapse.<sup>11, 19</sup> On whole-body magnetic resonance imaging (MRI) however, a complete patient-reported response to prednisolone has been shown to correlate with an extra-capsular pattern of inflammation, thereby confirming the existence of discrete phenotypic differences between glucocorticoid-responsive and -resistant PMR cases.<sup>20</sup> Identification of baseline NLR as a predictor of later glucocorticoid-resistance in this study therefore has certain clinical relevance. Not only does it add to the paucity of recognized adverse prognostic indicators in this condition (such as female sex, peripheral joint involvement and high ESR)<sup>2</sup>, but it also further characterizes the subset of patients with relapsing PMR whom may benefit from early disease modifying anti-rheumatic drug (DMARD) initiation.

Relying upon systemic markers of inflammation to assess disease activity in PMR can be problematic. Normal CRP and ESR results are observed in 14 and 27% of relapses respectively.<sup>21</sup> There is consequently an unmet need for a novel biomarker that accurately reflects the underlying inflammatory state in PMR. In research settings, the PMR-AS is considered a valid and reliable measure of disease activity; a value  $\geq 9.35$  is associated with a sensitivity of 96.6% and specificity of 90.7% for flare diagnosis.<sup>22</sup> The composite nature of this scoring system is however less conducive to use in everyday clinical practice. In this study, a statistically significant relationship existed between PMR-AS and both NLR and PLR at baseline, with PLR also being found to correlate with disease activity during follow-up. We therefore propose that these indices, which can be simply calculated from an FBE, represent readily accessible and inexpensive biomarkers with the potential to measure PMR disease activity more reliably than conventional inflammatory markers like CRP and ESR.

Several other studies have recently investigated trends in haematologic parameters in PMR. In their retrospective analysis of 94 PMR patients contrasted with 242 RA patients, Jung et al. found NLR and PLR to be significantly higher among PMR cases.<sup>8</sup> These levels subsequently diminished with treatment and were found to correlate with other measures of disease activity including CRP, however an association between NLR or PLR and a relapsing disease course was not identified in this instance. A Japanese study has however reported thrombocytosis as an adverse prognostic factor in PMR.<sup>23</sup> Using hierarchical cluster analysis, participants with a platelet count  $>450 \times 10^9/L$  were found to be less likely to exhibit a response to glucocorticoid therapy at one month. Finally, a change in leukocyte dynamics among patients with PMR and GCA compared with healthy and infection controls has been newly documented by van Sleen et al., with a shift towards the production of myeloid-lineage leukocytes noted prior to the commencement of prednisolone.<sup>24</sup> This bias ultimately persisted during treatment with a weaning schedule of glucocorticoid therapy and was even maintained in patients achieving drug-free remission.

Taken together, these results suggest that the inflammatory milieu which characterises PMR directly impacts neutrophil and platelet production within the bone marrow. As other authors have previously hypothesised, this likely occurs secondary to high levels of the key cytokine interleukin-6, given this pro-inflammatory mediator is additionally an independent regulator of granulopoiesis and stimulates thrombopoiesis through thrombopoietin.<sup>25, 26</sup> It is therefore entirely conceivable that haematologic parameters reported on an FBE may provide an accurate representation of underlying disease activity in PMR.

Whilst the precise mechanism behind the association of high NLR with adverse survival in cancer patients is not known, neutrophilia as an inflammatory response is understood to suppress other immune cells including lymphocytes, activated T cells and natural killer cells, whose infiltration of tumors is otherwise associated with positive cytotoxic treatment outcomes.<sup>4</sup> In RA, where a recent meta-analysis has demonstrated a consistent relationship between NLR and PLR, and the presence of active disease, these indices are similarly thought to reflect the pathogenic mechanisms at play rather than being surrogate measures of the body's overall inflammatory state.<sup>27</sup>

The pathogenesis of PMR remains comparatively unclear though – it is hypothesized to arise from an aberrant immune response that follows an interaction between environmental factors, possibly viral, and the innate immune system in genetically predisposed individuals.<sup>28</sup> Activated macrophages predominate in both synovial and arterial samples taken from PMR patients. In the related condition GCA however, neutrophils have been implicated as the promoters of an escaped proinflammatory disease phenotype.<sup>29</sup> More specifically, a subset of neutrophil granulocytes capable of suppressing T cell activity following the institution of high-dose prednisolone therapy have been demonstrated to lose this ability upon glucocorticoid weaning in the context of rising IL-17 and IL-6 levels. Loss of this neutrophil suppressor function is thought to result in unchecked T cell proliferation within the vessel wall and eventual disease relapse.

Whilst this mechanism provides a biologically plausible explanation for a predominance of neutrophils enabling an adverse prognostic outcome in PMR, baseline neutrophil counts for glucocorticoid-resistant patients in our study were not substantially different from their glucocorticoid-responsive counterparts. Rather, lymphocyte counts were lower in this subset thereby producing higher NLR values. In general, no difference in total lymphocyte numbers is observed when PMR cases are compared with healthy controls.<sup>30</sup> Circulating B-cell lymphopaenia secondary to redistribution or intravascular marginalization of predominantly pro-inflammatory B-effector cells has however been established to exist in newly diagnosed, steroid-naïve PMR.<sup>31</sup> This disturbance in B cell homeostasis corrects with glucocorticoid therapy and is sustained in clinical remission but reoccurs upon disease relapse. Unfortunately, we did not undertake lymphocyte subset testing as part of this study, hence it is unclear whether lower lymphocyte counts at baseline in glucocorticoid-resistant patients represented an exaggeration of this previously described B cell phenomenon. Further investigation of lymphocyte subsets and their association with glucocorticoid resistance in PMR is now planned.

There are several other limitations to this study. It involves a relatively small number of participants and consequently the results may not be generalizable to a larger, more heterogeneous PMR cohort. As glucocorticoids have the potential to impact upon measured neutrophil and platelet counts, it is similarly not known if NLR can predict glucocorticoid-resistant disease in PMR if calculated from an FBE obtained once the patient has commenced prednisolone. Finally, this study provides proof-of-concept for the utility of NLR and PLR in measuring PMR disease activity and predicting treatment response. For use in everyday practice however, cut-off values to aid clinical decision-making would be ideal. Unfortunately, this was beyond the scope of the current pilot and hence further validation of these biomarkers in a large, multi-center trial is necessary.

## CONCLUSION

Baseline NLR represents a readily accessible and inexpensive biomarker that can predict glucocorticoid resistance in newly diagnosed PMR. This finding further characterizes a distinct subgroup of patients with relapsing disease in whom early initiation of DMARD therapy may be appropriate. In addition, both NLR and PLR appear to be reliable measures of PMR disease activity, outperforming conventional inflammatory markers like CRP and ESR. Further studies are now needed to validate these biomarkers for implementation in routine clinical practice.

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**Table 1** – Baseline demographic information: values are means  $\pm$  standard deviation, unless otherwise stated; median values are reported with 25% and 75% quartiles.

| <b>Demographic</b>                            | <b>Patients</b><br>(n=32) |
|-----------------------------------------------|---------------------------|
| <b>Age</b> (years)                            | 69.0 $\pm$ 7.2            |
| <b>Male</b>                                   | 17 (53.1%)                |
| <b>Caucasian</b>                              | 31 (96.9%)                |
| <b>BMI</b> (kg/m <sup>2</sup> )               | 27.7 $\pm$ 5.1            |
| <b>Shoulder Pain</b>                          | 32 (100%)                 |
| <b>Hip Pain</b>                               | 28 (87.5%)                |
| <b>Median EMS</b> (mins)                      | 120 (67.5 – 195)          |
| <b>EULAR/ACR<br/>Clinical Algorithm Score</b> | 5.2 $\pm$ 0.6             |
| <b>Median CRP</b> (mg/L)                      | 42.9 (21.8 – 65.7)        |
| <b>Median ESR</b> (mm)                        | 47.5 (30.5 – 68)          |
| <b>PMR-AS</b>                                 | 74.2 $\pm$ 35.7           |
| <b>Median HAQ-DI</b>                          | 1.7 (1.1 – 2.1)           |

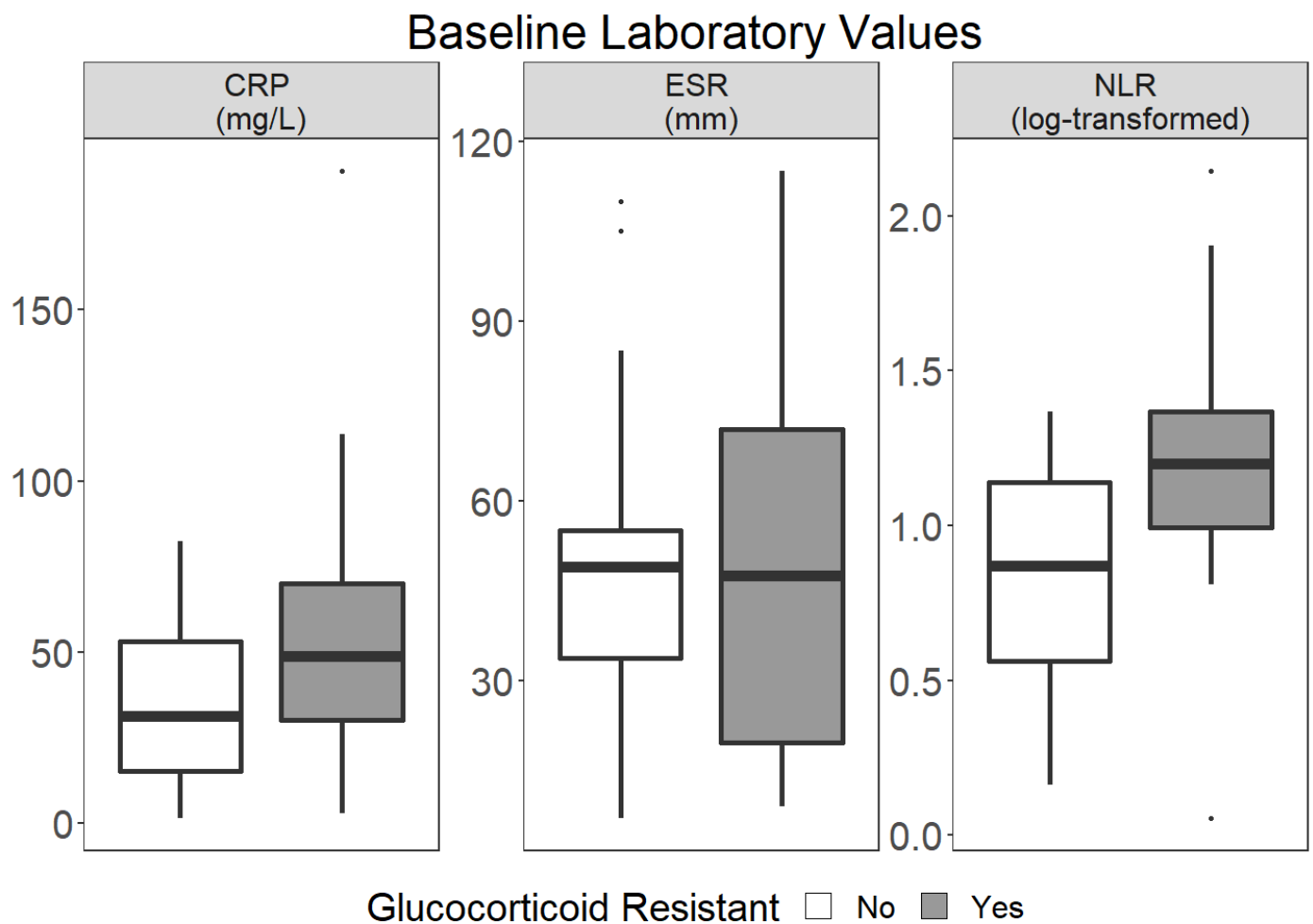
Abbreviations: BMI – body mass index; EMS – early morning stiffness; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PMR-AS – polymyalgia rheumatica-activity score; HAQ-DI – health assessment questionnaire-disability index.

**Table 2** – Demographic comparison of glucocorticoid-resistant and -responsive patients: values are means  $\pm$  standard deviation, unless otherwise stated; median values are reported with 25% and 75% quartiles.

| <b>Demographic</b>                               | <b>Glucocorticoid-Resistant</b><br>(n=16) | <b>Glucocorticoid-Responsive</b><br>(n=16) |
|--------------------------------------------------|-------------------------------------------|--------------------------------------------|
| <b>Age</b> (years)                               | 71.9 $\pm$ 7.0                            | 66.1 $\pm$ 6.4                             |
| <b>Gender:</b>                                   |                                           |                                            |
| - Female                                         | 10 (62.5%)                                | 5 (31.25%)                                 |
| - Male                                           | 6 (37.50%)                                | 11 (68.75%)                                |
| <b>CRP</b> (mg/L)                                | 59.3 $\pm$ 46.0                           | 36.4 $\pm$ 27.6                            |
| <b>ESR</b> (mm)                                  | 50.7 $\pm$ 28.6                           | 49.4 $\pm$ 30.1                            |
| <b>PMR-AS</b>                                    | 85.3 $\pm$ 35.3                           | 63.0 $\pm$ 33.7                            |
| <b>Median WCC</b> ( $\times 10^9/L$ )            | 8.55 (7.4 – 9.25)                         | 7.95 (7.0 – 9.23)                          |
| <b>Median neutrophils</b><br>( $\times 10^9/L$ ) | 5.5 (4.9 – 6.73)                          | 5.1 (3.8 – 5.9)                            |
| <b>Median lymphocyte</b><br>( $\times 10^9/L$ )  | 1.7 (1.6 – 1.8)                           | 2.1 (1.9 – 2.3)                            |
| <b>Median platelets</b> ( $\times 10^9/L$ )      | 362 (297 – 409)                           | 332 (264 – 448)                            |
| <b>NLR</b> (log-transformed)                     | 1.2 $\pm$ 0.4                             | 0.8 $\pm$ 0.4                              |
| <b>PLR</b> (log-transformed)                     | 5.37 $\pm$ 0.37                           | 5.12 $\pm$ 0.38                            |

Abbreviations: CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PMR-AS – polymyalgia rheumatica-activity score; WCC – white cell count; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio.

**Figure 1** – Box plots: The relationship between baseline CRP, ESR and NLR values, and glucocorticoid-resistant disease.



Abbreviations: CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; NLR – neutrophil to lymphocyte ratio.

# **Chapter 7: Developing an OMERACT Endorsed Core Outcome Measurement Set for Polymyalgia Rheumatica**

## **7.1 Preface**

In previous chapters, it was established that relapse is a common outcome amongst newly diagnosed PMR patients treated with a standardised weaning schedule of low-dose glucocorticoid therapy. Even though most participants were taking a prednisolone dose of  $\leq 5\text{mg}$  daily by the conclusion of the MPR-PMR study, their disease activity had begun to exhibit an upward trajectory. There is consequently a need to improve treatment outcomes in PMR and preferably do so with novel therapies which do not cause the same incidence of adverse events as glucocorticoids. In pursuit of this goal however, PMR researchers must remain cognisant that “clinical trials are only (ever) as credible as their endpoints”.<sup>(1)</sup>

OMERACT (Outcome Measures in Rheumatology) is an international network of clinicians, researchers and patient partners committed to improving outcome measures in rheumatology.<sup>(2)</sup> Dedicated Working Groups strive to validate study endpoints for use in clinical trials and observational research by employing an evidenced-based, iterative consensus process. As part of these teams, early career researchers serve as Fellows and are chiefly responsible for executing tests outlined in the OMERACT Filter<sup>(3)</sup> which determines the suitability of candidate instruments for inclusion in a final core outcome measurement set.

At the biennial OMERACT Conference held in 2018, the author of this thesis had the privilege of fulfilling the PMR Working Group Fellow role. In 2016, a set of core research domains were endorsed by OMERACT for PMR including pain, stiffness, physical function and systemic inflammation.<sup>(4)</sup> Next steps therefore comprised identifying those instruments mapping to these domains and evaluating their measurement properties for truth, discrimination and feasibility. In addition to assisting with a systematic literature review<sup>(5)</sup> and online respondent survey of PMR patients<sup>(6)</sup>, Fellow responsibilities included leading the raw data analysis utilising results from the MPR-PMR study and The PMR Cohort in the United Kingdom, and presenting findings from the three work streams to key stakeholders at the 2018 Conference’s PMR Special Interest Group.

The following journal article encapsulating this work was published in 2019 – Owen CE, Yates M, Twohig H, Muller S, Neill LM, Harrison E, Shea B, Simon LS, Hill CL & Mackie SL.

Toward a Core Outcome Measurement Set for Polymyalgia Rheumatica: Report from the OMERACT 2018 Special Interest Group. *Journal of Rheumatology*; 01:01.

## 7.2 Summary of Main Findings

- A literature review of all published articles found a lack of consistency in patient assessment in PMR studies, with only 2/10 randomised controlled trials and 12/23 prospective cohort studies measuring an outcome in each of the four predefined core domains.
- Systemic inflammation represented the most assessed domain, followed by pain, stiffness and physical function. Candidate instruments identified for possible inclusion in the core outcome measurement set included pain VAS/numeric rating scale (NRS), stiffness VAS/NRS and duration, CRP and ESR, and the HAQ-DI/mHAQ.
- An online respondent survey of PMR patients from three continents established that the candidate instruments were both a suitable match for the target domain and feasible to complete. Further assessment of their performance based on raw data analysis from the MPR-PMR study and The PMR Cohort similarly proved favourable for possible inclusion in the core outcome measurement set.
- Consensus was reached by attendees at the OMERACT 2018 PMR Special Interest Group that pain VAS/NRS, stiffness VAS and duration, ESR and CRP, and HAQ-DI/mHAQ were either green (“good to go”) or amber “(more work needed or a concern, but go”) for domain match and feasibility, and therefore should continue through the Filter(3).
- The focus of the PMR Working Group now shifts to appraising the existing evidence for each instrument’s measurement properties and addressing identified knowledge gaps by further analysing relevant datasets. The primary goal remains the development of an OMERACT endorsed core outcome measurement set.

## 7.3 Interpretation

The absence of a standardised approach to patient assessment in PMR represents yet another barrier to research advances in this rheumatic disease. A core outcome measurement set endorsed by OMERACT has the potential to vastly improve the quality of all future clinical trials and observational studies in PMR by ensuring validated endpoints are routinely employed.

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# Toward a Core Outcome Measurement Set for Polymyalgia Rheumatica: Report from the OMERACT 2018 Special Interest Group

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**ABSTRACT. Objective.** To report the progress of the Outcome Measures in Rheumatology (OMERACT) Polymyalgia Rheumatica (PMR) Working Group in selecting candidate instruments for a core outcome measurement set.

**Methods.** A systematic literature review identified outcomes measured and instruments used in PMR studies, and a respondent survey and raw data analysis assessed their domain match and feasibility.

**Results.** Candidate instruments were identified for pain [visual analog scale/numerical rating scale (VAS/NRS)], stiffness (VAS/NRS and duration), and physical function (Health Assessment Questionnaire–Disability Index/modified Health Assessment Questionnaire). Domain match and feasibility assessments were favorable; however, validation in PMR was lacking.

**Conclusion.** Further assessment of candidate instruments is required prior to recommending a PMR core outcome measurement set. (J Rheumatol First Release April 1 2019; doi:10.3899/jrheum.181050)

## Key Indexing Terms:

POLYMYALGIA RHEUMATICA

OUTCOMES

OMERACT

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Polymyalgia rheumatica (PMR) is an inflammatory disease characterized by subacute onset pain and stiffness in the shoulders and hips. Oral glucocorticoids represent the mainstay of treatment and while cessation of therapy is the ultimate goal, up to 50% of patients with PMR continue to require prednisolone 2–3 years after diagnosis<sup>1</sup>. It is unclear what starting dose or tapering schedule achieves the best outcome, or what benefit may be offered by putative glucocorticoid-sparing agents. Significant morbidity from glucocorticoid-induced complications is recognized and likely surpasses that seen in comparable rheumatic conditions<sup>2</sup>.

To our knowledge, there is currently no agreed core outcome measurement set for PMR clinical trials. A lack of consistency in definitions for domains or instruments used to assess patients with PMR is characteristic of the existing literature<sup>3</sup>. A core outcome measurement set for universal use in studies of PMR would improve the quality of future research.

In 2016, the Outcome Measures in Rheumatology (OMERACT) endorsed a core domain set for PMR. The inner core of the “onion,” signifying items to be measured in all PMR clinical trials, consisted of 4 domains: pain, stiffness, physical function, and systemic inflammation<sup>4</sup>. Here we report the progress of the PMR Working Group in identifying and evaluating suitable instruments mapping to these core domains. This work includes an updated systematic literature review, online respondent survey, and raw data analysis evaluating the domain match and feasibility of selected instruments in line with the first 2 signaling questions of the OMERACT Filter 2.1: Instrument Selection Algorithm<sup>5,6,7</sup>. The proceedings of the OMERACT 2018 PMR Special

Interest Group (SIG) are also detailed, in particular the major points discussed, and consensus reached regarding which candidate instruments should continue through the filter.

### Systematic Literature Review

To obtain all published articles reporting outcome measures mapping to the OMERACT-endorsed PMR Core Domain Set, 5 databases (MEDLINE, CINAHL, Embase, Web of Science, Cochrane Library) were searched from inception to September 30, 2017. This yielded 16,222 references, which was reduced to 90 full-text studies following removal of duplicates and screening abstracts. Forty-six studies were included in the review. Risk of bias was assessed using a modified Quality in Prognosis Studies (QUIPS) tool<sup>8</sup>. The systematic review protocol was registered with PROSPERO (CRD42017080058).

Two out of 10 randomized controlled trials and 12/23 prospective cohort studies measured outcomes in each of the 4 core domains. The most commonly assessed domain was systemic inflammation (43/46 studies), usually by erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Pain was measured in 32/46 studies, most often using a visual analog scale (VAS). Stiffness was measured in 28/46 studies, typically as duration of morning stiffness. Physical function was assessed in 22/46 of studies, most frequently using the elevation of upper limb score as part of the PMR activity score<sup>9</sup>, or the Health Assessment Questionnaire (HAQ). There was no association between higher-quality clinical research trials (assessed by QUIPS tool) and the number of outcomes measured from the core domain set.

### Online Respondent Survey

The patient perspective on candidate instruments for pain (VAS/numeric rating scale [NRS]), stiffness (VAS/NRS, and duration of morning stiffness), physical function [Health Assessment Questionnaire-Disability Index (HAQ-DI)/modified Health Assessment Questionnaire (MHAQ)], and systemic inflammation (ESR/CRP) were evaluated using a Web-based survey. Google Docs links were created and included in the Newswire newsletter of the charity PMRGCAuk (Polymyalgia Rheumatica and Giant Cell Arteritis UK), which is distributed to 1800 readers, and the HealthUnlocked Web forum consisting of 6986 members, yielding between 28 and 73 responses for each of the instruments examined. Patients were asked a series of questions addressing face validity and feasibility that had been developed by consensus of the PMR Working Group. Ethical approval was received from the University of East Anglia Research Ethics Committee (2017/18 – 81) and all respondents provided written informed consent to publish the results prior to survey completion.

Participants from 3 continents (Europe, North America, Australia/New Zealand) contributed 51 responses for pain

VAS/NRS, 51 for stiffness VAS/NRS, 51 for duration of morning stiffness, 73 for HAQ-DI, 28 for MHAQ, and 62 for ESR/CRP. Disease duration ranged from new diagnosis to 17 years; current prednisolone dose was 0–50 mg daily. Most respondents agreed candidate instruments were both a suitable match for the target domain and feasible to complete: approval for pain VAS was 68.6%/NRS 60.8%; stiffness VAS 62.8%/NRS 58.8%; duration of morning stiffness 58.8%; HAQ-DI 70%; MHAQ 53.6%; and ESR/CRP 54.8%. The free text responses further contextualized the numerical scores and will be the subject of a separate publication arising from this work.

### Raw Data Analysis

Two prospective observational cohort studies contributed raw data to further assess the domain match and feasibility of candidate instruments for pain, stiffness, and physical function: the Melbourne Predictors of Relapse in PMR (MPR-PMR) study, and The PMR Cohort<sup>10</sup>. Specifics pertaining to each of these studies' designs and baseline patient demographics are outlined in Table 1<sup>11,12</sup>. Ethical approval was received from the Austin Health Research Ethics Committee for the MPR-PMR study (HREC/14/Austin/158) and the Staffordshire Research Ethics Committee for The PMR Cohort (12/WM/0021v), with written informed consent including publication of results provided by all participants in both instances prior to study enrollment.

Statistical analysis was conducted using Stata<sup>11,12</sup>. A data completion rate > 80% was ensured for each instrument, prior to generating a frequency distribution histogram. The proportion (percentage) of participants with the lowest ("floor") and highest ("ceiling") values was recorded, and the normality of each distribution was assessed (based upon the coefficient of skewness where 0 = normal and –0.5 to 0.5 is about symmetric).

The data completion rate ( $\geq 96.3\%$ ) and time taken were deemed acceptable for all of the candidate instruments examined. Pain VAS/NRS and stiffness NRS were both associated with > 15% of respondents scoring the highest possible value (VAS/NRS = 10) at baseline, and the lowest value (VAS/NRS = 0) at multiple timepoints during treatment and followup. Both versions of the HAQ, but especially the MHAQ, were similarly characterized by floor effects (lowest value = 0) throughout but did not show the same ceiling problems (highest value = 3). The observed floor and ceiling patterns appeared consistent with the expected clinical course for patients with newly diagnosed PMR.

At baseline in both studies, pain levels were at the higher end of the scale (VAS/NRS), then appropriately trended to lower values following treatment (Figure 1). While the MPR-PMR study measured duration of morning stiffness, as compared with stiffness NRS in The PMR Cohort, the pattern of distribution was similar for both instruments and mirrored

Table 1. Study design and baseline demographic data for the MPR-PMR study and The PMR Cohort.

| Criterion                                    | MPR-PMR Study                                                                                                                                    | The PMR Cohort                                                                                                                           |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Study type                                   | Prospective, observational                                                                                                                       | Prospective, observational                                                                                                               |
| Setting                                      | Tertiary referral center                                                                                                                         | Primary care                                                                                                                             |
| Mode of survey distribution                  | Clinician administered                                                                                                                           | Mail                                                                                                                                     |
| Sample size, n                               | 37                                                                                                                                               | 652                                                                                                                                      |
| Mean age, yrs $\pm$ SD                       | 62.9 $\pm$ 24.6                                                                                                                                  | 72.4 $\pm$ 9.3                                                                                                                           |
| Female                                       | 46.0%                                                                                                                                            | 62.2%                                                                                                                                    |
| White                                        | 97.3%                                                                                                                                            | 97.0%                                                                                                                                    |
| Diagnostic criteria                          | 2012 EULAR/ACR <sup>11</sup>                                                                                                                     | Clinician diagnosis                                                                                                                      |
| Treatment                                    | BSR guideline <sup>12</sup>                                                                                                                      | Clinician discretion                                                                                                                     |
| Visit schedule                               | Weeks 0, 4, 8, 16, 24, 32, and 46                                                                                                                | Mos 0, 1, 4, 8, 12, 18, and 24                                                                                                           |
| Followup duration                            | 46 weeks                                                                                                                                         | 24 mos                                                                                                                                   |
| Instrument used to measure pain              | VAS                                                                                                                                              | NRS                                                                                                                                      |
| Pain VAS/NRS stem and anchors                | Please indicate on the scale below the severity of your current muscle/joint pain (where 0 is “no pain” and 10 is “pain as bad as it could be”). | How would you rate the overall level of pain from your PMR on a 0–10 scale, where 0 is “no pain” and 10 is “pain as bad as it could be”? |
| Instrument used to measure stiffness         | Duration of morning stiffness, min                                                                                                               | NRS                                                                                                                                      |
| Instrument used to measure physical function | HAQ-DI                                                                                                                                           | MHAQ                                                                                                                                     |

PMR: polymyalgia rheumatica; MPR-PMR: Melbourne Predictors of Relapse–Polymyalgia Rheumatica; MPR-PMR: Melbourne Predictors of Relapse–PMR; EULAR/ACR: European ; EULAR/ACR: European League Against Rheumatism/American College of Rheumatology; BSR: British Society of Rheumatology; VAS: visual analog scale; NRS: numerical rating scale; HAQ-DI: Health Assessment Questionnaire–Disability Index; MHAQ: modified Health Assessment Questionnaire.

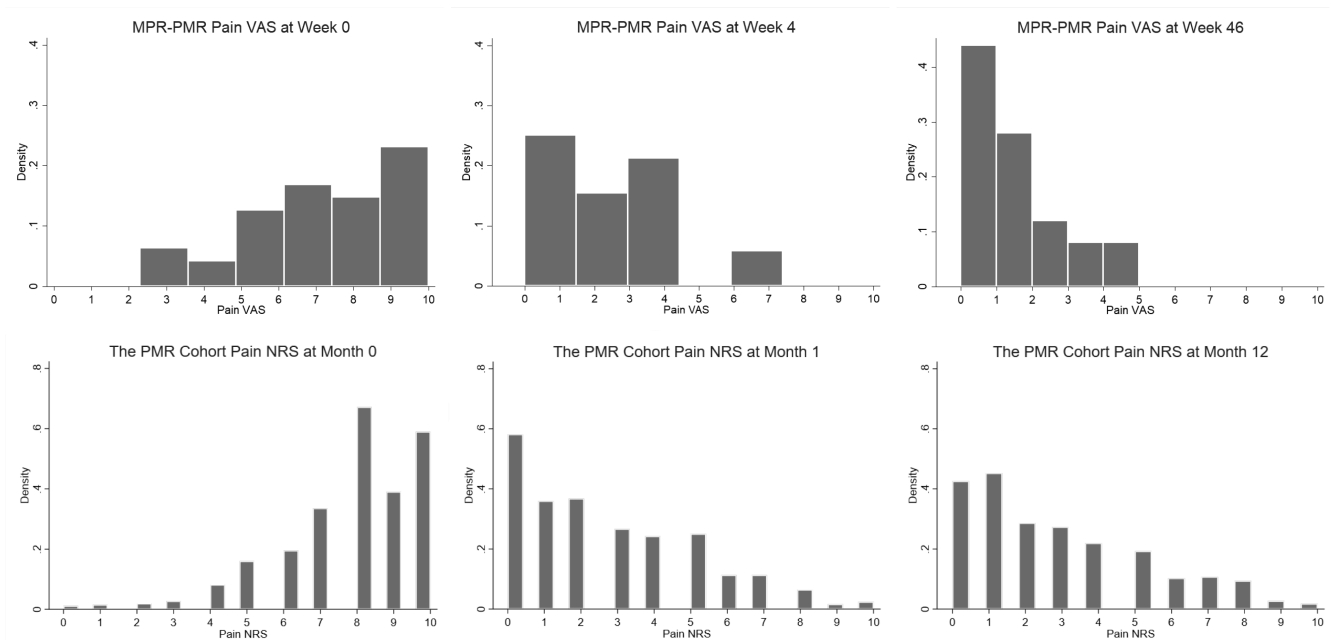


Figure 1. Frequency distribution histograms for pain VAS in the MPR-PMR study at weeks 0, 4, and 46 compared with pain NRS in The PMR Cohort at months 0, 1, and 12. On the Y axis, density refers to the average frequency of scores within the allocated interval. VAS: visual analog scale; MPR-PMR: Melbourne Predictors of Relapse–Polymyalgia Rheumatica; NRS: numerical rating scale.

that seen for pain VAS/NRS. MHAQ results at baseline in The PMR Cohort were typically lower than those recorded using HAQ-DI, which might be explained by the shorter

format of this instrument. During followup, no major differences were noted in the performance of the HAQ-DI compared with MHAQ (Figure 2).

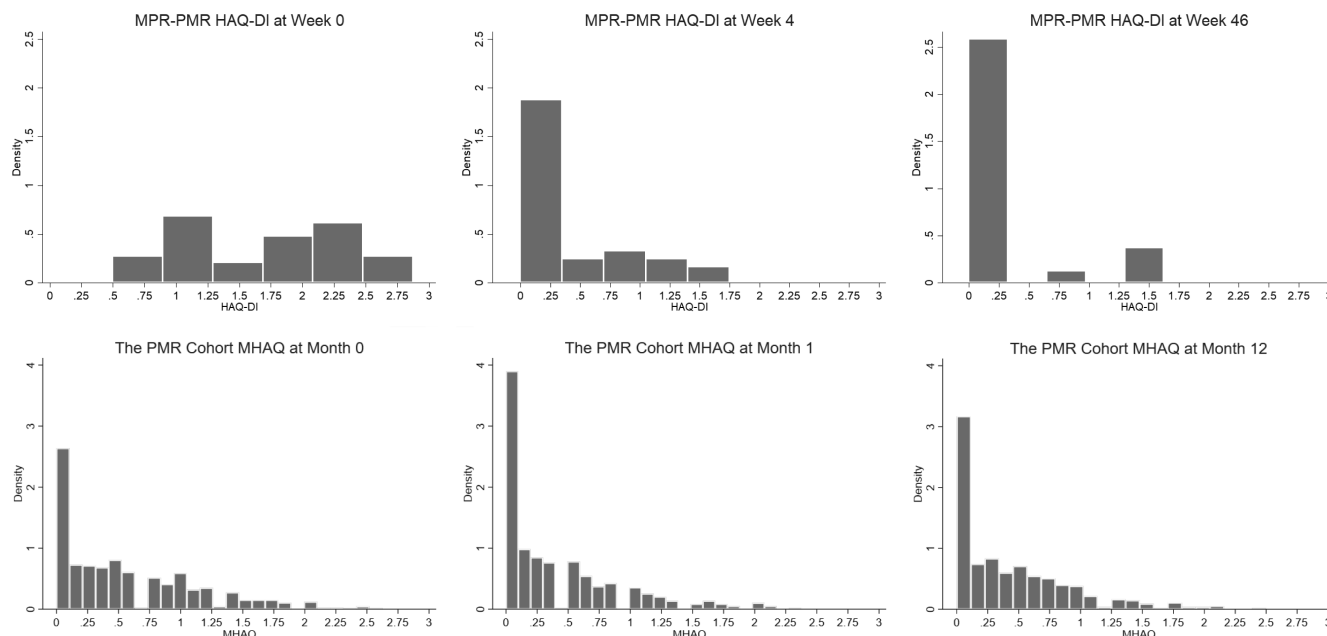


Figure 2. Frequency distribution histogram for HAQ-DI in the MPR-PMR study at weeks 0, 4, and 46 compared with MHAQ in The PMR Cohort at months 0, 1, and 12. On the Y axis, density refers to the average frequency of scores within the allocated interval. HAQ-DI: Health Assessment Questionnaire–Disability Index; MPR-PMR: Melbourne Predictors of Relapse–Polymyalgia Rheumatica; MHAQ: modified Health Assessment Questionnaire.

## Summary of the OMERACT 2018 PMR SIG

Participants including clinicians, researchers, and patient partners discussed the results of the 3 work streams in detail at the OMERACT 2018 PMR SIG. The purpose of the SIG was to establish whether instruments mapping to the 4 core domains had satisfied tests for domain match and feasibility, and if they should continue through the OMERACT 2.1 Filter<sup>5,6,7</sup>.

The major points of discussion were the interchangeability of VAS and NRS for the measurement of pain, the most suitable instrument to measure stiffness (VAS/NRS vs duration of morning stiffness), and the appropriateness of HAQ as a patient-reported outcome measure (PROM) across different age groups and in the modern day. Although the raw data analysis revealed no major differences in the performance of pain VAS and NRS in the 2 PMR populations studied, no head-to-head comparison was available, and this may require additional study. VAS/NRS and duration of morning stiffness were both acknowledged to possess limitations in their respective abilities to measure the patient experience of stiffness (particularly when eliciting responses from non-English speaking patients); this issue is common to many rheumatic diseases and no better alternative for measuring stiffness in PMR is currently described. While some HAQ questions may be less relevant to older persons (e.g., “Do chores such as vacuuming or yard work?”) or contextually out of date (e.g., “run errands?”), it is otherwise a well-validated instrument that in other diseases has been

shown to be responsive to change over time and capable of discriminating between groups of interest. The development of an entirely new instrument for the domain of physical function was therefore deemed unnecessary. However, it is recognized that the overall life impact of PMR reaches beyond the 4 core domains and there remains an unmet need for a disease-specific PROM for PMR.

## Future Research Agenda

At the end of the SIG, consensus was reached among the participants that candidate instruments for pain (VAS/NRS), stiffness (VAS/NRS and duration of morning stiffness), and physical function (HAQ-DI/MHAQ) were either green (“good to go”) or amber (“more work needed or a concern, but go”) for domain match and feasibility. The PMR Working Group will focus upon appraising the existing evidence for each instrument’s measurement properties before addressing any identified gaps by undertaking focused analysis of relevant datasets. Our objective is to generate a PMR Core Outcome Measurement Set for future endorsement by OMERACT.

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## Chapter 8: Discussion and Conclusion

### 8.1 Preface

In the final chapter, earlier results will first be summarised relative to the original aims of this thesis. Detailed discussion of the relevance of these findings in the context of the existing PMR literature will follow. Limitations of this work and areas for future research will also be outlined, prior to final conclusions being drawn.

### 8.2 Overview

In a prospective longitudinal cohort study of 35 newly diagnosed, steroid naïve PMR patients treated with a weaning schedule of low-dose glucocorticoid therapy as outlined in the BSR guideline(1), disease relapse occurred frequently. This outcome was more common among older participants and women. Imaging results further substantiated clinical diagnoses, however serial ultrasound during the 46-week follow-up period failed to refine individual relapse risk. By contrast, the presence of volar  $^{18}\text{F}$ -FDG uptake at the hand on whole body PET/CT conferred a distinct prognostic advantage.

Half of the study's patients met criteria for a PMR disease course characterised by glucocorticoid resistance. Again, predictors included older age and female sex, along with high BMI. A relationship between haematologic parameters and disease activity was also noted, with indices including NLR and PLR later confirmed as new biomarkers of clinical and prognostic significance in PMR.

Results from the MPR-PMR study additionally contributed to characterising PMR's underlying pathology by identifying hamstring peritendonitis as the anatomic correlate of abnormal  $^{18}\text{F}$ -FDG uptake adjacent to the ischial tuberosities and at the posteromedial knee on whole body PET/CT. High sensitivity and specificity values for diagnosing PMR were achieved with this imaging modality using a novel algorithm that incorporated just three musculoskeletal sites representing distinctive extra-capsular inflammation.

Finally, data was utilised in a preliminary validation exercise of candidate instruments mapping to the pre-specified OMERACT domains of pain, stiffness, physical function, and systemic inflammation.(2) These findings will now inform the development of a core outcome measurement set for use in all future clinical trials and observational studies of PMR.

In its entirety, this thesis provides a substantive contribution to the existing PMR literature. In particular, the body of work furthers our current understanding of those patients at increased risk of relapsing or glucocorticoid-resistant disease who are most likely to benefit from early initiation of a steroid-sparing agent. Furthermore, identification of precise anatomic correlates of abnormalities detected on whole body PET/CT brings new perspective to the musculotendinous pathology that defines PMR and ultimately sets it apart from other rheumatic diseases. Finally, affirmation of whole body PET/CT as a test with gold standard potential in PMR substantiates an alternate diagnostic approach, especially in research settings, that is not dependent upon clinical classification criteria.

## 8.3 Executive Summary of Thesis Findings

### 8.3.1 Primary Aim

- 1) To characterise the demographic, clinical, laboratory and imaging phenotype of patients with PMR that relapses with standardised, low-dose glucocorticoid therapy:
  - In the MPR-PMR study, the following statistically significant baseline predictors of disease relapse were identified:
    - Age (HR 1.07);
    - Female sex (HR 2.38).
  - Conversely, a volar pattern of  $^{18}\text{F}$ -FDG uptake at the hand on whole body PET/CT correlated with later time to first relapse/no relapse (HR 0.25).
  - Predictors of glucocorticoid-resistant disease similarly included older age and female sex, in addition to high BMI and high NLR.

### 8.3.2 Secondary Aims

- 1) To investigate the pathologic basis of PMR by determining precise anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake on whole body PET/CT:
  - Using PET/MRI fusion, hamstring peritendinitis was identified as the anatomical correlate of abnormalities detected adjacent to the ischial tuberosities and of posteromedial knee structures.
  - A volar pattern of abnormal  $^{18}\text{F}$ -FDG uptake at the hand corresponded with flexor tenosynovitis on MRI.
- 2) To determine the sensitivity and specificity of novel  $^{18}\text{F}$ -FDG whole body PET/CT findings for the diagnosis of PMR:
  - Posteromedial knee  $^{18}\text{F}$ -FDG uptake  $\geq 1$  was associated with a sensitivity of 75% and specificity of 80.1% for a diagnosis of PMR.

- In a nested case-control study evaluating the diagnostic potential of whole body PET/CT in PMR, the combination of abnormalities in a peri-articular distribution at the shoulders, interspinous bursa and adjacent to the ischial tuberosities achieved the highest sensitivity (93.9%) and specificity (97%) values.
  - A novel algorithm comprising pre-specified qualitative scores at just three musculoskeletal sites –  $^{18}\text{F}$ -FDG uptake  $\geq 2$  adjacent to the ischial tuberosities in combination with either abnormalities at the peri-articular shoulder or interspinous bursa – was developed, and found to possess a sensitivity of 90.9% and specificity of 92.4% for diagnosing PMR.
- 3) To ascertain the role of musculoskeletal ultrasound in evaluating treatment response and clinical remission in PMR:
- Musculoskeletal ultrasound findings responded to glucocorticoid therapy in the MPR-PMR study, however complete resolution of abnormalities was infrequent and did not equate with sustained clinical remission.
- 4) To evaluate the efficacy of a standardised low-dose glucocorticoid weaning schedule for the treatment of PMR:
- Use of the BSR guideline(1) in the MPR-PMR study was associated with disease relapse in 78% of participants, with an average of 1.2 events per patient.
  - Whilst median time to remission was 6.1 weeks with this schedule, disease activity exhibited an upward trajectory by the end of follow-up.
- 5) To identify a novel biomarker that accurately measures PMR disease activity:
- A statistically significant relationship existed between disease activity and both NLR and PLR at baseline in the MPR-PMR study.
  - During follow-up, PLR correlated with mean PMR-AS, with a trend towards significance observed between NLR and mean PMR-AS.
- 6) To utilise collected data for the preliminary validation of instruments used to measure outcomes in clinical trials and observational research involving patients with PMR:
- Candidate instruments mapping to the core domains of pain (VAS/NRS), stiffness (VAS/NRS), physical function (HAQ-DI/mHAQ) and systemic inflammation (CRP/ESR) passed tests for truth and feasibility based upon raw data analysis from the MPR-PMR study and The PMR Cohort, and can now continue through the OMERACT Filter 2.1(3).

## 8.4 Contextualisation

### 8.4.1 Predictors of Relapse

At the beginning of this thesis, it was hypothesised that PMR which relapses with standardised, low-dose glucocorticoid therapy represents a distinct, but as yet undefined, disease subset. The results from the MPR-PMR study outlined above substantiate this theory by identifying several predictors associated with either an increased risk or, alternatively, protection against relapse.

A systematic review has previously identified female sex, high ESR and the presence of peripheral arthritis as adverse prognostic factors in PMR.(4) Whilst relapse is commonly utilised as an endpoint in studies of PMR patients, few authors have investigated the relationship between baseline characteristics and time to first relapse in the existing literature. A variety of different relapse definitions are similarly employed, although the recurrence of polymyalgia symptoms in association with raised inflammatory markers is typical. Of course, this approach is problematic given it is known that normal CRP and ESR results are observed in up to 14 and 27% of relapses respectively.(5) Accordingly, disease relapse was defined for the purposes of the MPR-PMR study by a PMR-AS  $\geq 9.35$ , a cut-off previously established to possess a sensitivity of 96.6% and specificity of 90.7% for flare diagnosis.(6)

In the largest study to evaluate predictors of first relapse, Kremers et al. retrospectively investigated the disease course of 364 patients with newly diagnosed PMR.(7) A higher initial prednisolone dose and more aggressive glucocorticoid weaning schedule were associated with future relapse, however Cox proportional-hazards model results were not statistically significant for age at diagnosis (HR 1.08 [0.92 – 1.27]). Age as a variable was however grouped by per 10-year increase for this analysis. In the MPR-PMR study by comparison, older age predicted earlier relapse and similarly correlated with glucocorticoid-resistant disease. Despite recognition of a higher incidence-rate among more elderly patients(8), an association between older age and poor prognosis has not been previously demonstrated in PMR.(4)

The findings presented in this thesis concerning age should therefore be interpreted with caution. Firstly, the small sample size of the MPR-PMR study may have resulted in a spurious result and secondly, the magnitude of effect detected (ie. a 7% increase in relapse risk) is of uncertain clinical significance. That said, age-related changes in immune function provide one possible explanation for these observations being valid. “Inflamm-aging” describes the progressive increase in circulating pro-inflammatory mediators that coincides with normal aging.(9) Presumed to be the consequence of continuous antigenic stimulation throughout life, the secretion of TNF- $\alpha$ , IL-1 and IL-6 by senescent cells has been previously implicated in other

age-related diseases including RA.(10, 11) It therefore stands to reason, given the pivotal role played by cytokines such as IL-6 in the pathogenesis of PMR, that this phenomenon might serve to heighten disease activity in older patients and by doing so increase their likelihood of relapse.

The evidence for gender being a determinant of prognosis in PMR is far stronger.(4) More specifically, female sex has been consistently associated with adverse treatment outcomes in the existing literature including longer duration and lower discontinuation rates of glucocorticoid therapy, together with higher cumulative doses of prednisolone.(12-14) A greater proportion of female than male participants meeting the secondary endpoint of glucocorticoid resistance in the MPR-PMR study is therefore consistent with previous work in this area. A higher relapse rate has similarly been previously documented in female PMR patients, as it was in this thesis. Cimmino et al. evaluated gender differences in 80 consecutive, newly diagnosed patients finding a greater number of relapses among women.(14) No difference in baseline disease activity between the two sexes was observed, however female participants required higher doses of prednisolone to achieve symptom control and this resulted in an increased incidence of glucocorticoid-related side effects. The authors accordingly hypothesised that gender may influence corticosteroid responsiveness, noting that oestrogen's propensity to enhance autoimmunity provided an inadequate explanation for this observation given the majority of female PMR patients are post-menopausal.

BMI as a predictor of glucocorticoid-resistant PMR is a particularly noteworthy finding to arise from this thesis. In a large retrospective population-based cohort, no association was found between obesity and the subsequent development of PMR, a result that is in fact at odds with those described in comparable rheumatic conditions like RA.(15, 16) Elevated BMI also did not impact upon the likelihood of glucocorticoid discontinuation in this study, however other treatment outcomes were not specifically assessed. Conversely, body weight was identified as the main determinant of clinical response in a prospective study of 60 newly diagnosed PMR patients treated with an initial prednisolone dose of 12.5mg daily.(17) This association was attributed to the pharmacokinetic properties of glucocorticoids, specifically their high volume of distribution and lipophilic nature.

The production of pro-inflammatory mediators by adipocytes provides an additional mechanism by which low-dose glucocorticoid therapy may be less effective in obese PMR patients. Adipose tissue is increasingly recognised as a dynamic endocrine and immune organ with capacity to produce adipokines including the insulin-sensitiser adiponectin and satiety-master leptin, along with TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and the acute-phase reactant CRP.(18) The metabolic excess associated with obesity accordingly promotes and then maintains a state of chronic, low-

grade inflammation.(19) To date, the impact of adipokines on treatment outcomes in PMR has not been studied and hence it is not known whether the profiles of glucocorticoid-resistant patients possess discrete differences to their glucocorticoid-responsive counterparts. In RA by comparison, adiponectin and leptin levels are known to correlate with disease activity and obesity is associated with significantly lower odds of achieving clinical remission.(20)

Kreiner et al. did evaluate adipokine profiles before and after 14 days of treatment with prednisolone 20mg in a case-control study including 15 newly diagnosed PMR patients.(21) Adiponectin levels in the PMR cases were noted to be inversely proportional to pro-inflammatory cytokines at baseline and this abnormality appropriately corrected with glucocorticoid therapy. By contrast, leptin levels which were not significantly different between the groups at baseline, rose in both the cases and controls post treatment. This observation was consequently attributed to a direct prednisolone effect, however endogenous glucocorticoids and testosterone are known to inhibit leptin synthesis whilst ovarian sex steroids upregulate its production.(20) In truth, leptin's sexual dimorphism provides a biologically plausible explanation for female patients in the MPR-PMR study experiencing higher rates of disease relapse and a propensity toward glucocorticoid resistance. Importantly, leptin derives from the same long-chain helical cytokine family as IL-6 and modulates both innate and adaptive immune responses in a pro-inflammatory manner.(22) It therefore stands to reason that higher physiologic levels of this adipokine in women might result in more difficult to control PMR. Further study of leptin's potential contribution to disease pathogenesis and the impact of it and other adipokines on treatment outcomes in PMR is now indicated.

Peripheral manifestations have long represented a vexing issue for clinicians in the diagnosis of PMR. For some rheumatologists, their existence still mandates a change in classification to late-onset seronegative RA. This approach is not an evidence-based one though, with distal musculoskeletal involvement documented to exist in approximately one-half of PMR cases.(23, 24) In the MPR-PMR study, 17 patients (48.6%) indicated wrist and /or hand involvement at baseline. Using Cox proportional-hazards modelling however, peripheral joint symptoms and evidence of synovitis on clinical examination failed to predict subsequent disease relapse. By contrast, the presence of hand pain, peripheral synovitis and a volar pattern of  $^{18}\text{F}$ -FDG uptake on whole body PET/CT were found to confer a prognostic advantage.

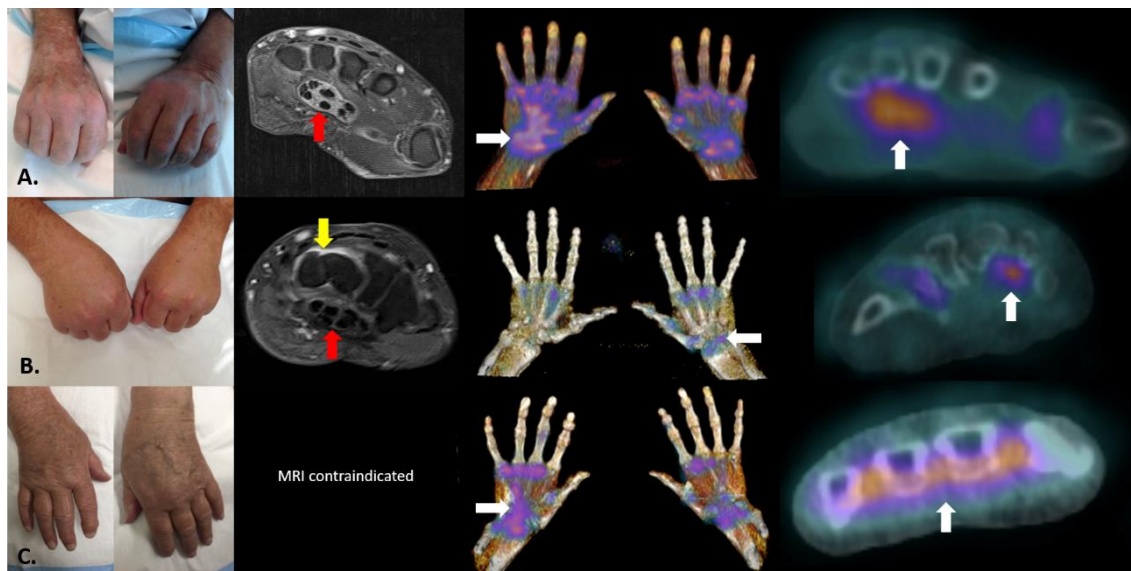
As previously outlined, peripheral arthritis is a recognised predictor of relapsing PMR and hence these results are at odds with the existing evidence.(4) In a prospective study of 177 patients, Salvarini et al. documented a relapse rate of 53% in patients with peripheral joint involvement compared with just 26% of those participants without this clinical manifestation

( $p=0.002$ ).<sup>(25)</sup> Female patients notably exhibited this pattern of disease more commonly than their male counterparts (67% cf. 33%). Another noteworthy point to arise from this study though was a significant difference in prognosis among participants with “distal extremity swelling with pitting oedema”. More specifically, these individuals were found to have a more benign disease course as evidenced by a lower cumulative prednisolone dose and shorter overall duration of glucocorticoid therapy. Undoubtedly, this observation has certain relevance to the disparate effects of peripheral manifestations upon prognosis that has been observed in this thesis.

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome describes a clinical entity characterized by an exquisitely steroid-responsive polysynovitis of the hands and/or feet that occurs in association with swelling of the extremities.<sup>(26)</sup> Originally considered a distinct subset of seronegative RA, RS3PE has now been reported in association with a range of rheumatic conditions including PMR, where it is increasingly accepted as part of the disease spectrum.<sup>(27)</sup> On MRI, tenosynovial sheath inflammation represents the imaging hallmark of this presentation, with concomitant joint synovitis also present in some cases.<sup>(26)</sup> In the MPR-PMR study, three participants (two male and one female) were noted to have RS3PE syndrome at enrolment. On whole body PET/CT in each of these individuals, intense  $^{18}\text{F}$ -FDG uptake was visualized at the hand and wrist in a volar distribution, with MRI in two cases (contraindicated in the third) confirming the presence of flexor tenosynovitis and inter-carpal synovitis (Figure 8.1).

Taken together, these findings suggest that RS3PE syndrome confers a definite prognostic advantage in PMR. A volar pattern of  $^{18}\text{F}$ -FDG uptake is also re-affirmed as the PET/CT correlate of flexor tenosynovitis. Given that volar  $^{18}\text{F}$ -FDG uptake correlated with a significantly reduced risk of relapse in the MPR-PMR study (HR 0.25), it is accordingly hypothesized that this PET/CT abnormality signifies a more glucocorticoid-responsive disease subset. This viewpoint is further substantiated by the existing literature where a symmetrical extra-capsular pattern of inflammation on MRI adjacent to the greater trochanter, acetabulum, ischial tuberosity and/or pubic symphysis has been previously associated with a complete, patient-reported response to prednisolone.<sup>(28)</sup> Consequently, it seems clear that peripheral manifestations cannot be universally assumed to predict a more severe disease course in PMR. Rather, joint synovitis represents an adverse prognostic factor, but the existence of tenosynovitis portends a more favorable treatment outcome.

**Figure 8.1:** Clinical photography, MRI and whole body PET/CT images of the hands in three patients (A-C) with RS3PE syndrome. Red and yellow arrows indicate flexor tenosynovitis and intercarpal synovitis respectively on MRI. White arrows highlight corresponding areas of  $^{18}\text{F}$ -FDG uptake in a distinctive volar distribution.



Abbreviations: MRI – magnetic resonance imaging; PET/CT – positron emission tomography/computed tomography; RS3PE - remitting seronegative symmetrical synovitis with pitting oedema;  $^{18}\text{F}$ -FDG –  $^{18}\text{F}$ -Fluorodeoxyglucose.

### 8.4.2 Underlying Pathology

The following discussion is adapted from an editorial published in 2019 – Owen CE, Liew DFL & Buchanan RRC. Musculotendinous Inflammation: The Defining Pathology of Polymyalgia Rheumatica? *The Journal of Rheumatology*; 46(12):1552-5. The full text version of this publication is included in Appendix 5.

To this day, the precise pathology underpinning PMR remains unclear from histological studies.(29) On modern imaging however, an extra-capsular pattern of inflammation has been identified as a point of difference between PMR and other rheumatic conditions, with utility in both diagnostic and prognostic settings.(28, 30, 31) Characterisation of the inflamed structures that correlate with these findings anatomically consequently provides a means by which to shed new light on the mystery that is PMR's true pathology.

In chapter 3 of this thesis, results from a proof-of-concept PET/MRI fusion study were presented. Having observed distinctive abnormalities on whole body PET/CT adjacent to the ischial tuberosities and of posteromedial knee structures in newly diagnosed PMR patients, MRI was undertaken to confirm suspected involvement of the hamstring tendons.(32) Bilateral and symmetric high T2 signal surrounding the proximal hamstring tendon origins of the semimembranosus and the conjoint tendon of the semitendinosus and biceps femoris was subsequently visualised at the pelvis, with peritendinitis of the semitendinosus and to a lesser extent gracilis tendons noted at the knee. Using PET/MRI fusion, hamstring peritendinitis was identified as the anatomical correlate of <sup>18</sup>F-FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures.

Since publication of this work, PMR's predilection for tendinous structures has been further substantiated by Fruth et al.(33) In a retrospective study of 40 patients who underwent contrast-enhanced pelvic MRI as part of their diagnostic work-up, areas of previously mentioned extra-capsular inflammation were studied in detail in the hopes of identifying a disease-specific pattern. Mostly bilateral enhancement of tendinous structures in the pelvis corresponded with these regions of interest in all cases and the pathology encompassed a spectrum ranging from circumferential peritendinous inflammation to complete intratendinous involvement up to the level of the musculotendinous junction. The authors therefore hypothesised that the peritendineum represented the primary anatomic target of PMR's inflammatory response.

This paper also notably documented linear enhancement of the intramuscular perimysium at the gluteus maximus in two patients; an observation that has been subsequently explored in more

detail by a French group as part of the post-hoc analysis of the TENOR study.(34) Laporte et al. reviewed short T1 inversion recovery (STIR) weighted MRI of the shoulder and pelvic girdle in 18 active PMR patients at baseline, 2 and 12 weeks post treatment with the IL-6 receptor blocker tocilizumab to ascertain the prevalence of localised myofascial lesions. Myofascial inflammation was defined as high T2-STIR signal within the affected muscle or forming a line around it. In addition to an anticipated high frequency of synovitis and bursitis, at least one shoulder girdle and at least one pelvic girdle myofascial inflammatory lesion was detected at baseline in 71.4% and 86.7% of cases respectively. The hip musculature was most commonly involved (86.7%), followed by the adductors at the pubic symphysis (80.0%), shoulder musculature (71.4%) and muscles adjacent to the ischial tuberosities, specifically semitendinosus, semimembranosus and the long head of biceps femoris (60.0%). Improvement in these lesions was subsequently noted in 64.1% of muscle groups at 12 weeks, thereby confirming the responsiveness of this newly identified pathology in PMR to a therapy with established efficacy.(35)

In their discussion, Fruth et al. rightly highlight the contiguous relationship that exists between muscle perimysium and peritendineum, whilst the provided images confirm a seamless transition between hip capsulitis and adjacent peritendinous enhancement.(33) The close anatomic proximity of the subacromial bursa to the supraspinatus tendon of the shoulder should also be remembered in this context. This bursa does not consist of a distinct sac, but rather its synovial layers blend with and are firmly attached to the underlying rotator cuff.(36) The possibility that the mild joint synovitis associated with PMR may represent a secondary phenomenon that arises from adjacent extra-articular inflammation has been previously proposed.(37) That bursitis in this condition could similarly reflect a primary pathology within the tendon itself should now be considered. Certainly, there can be little doubt amid this accumulating evidence of the involvement of the connective tissues surrounding the tendons and muscles of the shoulder and pelvic girdle in the pathogenesis of PMR. Musculotendinous inflammation thus appears to be the defining pathology of PMR, providing not only a unifying anatomic basis for established disease manifestations including capsulitis and bursitis, but also an explanation for the profound myalgia typically experienced by patients, which has been so inadequately accounted for by our understanding of this condition to date.

Imaging, of course, cannot characterise histopathology and dedicated studies are needed to confirm the existence of musculotendinous inflammation in PMR. Some of the very first biopsy reports in this condition did however document oedema and perivascular chronic inflammatory cell infiltration of the muscular fascia and its tendinous septum.(38) Similar inflammatory changes were identified at the shoulder joint capsule and bursa, whilst many arterioles exhibited

active intimal endothelial cell proliferation raising a possible patho-aetiological link between PMR and GCA. An immunofluorescence study of biceps biopsy samples similarly revealed immune complex and fibrinogen deposition in the perifascicular areas of the perimysium.(39) The authors concluded that muscle pathology in PMR was likely characterised by inflammation of the interstitial tissues. Finally, a more recent microdialysis study documented increased interstitial concentrations of key cytokines including IL-6 in the symptomatic trapezius and vastus lateralis muscles of PMR patients.(40) These abnormal levels normalized after prednisolone treatment and this correlated with complete symptom resolution, providing further proof of the response of inflammation within muscle connective tissues in PMR to conventional therapy and linking its resolution to positive clinical outcomes.

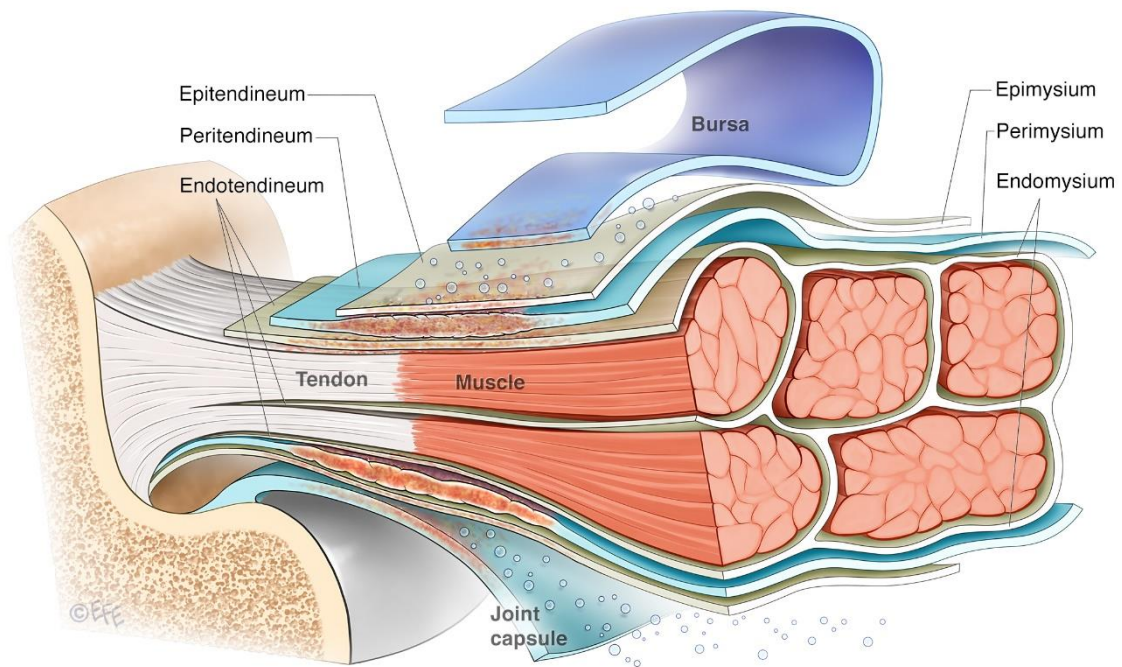
Overall, it is increasingly apparent from recent publications that the extra-capsular pattern of inflammation noted on imaging in PMR corresponds with musculotendinous structures of the shoulder and pelvic girdle. Musculotendinous inflammation therefore represents the defining pathology of PMR, given that extra-capsular abnormalities have previously been identified as the point of difference between PMR and other rheumatic conditions. The connective tissues surrounding the tendons and muscles, namely the peritendineum and perimysium, likely represent the anatomic target of PMR's inflammatory response, with secondary involvement of adjacent structures including the joint capsule and bursa (Figure 8.2). Although more detailed histological studies are necessary to confirm its precise immuno-pathology, these developments mean PMR should now be described as a chronic, inflammatory disease of musculotendinous structures rather than a vague syndrome of shoulder and pelvic girdle pain, and stiffness.

### 8.4.3 Diagnosis and Assessment of Disease Activity

In the absence of a gold standard investigation, clinicians can find it difficult to diagnose PMR with confidence. Central to this issue lies the fact that a shift in diagnosis is observed in 5-23% of PMR patients after long-term follow-up.(41, 42) In 2012, the consensus-based EULAR/ACR classification criteria were developed in order to standardize the definition of PMR. Whilst their sensitivity has since been demonstrated to be comparable to previous criteria, the specificity of the clinical scoring algorithm proved low for diagnostic purposes at 81.5% overall and 79.7% when attempting to distinguish PMR from late-onset RA.(43) Improvement in these figures to more acceptable levels of 91.3% and 89.9% respectively was though achieved with the addition of musculoskeletal ultrasound results.

Given the evolving evidence-base of distinct differences in the anatomic distribution of PMR relative to other rheumatic conditions, it stands to reason that imaging might be capable of

**Figure 8.2:** A depiction of musculotendinous pathology in PMR arising from the connective tissues of the tendons and muscles, namely peritendineum and perimysium, to involve adjacent structures including the joint capsule and bursa.(44)



improving the reliability of this diagnosis. As outlined, ultrasound is one modality that theoretically possesses this potential, however the low specificity for PMR of isolated findings like subacromial bursitis, biceps tenosynovitis and trochanteric bursitis mean it is unsuitable as a gold standard diagnostic test.(45) Furthermore, one study evaluating the contribution of musculoskeletal ultrasound to PMR diagnosis actually failed to demonstrate superior sensitivity with this approach.(46) Inherent advantages include lack of radiation exposure and ready accessibility, although application of the 2012 EULAR/ACR ultrasound scoring algorithm is presumably limited in clinical practice to those rheumatologists with scanning expertise.

By contrast, both MRI and whole body PET/CT are more capable of detecting those extra-capsular findings unique to PMR. Recent documentation of peritendinous enhancement on MRI as an imaging hallmark of PMR adds credence to this modality's diagnostic capacity, as does follow-up work by the same authors finding a sensitivity of 95.8% and specificity of 97.1% when  $\geq 10$  inflamed sites were identified throughout the pelvis.(33, 47) But whilst MRI, like ultrasound, is more readily available and does not involve radiation, PET/CT remains the only test that can image the whole body at once. Moreover, relevant differential diagnoses such as infection and malignancy can be excluded, and concomitant large vessel (LV)-GCA detected. Given the association between large vessel involvement and increased mortality due to vascular complications in GCA, identification of this PMR subgroup is especially desirable.(48)

One of the objectives of this thesis was to determine the sensitivity and specificity of PET/CT findings for diagnosing PMR. Two other groups have previously evaluated the performance of this imaging modality as a diagnostic tool. In their retrospective analysis of 50 patients with newly diagnosed or relapsing PMR compared with 53 malignancy controls, Sondag et al. established a sensitivity of 74% and specificity of 79% based upon the presence of abnormalities at  $\geq 3$  musculoskeletal sites.(49) A strongly statistically significant difference in mean  $^{18}\text{F}$ -FDG uptake score was also noted between the case and control groups (1.12 cf. 0.34  $p = <0.00001$ ) leading the authors to conclude that the number of sites involved and degree of  $^{18}\text{F}$ -FDG uptake were key in diagnosing PMR on whole body PET/CT. Subsequent to this, a prospective study of 99 consecutive patients with a possible clinical diagnosis of PMR found a total skeletal score  $>16$  (calculated from summing  $^{18}\text{F}$ -FDG uptake scores at 12 articular regions) possessed a sensitivity of 85.1% and specificity of 87.5% for differentiating between cases and controls.(50) In addition, this work specifically evaluated the performance of individual musculoskeletal sites but found acceptable sensitivity values often occurred at the expense of specificity, and vice versa. Combining sites corresponding to extra-capsular pathology did however partly address this limitation, with PET avidity at the cervical

interspinous bursa plus ischial tuberosities yielding a sensitivity of 62.7% and specificity of 96.6% for diagnosing PMR.

Based upon these findings, the potential of whole body PET/CT as a diagnostic test for PMR seems clear, with greatest certainty likely to occur in the presence of intense  $^{18}\text{F}$ -FDG uptake at a combination of pathognomonic musculoskeletal sites. In chapter 4, results from a study comparing the PET/CT scans of 33 newly diagnosed, steroid naïve PMR patients with 132 age- and sex-matched historic controls were presented. As anticipated, mean reference score compared to normal liver and  $\text{SUV}_{\text{max}}$  values were significantly higher in cases at the peri-articular shoulder, interspinous bursa, peri-articular hip, adjacent to the ischial tuberosities and posteromedial knee, with abnormalities at the peri-articular shoulder plus interspinous bursa and ischial tuberosities performing best in the ROC analysis (sensitivity 93.9%, specificity 97.0%). Combinations incorporating  $^{18}\text{F}$ -FDG uptake at the posteromedial knee similarly performed well (peri-articular shoulder + ischial tuberosities + posteromedial knee – sensitivity 93.9%, specificity 91.7%; interspinous bursa + ischial tuberosities + posteromedial knee – sensitivity 93.9%, specificity 92.4%), thereby validating this novel finding as an additional imaging feature specific to PMR. Images of the knees should accordingly be routinely acquired in cases of suspected PMR so as to optimise the diagnostic performance of PET/CT for this indication.

A major limitation of the composite scoring systems proposed by other authors is their diminished utility for everyday practice. In their discussion, Sondag et al. raise the possibility of whole body PET/CT findings being incorporated into a clinical decision tree and hence a secondary aim of the nested case-control presented in chapter 4 was to generate a diagnostic algorithm for PMR based upon pre-specified qualitative scores at a minimum number of musculoskeletal sites. Using CART modelling, abnormal  $^{18}\text{F}$ -FDG uptake  $\geq 2$  at the ischial tuberosities in association with either the peri-articular shoulder or interspinous bursa was subsequently found to possess a sensitivity of 90.9% and specificity of 92.4% for a diagnosis of PMR. Such results surpass those achieved using up to 17 articular regions and by doing so further substantiate the uniqueness of extra-capsular pathology to this condition. Clinicians can henceforth feel confident of a PMR diagnosis when these features alone are present on whole body PET/CT.

The question remains though as to whether whole body PET/CT represents a viable gold standard investigation for PMR. Certainly, it has very real potential when compared to existing classification criteria and probably should be a standard undertaking to ensure population homogeneity in research settings. A dedicated prospective study of whole body PET/CT's ability to distinguish PMR from other relevant rheumatic differentials like late-onset RA and

spondyloarthritis is next needed, along with a cost-benefit analysis of the test's appropriateness for use in the mainstream. Until then, its role will presumably remain limited to tertiary referral centres and patients with atypical presentations or suspected concomitant LV-GCA.

The absence of a validated diagnostic, monitoring and/or prognostic biomarker specific to PMR has long been a significant barrier to the proficient management of patients with this rheumatic condition. Ideally, a biomarker should provide an objective indication of the underlying disease state, which can be accurately and reliably reproduced.<sup>(51)</sup> Ease of access and low cost represent additional desirable characteristics for such a test, and likely go some way to explaining why the systemic inflammatory markers ESR and CRP remain the typical means by which to measure PMR disease activity to this day. However, whilst a higher baseline ESR has been previously linked to a lower probability of long-term glucocorticoid discontinuation, its performance, like that of CRP, as a monitoring biomarker in PMR is far from perfect with normal values observed in 27 and 14% of relapses respectively.<sup>(4, 5)</sup> An unmet need therefore persists for a test that can precisely measure the patient's current inflammatory condition and, by doing so, provide information that assists with clinical decision-making.

Several other candidate biomarkers have been proposed by other authors. In a 5-year prospective cohort study of 176 PMR patients, high plasma viscosity at diagnosis was found to correlate with a protracted steroid course and later development of concomitant GCA.<sup>(52)</sup> Unfortunately, this level was not repeated serially during follow-up, nor was its relationship to conventional disease activity measures explored. By contrast, McCarthy et al. evaluated whether plasma fibrinogen, given its close relationship to IL-6 production, represented a superior biomarker of disease activity in PMR to ESR and CRP.<sup>(5)</sup> In their prospective study of 25 newly-diagnosed and 35 inactive patients assessed at weeks 0 and 6, fibrinogen levels proved more specific than either ESR or CRP for gauging treatment response and diagnosing clinical remission. Inherent advantages of this biomarker include its ready availability and inexpensive nature, although its performance in a larger cohort of longer duration requires study prior to consideration of its application in routine clinical practice. Finally, a novel marker of angiogenesis, angiopoietin-2, has most recently been evaluated for its ability to predict concomitant vascular inflammation and time to glucocorticoid cessation in 39 newly diagnosed, steroid-naïve PMR patients.<sup>(53)</sup> Results included a strong correlation between high angiopoietin-2 levels at baseline and the presence of concomitant GCA, along with a tendency for PMR patients with higher values to exhibit a more complicated disease course (presumably due to the presence of surreptitious vasculitis). Not surprisingly, angiopoietin-2 was also found in this work to be more sensitive and specific than ESR or CRP for the detection of vascular

inflammation, however whether it can play any role in generally monitoring PMR disease activity remains yet unclear.

Earlier in this thesis, the relationship between NLR and PLR, and disease activity in the MPR-PMR study was explored. In this proof-of-concept study, a statistically significant relationship was identified between these haematologic indices and the PMR-AS at baseline, with PLR also found to correlate with mean PMR-AS values during follow-up and NLR exhibiting a trend toward significance. Furthermore, baseline NLR proved to be a predictor of glucocorticoid-resistant PMR (OR 14.01) suggesting that these biomarkers, which can be simply calculated from a routine FBE, possess both monitoring and prognostic capabilities. In truth, such potential has rarely been identified among other candidate tests in this condition, certainly not from one that would necessitate no additional healthcare expenditure. Moving forward, the validation of these biomarkers in large, multi-centre trials of PMR is key, with other considerations including study of their ability to aid clinical decision-making surrounding glucocorticoid weaning and early DMARD initiation.

Outside of biomarkers, imaging theoretically provides another means by which to assess treatment response in PMR. Ultrasound seems the logical modality for this application given the ease with which serial examinations can be performed, with one prior study finding it exhibited similar or better sensitivity to change than clinical and laboratory variables.<sup>(54)</sup> A secondary aim of this thesis therefore involved ascertaining the relationship between resolution of musculoskeletal ultrasound findings and clinical remission in PMR.

When compared with similar work by Macchioni et al. evaluating the role of ultrasound in identifying patients with relapsing disease, the incidence of subacromial bursitis observed at baseline in the MPR-PMR cohort proved comparable (85.7% cf. 91.2%).<sup>(55)</sup> A lesser rate of abnormalities at the long head of biceps tendon (65.7% cf. 98.2%) and glenohumeral joint (2.8% cf. 35.1%) were though appreciated, although inherent differences existed in the definitions used for a positive result. Following the commencement of prednisolone, the frequency of abnormal findings detected on ultrasound declined significantly, an observation that is also consistent with several other studies in this area.<sup>(54-57)</sup> Persistent bilateral subacromial bursitis and biceps tenosynovitis were subsequently identified in 13.3 and 24% of patients at week 46. Again, such results only serve to reinforce the assertion by others that subclinical inflammation persists on ultrasound in a percentage of PMR patients despite successful treatment with low-dose glucocorticoid therapy.<sup>(55, 56)</sup>

The possibility of ultrasound abnormalities predicting a relapsing disease course in PMR has been previously hypothesised.(55) To that end, Macchioni et al. found a statistically significant correlation between the presence of Power Doppler signal at diagnosis and a higher risk of relapse during follow-up. There was however no difference observed in the incidence of this outcome among patients with persistent subclinical ultrasound findings at the shoulder and those without. A more recent study of 66 patients with newly diagnosed PMR similarly failed to identify a relationship between residual subacromial bursitis and/or biceps tenosynovitis at 6 months, and laboratory relapse at 12 months.(57) The authors accordingly concluded that these findings represented “bystander manifestations”, which should not be relied upon to make management decisions.

Despite taking a somewhat different approach, the results of the MPR-PMR study also fall short of endorsing ultrasound as a test with clear-cut disease monitoring and prognostic potential in PMR. At week 16, 21/30 (70%) participants had achieved clinical remission according to the PMR-AS, yet only one of these individuals exhibited no abnormalities at the shoulder on ultrasound. This correlation did improve by the end of the study (of the 13/25 [52%] participants in clinical remission at week 46, six had normal scan results), however the combination of a PMR-AS <9.35 and resolution of ultrasound abnormalities ultimately failed to protect against later disease relapse. It can therefore be concluded that findings such as subacromial bursitis and biceps tenosynovitis, whilst useful at diagnosis, provide little additional information thereafter about the patient’s inflammatory state than conventional disease activity measures. Of course, the high rate of ultrasound abnormalities detected at the shoulder among asymptomatic controls provides one possible explanation as to why this phenomenon is observed.(58) Furthermore, if bursitis does not represent a primary manifestation of PMR as proposed earlier in this thesis, then it stands to reason that its resolution may not closely parallel improvement in other clinical parameters. Given MRI has already proven more capable of detecting musculotendinous inflammation than ultrasound, future efforts should now concentrate on delineating its role in monitoring PMR disease activity and predicting long-term treatment outcomes.

#### 8.4.4 Therapeutic Paradigm

Unlike most other inflammatory rheumatic diseases in the 21<sup>st</sup> century, prednisolone monotherapy remains the treatment of choice for PMR. This is despite evidence of a prolonged “symptom tail” in this condition, whereby up to one-quarter of patients receive more than four years of glucocorticoid therapy.(8) Not surprisingly, such high cumulative doses of prednisolone have been previously equated with increased rates of glucocorticoid-induced

complications compared to other rheumatic diseases like RA.(59) The absence of evidence for the use of a steroid-sparing agent from diagnosis is without doubt a major contributor to this scenario. But whilst results from such studies may be accurate, it is similarly possible given the lack of validated instruments to measure outcomes in clinical trials of PMR that effective therapeutic options have been mistakenly discounted.

To the author's knowledge, this thesis provides first documentation of the efficacy of the BSR guideline for the management of PMR. Twenty-five patients (78.1%) met the primary outcome measure of disease relapse as defined by the PMR-AS, a composite measure with established validity for flare diagnosis.(6) Such an incidence rate does exceed that reported in other studies, however these comparisons are limited by heterogeneity in the schedule of low-dose glucocorticoid therapy prescribed and the definition of relapse employed.(60) One previous study did evaluate clinical outcomes in the first year following PMR diagnosis.(61) 129 steroid-naïve patients were prospectively recruited from eight hospital-based rheumatology clinics in the UK, with treatment comprising a weaning course of prednisolone not dissimilar to the BSR guideline. Forty-six relapses were documented in 40 patients (31%) over the ensuing 12 months, although this endpoint was arbitrarily defined by the return of PMR symptoms requiring an increase in steroid dose. A more recent 5-year prospective study of 169 PMR patients using the same relapse definition similarly found 49.1% of participants experienced at least one event, 81/83 (97.6%) of these occurring within the first two years of steroid therapy.(52) Given a more stringent approach to measuring disease activity was utilised in the MPR-PMR study, a comparatively higher relapse rate in newly diagnosed PMR patients than that documented by earlier studies would appear to an expected finding.

On this basis, it seems abundantly clear that a weaning schedule of low-dose glucocorticoid therapy like that outlined in the BSR guideline falls short of achieving sustained clinical remission in a significant proportion of cases. Rather, the disease course of PMR is typically characterised by an impressive initial response to higher doses of prednisolone with a median time to remission of just 6.1 weeks. Unfortunately, a progressive trend toward increasing disease activity tends to follow upon glucocorticoid weaning, with relapse being documented most commonly at week 24 in this thesis, by which point in time participants were taking a median prednisolone dose of 7mg. The question therefore arises as to whether glucocorticoid therapy truly modifies the disease course of PMR or just temporarily diminishes its activity at musculotendinous structures to more clinically acceptable levels.

Naturally, the other contention with prednisolone monotherapy in PMR relates to its propensity to cause glucocorticoid-induced complications. The MPR-PMR study proved no exception in

this regard recording an average event rate of 3.2 side effects per participant. Only two patients denied experiencing any steroid-related adverse effects during the 46-week follow-up period. This high incidence again exceeds those figures published by other authors in larger, population-based studies. In two retrospective analyses of adverse outcomes among PMR patients treated with glucocorticoids, 43 and 65% encountered at least one adverse event after a mean duration of 2.6 and 1.6 years of treatment respectively.(62, 63) Complications in both of these studies were however determined by medical record review, meaning the types of events documented proved more serious (eg. Osteoporosis, diabetes mellitus, hypertension) than the patient-reported side effects common to this thesis (eg. Weight gain, cosmetic changes, insomnia). By contrast, only one fracture was sustained among the MPR-PMR cohort, although such a low incidence would seem expected given the shorter duration of follow-up employed.

In a recent study comparing steroid-related side effects in 359 PMR patients age- and sex-matched to general population comparators, no difference was observed in adverse event rates for diabetes mellitus, hypertension, hyperlipidaemia or osteoporotic fracture.(64) More specifically, only the cumulative incidence of cataracts was higher in the PMR group at 5 years (41% cf. 27.3%, HR 1.72). Whilst such results could be interpreted as evidence for the safety of long-term low-dose glucocorticoid therapy, a EULAR taskforce found uncertainty in the literature surrounding the risks associated with prolonged exposure to >5mg but <10mg/day of prednisolone.(65) Instead, it went on to identify a range of patient-specific factors recognised to increase harm, age >60 years and female sex being chief among them. Given the PMR patient demographic, it would accordingly seem questionable to persist with a therapeutic paradigm in this condition that prioritises prednisolone use. Identifying an alternate treatment approach that is both efficacious and without substantial morbidity remains a key research priority, a fact also reflected in the results of two surveys from the UK evaluating the main concerns of patients living with PMR.(66, 67)

In truth, there are many therapeutic options that should be further explored in PMR. Aside from re-visiting the role of synthetic DMARDs like methotrexate and leflunomide in well-designed randomised controlled clinical trials, there is the need to expand upon impressive results from an open-label prospective longitudinal study of tocilizumab.(35) Additional considerations include small molecules like the JAKinibs which are capable of blocking discrete pathways downstream from IL-6, or even monoclonal antibodies targeting granulocyte-macrophage colony-stimulating-factor (GM-CSF) based upon the potential pathogenic role of neutrophils in PMR discussed in chapter 5.(68, 69) It is however imperative that future studies evaluating the efficacy of novel therapeutic agents are carried out in a manner that optimises their chances of

achieving a positive result. Central to this issue lies the need for consistency in patient assessment across all PMR clinical trials and the utilisation of validated outcome measures.

In the last chapter of this thesis, work involving the preliminary validation of instruments used to measure outcomes in clinical trials of patients with PMR was presented. Three workstreams comprising a systematic literature review, respondent survey and raw data analysis resulted in the identification of candidate instruments mapping to the pre-specified core domains of pain, stiffness, physical function and systemic inflammation.(2) Pain VAS/NRS, stiffness VAS/NRS and duration, ESR and CRP, and HAQ-DI/mHAQ were subsequently endorsed for domain match and feasibility by participants including clinicians, researchers and patient partners at the OMERACT 2018 PMR Special Interest Group. In line with an established methodology, next steps now include appraisal of the evidence supporting the use of these instruments in PMR and evaluation of their measurement properties relative to the OMERACT Good Methods Checklist.(3) Long-term, the finalisation of a core outcome measurement set for use in all PMR clinical research is expected to significantly improve the quality and reliability of studies undertaken, thereby addressing a major barrier to therapeutic advances in this condition.

## 8.5 Limitations

There are several limitations to the work which has been presented throughout this thesis. First and foremost, the MPR-PMR study was a small, investigator-initiated pilot carried out at a single tertiary referral centre. Its results may therefore not be generalisable to a larger, more heterogeneous population of PMR patients being evaluated in primary care. Presumably due to small numbers, a larger proportion of men were included in the study than would usually be anticipated. The original recruitment goal of 60 participants also required revision down to 35 based upon the feasibility of enrolling only newly diagnosed, steroid naïve PMR patients within the specified timeframe for this research. It is conceivable that this approach may have additionally introduced selection bias.

Due to scanner availability, ultrasound assessments were not blinded. This meant that the investigator was privy to clinical information and hence these results are subject to observer bias. That being said, no significant correlation was identified between ultrasound findings and disease activity in the MPR-PMR study, suggesting the impact of this methodological flaw was negligible.

Similar issues pertaining to scoring apply to the nested case-control study evaluating the diagnostic potential of whole body PET/CT in PMR presented in chapter 4. Whilst the two

nuclear medicine physicians involved were not responsible for clinical assessments or medical record review, the designation of patients as cases or controls was nonetheless readily apparent to them. In an ideal world, images would be de-identified and mixed together to improve objectivity, and age- and sex-matched controls prospectively recruited rather than derived from historic data.

Finally, it is unclear what impact the initiation of low-dose steroid therapy would have upon the utility of whole body PET/CT as a diagnostic tool or NLR as a predictor of glucocorticoid resistant disease. Certainly, in GCA, it is well established that just three days of treatment attenuates large vessel  $^{18}\text{F}$ -FDG uptake, however significantly higher prednisolone doses are routinely used in this condition than PMR.(70) Limited impact upon diagnostic accuracy was though identified in this study if the scan was undertaken within 72 hours. Regardless, there remains the need for caution when extrapolating results from the MPR-PMR study to patients who have already commenced glucocorticoid therapy, as is commonly the case in everyday clinical practice.

## 8.6 Future Directions

Throughout this thesis, numerous areas of future research have been identified. A summary of these are provided below:

- Characterisation of precise anatomic correlates of abnormal  $^{18}\text{F}$ -FDG uptake within the shoulder girdle using the PET/MRI fusion technique described in chapter 3.
- Histopathological examination of sites corresponding to extra-capsular pathology detected on imaging, with a view to confirming musculotendinous inflammation as the defining pathology of PMR.
- Evaluation of whole body PET/CT's ability to distinguish PMR from relevant rheumatic differentials including late-onset RA and spondyloarthritis.
- Testing the diagnostic performance of the novel PET/CT algorithm outlined in chapter 4 in a prospective, longitudinal study of patients presenting with polymyalgia.
- Further validation of NLR and PLR as monitoring and prognostic biomarkers in PMR including exploration of an alternate therapeutic paradigm among individuals with high baseline NLR given its association with glucocorticoid resistance.
- Comparison of lymphocyte subsets in glucocorticoid-responsive versus glucocorticoid-resistant patients to ascertain whether disturbances in B cell homeostasis contribute to phenotypic differences in PMR.

- Following on from identification of BMI as an adverse prognostic factor in PMR, a proof-of-concept study to investigate the relationship between adipokines and, disease activity and treatment outcomes.
- Investigation of the precision exhibited by imaging modalities such as MRI for diagnosing active PMR relative to conventional measures like the PMR-AS and systemic inflammatory markers.
- Development of a core outcome measurement set for use in all PMR clinical research studies, based upon the methodology outlined in the OMERACT Filter 2.1.(3)

## 8.7 Conclusion

In a prospective, single-centre study of newly diagnosed, steroid-naïve PMR patients treated with a standardised schedule of low-dose glucocorticoid therapy, relapse was found to be commonplace. As hypothesised, discrete differences existed between these patient subsets, with age and female sex proving statistically significant predictors for the study's primary outcome. In contrast, abnormal  $^{18}\text{F}$ -FDG uptake at the volar hand correlated with later time to first relapse/no relapse, thereby substantiating earlier work espousing the prognostic benefits of an extra-capsular pattern of inflammation in this condition.

The pathology underlying PMR has long remained a mystery, however its predilection for musculotendinous structures has become increasingly apparent throughout this thesis. The distinctive nature of these abnormalities additionally means there is hope of eliminating the diagnostic uncertainty that has traditionally shrouded this rheumatic disease. Indeed, whole body PET/CT can now be considered a test exhibiting high sensitivity and specificity for PMR, with abnormalities detected at just three musculoskeletal sites providing sufficient evidence for this diagnosis.

Early detection of glucocorticoid-resistance is another vexing management issue in PMR, along with accurate disease activity assessment in the absence of a reliable and reproducible biomarker. Baseline NLR was hence identified as a predictor of glucocorticoid-resistant disease in this work, whilst PLR was found to correlate with both baseline and mean PMR-AS values during follow-up. Such findings delineate a discrete patient population that may benefit from early DMARD initiation and provide a simple and cheap means for prognostication and monitoring, the likes of which has not been previously identified in this condition.

Ultimately, there is still much work to be done before our understanding of PMR will parallel that of comparable rheumatic diseases like RA. The development of a core outcome

measurement set for use in all PMR clinical research represents a key step towards homogenising study endpoints and advancing a therapeutic paradigm, which can best be described as antiquated. This thesis has contributed to the existing literature across a breadth of topics including pathology, diagnosis, monitoring and management, and identified several gaps in the knowledge base for future investigation. In the long-term, it is sincerely hoped that the advances made here will potentiate further improvement in the standard of care delivered to patients living with PMR.

## 8.8 References

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## INTERNAL MEDICINE JOURNAL



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## REVIEW

## Recent advances in polymyalgia rheumatica

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## Key words

polymyalgia rheumatica, whole body positron emission tomography/computed tomography, ultrasound, prednisolone.

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## Abstract

Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder of unknown cause characterised by the subacute onset of shoulder and pelvic girdle pain, and early morning stiffness in men and women over the age of 50 years. Due to the lack of a gold standard investigation, diagnosis is based on a clinical construct and laboratory evidence of inflammation. Heterogeneity in the clinical presentation and disease course of PMR has long been recognised. Aside from the evolution of alternative diagnoses, such as late-onset rheumatoid arthritis, concomitant giant cell arteritis is also recognised in 16–21% of cases. In 2012, revised classification criteria were released by the European League Against Rheumatism and American College of Rheumatology in order to identify a more homogeneous population upon which future studies could be based. In this article, we aim to provide an updated perspective on the pathogenesis and diagnosis of PMR, with particular focus on imaging modalities, such as ultrasound and whole body positron emission tomography/computed tomography, which have advanced our current understanding of this disease. Future treatment directions, based on recognition of the key cytokines involved in PMR, will also be explored.

## Introduction

Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder of unknown cause that ranks second only to rheumatoid arthritis (RA) in terms of its lifetime incidence risk (estimated at 2.43% for women and 1.66% for men).<sup>1</sup> It typically affects men and women over the age of 50 years and is characterised by the subacute onset of shoulder and pelvic girdle pain, and early morning stiffness.

Due to the lack of a gold standard investigation, diagnosis is based on a clinical construct and laboratory evidence of systemic inflammation. Controversy exists though as to whether PMR represents a disease in its own right or is an umbrella term that encapsulates a clinical presentation common to a range of related conditions. For example, an initial 'polymyalgic' presentation may evolve to an alternative diagnosis, such as late-onset RA or spondyloarthritis. Similarly, concomitant giant cell arteritis (GCA) is recognised in 16–21% of PMR cases.<sup>2</sup>

In 2012, collaboration between the European League Against Rheumatism and American College of Rheumatology (EULAR/ACR) resulted in standardised classification criteria being released in order to improve the

homogeneity of this population for future study.<sup>3</sup> In this article, we aim to provide an updated perspective on the pathogenesis and diagnosis of PMR, with particular focus on imaging modalities, such as ultrasound and whole body positron emission tomography/computed tomography (PET/CT), which have advanced our current understanding of this disease. Future treatment directions, based on recognition of the key cytokines involved in PMR, will also be explored.

## Pathogenesis

The pathogenesis of PMR remains poorly understood, but several genetic polymorphisms have been linked to the condition. In individuals of Northern European descent who exhibit the highest disease incidence, there is a clear association with HLA-DRB1\*04.<sup>4,5</sup> The same HLA gene is seen in increased frequency in both GCA and RA.<sup>6</sup> Ethnic variation is appreciated though, as HLA-DRB1\*04 is infrequently identified in Southern European patients. Instead, genes involved in the inflammatory cascade, such as a microsatellite polymorphism of tumour necrosis factor (TNF) b3, is strongly linked with PMR in Spain, and this association exists independent of HLA-DRB1\*04.<sup>7</sup> Similarly, intercellular adhesion molecule 1 polymorphism has been proposed as a susceptibility factor in an Italian study.<sup>8</sup>

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More recent efforts have focussed on the role of the innate inflammatory pathway. Increased expression of Toll-like receptor (TLR) 7 and TLR 9 has been demonstrated in the peripheral mononuclear blood cells of both PMR and GCA patients when compared with healthy controls.<sup>9</sup> Subsequent work assessing TLR9 polymorphisms has failed however to demonstrate a significant difference in allele frequencies in either condition.<sup>10</sup>

Despite various infectious agents being implicated as possible triggers of PMR, no microorganism has been consistently linked to its pathogenesis.<sup>4</sup> Other studies have reported seasonal variations or cycles of incidence, but the precise environmental cause for these findings remains unclear.<sup>11</sup>

In GCA, immunohistological evidence exists of dendritic cell activation at the adventitia-media border of large vessels followed by CD4+ T-cell and macrophage interaction to produce a T helper (Th) 1 predominant cytokine milieu.<sup>12</sup> In a recent review, increased expression of Th17 T-cells in untreated GCA patients has been similarly reported, with suppression observed following glucocorticoid therapy.<sup>13,14</sup> PMR has been previously suggested to represent a 'forme fruste' of GCA whereby systemic inflammation predominates and vasculitis is either absent or remains subclinical.<sup>13</sup> Indeed, the profile of T-cell and macrophage-derived cytokines in temporal artery biopsy specimens from patients with PMR resemble those of GCA, with the exception of interferon- $\gamma$  production.<sup>15</sup> It therefore appears that interferon- $\gamma$  expression may be the key determinant in the clinical phenotype of GCA versus PMR.

The precise location of the inflammatory process in PMR is still debated based on available histological studies. A mild synovitis with CD4+ T-cell and macrophage infiltration characterises the pathology within the glenohumeral joint; however, there is evidence that peri-articular structures, including the muscle, are similarly affected.<sup>16</sup> In one recent study, the concentrations of IL-1 $\beta$  and IL-6, but not TNF $\alpha$  in the symptomatic trapezius and vastus lateralis muscles, were significantly higher among patients with PMR than controls.<sup>17</sup>

In the peripheral blood, PMR is characterised by hyperproduction of IL-6; however, serum levels of IL-1 $\beta$  and TNF $\alpha$  are not raised compared with controls.<sup>18</sup> The source of IL-6 is therefore unclear, with a similar percentage of circulating monocytes seen and no significant difference was observed in cytokine production following *ex vivo* stimulation. Similarly, CD3+ T lymphocytes from patients with PMR express similar amounts of intracellular cytokines to controls.

## Clinical presentations and related conditions

Sudden-onset bilateral shoulder girdle pain is the presenting complaint in 70–95% of PMR patients and is typically accompanied by prolonged early morning stiffness (>45-min duration).<sup>19</sup> Involvement of the hip region is less common (50–70%). Despite this textbook description, non-classical features occur in a substantial proportion of PMR cases. In particular, distal manifestations are seen in up to one-half of patients, including peripheral arthritis and RS3PE (remitting seronegative symmetrical synovitis with pitting oedema) syndrome.<sup>3</sup> Distinguishing this group from late-onset RA at presentation is especially difficult, although the combination of wrist and metacarpophalangeal or proximal interphalangeal synovitis is significantly more common in RA than PMR.<sup>20</sup> The peripheral arthritis of PMR is also typically a short-lived phenomenon that exhibits a rapid response to treatment with prednisolone and seldom recurs.

With concomitant GCA recognised in 16–21% of PMR cases, another challenge is differentiating between a 'polymyalgic' presentation of large vessel vasculitis and isolated PMR.<sup>2</sup> GCA can develop before, during or after PMR. Typical features, such as headache, scalp tenderness, jaw claudication and visual change, may not always be present; hence, an underlying vasculitic process should be suspected in patients with persistent constitutional symptoms, including fever and inflammatory markers that fail to respond to treatment.

Despite best efforts, a shift in diagnosis is observed in 5–23% of PMR patients after a long-term follow-up.<sup>21,22</sup> A range of mimics, including infection, malignancy and other inflammatory conditions, such as spondyloarthritis or ANCA vasculitis, have been reported.<sup>20</sup> The consensus-based 2012 EULAR/ACR Classification Criteria were developed to standardise the definition of PMR and thereby address the uncertainty that commonly surrounds its diagnosis.<sup>3</sup> Age at onset  $\geq 50$  years, bilateral shoulder aching, and abnormal erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) represent the required criteria with an additional scoring algorithm as outlined in Table 1. A score of  $\geq 4$  points on the clinical algorithm is indicative of PMR.

Macchioni and colleagues have since compared the performance of these with six other classification/diagnostic criteria, concluding that the 2012 EULAR/ACR criteria were the most sensitive (92.6%) and exhibited comparable specificity (81.5%).<sup>23</sup> When utilised to distinguish PMR from late-onset RA, the 2012 EULAR/ACR classification criteria similarly performed well (sensitivity 86%, specificity 91%). Although higher specificities were observed with both the Jones and the Nobunaga criteria

**Table 1** The 2012 EULAR/ACR classification criteria scoring algorithm for PMR without and including ultrasound<sup>3</sup>

| Features                                                                                                                                                     | Clinical criteria<br>(without<br>ultrasound) | Criteria<br>including<br>ultrasound |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------|
| Morning stiffness >45 min                                                                                                                                    | 2 points                                     | 2 points                            |
| Hip pain or limited range of movement                                                                                                                        | 1 point                                      | 1 point                             |
| Normal Rh factor or ACPA                                                                                                                                     | 2 points                                     | 2 points                            |
| Absence of other joint pain                                                                                                                                  | 1 point                                      | 1 point                             |
| Ultrasound:                                                                                                                                                  |                                              |                                     |
| At least 1 shoulder with subdeltoid bursitis +/- biceps tenosynovitis +/- glenohumeral synovitis AND at least 1 hip with synovitis +/- trochanteric bursitis | N/A                                          | 1 point                             |
| Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis                                                                      | N/A                                          | 1 point                             |

Required criteria are age  $\geq 50$  years, bilateral shoulder aching and abnormal C-reactive protein and/or erythrocyte sedimentation rate. A score of  $\geq 4$  or more without an ultrasound examination and a score of  $\geq 5$  or more with an ultrasound examination is indicative of PMR. ACPA, anti-citrullinated peptide antibody; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; N/A, not applicable; PMR, polymyalgia rheumatica.

(96.7% and 97.8%, respectively), mostly due to their emphasis on the absence of peripheral arthritis, this occurred at the expense of their sensitivity values (63.1% and 58.2%).

## Laboratory tests

The inflammatory markers, CRP and ESR, are typically elevated by 2–10 times the upper limit of normal in patients with PMR; however, 7–20% of cases have been reported to have normal results.<sup>24</sup> Levels should respond and eventually normalise following treatment with prednisolone; hence, persistently abnormal ESR and CRP values are concerning and may represent an alternative diagnosis.

Additional investigations should aim to exclude those conditions that may mimic PMR, including other inflammatory conditions (e.g. myositis), metabolic disorders (e.g. hypothyroidism), infection and malignancy. Simple measures, such as full blood count, calcium, creatinine kinase and thyroid function tests, are advisable. Detection of rheumatoid factor and/or anti-citrullinated peptide antibodies is consistent with late-onset RA, although the absence of these antibodies does not necessarily rule out this differential diagnosis given that up to 35% of subjects are seronegative.<sup>25</sup>

## Imaging

Significant progress in the understanding of disease pathogenesis in PMR has come courtesy of the imaging modalities. Ultrasound has been advocated to form part of an optional scoring algorithm in the 2012 EULAR/ACR classification criteria (Table 1).<sup>3</sup> Bilateral subacromial-subdeltoid bursitis is considered the hallmark lesion of PMR.<sup>26</sup> Findings of bilateral shoulder abnormalities or abnormalities in one shoulder and hip significantly

improve the specificity of the criteria from 81.5% to 91.3%.<sup>23</sup>

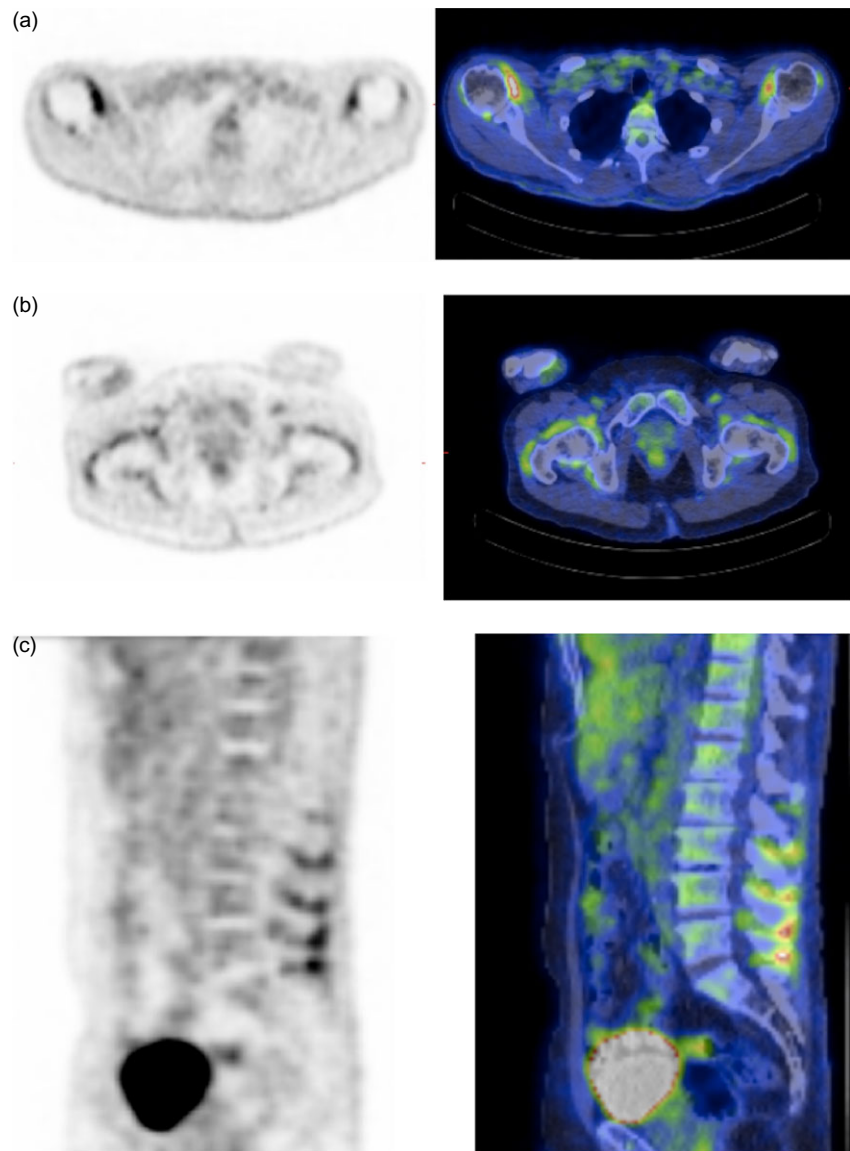
The site of inflammatory change may help differentiate PMR from late-onset RA. One study found that peri-articular inflammation (subacromial-subdeltoid bursitis and biceps tenosynovitis) was significantly more common in PMR patients, whilst intra-articular inflammation (glenohumeral synovitis) was more frequent in RA.<sup>27</sup> Furthermore, Falsetti and colleagues showed a lower intensity of power Doppler signal in the shoulders and wrists of patients with PMR than late-onset RA, and magnetic resonance imaging in PMR patients with distal involvement suggests that tenosynovitis rather than synovitis is the predominant radiological finding.<sup>28,29</sup>

Taken together, these results support the hypothesis that peri-articular, not intra-articular, inflammation is the prevailing pathology in PMR.<sup>29</sup> Oedema of the tendon sheath rather than synovial cellular proliferation also seems characteristic, thereby explaining the rapid resolution of joint symptoms that typically accompanies glucocorticoid treatment.<sup>28</sup>

The use of PET/CT scanning is similarly fast evolving in PMR due to its unique ability to document the distribution of inflammation (bursitis, synovitis, vasculitis) throughout the whole body. Fluorodeoxyglucose (FDG) uptake is characteristically increased at the shoulders, hips and interspinous processes (Fig. 1), the latter shedding light on the aetiology of pain in the cervical and lumbar spine among the affected patients. In up to one-third of cases, involvement of the large vessel vasculature is also seen.<sup>30</sup> This serves as another reminder of the relationship that exists between GCA and PMR. However, the significance of low-grade large vessel FDG uptake in patients with clinically isolated PMR and implications for therapy remain as yet unclear.<sup>31</sup>

Another inherent advantage of whole body PET/CT is its ability to detect recognised mimics, such as infection and

**Figure 1** PET/CT demonstrating characteristic increased FDG uptake in the (a) shoulders; (b) hips; and (c) interspinous processes of a polymyalgia rheumatica patient. FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.



malignancy. Consequently, this modality was recently proposed as a ‘one stop shop’ for diagnosing PMR.<sup>32</sup> Similarities of and differences in PET/CT among patients with PMR, RA and spondyloarthritis have also been studied.<sup>29</sup> Detection of inflammation in the ischial tuberosities, greater trochanters and interspinous processes was found to discriminate between PMR and RA, but not between PMR and spondyloarthritis. Higher FDG intensity was however detected in PMR patients compared with both RA and spondyloarthritis. Disadvantages to the use of whole body PET/CT for the diagnosis of PMR include radiation exposure, accessibility and cost. At present, Medicare reimbursement is not available in Australia for this indication or the investigation of suspected large

vessel vasculitis. The role of imaging in assessing treatment response in PMR is presently poorly delineated. In a longitudinal study examining the role of shoulder ultrasound in assessing remission, 60% of patients exhibited persistent inflammatory change.<sup>33</sup> The significance of these subclinical findings is unknown.

## Treatment

To this day, glucocorticoids constitute the mainstay of treatment for PMR. The ideal approach for prednisolone therapy remains controversial, as studies examining different starting doses and weaning schedules are lacking. Recently, the British Society for Rheumatology (BSR)

recommended a consensus-based regimen for low-dose glucocorticoid treatment, starting with prednisolone at 15 mg daily for 3 weeks.<sup>34</sup> The dose is then tapered to 12.5 mg daily for an additional 3 weeks, 10 mg for 4–6 weeks and finally reduced by 1 mg every 4–8 weeks thereafter. In the event of disease relapse (arbitrarily defined by the recurrence of symptoms and elevated inflammatory markers), the dose of prednisolone should be increased to the previous level for several weeks before the weaning schedule is reinstated.

The disease course of patients with PMR typically exhibits heterogeneity. Some individuals respond rapidly and require therapy for less than 1 year, whereas others experience initial response failure or subsequent disease relapse.<sup>35</sup> A steroid-sparing agent or disease modifying anti-rheumatic drug (DMARD) is often initiated in the latter group; however, there is little high-level evidence to support the efficacy of this approach. Furthermore, the baseline characteristics of those PMR patients with refractory disease that may benefit from these medications are incompletely known.

To date, there have been three randomised controlled trials assessing the efficacy of methotrexate for initial treatment of PMR.<sup>36</sup> Overall, the results have been mixed with a steroid-sparing effect and reduction in risk of disease relapse observed in only two of the studies.<sup>37–39</sup> Low doses of methotrexate were utilised ( $\leq 10$  mg weekly) and patients with GCA were included in the trial population, which may have influenced the results. In the BSR guidelines, commencement of methotrexate is suggested in the event that a patient has relapsed with prednisolone on more than two occasions.<sup>34</sup>

Other DMARDs have been tried in PMR, including leflunomide, which is a small molecule inhibiting pyrimidine synthesis with immunomodulatory and anti-inflammatory effects, and proven efficacy in RA. Interest in the use of leflunomide in PMR however arises from its lesser-known effect on inhibition of aberrant dendritic cell activation and downstream modulation of cytokine production, including IL-6.<sup>40</sup> Two recent case series have supported its efficacy as a steroid-sparing agent in patients with difficult to treat disease.<sup>41,42</sup> A randomised controlled trial examining the role of leflunomide in achieving sustained clinical remission in PMR is now underway.<sup>43</sup>

Due to the unprecedented success of TNF-blockade in RA, TNF inhibitors have also been trialled in refractory PMR. In a recent review of 99 cases with persistent disease activity or glucocorticoid-induced complications, a modest steroid-sparing effect was reported.<sup>44</sup> Based on biological plausibility and its success in GCA, there is growing interest in the use of tocilizumab, a humanised monoclonal immunoglobulin G antibody that binds

directly to the IL-6 receptor. At present, experience in PMR is limited to a handful of case reports; however, there has been reported benefit when used either as monotherapy or in combination with glucocorticoids.<sup>45</sup> A recombinant antibody that neutralises IL-1 $\beta$  called gevokizumab has also been considered in a randomised controlled trial for GCA.<sup>46</sup> Its therapeutic indication may extend to PMR in the future.

## Prognosis

In PMR, mortality does not appear to be increased. Strangely, a large prospective study found improved survival in cases when compared with age- and sex-matched controls.<sup>47</sup> This finding is thought to reflect superior medical surveillance following diagnosis.<sup>48</sup> Among the subset of patients with large vessel involvement however, an increased mortality is observed from aortic aneurysm/dissection (hazard ratio 3.4, 95% confidence interval 2.2–5.4).<sup>49</sup> The detection of subclinical large vessel vasculitis in patients with PMR therefore has significant prognostic implications.

Glucocorticoid-induced complications are a significant cause of morbidity in PMR. It has been reported that most patients experience an adverse event within 2 years of commencing prednisolone therapy.<sup>50</sup> Older age at diagnosis, female sex and higher cumulative glucocorticoid dose represent independent risk factors, with the incidence of diabetes mellitus, vertebral and hip fractures two to five times greater in PMR patients compared with healthy controls. Accordingly, monitoring and treating glucocorticoid-induced complications must be a management priority while new strategies to limit the dose and duration of exposure are developed.

## Conclusion and future directions

From a clinical syndrome characterised by subacute onset bilateral shoulder and pelvic girdle pain together with raised inflammatory markers, our concept of PMR has evolved. Aided by imaging technology, the prevailing pathology is increasingly appreciated to be peri-articular, rather than intra-articular, in origin. A paradigm shift in therapeutics is also anticipated following recognition of key differences in inflammatory cytokine profiles in PMR, late-onset RA and GCA.

In the future, work must focus on further defining PMR as a distinct disease entity. The use of whole body PET/CT may assist in determining the significance of low-grade large vessel FDG uptake and intra- versus peri-articular involvement in patients with clinically isolated PMR. Ultrasound should continue to be evaluated as a tool to assess disease activity and the prognostic implications of

subclinical inflammatory findings explored. Finally, the subset of patients with PMR that relapse with standard prednisolone therapy requires characterisation in order to facilitate further study of DMARDs and prevention of glucocorticoid-induced complications.

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# PROTOCOL

## Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoids

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Protocol Number (if applicable): 1

Version: #3

Date: 29/07/2014

**Author/s:**

Dr Claire Owen, A/Prof. Russell Buchanan

**Sponsor/s:**

N/A

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This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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## 1. GLOSSARY OF ABBREVIATIONS & TERMS

| Abbreviation | Description (using lay language)          |
|--------------|-------------------------------------------|
| ACPA         | Anti-Citrullinated Peptide Autoantibodies |
| BMI          | Body Mass Index                           |
| BSR          | British Society of Rheumatology           |
| CRP          | C Reactive Protein                        |
| CT           | Computed Tomography                       |
| DMARD        | Disease Modifying Anti-Rheumatic Drug     |
| ESR          | Erythrocyte Sedimentation Rate            |
| FDG          | Fludeoxyglucose                           |
| GCA          | Giant Cell Arteritis                      |
| MRI          | Magnetic Resonance Imaging                |
| PGS          | Physician Global Score                    |
| PET          | Positron Emission Tomography              |
| PMR          | Polymyalgia Rheumatica                    |
| PMR-AS       | Polymyalgia Rheumatica- Activity Score    |
| RA           | Rheumatoid Arthritis                      |
| TVS          | Total Vascular Score                      |
| VAS          | Visual Analogue Scale                     |

## 2. STUDY SITES

### 2.1 STUDY LOCATION/S

| Site                    | Address                                     | Contact Person | Phone      | Email                  |
|-------------------------|---------------------------------------------|----------------|------------|------------------------|
| Austin Hospital         | 145 Studley Road,<br>Heidelberg<br>VIC 3084 | Dr Claire Owen | 0439615058 | claireowen85@gmail.com |
| Heidelberg Repatriation | 300 Waterdale Road,                         | Dr Claire Owen | 0439615058 | claireowen85@gmail.com |

**Study Name:** Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoids

**Protocol Number:** 1

**Version & date:** 3; 29/07/2014

|          |                                |  |  |  |
|----------|--------------------------------|--|--|--|
| Hospital | Heidelberg<br>West<br>VIC 3081 |  |  |  |
|----------|--------------------------------|--|--|--|

### 3. INTRODUCTION/BACKGROUND INFORMATION

#### 3.1 LAY SUMMARY

Despite the fact that Polymyalgia Rheumatica (PMR) is the most common inflammatory rheumatic disease of the elderly, it is poorly understood. With no diagnostic tests available, diagnosis is dependent upon a history of muscle pain and stiffness in the hip and shoulder regions, combined with raised inflammation levels in the blood. Treatment consists of Prednisolone (commonly referred to as “cortisone”) prescribed in a “one size fits all” approach. However, the way in which PMR patients’ symptoms respond is very variable; some improve almost overnight, whilst other individuals require higher doses for much longer periods of time. Unfortunately, such long-term Prednisolone use can result in many complications including osteoporosis, weight gain, high blood pressure and diabetes. Similarly, uncontrolled PMR is associated with increased risk of heart attacks and stroke.

This project therefore aims to identify the characteristics of PMR patients that fail to respond adequately to standard Prednisolone treatment. Patients with suspected PMR attending the Austin Hospital or referred by primary care providers and Rheumatologists in the Hospital’s catchment area (north-eastern suburbs of Melbourne, Victoria), will be invited to partake. After appropriate consent, demographic data, a questionnaire on symptoms and general physical examination will be carried out. Participants will also have baseline blood tests, hand x-rays, an ultrasound performed of their hands, shoulders and hips, and (in selected cases) targeted Magnetic Resonance Imaging (MRI) of their pelvis and a whole body Positron Emission Tomography (PET)/Computed Tomography (CT) scan (a test capable of detecting active inflammation in the body) within the first 7 days (first visit time commitment 3-4 hours). Treatment with Prednisolone will then be commenced, with the dose reduced every 3-4 weeks. Participants will return to the clinic at week 4, week 16, week 32 and week 46 for follow-up visits. A questionnaire on symptoms, general physical examination, blood test and ultrasound (week 4, week 16 and week 46 only) will be repeated on each occasion (follow-up visit time commitment 2 hours). Additional clinic visits can also be arranged if the need arises between scheduled reviews. In the event that a participant’s PMR relapses with standard treatment, the Prednisolone dose will be increased or additional medication added as in usual clinical practice.

At the conclusion of the study, those participants that responded to the standard Prednisolone treatment will be compared with those whose disease relapsed and required higher doses or additional medication. It is hypothesised that this information will delineate a distinct subset of patients refractory to the “one size fits all” approach, thereby permitting further study of alternate therapy in this group and minimising the side effects of long-term Prednisolone use.

#### 3.2 INTRODUCTION

PMR is a common chronic inflammatory disorder affecting men and women over the age of 50 years characterized by subacute onset shoulder and hip girdle pain, and early morning stiffness. Diagnosis is based upon a clinical construct and laboratory evidence of systemic inflammation, whilst treatment entails a weaning course of low-dose glucocorticoid therapy with Prednisolone.

Great heterogeneity in the disease course of PMR and its response to standard treatment is well-recognized. In particular, evolution to an alternate diagnosis such as late-onset

Rheumatoid Arthritis (RA) or the development of concomitant Giant Cell Arteritis (GCA) may occur. Furthermore, a subset of patients experience an incomplete response or relapse with treatment, resulting in an inability to dose-reduce Prednisolone and the need for Disease Modifying Anti-Rheumatic Drugs (DMARDs) like Methotrexate. No study has previously characterized this group of “refractory” patients within the PMR population.

Musculoskeletal ultrasound and whole body PET/CT scanning are evolving investigative tools in PMR. Findings of bilateral shoulder abnormalities (subacromial bursitis, bicipital tenosynovitis, glenohumeral effusion) or abnormalities in one shoulder and hip (hip effusion, trochanteric bursitis) significantly improve the specificity of the 2012 EULAR/ACR Classification Criteria.<sup>1</sup> Similarly, abnormal Fludeoxyglucose (FDG) uptake in PMR is seen at the shoulders, interspinous processes and vasculature on PET scanning in 93.4%, 51.4% and 31.4% respectively.<sup>3</sup> The ability of these imaging modalities to prognosticate and measure treatment response has been incompletely explored by research groups.

This study therefore intends to prospectively follow patients with a new diagnosis of PMR as they are treated with standardized low-dose glucocorticoid therapy. The demographic, clinical, laboratory and radiographic characteristics (on musculoskeletal ultrasound, MRI and whole body PET/CT scan) of patients whose disease relapses (as defined by the PMR-Activity Score [PMR-AS]) will be compared with those in sustained disease remission. Identification of this “refractory” subset of patients will permit future treatment to be tailored to individual risk of disease relapse and prevent complications arising from unnecessarily prolonged glucocorticoid therapy.

### 3.3 BACKGROUND INFORMATION

PMR is a chronic, inflammatory disorder of unknown cause that ranks second only to RA in terms of its lifetime incidence risk (estimated at 2.43% for women and 1.66% for men).<sup>2</sup> Characterized by the presence of persistent shoulder and hip girdle pain, and early morning stiffness, there are no specific diagnostic tests. Instead, diagnosis is based upon a clinical construct and laboratory evidence of systemic inflammation.

Heterogeneity in the clinical features and disease course of PMR has been long recognized. Aside from the evolution of alternate diagnoses such as late-onset RA and spondyloarthritis that may follow an initial polymyalgic presentation, concomitant GCA is also recognized in 16-21% of cases.<sup>2</sup> Furthermore, approximately half of patients diagnosed with PMR may exhibit distal manifestations including peripheral synovitis, tenosynovitis, pitting oedema and carpal tunnel syndrome.<sup>1</sup>

In 2012, the EULAR/ACR Classification Criteria for PMR were released in order to classify this clinical syndrome as a distinct disease entity and thereby differentiate it from other rheumatic diseases. Age at onset  $\geq 50$  years, bilateral shoulder aching and abnormal C Reactive Protein (CRP) and/or Erythrocyte Sedimentation Rate (ESR) represent required criteria with an additional scoring algorithm developed for early morning stiffness (2 points), hip pain or limited range of movement (1 point), negative rheumatoid factor or Anti-

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<sup>1</sup> Dasgupta, B. (2012). ‘2012 Provisional classification criteria for polymyalgia rheumatica’, *Arthritis and Rheumatism*, 64(4): 943-54.

<sup>2</sup> Kermani, T.A. (2013). ‘Polymyalgia rheumatica’, *Lancet*, 381:63-72.

Citrullinated Peptide Autoantibodies (ACPA) (2 points) and lack of other joint involvement (1 point).<sup>2</sup> In the absence of competing diagnoses, a score of 4 or greater is indicative of PMR (sensitivity 72% and specificity 65%).<sup>1</sup>

The algorithm can also be extended to include musculoskeletal ultrasound results where possible. Findings of bilateral shoulder abnormalities (subacromial bursitis, bicipital tenosynovitis, glenohumeral effusion) or abnormalities in one shoulder and hip (hip effusion, trochanteric bursitis) significantly improve the specificity (70%) of the clinical criteria.<sup>1</sup> Indeed, imaging with ultrasound is one of the most appealing techniques with which to further study PMR. Whilst its inappropriateness as a diagnostic test has been long recognized, the potential to prognosticate and measure treatment response has been incompletely explored.<sup>1</sup>

The role of whole body PET/CT scanning is similarly fast-evolving in PMR with recent studies documenting the characteristic distribution of increased Fluorodeoxyglucose (FDG) uptake at the shoulders (93.4%), interspinous processes (51.4%) and vasculature (31.4%) in this condition.<sup>3</sup> Consequently, this modality offers a tool with which to document the distribution of disease activity (bursitis, synovitis, vasculitis) and potentially prognosticate about risk of relapse with low-dose glucocorticoid therapy (for instance, conventional Rheumatology teaching dictates both vasculitis and synovitis are unlikely to be successfully treated with only Prednisolone 15mg). As yet, no study has documented the longitudinal outcomes of new diagnosis PMR patients in relation to whole body PET/CT scan findings.

Despite certain advances, PMR is still subject to wide variations of clinical practice. Glucocorticoids represent the mainstay of treatment, however randomized controlled trials are lacking. As a result, the efficacy of different initial doses or drug tapering regimes is unknown. The British Society for Rheumatology (BSR) Guidelines for Management of PMR represent a recently developed consensus-based regimen for low-dose glucocorticoid treatment. Prednisolone 15mg daily is initiated for 3 weeks, weaned to 12.5mg for a further 3 weeks, then 10mg for 4-6 weeks, and finally reduced by 1mg every 4-8 weeks thereafter.<sup>3</sup>

However, even patients with a classic presentation of PMR may vary in their response to low-dose glucocorticoids with female sex and Body Mass Index (BMI) previously identified as key determinants.<sup>2</sup> Treatment dilemmas arise from incomplete, poorly-sustained or non-response, inability to dose-reduce and the need for prolonged therapy beyond 2 years. The role of steroid-sparing agents in PMR is also unclear with mixed results from randomized clinical trials assessing the efficacy of Methotrexate for initial treatment.<sup>2</sup> As yet, no study has managed to characterize the subset of “refractory” patients within the PMR population likely to require Disease Modifying Anti-Rheumatic Drugs (DMARDs).

Long-term, a diagnosis of PMR is associated with increased prevalence of cardiovascular comorbidities including coronary artery disease, peripheral arterial disease and cerebrovascular disease. As in other inflammatory conditions eg. RA and Systemic Lupus Erythematosus, disease control is the basis for prevention of this outcome. Conversely, complications of glucocorticoid therapy such as diabetes mellitus, vertebral and hip fractures

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<sup>3</sup> Dasgupta, B. (2009). ‘BSR and BHPR guidelines for management of polymyalgia rheumatica’, *Rheumatology*; 49:186-90.

(associated with a 2.5 fold increased risk<sup>4</sup>) must be minimized. In an age where personalized medicine is an increasing possibility, PMR therapy tailored to individual risk of disease relapse and prevention of treatment complications warrants further investigation.

## **4. STUDY OBJECTIVES**

### **4.1 HYPOTHESIS**

That PMR which relapses with low-dose glucocorticoid therapy represents a distinct, but as yet undefined, disease subset.

### **4.2 STUDY AIMS**

- a. To identify PMR patients that relapse (as defined by the PMR-AS) with standardised, low-dose glucocorticoid therapy;
- b. To characterise the demographic, clinical, laboratory and radiologic features (using musculoskeletal ultrasound and [in selected cases] targeted MRI and whole body PET/CT scan) of this group that is refractory to standardised treatment;
- c. To ascertain the role of musculoskeletal ultrasound in evaluating treatment response and clinical remission in PMR.

### **4.3 OUTCOME MEASURES**

- a. Primary Outcome Measure:  
The primary outcome measure will be relapse as defined by the PMR-AS (>9.35 or change in PMR-AS >6.6).
- b. Secondary Outcome Measures:  
Secondary outcome measures will include:
  - Non-response to a Prednisolone dose of 15mg daily;
  - Prednisolone dose of <5mg daily at week 46;
  - Evolution of abnormalities (including bursitis, tenosynovitis, synovitis and joint effusions) on musculoskeletal ultrasound with treatment and in clinical remission.

## **5. STUDY DESIGN**

### **5.1 STUDY TYPE & DESIGN & SCHEDULE**

In a prospective, single-centre, cohort study, patients with suspected PMR will be consecutively recruited to an early referral clinic located in the Rheumatology Department at Heidelberg Repatriation Hospital. Referral sources will include the Austin Hospital Emergency Department and inpatient units, along with primary care providers and Rheumatologists in the Hospital's catchment area (north-eastern suburbs of Melbourne, Victoria). Recruitment is anticipated for 12 months following ethics approval.

The initial clinic visit (performed by the Principle Investigator) shall comprise screening to ensure the patient meets key inclusion criteria, specifically a new diagnosis of PMR as

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<sup>4</sup> Gabriel, S.E. et al. (1997). 'Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica', *Arthritis Rheum*;40:1873–8.

defined by the 2012 EULAR/ACR Classification Criteria (age at onset  $\geq 50$  years, bilateral shoulder aching and abnormal CRP and/or ESR, combined with a scoring algorithm including early morning stiffness, hip pain or limited range of movement, negative rheumatoid factor or ACPA and lack of other joint involvement). Patients with symptoms suggestive of GCA (headache, jaw claudication, scalp tenderness or visual disturbance) will be excluded, along with cases of cancer within the past 5 years, neuromuscular disease, active infection, other inflammatory conditions (eg. RA), chronic pain syndromes and uncontrolled psychiatric conditions, hypertension or diabetes. Treatment with glucocorticoids for  $>7$  days prior to screening or a dose  $>15\text{mg/day}$ , and concomitant DMARD therapy will also not be permitted. Patients deemed ineligible for the study will be referred to an appropriate Austin Health Rheumatology Clinic for ongoing management.

Information outlining the research project's purpose and participant involvement will then be provided to eligible patients (see Appendix). Time for the individual to discuss the study with their family members and/or general practitioner will be provided, whilst the Principle Investigator will be contactable via phone to answer any questions that arise. Following written consent (see Appendix), a unique study identification number will be assigned to each participant to facilitate de-identification of all data and permit blinded evaluations to occur at a later date.

At the first study visit after enrollment (week 0), baseline demographic data shall be collected including date of birth, gender, race, co morbidities, BMI and smoking status (lifelong non-smoker, current smoker or ex-smoker). Disease onset, distribution of joint involvement, duration of early morning stiffness (mins), presence of constitutional symptoms (loss of weight [kg], fever and fatigue) and, duration and dose of glucocorticoid treatment will also be recorded. A standard physical examination including vital signs and BMI shall be carried out with specific focus upon the presence of active synovitis or effusions of the peripheral joints and range of motion at the shoulders bilaterally (Elevation of Upper Limb score). In order to generate a PMR-AS, participants will also fill in a Visual Analogue Scale (VAS) and the investigator will complete a Physician Global Score (PGS).

Baseline investigations will comprise pathology (FBE, UEC, LFTs, CRP, ESR, rheumatoid factor, ACPA, ANA, ANCA, CK, TSH, Vitamin D, fasting blood glucose, HbA1C) and plain x-ray of bilateral hands (to assess for erosive change, performed in the Radiology Department at Heidelberg Repatriation Hospital). Within 7 days of the screening visit, a musculoskeletal ultrasound, targeted MRI scan and whole body PET/CT scan will also be arranged. In the case of whole body PET/CT scanning, this will only be carried out on participants who are glucocorticoid naïve (ie. Have not received any glucocorticoid in the 7 days prior to screening) due to the FDG uptake being significantly reduced following Prednisolone exposure. Similarly, targeted MRI scanning will only be performed in glucocorticoid-naïve patients in whom there are no contraindications (for example metallic implants and claustrophobia).

Musculoskeletal ultrasound (performed by the Principle Investigator at Heidelberg Repatriation Hospital) shall involve B-mode and Power Doppler scanning of bilateral hands and wrists (to assess for active synovitis, joint effusions, tenosynovitis and erosions), shoulders (to assess for subacromial bursitis, long head of biceps tenosynovitis,

glenohumeral synovitis and joint effusion) and hips (to assess for trochanteric bursitis, hip synovitis and joint effusion).

Targeted MRI of the hamstring origins in the pelvis will take place in the Radiology Department at Austin Hospital using the 1.5T Siemens MRI. Fusion of the PET/CT and MRI images with detailed evaluation of the hamstring origins will be performed by two experienced Musculoskeletal Radiologists, with any differences in results to be resolved by consensus.

Whole body PET/CT scanning will take place in the Nuclear Medicine and Centre for PET at the Austin Hospital using the Phillips PET/CT camera. Qualitative evaluation of joint and vascular FDG uptake (including Total Vascular Score [TVS]) will be performed, along with a semi-quantitative analysis of joint and vascular uptake. Analysis of all PET/CT images will be undertaken by two experienced Nuclear Medicine Physicians (for qualitative evaluation), with any differences in results resolved by consensus.

The standardised schedule of low-dose glucocorticoid therapy for PMR as outlined in the BSR Guidelines will be initiated thereafter:

- Prednisolone 15mg oral daily for 3 weeks;
- Prednisolone 12.5mg oral daily for 3 weeks;
- Prednisolone 10mg oral daily for 4 weeks, then wean by 1mg every 4 weeks until cessation (total course 46 weeks).

In the event a patient is significantly disabled by joint pain and stiffness at baseline however, treatment will be initiated immediately ie. Prior to musculoskeletal ultrasound.

Subsequent clinic visits for data collection at Heidelberg Repatriation Hospital (performed by Sub-Investigators) will be scheduled for week 4, week 8, week 16, week 24, week 32 and week 46 post enrollment and comprise the same standardised format. Distribution of joint involvement, duration of early morning stiffness (mins), presence of constitutional symptoms (loss of weight [kg], fever, fatigue), development of symptoms suggestive of GCA (headache, jaw claudication, scalp tenderness or visual disturbance) and current dose of glucocorticoid treatment will be recorded. Physical examination of the peripheral joints and range of motion at the shoulders bilaterally will be repeated (Elevation of Upper Limb score), along with vital signs, body weight and random blood glucose level. Recalculation of PMR-AS will occur following repeat participant VAS, PGS and measurement of inflammatory markers (CRP and ESR) on pathology.

Musculoskeletal ultrasound of bilateral hands and wrists, shoulders and hips will also be repeated at week 4, week 16 and week 46. The Principal Investigator will remain blinded to participant laboratory results prior to undertaking musculoskeletal ultrasound assessments, thereby ensuring the integrity of these results.

A PMR-AS score of  $>9.35$  or change in PMR-AS  $>6.6$  will constitute the definition of disease relapse. In the event this occurs, the participant's Prednisolone dose will be increased to the previous higher dose for 4 weeks before the weaning schedule is reinstated. If this occurs on more than two occasions, additional immunosuppression will be introduced eg.

Methotrexate. This management approach is again in keeping with the BSR Guidelines for Management of PMR.<sup>4</sup>

Should the participant experience relapse between scheduled visits, an unscheduled clinic visit will be arranged upon request. This visit shall again comprise the standard format as outlined above. Upon confirmation of relapse as defined by PMR-AS, musculoskeletal ultrasound will also be arranged.

If a participant develops symptoms suggestive of GCA at any point in the study, the Prednisolone dose will be immediately increased to 50mg oral daily and a temporal artery biopsy urgently arranged. Participants with biopsy-confirmed GCA will continue to be treated with high-dose glucocorticoids as per standard clinical practice, whilst those with negative results will be weaned back to their previous PMR Prednisolone dose.

At the conclusion of the study (46 weeks), participants will be provided ongoing follow-up and management at an appropriate Austin Health Rheumatology Clinic.

This project will form the basis of the Principal Investigator's Doctor of Philosophy Research degree at the University of Melbourne.

| Assessment/Procedure                                           | Visit 1<br>(Week 0)                                                                                                                            | Visit 2<br>(Week 4)                         | Visit 3<br>(Week 8)                         | Visit 4<br>(Week 16)                        | Visit 5<br>(Week 24)                        | Visit 6<br>(Week 32)                        | Visit 7<br>(Week 46)                        | Unscheduled<br>visit                  |
|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------|
| Informed Consent                                               | X                                                                                                                                              |                                             |                                             |                                             |                                             |                                             |                                             |                                       |
| Demographic Information                                        | X                                                                                                                                              |                                             |                                             |                                             |                                             |                                             |                                             |                                       |
| Symptom Questionnaire                                          | X                                                                                                                                              | X                                           | X                                           | X                                           | X                                           | X                                           | X                                           | X                                     |
| Physical Examination                                           | X                                                                                                                                              | X                                           | X                                           | X                                           | X                                           | X                                           | X                                           | X                                     |
| Pathology                                                      | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR, Rh<br>factor,<br>ACPA,<br>ANA,<br>ANCA,<br>CK, TSH,<br>Vitamin<br>D, fasting<br>glucose,<br>HbA1C) | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR) | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR) | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR) | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR) | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR) | X<br>(FBE,<br>UEC,<br>LFTs,<br>CRP,<br>ESR) | X<br>(FBE, UEC,<br>LFTs, CRP,<br>ESR) |
| Hand X-Rays                                                    | X                                                                                                                                              |                                             |                                             |                                             |                                             |                                             |                                             |                                       |
| Musculoskeletal U/S                                            | X                                                                                                                                              | X                                           |                                             | X                                           |                                             |                                             | X                                           | X                                     |
| Targeted MRI Scan of<br>the Hamstring Origins in<br>the Pelvis | X<br>(in<br>selected<br>cases)                                                                                                                 |                                             |                                             |                                             |                                             |                                             |                                             |                                       |
| Whole Body PET/CT<br>Scan                                      | X<br>(in<br>selected<br>cases)                                                                                                                 |                                             |                                             |                                             |                                             |                                             |                                             |                                       |

## 5.2 STANDARD CARE AND ADDITIONAL TO STANDARD CARE PROCEDURES

| Standard Care Procedures                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Procedure                                                                                                       | Time/Visit                                                                                                                                                                                                                                                                                                                                                                                  | Dosage/Volume                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical Review:</b> <ul style="list-style-type: none"> <li>History</li> <li>Physical Examination</li> </ul> | <b>Standard Care:</b> <ul style="list-style-type: none"> <li>Baseline</li> <li>Week 4 and ~3-4 monthly thereafter</li> </ul> <b>Study:</b> <ul style="list-style-type: none"> <li>Baseline</li> <li>Week 4, week 8, week 16, week 24, week 32 &amp; week 46</li> </ul>                                                                                                                      | N/A                                                                                                                                                                                                                                                                                                                                             |
| <b>Pathology</b>                                                                                                | <b>Standard Care:</b> <ul style="list-style-type: none"> <li>Baseline – FBE, UEC, LFTs, CRP, ESR, Rh factor, ACPA, fasting glucose, HbA1C</li> <li>Week 4 and ~3-4 monthly thereafter – FBE, UEC, LFTs, CRP, ESR</li> </ul> <b>Study:</b> <ul style="list-style-type: none"> <li>Baseline – as above</li> <li>Week 4, week 8, week 16, week 24, week 32 &amp; week 46 – as above</li> </ul> | N/A                                                                                                                                                                                                                                                                                                                                             |
| <b>Prednisolone</b>                                                                                             | <b>Standard Care:</b> <ul style="list-style-type: none"> <li>Weaning schedule similar to the BSR Guidelines</li> </ul> <b>Study:</b> <ul style="list-style-type: none"> <li>Weaning schedule as per BSR Guidelines</li> </ul>                                                                                                                                                               | <b>Standard Care:</b> <ul style="list-style-type: none"> <li>Prednisolone 15mg oral daily for 3 weeks</li> <li>Prednisolone 12.5mg oral daily for 3 weeks</li> <li>Prednisolone 10mg oral daily for 4 weeks, then wean by 1mg every 4 weeks until cessation</li> </ul> <b>Study:</b> <ul style="list-style-type: none"> <li>As above</li> </ul> |

| Additional to Standard Care Procedures |                                                                                             |               |
|----------------------------------------|---------------------------------------------------------------------------------------------|---------------|
| Procedure                              | Time/Visit                                                                                  | Dosage/Volume |
| <b>Bilateral Hand X-Rays</b>           | <ul style="list-style-type: none"> <li>Baseline</li> </ul>                                  | 0.0015mSv     |
| <b>Musculoskeletal U/S</b>             | <ul style="list-style-type: none"> <li>Baseline</li> <li>Week 4</li> <li>Week 16</li> </ul> | N/A           |

|                                                          |                                                              |         |
|----------------------------------------------------------|--------------------------------------------------------------|---------|
|                                                          | <ul style="list-style-type: none"> <li>• Week 46</li> </ul>  |         |
| Targeted MRI Scan of the Hamstring Origins in the Pelvis | <ul style="list-style-type: none"> <li>• Baseline</li> </ul> | N/A     |
| Whole Body PET/CT Scan                                   | <ul style="list-style-type: none"> <li>• Baseline</li> </ul> | 9.05mSv |

### 5.3 RANDOMISATION

No randomisation is necessary for this study.

All clinic visits after screening will be performed by study Investigators. The Principle Investigator will remain blinded to participant laboratory results prior to undertaking musculoskeletal ultrasound assessments, thereby ensuring the integrity of these results at weeks 4, 16 and 46.

### 5.4 STUDY METHODOLOGY

- Symptom questionnaire (see Appendix):
  - Distribution of joint involvement;
  - Duration of early morning stiffness;
  - Presence of constitutional symptoms (loss of weight [kg] and fatigue)
  - Duration and dose of glucocorticoid treatment.
- Physical examination:
  - Vital signs (blood pressure, heart rate, temperature);
  - BMI;
  - Peripheral joints (synovitis, effusions);
  - Cardiovascular;
  - Respiratory;
  - Gastrointestinal.
- Laboratory:
  - FBE;
  - UEC;
  - LFTs;
  - CRP;
  - ESR;
  - Rh factor;
  - ACPA;
  - ANA;
  - ANCA;
  - CK;
  - TSH;
  - Vitamin D;
  - Fasting glucose;
  - HbA1C.
- Hand X-Ray:
  - Participants will undergo AP view, lateral and “ball catcher’s” projection;
  - All images will be taken using a Shimadzu X-ray unit with a Shimadzu DR retrofit.
- Musculoskeletal ultrasound:
  - Participants will undergo B mode and Power Doppler scanning;

- All images will be taken using a General Electric Logic e ultrasound machine.
- Bilateral hands and wrists (to assess for active synovitis, joint effusions, tenosynovitis and erosions), shoulders (to assess for subacromial bursitis, long head of biceps tenosynovitis, glenohumeral synovitis and joint effusion) and hips (to assess for trochanteric bursitis, hip synovitis and joint effusion) will be scanned.
- Targeted MRI scan:
  - Volume 3D space T1-weighted isotropic voxel of the pelvis;
  - Hamstring origins (both): Axial PD, Axial PD fat sat, Coronal PD, Coronal PD fat sat, Sag PD;
  - Qualitative evaluation of the hamstring origins will be performed following fusion with PET/CT images.
- Whole body PET/CT scan:
  - Participants will undergo a low radiation whole body protocol;
  - All images will be taken using the Phillips PET/CT camera;
  - Qualitative evaluation of joint and vascular FDG uptake (including Total Vascular Score [TVS]) will be performed, along with a semi-quantitative analysis of joint and vascular uptake.

## 6. STUDY POPULATION

### 6.1 RECRUITMENT PROCEDURE

Participants will be recruited from the Austin Hospital's Emergency Department and inpatient units, along with primary care providers and Rheumatologists in the Hospital's catchment area (north-eastern suburbs of Melbourne, Victoria). The Principle Investigator will be available via phone (94964038, with diversion to mobile after hours) for new referrals.

At the Austin Hospital, a brief oral presentation at study commencement will be arranged at the Rheumatology Unit weekly meeting. A similar approach is intended to inform clinicians working in the Emergency Department and General Medicine. For primary care providers and Rheumatologists in the Hospital's catchment area, information outlining study specifics will be circulated via mail (see Appendix).

### 6.2 INCLUSION CRITERIA

- New diagnosis of PMR as defined by the 2012 EULAR/ACR Classification Criteria:
  - Age  $\geq$  50 years;
  - AND
  - Bilateral shoulder aching;
  - AND
  - Abnormal ESR and/or CRP;
  - PLUS a score of  $\geq$ 4 based upon a scoring algorithm:
    - Morning stiffness duration  $>$ 45 mins (2 points);
    - Hip pain or limited range of movement (1 point);
    - Negative rheumatoid factor and/or ACPA (2 points);
    - Absence of peripheral joint pain (1 point).

### 6.3 EXCLUSION CRITERIA

- Inability to provide informed consent;

- Symptoms suggestive of GCA (headache, jaw claudication, scalp tenderness or visual disturbance);
- Cancer within the past 5 years;
- Neuromuscular disease;
- Active infection;
- Other inflammatory conditions eg. RA;
- Chronic pain syndromes;
- Uncontrolled psychiatric conditions, hypertension or diabetes;
- Treatment with glucocorticoids for >7 days prior to screening or a dose >15mg/day.
- Treatment with concomitant DMARDs.

## 6.4 CONSENT

Individual consent will be obtained from all eligible patients following the provision of information regarding the study's purpose and participant requirements.

## 7. PARTICIPANT SAFETY AND WITHDRAWAL

### 7.1 RISK MANAGEMENT AND SAFETY

Investigators will be responsible for monitoring the safety of the study participants and instituting appropriate medical care.

If an adverse event should occur, the patient will be followed until the event is resolved. This shall occur even if the patient withdraws before study completion.

In addition to records of scheduled observations, unexpected symptoms and physical signs will be noted, and irregular investigation results actioned. Further appropriate medical assessments may take place during the study as clinically indicated.

#### *Safety Parameters Assessed*

- Symptom Questionnaire:  
At each visit, participants will complete a questionnaire detailing their progress since the previous review. Investigators will also ask patients about any issues or concerns that have developed.
- Physical Examination:  
Vital signs including temperature, blood pressure and heart rate will be collected at each visit. Body weight will also be measured (obtained with the patient wearing undergarments or light clothing, using the same scale). A complete physical examination will be performed at the initial visit. Any clinically significant abnormalities that subsequently arise will be recorded.
- Pathology:
  - Haematology (all visits):  
Including haemoglobin, white blood cell count with differential and platelet count.
  - Biochemistry (all visits):  
Including sodium, potassium, urea and creatinine.
  - Liver function tests (all visits):

Including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), albumin and total bilirubin.

- Fasting blood glucose and HbA1C (baseline).

#### *Adverse Events*

- Giant Cell Arteritis:

Given that concomitant GCA is recognized in 16-21% of PMR cases, participants will be questioned at each visit regarding the new development of suggestive symptoms (headache, jaw claudication, scalp tenderness, visual loss). In the event of a positive history, the Prednisolone dose will be immediately increased to 50mg oral daily and a temporal artery biopsy urgently arranged. Participants with biopsy-confirmed GCA will continue to be treated with high-dose glucocorticoids as per standard clinical practice, whilst those with negative results will be weaned back to their previous PMR Prednisolone dose.

The same steps will be taken if FDG uptake consistent with large vessel vasculitis (as seen in GCA) is detected on whole body PET/CT scan.

- Complications of Glucocorticoids:

Long-term glucocorticoid use is associated with side effects including osteoporosis, hypertension and diabetes.

As in usual clinical practice, a Bone Mineral Density scan will be performed if the participant takes >7.5mg of Prednisolone daily for >3 months duration. In patients with a T score -1.5, appropriate bone protection therapy will be commenced.

Vital signs including blood pressure will be recorded at each visit. Anti-hypertensive medications may be started or adjusted as needed.

Fasting glucose and HbA1C will be performed at baseline for all participants. A random blood glucose level will also be checked at each subsequent visit. In the event of a new diagnosis of diabetes, appropriate management and Endocrinology referral (where necessary) will be instituted. If the participant has a past history of diabetes, blood sugar control will be monitored at each visit and medication adjustments made where required.

Infrequently, altered mood can occur with glucocorticoids. Individuals with uncontrolled psychiatric conditions will therefore be excluded from the study. In the event the participant reports symptoms including a depressed, elevated or agitated mood, referral to a psychologist, general practitioner or psychiatrist will be arranged as deemed clinically appropriate. Minimization of Prednisolone dose and early introduction of a DMARD will also occur, as in standard clinical practice.

- Radiation:

The radiation exposure associated with bilateral hand x-ray is 0.0015 mSv, whilst a whole body PET/CT scan equates to 9.05. Overall, the dose is comparable to that received from many diagnostic medical x-ray and nuclear medicine procedures. At

this dose, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. The risk is therefore believed to be low.

- Incidental detection of FDG-avid lesions on whole body PET/CT scanning  
Incidental findings on whole body PET/CT scanning may occur in the course of this research project. Should this eventuate, the investigator will ensure other investigations and an appropriate referral occurs as clinically necessary. For example, if an FDG-avid lung lesion were detected, a CT Chest and urgent referral to the Respiratory Clinic would be arranged.
- Psychological distress:  
Given the observational nature of the study, the potential for psychological distress to the participants involved is deemed minimal. However, if a participant does experience any such symptoms as a direct result of involvement in this research project, referral to a psychologist, general practitioner or psychiatrist will be arranged as deemed clinically appropriate.

## 7.2 HANDLING OF WITHDRAWALS

The criteria for enrolment will be followed explicitly. If a participant who does not meet these criteria is inadvertently enrolled, treatment with low-dose glucocorticoid therapy will be safely discontinued. The patient will then be referred to an appropriate Austin Health Rheumatology Clinic for ongoing management.

In addition, participants will be withdrawn from the study in the following circumstances:

- The patient requests to be withdrawn from the study;
- The patient experiences a severe adverse event that results in significant alterations to the low-dose glucocorticoid weaning schedule or the early addition of a DMARD;
- The patient develops a significant medical condition that meets one of the exclusion criteria;
- The patient, for any reason, requires extended treatment with Prednisolone >15mg/day;
- The Investigator stops the study or stops the patient's participation in the study for medical, safety or other reasons.

Patients who withdraw due to the aforementioned reasons will continue to be followed-up, with visits scheduled as clinically appropriate.

## 7.3 REPLACEMENTS

Withdrawn participants will be replaced in the study.

# 8. STATISTICAL METHODS

## 8.1 SAMPLE SIZE ESTIMATION & JUSTIFICATION

## 8.2 POWER CALCULATIONS

Due to a lack of literature indicating anticipated effect size in a pilot study such as this, sample size calculation is difficult. That said, a similar study design by Cimmino et al. (2011) did achieve a statistically significant result with enrolment of 60 patients.<sup>5</sup>

### **8.3 STATISTICAL METHODS TO BE UNDERTAKEN**

At study completion, statistical analyses will be undertaken using Stata 13.0 to compare those PMR patients who relapsed with those who remained in remission with standardized low-dose glucocorticoid therapy. Parametric data will be compared using t-tests, while non-parametric data will be compared using the chi-square test or Kruskal-Wallis one-way analysis of variance. P-values of < 0.05 will be classified as statistically significant. A more detailed multivariable and conditional logistic regression is also planned to control for the effects of variables such as gender, BMI and smoking status.

## **9. STORAGE OF BLOOD AND TISSUE SAMPLES**

### **9.1 DETAILS OF WHERE SAMPLES WILL BE STORED, AND THE TYPE OF CONSENT FOR FUTURE USE OF SAMPLES**

Blood samples will be collected at the times specified in the study design and analysed at the Austin Hospital's Pathology Department. No genetic testing will be performed, nor will specimens be stored for use in future research. Samples will only be retained in the Pathology Department if necessary to comply with applicable laws, regulations or laboratory certification standards.

## **10. DATA SECURITY & HANDLING**

### **10.1 DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED**

All records will be stored securely in a locked office for a minimum period of 7 years within the Rheumatology Department at Heidelberg Repatriation Hospital, 300 Waterdale Road, Heidelberg West VIC 3081.

### **10.2 CONFIDENTIALITY AND SECURITY**

Study data in storage will be re-identifiable using the participant's unique identification number. A separate password-protected decoding document will be maintained on a computer within the locked Rheumatology Department office. Only study Investigators will be provided with the password for this document.

### **10.3 ANCILLARY DATA**

Hand x-rays and targeted MRI scan images obtained during the study will be archived by the Austin Hospital's Radiology Department in accordance with applicable laws and regulations. Musculoskeletal ultrasound images obtained by the Principle Investigator will be saved in a re-identifiable manner onto a hard drive and stored securely within the Rheumatology Department, also for a minimum period of 7 years. Whole body PET/CT images will be archived by the Austin Hospital's Centre for PET in accordance with applicable laws and regulations.

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<sup>5</sup>Cimmino, M. et al. (2011). 'The correct Prednisolone starting dose in polymyalgia rheumatica is related to body weight but not disease severity', *BMC Musculoskeletal Disorders*; 12:94.

## **11. APPENDIX**

### **List of Attachments included:**

| <b>Document Name</b>                                                          | <b>Version Number</b> | <b>Date (e.g., 18 January 2012)</b> |
|-------------------------------------------------------------------------------|-----------------------|-------------------------------------|
| 20150729 SUMMARY - Protocol Changes v2                                        | 2                     | 29/7/2015                           |
| 20150804 FORM - Radiology v2                                                  | 2                     | 4/8/2015                            |
| 20150819 FORM - Patient Information Consent Form v4 Changes Tracked and Clean | 4                     | 19/8/2015                           |
| 20150819 OUTLINE - Budget v2                                                  | 2                     | 19/8/2015                           |

## **12. REFERENCES**

As above.





Place Patient Label Here

**Participant Information Sheet/Consent Form**  
**Interventional Study - Adult providing own consent**

Austin Hospital and Heidelberg Repatriation Hospital

|                                                                |                                                                                                       |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Title                                                          | Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoid therapy |
| Protocol Number                                                | 1                                                                                                     |
| Coordinating Principal Investigator/<br>Principal Investigator | Dr Claire Owen                                                                                        |
| Associate Investigators                                        | A/Prof Russell Buchanan<br>Dr Simon Lam                                                               |
| Location                                                       | Austin Hospital and Heidelberg Repatriation Hospital                                                  |

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**Part 1 What does my participation involve?**

**1 Introduction**  
 You are invited to take part in this research project. This is because you have a new diagnosis of Polymyalgia Rheumatica (PMR). This research project is designed to identify patient factors that predict a lack of response to standard treatment with Prednisolone (or "cortisone").  
  
 This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.  
  
 Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.  
  
 Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.  
  
 If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
 

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

 You will be given a copy of this Participant Information and Consent Form to keep.

Master Participant Information Sheet/Consent Form v4 19/8/2015

Page 1 of 8



## **2 What is the purpose of this research?**

Despite the fact that PMR is a very common disease, it is poorly understood. With no specific diagnostic tests available, diagnosis is based upon symptoms and raised inflammation levels in the blood. Treatment consists of a course of Prednisolone or “cortisone” prescribed in a “one size fits all” approach. However, the way in which PMR patients’ respond to treatment is highly variable; some improve overnight, whilst others require higher doses for much longer periods of time. Unfortunately, such long-term Prednisolone use can result in complications including osteoporosis, weight gain, high blood pressure and diabetes.

This research project is designed to identify patient factors that predict a lack of response to standard treatment with Prednisolone. Identifying these factors will permit further study of alternative treatment approaches in this group and facilitate PMR therapy tailored to the individual patient long-term.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Prednisolone is approved in Australia to treat PMR.

This research has been initiated by the study doctor, Dr Claire Owen. Its results will be used to obtain a Doctor of Philosophy degree.

Funding has been provided for this research by Arthritis Australia and Austin Medical Research Foundation.

## **3 What does participation in this research involve?**

If you agree to participate in the research project, the attached Consent Form must first be signed.

The first study visit (week 0) will comprise a questionnaire on demographic information and symptoms, and a general physical examination. You will also have baseline bloods tests (17mLs [approximately 2 teaspoons] of blood will be collected) and hand x-rays, an ultrasound performed of your hands, shoulders and hips, a whole body Positron Emission Tomography /Computed Tomography scan (PET/CT) and a Magnetic Resonance Imaging (MRI) scan of your pelvis within the next 7 days.

A whole body PET/CT scan is a form of imaging which demonstrates the metabolism of the body’s tissues. It is therefore able to detect areas of active inflammation such as in PMR. You will need to fast for 6 hours before the scan (water is allowed). An injection of a radioactive glucose will be given into a vein in your arm, followed by a rest period where you will lie quietly for 60 minutes. Pictures will then be taken on a camera that resembles a CT scanner. The whole body PET/CT scan will be conducted at the Nuclear Medicine and Centre for PET at the Austin Hospital. However, it will only be conducted if you have not already started Prednisolone treatment due to the effect of this medication on scan results.

An MRI scanner uses a powerful magnet to produce superbly detailed images of the body. It is therefore also able to demonstrate areas of inflammation in specific muscles and joints in PMR. MRI does not use radiation, unlike x-ray and CT. Like the PET/CT scan, you will be required to lie quietly for 30 minutes. The MRI scan will be conducted at the Radiology Department at the Austin Hospital. However, it will also only be conducted if you have not already started Prednisolone treatment due to the effect of this medication on scan results. Similarly, participants who have mental implants in their body or claustrophobia will not be eligible.

The estimated time commitment for the first study visit is 3-4 hours.



Place Patient Label Here

A course of oral Prednisolone will then be commenced to treat your PMR, with the dose reduced every 3-4 weeks as in standard clinical practice (15mg for 3 weeks, 12.5mg for 3 weeks, 10mg for 4 weeks, then reduce by 1mg every 4 weeks until cessation).

You will be expected to return to the clinic at week 4, week 8, week 16, week 24, week 32 and week 46 for follow-up visits. A questionnaire on symptoms, general physical examination, blood test (13mLs [approximately one teaspoon] of blood will be collected at each visit) and ultrasound (week 4, week 16 and week 46 only) will be repeated on each occasion. Follow-up visits are estimated to take 1-2 hours.

Additional clinic visits can also be arranged if the need arises between scheduled reviews.

You will be involved in the research project for a total of 46 weeks. Ongoing follow-up will be provided at an appropriate Austin Health Rheumatology Clinic thereafter. The entire research project is expected to be completed over a two year period.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. No reimbursement will be provided for travel costs. All tests and medical care required will be provided free of charge. A PBS prescription for Prednisolone will incur the standard out-of-pocket cost when filled at a pharmacy of your choice.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

The progress of this project will be monitored by the Austin Hospital's Rheumatology Department at 4-monthly dedicated research meetings.



Place Patient Label Here

| Assessment/Procedure                    | Visit 1<br>(Week 0)                                | Visit 2<br>(Week 4)      | Visit 3<br>(Week 8)      | Visit 4<br>(Week 16)     | Visit 5<br>(Week 24)     | Visit 6<br>(Week 32)     | Visit 7<br>(Week 46)     | Unscheduled<br>visit     |
|-----------------------------------------|----------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Visit Date                              | <Insert>                                           | <Insert>                 | <Insert>                 | <Insert>                 | <Insert>                 | <Insert>                 | <Insert>                 | <Insert>                 |
| Visit Duration                          | 3-4 hours                                          | 2 hours                  | 1 hour                   | 2 hours                  | 1 hour                   | 1 hour                   | 2 hours                  | 2 hours                  |
| Demographic Information                 | X                                                  |                          |                          |                          |                          |                          |                          |                          |
| Symptom Questionnaire                   | X                                                  | X                        | X                        | X                        | X                        | X                        | X                        | X                        |
| Physical Examination                    | X                                                  | X                        | X                        | X                        | X                        | X                        | X                        | X                        |
| Blood Test                              | X<br>***Fasting required***                        | X<br>No fasting required | X<br>No fasting required | X<br>No fasting required | X<br>No fasting required | X<br>No fasting required | X<br>No fasting required | X<br>No fasting required |
| Hand X-Rays                             | X                                                  |                          |                          |                          |                          |                          |                          |                          |
| Ultrasound of Hands, Shoulders and Hips | X                                                  | X                        |                          | X                        |                          |                          | X                        | X                        |
| Whole Body PET/CT Scan                  | X<br>(in selected cases)<br>***Fasting required*** |                          |                          |                          |                          |                          |                          |                          |
| MRI Scan of Pelvis                      | X<br>(in selected cases)                           |                          |                          |                          |                          |                          |                          |                          |

#### 4 What do I have to do?

You are unable to participate or continue in this research project if:

- You are unable to speak and read English proficiently;
- You have symptoms suggestive of the serious, related condition Giant Cell Arteritis, including headache, scalp tenderness, jaw pain on chewing or visual disturbance;
- You have been diagnosed with cancer within the past 5 years;
- You have a neuromuscular disease;
- You have a serious infection;
- You have another inflammatory condition eg. Rheumatoid arthritis;
- You have a chronic pain syndrome;
- You have an uncontrolled psychiatric condition;
- You have uncontrolled hypertension or diabetes;
- You have been taking Prednisolone for longer than the past 7 days or a Prednisolone dose greater than 15mg daily;
- You are taking a Disease Modifying Anti-Rheumatic Drug.

Throughout the research project, you will be expected to take Prednisolone as prescribed. You can also continue to take your other regular medications. A prolonged course (longer than 7 days) of high dose (greater than 25mg daily) Prednisolone for another medical condition is not permitted and will result in your withdrawal from the research project.

**If you develop headache, scalp tenderness, jaw pain on chewing or visual disturbance during the research project, you must notify the researchers immediately as this may represent the development of Giant Cell Arteritis (a serious condition related to PMR).**



You will not be subjected to any lifestyle or dietary restrictions in this research project.

### **5 Other relevant information about the research project**

This is a single-site research project expected to involve approximately sixty participants at the Austin Hospital and Heidelberg Repatriation Hospital. All participants will receive the same standard course of Prednisolone treatment and undergo the same assessments, except for the whole body PET/CT and MRI scans which will only be performed on individuals who have not already started Prednisolone.

### **6 Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Austin Health.

### **7 What are the possible benefits of taking part?**

There will be no additional benefit to you personally from your participation in this research, as you will receive treatment and follow-up as in standard clinical practice for PMR. However, this project is thought to have the potential to significantly advance our understanding of PMR and thereby improve the care available to future sufferers of this condition.

### **8 What are the possible risks and disadvantages of taking part?**

#### *Radiation Exposure*

This research project involves exposure to a very small amount of radiation from bilateral hand x-rays and whole body CT/PET scanning. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 9.05mSv. The dose from this research project is comparable to that received from many diagnostic medical x-ray and nuclear medicine procedures. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk is therefore believed to be low.

### **9 What will happen to my test samples?**

As in standard clinical practice, blood will be collected from all participants to monitor inflammation levels at the first study visit (week 0), week 4, week 16, week 32 and week 46. All samples will be analysed at the Austin Hospital's Pathology Department. No genetic testing will be performed, nor will specimens be stored for use in future research. Samples will only be retained in the Pathology Department if necessary to comply with applicable laws, regulations or laboratory certification standards.

### **10 What if I withdraw from this research project?**

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information



Place Patient Label Here

already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law.

### **11 What happens when the research project ends?**

After 46 weeks, ongoing clinical follow-up will be provided at an appropriate Austin Health Rheumatology Clinic.

All participants will be provided with a summary of the research project's results following its completion and appropriate statistical analysis (estimated date February 2016). Publications and/or presentations that have arisen from the research project will be specifically outlined in this document.

## **Part 2 How is the research project being conducted?**

### **12 What will happen to information about me?**

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. You will be assigned a unique identification number, which will be the only identifier kept in association with your records. A separate password-protected decoding document will be kept on a computer in the locked Rheumatology Department at Heidelberg Repatriation Hospital. Only researchers involved in the project will have access to this. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. All records will also be stored securely in a locked office within the Rheumatology Department for a minimum period of 7 years before being destroyed (shredded).

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities, the institution relevant to this Participant Information Sheet, Austin Health, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided about the research cohort as a whole. Individual outcomes will not be reported, unless your permission is specifically sought.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

### **13 Complaints and compensation**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.



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If you have a complaint regarding the project or treatment provided by a researcher, you should contact the Austin Health Research Ethics office.

#### 14 Who is organising and funding the research?

This research project is being conducted by Dr Claire Owen, Rheumatology Clinical Research Fellow.

Funding for this research project has been provided by Arthritis Australia and Austin Medical Research Foundation.

#### 15 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Austin Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

#### 16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor:

##### Clinical contact person

|           |                                                              |
|-----------|--------------------------------------------------------------|
| Name      | Dr Claire Owen                                               |
| Position  | Principal Investigator/Rheumatology Clinical Research Fellow |
| Telephone | 94964038                                                     |
| Email     | claire.owen@austin.org.au                                    |

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

##### Complaints contact person

|           |                                        |
|-----------|----------------------------------------|
| Name      | Sianna Panagiotopoulos                 |
| Position  | Manager, Austin Health Research Ethics |
| Telephone | 94965088                               |
| Email     | research@austin.org.au                 |



Place Patient Label Here

**Consent Form - Adult providing own consent**

**Title** Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoids

**Protocol Number** 1

**Coordinating Principal Investigator/  
Principal Investigator** Dr Claire Owen

**Associate Investigators** A/Prof Russell Buchanan  
Dr Simon Lam

**Location** Austin Hospital and Heidelberg Repatriation Hospital

**Declaration by Participant**

- I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
- I understand the purposes, procedures and risks of the research described in the project.
- I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
- I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Witness\* to Participant's  
Signature (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

\* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/  
Senior Researcher† (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

† A senior member of the research team must provide the explanation of, and information concerning, the research project.  
Note: All parties signing the consent section must date their own signature.

I consent to the use of blood samples taken from me for laboratory testing, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project.

Name of Participant (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Witness\* to Participant's  
Signature (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

\* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/  
Senior Researcher† (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.



Place Patient Label Here

## Form for Withdrawal of Participation - *Adult providing own consent*

**Title** Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoids

**Protocol Number** 1

**Coordinating Principal Investigator/  
Principal Investigator** Dr Claire Owen

**Associate Investigator(s)** A/Prof Russell Buchanan  
Dr Simon Lam

**Location** Austin Hospital and Heidelberg Repatriation Hospital

### **Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Austin Health.

Name of Participant (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

### **Declaration by Study Doctor/Senior Researcher<sup>†</sup>**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/  
Senior Researcher<sup>†</sup> (please print) \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

<sup>†</sup> A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.



**Austin Health**

**Participant Questionnaire**

**Week 0**

Study ID no.: \_\_\_\_\_

---

**Title**

**Principle Investigator**

**Associate Investigators**

**Location**

Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoid therapy

Dr Claire Owen

A/Prof Russell Buchanan and Dr Simon Lam

Austin Hospital and Heidelberg Repatriation Hospital

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**DEMOGRAPHICS**

Gender: ☐ Male ☐ Female

Date of birth: \_\_\_\_/\_\_\_\_/\_\_\_\_  
DD MM YYYY

Race: ☐ Caucasian ☐ Aboriginal/Torres Strait Islander  
☐ Pacific Islander ☐ North East Asian eg. Chinese, Korean, Japanese  
☐ Central Asian eg. Armenian, Uzbek ☐ Indian Sub-Continent  
☐ Other (specify): \_\_\_\_\_

---

**MEDICAL HISTORY**

The following is a list of common problems. Please indicate if you **CURRENTLY** have the problem in the first column. If you do not have the problem, skip to the next problem.

If you **DO** have the problem, please indicate in the second column if you receive medication or some other type of treatment for the problem. For example, if you have high blood pressure that is under good control with medication, you should check "yes" in columns 1 and 2.

Finally, indicate all medical conditions that are not listed under "other medical problems" on the next page.

| Problem                        | Do you have the problem? |    | Do you receive treatment? |    |
|--------------------------------|--------------------------|----|---------------------------|----|
|                                | Yes                      | No | Yes                       | No |
| Heart disease                  | Y                        | N  | Y                         | N  |
| High blood pressure            | Y                        | N  | Y                         | N  |
| High cholesterol               | Y                        | N  | Y                         | N  |
| Diabetes                       | Y                        | N  | Y                         | N  |
| Lung disease                   | Y                        | N  | Y                         | N  |
| Ulcer or stomach disease       | Y                        | N  | Y                         | N  |
| Kidney disease                 | Y                        | N  | Y                         | N  |
| Liver disease                  | Y                        | N  | Y                         | N  |
| Anaemia or other blood disease | Y                        | N  | Y                         | N  |
| Cancer                         | Y                        | N  | Y                         | N  |

Participant Questionnaire v2 12/5/2014

| Problem                 | Do you have the problem? |    | Do you receive treatment? |    |
|-------------------------|--------------------------|----|---------------------------|----|
|                         | Yes                      | No | Yes                       | No |
| Depression              | Y                        | N  | Y                         | N  |
| Osteoarthritis          | Y                        | N  | Y                         | N  |
| Gout                    | Y                        | N  | Y                         | N  |
| Other medical problems: | Y                        | N  | Y                         | N  |
|                         | Y                        | N  | Y                         | N  |
|                         | Y                        | N  | Y                         | N  |
|                         | Y                        | N  | Y                         | N  |
|                         | Y                        | N  | Y                         | N  |

**Medications:**

Please fill in the details below of **ALL** the medications you are **CURRENTLY** taking.

| Medication | Dose | Frequency |
|------------|------|-----------|
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |
|            |      |           |

**Smoking status:**
☐ Current smoker

☐ Ex-smoker

☐ Never smoked

If you **ARE** a current smoker or ex-smoker:

How many cigarettes per day do/did you smoke?

\_\_\_\_\_ Cigarettes

How long have/did you smoker for?

\_\_\_\_\_ Years

**SYMPTOMS**

When did you first notice pain and stiffness in your shoulders/hips?

\_\_\_\_\_ Days/Weeks/Months  
CIRCLE

How long do you experience muscle/joint stiffness in the morning?

\_\_\_\_\_ Minutes/Hours  
CIRCLE

Do you feel fatigued? ☐ Yes

☐ No

Have you been experiencing fevers?

☐ Yes

☐ No

**SYMPTOMS cont'd**Have you lost weight? ☐ Yes☐ NoIf you **HAVE** lost weight:

How much weight have you lost? \_\_\_\_\_ Kg

Have you been experiencing headaches or scalp tenderness?

☐ Yes☐ No

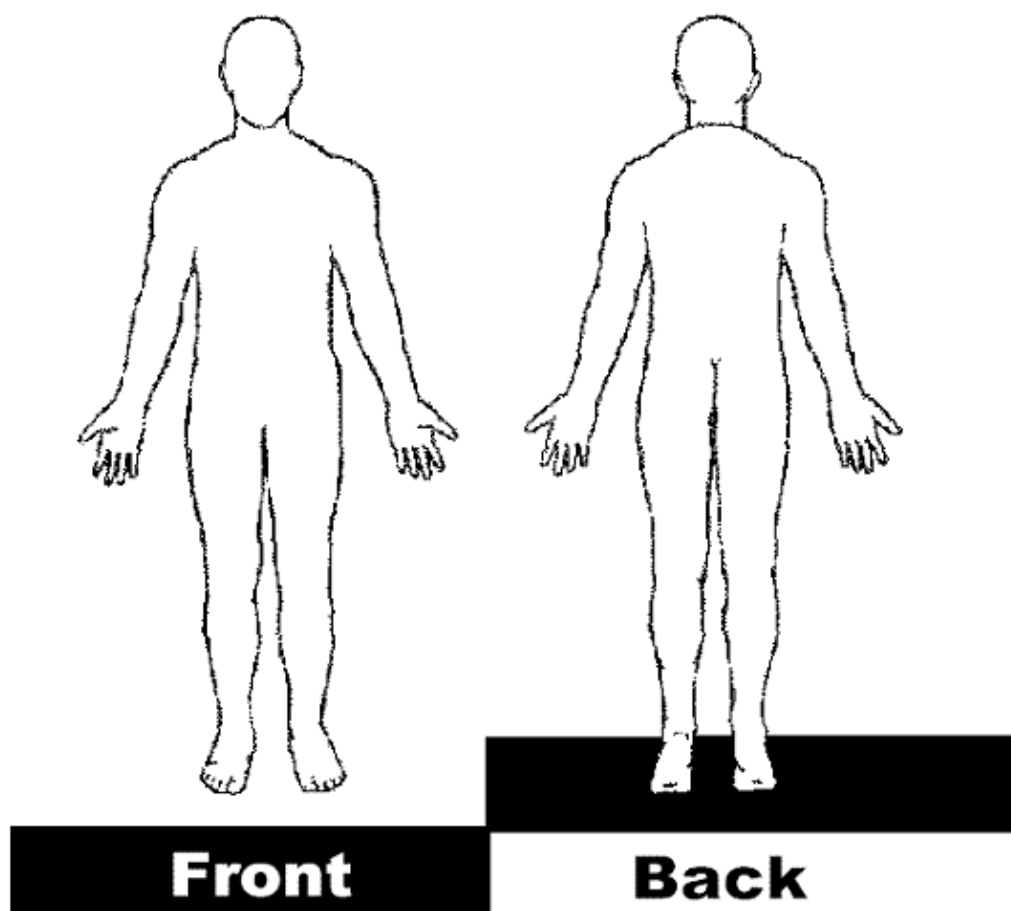
Do you have pain in your jaw when you chew?

☐ Yes☐ No

Have you experienced a change in your vision?

☐ Yes☐ No

On the picture below, please indicate where you are **CURRENTLY** experiencing muscle/joint pain and stiffness?



### HAQ-DI

The following questions relate to your ability to do everyday tasks. Please **CIRCLE THE NUMBER** which best describes your abilities over the past four weeks.

| Are you able to:                                               | Without any difficulty | With SOME difficulty | With MUCH difficulty | Unable to do |
|----------------------------------------------------------------|------------------------|----------------------|----------------------|--------------|
| 1. Dress yourself including tying shoelaces and doing buttons? | 1                      | 2                    | 3                    | 4            |
| 2. Shampoo your hair?                                          | 1                      | 2                    | 3                    | 4            |
| 3. Stand from an armless chair?                                | 1                      | 2                    | 3                    | 4            |
| 4. Get in and out of bed?                                      | 1                      | 2                    | 3                    | 4            |
| 5. Cut your meat?                                              | 1                      | 2                    | 3                    | 4            |
| 6. Lift a full cup or glass to your mouth?                     | 1                      | 2                    | 3                    | 4            |
| 7. Open a new milk carton?                                     | 1                      | 2                    | 3                    | 4            |
| 8. Walk outdoors on flat ground?                               | 1                      | 2                    | 3                    | 4            |
| 9. Climb five steps?                                           | 1                      | 2                    | 3                    | 4            |
| 10. Wash and dry your entire body?                             | 1                      | 2                    | 3                    | 4            |
| 11. Take a bath?                                               | 1                      | 2                    | 3                    | 4            |
| 12. Get on and off the toilet?                                 | 1                      | 2                    | 3                    | 4            |
| 13. Reach and get down a 2kg object from above your head?      | 1                      | 2                    | 3                    | 4            |
| 14. Bend down to pick clothing off the floor?                  | 1                      | 2                    | 3                    | 4            |
| 15. Open car doors?                                            | 1                      | 2                    | 3                    | 4            |
| 16. Open jars which have been previously opened?               | 1                      | 2                    | 3                    | 4            |
| 17. Turn taps on and off?                                      | 1                      | 2                    | 3                    | 4            |
| 18. Run errands and shop?                                      | 1                      | 2                    | 3                    | 4            |
| 19. Get in and out of the car?                                 | 1                      | 2                    | 3                    | 4            |

**HAQ-DI cont'd**

| Are you able to:                                               | Without any difficulty | With SOME difficulty | With MUCH difficulty | Unable to do |
|----------------------------------------------------------------|------------------------|----------------------|----------------------|--------------|
| 20. Do chores such as vacuuming, housework or light gardening? | 1                      | 2                    | 3                    | 4            |

---

**VAS**

Please indicate on the scale below the severity of your **CURRENT** muscle/joint pain.



---

**END OF QUESTIONNAIRE**

**Participant Questionnaire****Week 4/Week 8/Week 16/Week 24/Week 32/Week 46/Unscheduled Visit**

|                                |                                                                                                       |
|--------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Title</b>                   | Predictors of relapse in Polymyalgia Rheumatica patients treated with low-dose glucocorticoid therapy |
| <b>Principle Investigator</b>  | Dr Claire Owen                                                                                        |
| <b>Associate Investigators</b> | A/Prof Russell Buchanan and Dr Simon Lam                                                              |
| <b>Location</b>                | Austin Hospital and Heidelberg Repatriation Hospital                                                  |

**SYMPTOMS**

How long do you experience muscle/joint stiffness in the morning? \_\_\_\_\_ Minutes/Hours  
CIRCLE

Do you feel fatigued? ☐ Yes ☐ No

Have you been experiencing fevers?  
☐ Yes ☐ No

Have you lost weight? ☐ Yes ☐ No

If you **HAVE** lost weight:

How much weight have you lost? \_\_\_\_\_ Kg

Have you been experiencing headaches or scalp tenderness?  
☐ Yes ☐ No

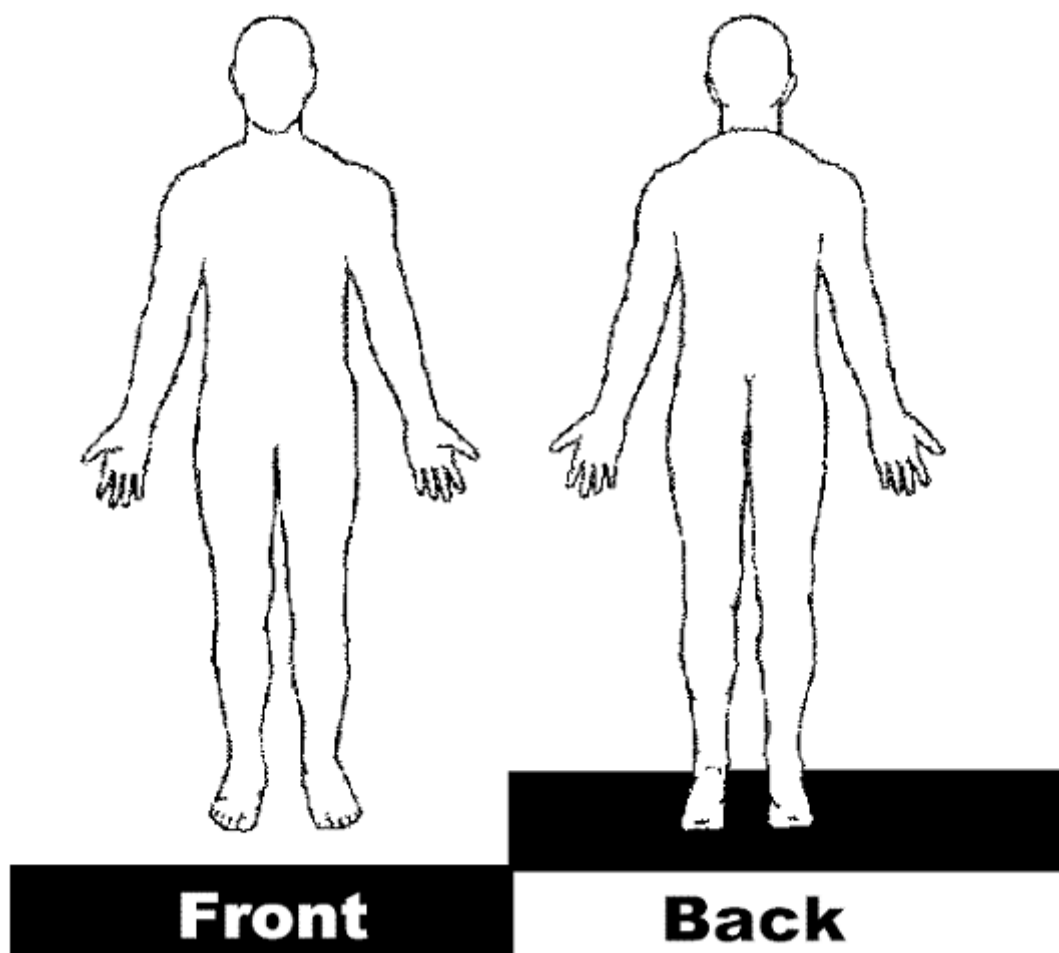
Do you have pain in your jaw when you chew?  
☐ Yes ☐ No

Have you experienced a change in your vision?  
☐ Yes ☐ No

**Cont'd over page**

### SYMPTOMS cont'd

On the picture below, please indicate where you are **CURRENTLY** experiencing muscle/joint pain and stiffness?



### HAQ-DI

The following questions relate to your ability to do everyday tasks. Please **CIRCLE THE NUMBER** which best describes your abilities over the past four weeks.

| Are you able to:                                               | Without any difficulty | With SOME difficulty | With MUCH difficulty | Unable to do |
|----------------------------------------------------------------|------------------------|----------------------|----------------------|--------------|
| 1. Dress yourself including tying shoelaces and doing buttons? | 1                      | 2                    | 3                    | 4            |
| 2. Shampoo your hair?                                          | 1                      | 2                    | 3                    | 4            |
| 3. Stand from an armless chair?                                | 1                      | 2                    | 3                    | 4            |
| 4. Get in and out of bed?                                      | 1                      | 2                    | 3                    | 4            |

**HAQ-DI cont'd**

| Are you able to:                                               | Without any difficulty | With SOME difficulty | With MUCH difficulty | Unable to do |
|----------------------------------------------------------------|------------------------|----------------------|----------------------|--------------|
| 5. Cut your meat?                                              | 1                      | 2                    | 3                    | 4            |
| 6. Lift a full cup or glass to your mouth?                     | 1                      | 2                    | 3                    | 4            |
| 7. Open a new milk carton?                                     | 1                      | 2                    | 3                    | 4            |
| 8. Walk outdoors on flat ground?                               | 1                      | 2                    | 3                    | 4            |
| 9. Climb five steps?                                           | 1                      | 2                    | 3                    | 4            |
| 10. Wash and dry your entire body?                             | 1                      | 2                    | 3                    | 4            |
| 11. Take a bath?                                               | 1                      | 2                    | 3                    | 4            |
| 12. Get on and off the toilet?                                 | 1                      | 2                    | 3                    | 4            |
| 13. Reach and get down a 2kg object from above your head?      | 1                      | 2                    | 3                    | 4            |
| 14. Bend down to pick clothing off the floor?                  | 1                      | 2                    | 3                    | 4            |
| 15. Open car doors?                                            | 1                      | 2                    | 3                    | 4            |
| 16. Open jars which have been previously opened?               | 1                      | 2                    | 3                    | 4            |
| 17. Turn taps on and off?                                      | 1                      | 2                    | 3                    | 4            |
| 18. Run errands and shop?                                      | 1                      | 2                    | 3                    | 4            |
| 19. Get in and out of the car?                                 | 1                      | 2                    | 3                    | 4            |
| 20. Do chores such as vacuuming, housework or light gardening? | 1                      | 2                    | 3                    | 4            |

**VAS**

Please indicate on the scale below the severity of your **CURRENT** muscle/joint pain.



**END OF QUESTIONNAIRE**

## Editorial

## Musculotendinous Inflammation: The Defining Pathology of Polymyalgia Rheumatica?



Despite being the most common inflammatory rheumatic disease of the elderly, and despite significant scientific breakthroughs in the related condition giant cell arteritis (GCA), the paradigm of polymyalgia rheumatica (PMR) has failed to progress beyond its earliest descriptions as a glucocorticoid-responsive syndrome of shoulder and pelvic girdle pain and stiffness. In the absence of a gold standard test, diagnosis is based on laboratory evidence of systemic inflammation and the exclusion of other relevant differentials. Ultrasound findings including subacromial bursitis, biceps tenosynovitis, and glenohumeral synovitis at the shoulders, and synovitis and trochanteric bursitis at the hips, improve the specificity of clinical classification criteria<sup>1</sup>. However, the precise pathology underpinning PMR remains unclear<sup>2</sup>. A mild synovitis with CD4+ T cell and macrophage infiltration characterizes arthroscopic biopsies taken from the glenohumeral joints of patients with PMR, while histopathologic studies of muscle have consistently revealed only minor immunologic abnormalities<sup>3,4</sup>. Such uncertainty surrounding disease pathophysiology has undoubtedly hindered therapeutic advances in PMR, with the majority of patients still condemned to long-term prednisolone treatment and its attendant glucocorticoid-related complications.

Modern advances in our understanding of PMR as a distinct disease entity have come largely courtesy of imaging. McGonagle, *et al* first reported an anatomical difference in the distribution of inflammation in their magnetic resonance imaging (MRI) study contrasting the shoulders of PMR and rheumatoid arthritis (RA) patients<sup>5</sup>. Extracapsular soft tissue edema differentiated the PMR group from its RA counterpart, whereas bursitis, tenosynovitis, and joint effusion did not. A subsequent study by the same authors investigating MRI findings at the metacarpophalangeal joints in PMR and RA similarly documented comparable rates of synovitis, tenosynovitis, and even bone erosions, with a much greater degree

of gadolinium-enhancement noted in the extracapsular soft tissues of patients with PMR<sup>6</sup>. More recently, a symmetrical extracapsular pattern of inflammation adjacent to the greater trochanter, acetabulum, ischial tuberosity, and/or pubic symphysis has been associated with a complete, patient-reported response to glucocorticoid therapy<sup>7</sup>. Taken together, these findings implicate extracapsular inflammation as a point of difference between PMR and other rheumatic conditions, with utility in both diagnostic and prognostic settings. Delineation of the inflamed anatomical structures responsible for this imaging pattern also possesses the very real potential to shed new light on the mystery that is PMR's true pathology.

In this edition of *The Journal*, Laporte, *et al*<sup>8</sup> provide first documentation of the prevalence of localized myofascial lesions in patients with active PMR and their response to the interleukin (IL)-6 receptor blocker tocilizumab (TCZ), which has previously been established as an effective therapy for this condition<sup>9</sup>. T1- and T2-short-tau inversion recovery (STIR)-weighted MRI of the shoulder and pelvic girdle were undertaken at baseline and at weeks 2 and 12 posttreatment, with myofascial inflammation defined as high T2-STIR signal within the affected muscle or forming a line around it. In addition to an anticipated high frequency of synovitis and bursitis, at least 1 shoulder girdle and at least 1 pelvic girdle myofascial inflammatory lesion was detected at baseline in 71.4% and 86.7% of cases, respectively. The hip musculature was most commonly involved (86.7%), followed by the adductors at the pubic symphysis (80.0%), shoulder musculature (71.4%), and muscles adjacent to the ischial tuberosities, specifically semitendinosus, semimembranosus, and the long head of biceps femoris (60.0%). Improvement in these lesions was subsequently noted in 64.1% of muscle groups following 12 weeks of TCZ, thereby confirming the responsiveness of this newly identified pathology in PMR to biologic therapy.

See Polymyalgia rheumatica and TCZ therapy, page 1619

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The close parallels between the anatomic distribution of the myofascial inflammatory lesions seen by Laporte, *et al*<sup>8</sup> and the previously described extracapsular pattern of inflammation typical of PMR cannot be denied. These findings similarly add to a growing body of evidence from other recent imaging studies documenting the involvement of musculotendinous structures in this condition. A Japanese whole-body positron emission tomography/computed tomography (PET/CT) study first noted abnormal fluorodeoxyglucose (FDG) uptake at the tendon attachment sites of the pelvic girdle as a feature unique to PMR<sup>10</sup>. Subsequent to this, Rehak, *et al* investigated the response of prepubic 18F-FDG accumulation to glucocorticoid therapy<sup>11</sup>. Like Laporte, *et al*<sup>8</sup>, improvement in these abnormalities was noted in all treated patients, with the authors hypothesizing that the observed PET findings represented “another type of extra-articular inflammation” in PMR (i.e., enthesitis and tenosynovitis of the pectineus and adductor longus muscles).

The low image resolution typical of whole-body PET/CT, however, has represented a barrier to the identification of precise anatomic correlates of abnormal 18F-FDG uptake in PMR. Having observed a distinctive pattern of PET avidity adjacent to the ischial tuberosities and of posteromedial knee structures in our own prospective study of 22 newly diagnosed, steroid-naïve patients, we performed MRI to confirm involvement of the hamstring tendons<sup>12</sup>. Bilateral and symmetric high T2 signal surrounding the proximal hamstring tendon origins of the semimembranosus and the conjoint tendon of the semitendinosus and biceps femoris was subsequently visualized at the pelvis, with peritendinitis of the semitendinosus and to a lesser extent gracilis tendons noted at the knee. Using PET/MRI fusion, hamstring peritendinitis was identified as the anatomical correlate of 18F-FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures, and PMR’s predilection for tendinous structures was confirmed.

Most recently, Fruth, *et al* has replicated these findings at the hamstrings and proposed peritendinous enhancement of the pelvic girdle tendons as the imaging hallmark of PMR<sup>13</sup>. In a retrospective study of 40 patients with PMR who underwent contrast-enhanced pelvic MRI as part of their diagnostic investigation, areas of previously mentioned extracapsular inflammation were studied in detail in the hopes of identifying a disease-specific pattern. Mostly bilateral enhancement of tendinous structures in the pelvis corresponded with these regions of interest in all cases and the pathology identified encompassed a spectrum ranging from circumferential peritendinous inflammation to complete intratendinous involvement up to the level of the musculotendinous junction. While Laporte, *et al* have documented the prevalence of localized myofascial lesions for the first time in PMR<sup>8</sup>, this publication also notably recorded the presence of linear enhancement of the intramuscular perimysium at the gluteus maximus in 2 patients.

It is with good reason that Fruth, *et al* highlight the contiguous relationship that exists between peritendineum and perimysium, with inflammation of the hip capsule similarly observed to merge seamlessly with peritendinous enhancement of adjacent muscles in the provided images<sup>13</sup>. The close anatomic proximity of the subacromial bursa to the supraspinatus tendon of the shoulder should also be remembered in this context. This bursa does not consist of a distinct sac, but rather its synovial layers blend with and are firmly attached to the underlying rotator cuff<sup>14</sup>. The possibility that the mild joint synovitis associated with PMR may represent a secondary phenomenon that arises from adjacent extra-articular inflammation has been previously proposed<sup>15</sup>. That bursitis in this condition could similarly reflect a primary pathology within the tendon itself should now be considered. Certainly there can be little doubt, amid this accumulating evidence, of the involvement of the connective tissues surrounding the tendons and muscles of the shoulder and pelvic girdle in the pathogenesis of PMR. Musculotendinous inflammation as the defining pathology of PMR not only provides a unifying anatomic basis for established disease manifestations including capsulitis and bursitis, but also goes some way toward finally explaining the profound myalgia experienced by patients with PMR, which has been so inadequately accounted for by our understanding of this condition to date.

Imaging, of course, cannot characterize histopathology, and dedicated studies are needed to confirm the existence of musculotendinous inflammation in PMR. Some of the very first biopsy reports in this condition did document edema and perivascular chronic inflammatory cell infiltration of the muscular fascia and its tendinous septum<sup>16</sup>. Similar inflammatory changes were identified at the shoulder joint capsule and bursa, while many arterioles exhibited active intimal endothelial cell proliferation, raising a possible pathoetiological link between PMR and GCA. An immunofluorescence study of biceps biopsy samples similarly revealed immune complex and fibrinogen deposition in the perifascicular areas of the perimysium<sup>17</sup>. The authors concluded that muscle pathology in PMR was likely characterized by inflammation of the interstitial tissues. Finally, a more recent microdialysis study documented increased interstitial concentrations of key cytokines including IL-6 in the symptomatic trapezius and vastus lateralis muscles of patients with PMR<sup>4</sup>. Once again, these abnormal levels normalized after prednisolone treatment and this correlated with complete symptom resolution, providing further proof of the response of inflammation within muscle connective tissues in PMR to conventional therapy and linking its resolution to positive clinical outcomes.

It is increasingly apparent from recent publications including Laporte, *et al*<sup>8</sup> that the extracapsular pattern of inflammation previously identified on imaging in PMR corresponds with musculotendinous structures of the shoulder and

pelvic girdle. Musculotendinous inflammation therefore represents the defining pathology of PMR, given that extra-capsular abnormalities have previously been identified as the point of difference between PMR and other rheumatic conditions. The connective tissues surrounding the tendons and muscles (peritendineum and perimysium) appear to represent the anatomic basis of PMR's pathology, with secondary

involvement of adjacent structures including the joint capsule and bursa. In Figure 1, we note the close proximity of hamstring peritendonitis to newly recognized localized myofascial lesions in a patient with PMR from our own study<sup>12</sup>, and present a detailed illustration depicting sites of musculotendinous inflammation in this condition. Ultimately, more detailed histological studies are necessary to elucidate

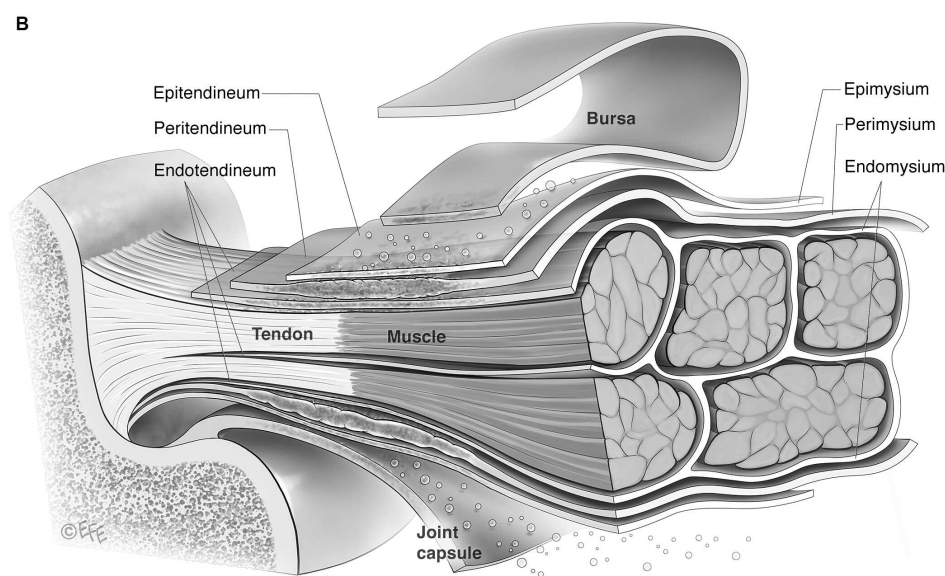
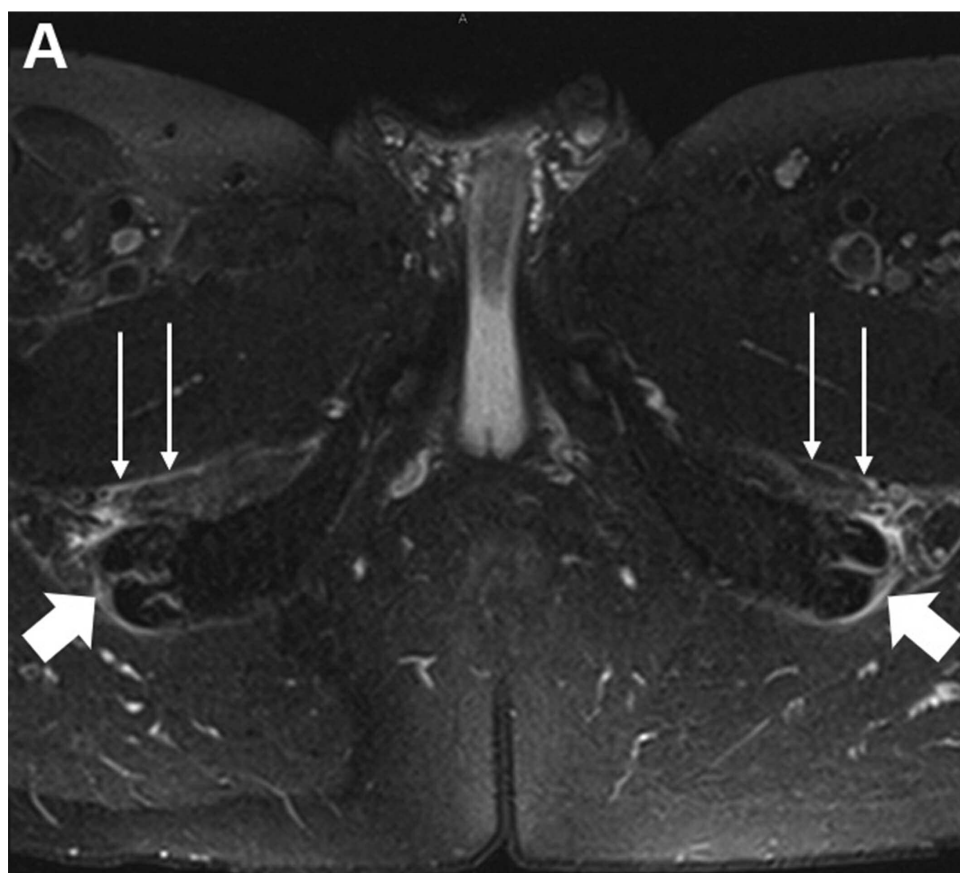


*Figure 1. Musculotendinous inflammation in polymyalgia rheumatica (PMR). A. T2-weighted FS MRI reveals the close anatomical relationship between previously documented proximal hamstring peritendonitis (thick arrows) and newly recognized localized myofascial inflammation of the obturator externus (thin arrows) in a patient with PMR. B. A depiction of musculotendinous pathology in PMR arising from the connective tissues of the tendons and muscles (peritendineum and perimysium) to involve adjacent structures including the joint capsule and bursa. Used with permission.*

the precise immunopathologic profile of PMR and enable long-overdue therapeutic advances in this condition. In the interim, PMR should be recognized for what it truly is — not a syndrome of shoulder and pelvic girdle pain and stiffness, but a chronic, inflammatory disease of musculotendinous structures.

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