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Abstract

Total joint arthroplasty (TJA) is an effective treatment for end stage osteoarthritis (OA), which aims to alleviate pain and improve function and mobility. Despite the remarkable success of TJA, complications can arise, leading to unplanned hospital readmission, implant failure, morbidity and mortality. Recently, there has been a growing interest in analysing sex-based differences in diseases and response to medical interventions. This review summaries evidence pertaining to the widening gap between men and women regarding the utilisation and outcome of TJA surgery. Interactions between sex and patient-reported outcome, implant failure and medical complication are complex and often demonstrates conflicting results. Significantly, there is a global consensus that men are at a higher risk of developing prosthetic joint infection (PJI) following joint arthroplasty. Guided by the literature, there is a clear need for standardised methods of collecting, analysing and reporting sex-specific data to improve outcomes for both men and women who undergo TJA.

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Main Text

Introduction

Published data has made it increasingly clear that males and females differ in the vulnerability to diseases, injuries and response to medical interventions. Within musculoskeletal health, women have a higher prevalence of osteoarthritis (OA), spinal disorders and certain soft tissue tumours(1, 2); the incidence of anterior cruciate ligament (ACL) injury is significantly higher in women compared to men(3); and differences in the efficacy of analgesics to treat conditions such as arthritis has been previously described(4). It is noteworthy that females remain underrepresented in clinical trials and animal models of disease, and in addition, studies are often limited by the fact that results are not analysed or reported separately by sex(5). As a result, the knowledge pertaining to the effect of female physiology, biology and responses to medical interventions is less well known when compared to males(5).

Total joint arthroplasty (TJA) is considered the gold standard treatment for OA, a leading cause of disability(6), and offers to improve patients' mobility, independence and quality of life (QoL)(7). In Australia alone, 66,346 and 50,784 total knee and total hip arthroplasties (TKA, THA) were performed in 2019 respectively(8). By 2030, the incidence of TKA and THA is forecasted to increase by 276% and 208% respectively, at a total cost to the Australian healthcare system of $AUD5.32 billion(9). Due to an aging population and

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growing obesity rates, this upward trend is expected to continue in in both Australia and worldwide(7, 8).

This narrative review highlights the importance of investigating sex in TJA research and identifies reported differences between men and women in the utilisation of surgery, patient reported outcomes, implant survival, medical complications and infection following hip and knee arthroplasty. Bringing awareness to the themes and issues in the TJA literature, we intend to lay the foundation for future research to further investigate the implications of sex differences for diagnosis and treatment of complications, and by doing so help clinicians to facilitate equitable delivery of medical information and treatment resources to patients.

Why is Sex-Specific Analysis and Reporting Important in Research?

The terms ‘sex’ and ‘gender’ are controversial in research and often inappropriately conflated in scientific literature and public media. In accordance to the Institute of Medicine(10), this review defines ‘sex’ as a biological classification generally as male or female according to their reproductive organs and function assigned at birth and ‘gender’ pertains to the socially constructed roles and behaviours which render an individual’s self-presentation as male, female, woman, man or gender diverse. While both biological (sex) and social/cultural (gender) differences are important, this review focuses on how patients’ sex can impact health, disease and treatment outcome.

Accounting sex as a key biological factor in research is crucial to promoting reproducibility through rigor and transparency and yet, only a decade ago, 70% of the orthopaedic literature failed to conduct sex-specific analysis and reporting(11). The historical underrepresentation of females in human clinical trials and animal models of disease has generated incomplete data relating to the aetiology, presentation and treatment of diseases which have been traditionally examined in the context of the male sex(11). As a result, treatment guidelines are

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generated with a substantial male bias, which has important consequences. This was highlighted in 2005 when 80% of drugs withdrawn from the USA market were due to adverse reactions affecting women that weren't captured during initial trials(2).

In 1993, the National Institutes of Health (NIH) Revitilisation Act mandated appropriate inclusion of women in clinical trials(11). Almost 30 years have elapsed and sex-specific reporting and analysis remains inadequate(5). The common practice of adjusting results by sex means the average combined male and female data can mask existing variances, and therefore clinically relevant differences related to the efficacy of medical devices may be obscured(2). In order to examine these differences, investigators should: (i) consider sex when formulating research questions and hypothesis testing, (ii) appropriately enrol a sufficient number of males and females within the sample cohort, (iii) analyse and report data separately for males and females and (iv) consider the influence of sex when interpreting and generalising research findings(12). As opposed to a one-size-fits-all approach, highlighting differences between men and women in medical research provides clinicians with an enhanced understanding of disease mechanisms, thereby facilitating shared decision-making and empowering patients to exercise control over their healthcare journey.

Sex, Gender and the Utilisation of TJA

The treatment of OA has become a global healthcare challenge. Not only do women have a higher overall prevalence of OA(13), but they also experience worse symptoms and disability compared to man despite sharing similar radiographic severity(13, 14). While the mechanisms remain unclear, declining levels of oestrogen, as seen in postmenopausal women, has been associated with reduced adult cartilage health(6). In addition, women presenting for TJA tend to be at a more advanced stage of their disease trajectory(15), while also being older and more obese, both of which are known risk factors for OA(6). Despite the greater need for joint arthroplasty in women, both utilisation and willingness to undergo TJA surgery is less for women than men (16-18). In this regard, a pronounced gender bias has

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been reported when it comes to the clinical decision making of elective surgery. A prior study indicates that in clinical practice, a physician and orthopaedic surgeon is less likely to refer a knee arthroplasty to a female patient compared to a male(18). Possible explanations for this finding include, gender norms that are reflected in healthcare in which clinicians have been reported to not take women's pain seriously and assign symptoms to psychological rather than physical causes(19) and the stereotype that women don't receive the same benefit from joint arthroplasty when compared to men. In addition, women are typically the primary family caregiver which might partially explain why women are more likely to accept persistent functional decline and delay in treatment(20). This indicates that women are potentially at a more advanced stage in their disease trajectory when presenting for TJA than males, which is important since those with more severe OA preoperatively report worse postoperative outcomes(21). Moreover, linking the anatomical sex-differences of the hip and knee to normal limb/joint kinematics and function has led to the development and use of sex-specific implant designs which to date have failed to demonstrate superiority in functional, pain or implant survival outcomes(22).

Sex in TJA and Postoperative Outcomes

Patient-reported Outcomes

Women show a greater risk of moderate to severe postoperative pain at two and five years after TKA(23). Possible mechanisms that might contribute to this difference are found in studies that report women are more sensitive to painful stimuli and are more likely to report high levels of distress and pain symptoms as opposed to men(24). However, in a sex-specific analysis, Nandi et al(24) found that by six weeks postoperatively, differences in reported pain between men and women were no longer evident. Importantly, due to the underrepresentation of females in clinical research, the influence of sex on anaesthetic and pain medication

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remains scant and unclear(25). Nevertheless, evidence suggests numerous physiological and pharmacological differences between male and females which might impact the safety and effectiveness of certain pain medication and therefore contribute to the observed differences in postoperative pain(25). Aside from pain, postoperative quality of life and functional status can also be indicated by clinical rating scores and self-reported questionnaires(26). For both six months and two years following knee surgery, women report to have greater improvements in Oxford Knee Score, Knee Society Score and Short Form-36 Health Survey (SF-36), however men report higher overall clinical scores as well as better knee flexion(27). This suggests women achieve greater improvements of function than men following TKA, but do not attain the same final level of function. For hips, Singh and Lewallen(28) found that female sex was associated with significantly higher dependence on walking aids and activity limitation at two- and five-years postoperatively. It has been postulated that increased severity of postoperative pain in women could potentially interfere with their functional recovery.

Survivorship Free of TJA Revision

Along with pain relief, an increasing number of patients seek TJA to maintain an active lifestyle, regain the ability to participate in various sporting activities and maintain general health(29). Despite the remarkable success of the procedure, some implants will fail which can require additional surgeries and burden the healthcare system(30). The impact of sex on TJA revision rates from aseptic causes varies in the literature. An earlier systematic review found that men experiences an increased the risk of aseptic revision(30). Age has been suggested as a driver of aseptic failure in men because they tend to present for TJA at a younger age(30) and reported to be more active than women(31). In this regard, the elevated muscular strength from physical activity among men could result in increased torsional forces on femoral components which might influence aseptic loosening, but this was examined in

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rheumatoid patients rather than osteoarthritic patients(32). Some implants have been shown to perform worse in women than men such as the metal-on-metal (MoM) hip implants where a large UK registry-based study reported poorer implant survivorship in women (33). However, controversy remains over MoM hip replacements with concerns involving metallosis and adverse reactions which increase the risk of aseptic and seems to be more prevalent in female patients(34, 35). Interestingly, another systematic review and meta-analysis found geographic variability with regards to sex and implant failure(36). In this study, males in Europe had an increased risk of THA revision, whereas males in the US had a decreased risk. The causes for this are unclear but the authors suggest it could partially be due to varying criteria for revision between the two regions(36-38).

Considering implant dislocation, Kim et al concluded that females were 2.5 times more likely to dislocate their hip implant compared to males(39). However, the substantial underrepresentation of females in the sample (n=464) as compared to males (n=804) gives rise to a potential source of bias which can lead to a systematic over- or under-estimation of dislocation rates across sex groups. In contrast, a study done in Australia(40) reported no significant effect of sex on dislocation outcomes. However, not only was a sex-specific analysis and reporting absent from the methodology, but the true dislocation rate remains unknown. The study's variable of interest was dislocation resulting in revision surgery and therefore fails to account for patients who incur a dislocation but are unable or unwilling to undergo a revision surgery.

Medical complications

While the impact of sex on medical complications has been widely published in literature pertaining to vascular surgery(41), this is not the case for TJA. In addition to the paucity of sex-specific analysis and reporting, the absence of a standardised grading system for postoperative TJA complications can lead to confusion and hamper accurate interpretation of surgical outcomes(42). For instance, Basques et al(43) investigated 6,123,637 TKA and THA

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patients and concluded that women had increased overall adverse events, however, this was primarily due to a higher frequency of urinary tract infections (UTI). In the same study, men had increased rates of infection, cardiac arrest, myocardial infarction, pneumonia and mortality. This is important since infection and cardiovascular event are leading reasons for 30-day readmission following TJA(44) and also because cardiac arrest and pneumonia are frequently occurring complications among those who die following THA(45). Other findings include, women showing higher rates of deep vein thrombosis, pulmonary embolism and blood transfusions(46, 47).

Notably, most studies that focus on the influence of sex on medical complications are (i) conducted in the US, (ii) have extracted data from the same registry, the American College of Surgeons National Surgical Quality Improvement Program, and (iii) are conducted within overlapping years(43, 45, 47). While it is possible for authors to perform different or more complex analyses with the same dataset, looking into sample groups from other global locations, such as Australia, could add meaningful information due to factors such as geographic variability.

Surgical Site Infection

‘‘Postoperative infection after total hip replacement is the saddest of all complications”. - Sir John Charnley at the Hip Society, 1982(48).

Surgical site infections (SSI) can be superficial, deep incisional, organ/space or implant infections and are known to inflict deep physical, mental and economic suffering(49). While evidence of sex differences for other complications seem to be inconsistent, it is increasingly clear that males are at a substantially higher risk of developing infections after TJA

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surgery(50). This phenomenon might be explained by the varying influence of sex-specific hormones on immune response, in that oestrogen increases antibody production while testosterone decreases antibody production(51). Not to mention, men have significantly longer operative time for TJA surgery and prolonged operative time is associated with increased risk of joint infection(52). A Norwegian study reported that males are 2.4 times more likely to have a revision for joint infection when compared to females (95% CI 1.8-3.1 P<0.001)(53) and at the 2013 International Consensus Meeting on Prosthetic Joint Infections (PJI), experts agreed that male sex increased the risk for surgical site infections (SSI) and in particular PJI following TJA(50). Along with the devastating impact on patients' physical and mental health, there are substantial economic costs associated with PJI. Joint infection is the leading cause of implant failure in the United States(54), while in Australia, revision surgeries due to infection has increased 72% from 2006-2012 to 2013-2018(8).

Importantly, comorbidities such as obesity and blood transfusions, have also been cited as risk factors for PJI development(49). However, despite higher infection rates in men, the literature suggests that female TJA patients present with significantly higher rates of obesity, morbid obesity and postoperative transfusions rates than male TJA patients(46, 55). In addition, evidence has associated diabetes mellitus (DM) with increased risk of joint infection, and worse QoL after TKA, with females experiencing poorer outcomes compared to males(56). This highlights the complex interactions among covariates that could potentially lead to infection. Moreover, in a meta-analysis investigating TJA infection rates, Chen et al(57) noted that "gender-specific effect estimates were rarely concluded", implying that there is a need for increased methodological rigor and sex-specific analysis to improve the quality of evidence to draw conclusions.

Summing Up: The Need for Further Research

Investigating differences between men and women is a pressing issue in orthopaedics, a field in which substantial sex differences are demonstrated in the prevalence of osteoarthritis,

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utilisation of arthroplasty and baseline pain and function of patients presenting for TJA. In addition, the interaction between sex and postoperative outcomes of TJA is complex. Women report more severe postoperative pain and reduced overall functional ability compared to men. The risk of an adverse event is greater for women, but this is mainly due to the higher frequency of UTIs in this group, whereas men show higher rates of cardiac events and mortality following surgery. Evidence regarding sex and risk of aseptic revisions, is inconsistent. Nevertheless, there is a global consensus that men have a significantly higher risk for developing joint infection following TJA. PJI is a major cause for revision surgery worldwide and a significant burden for both patients and surgeons. To the best of our knowledge there is a paucity of literature that investigates the characteristics of joint infection between men and women or sex differences in PJI treatment outcomes. Given the growing evidence that men and women often experience disparate outcomes following TJA, there is a clear need for standardised methods of collecting, analysing and reporting sex specific information to improve outcomes for both men and women who undergo TJA.

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Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution Statement

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All authors contributed to the conception, design of the study, and interpretation of the data. AC and CS were responsible for data and literature acquisition. AC wrote the first draft. All authors contributed to revising the manuscript for critically important intellectual content, read, and approved the submitted version.

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