

## **Too Fit To Fracture: A consensus on future research priorities in osteoporosis and exercise**

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## Mini-abstract

An international consensus process identified the following research priorities in osteoporosis and exercise: study of exercise in high risk cohorts; evaluation of multimodal interventions; research examining translation into practice, and a goal to examine fracture outcomes.

## Abstract

**Purpose:** To identify future research priorities related to exercise for people with osteoporosis or an osteoporotic spine fracture via international consensus.

**Methods:** An international expert panel and representatives from Osteoporosis Canada led the process and identified opinion leaders or stakeholders to contribute. Four patient advocates identified quality of life, mobility, activities of daily living, falls, bone mineral density, and harms as outcomes important for decision-making. Seventy-five individuals were invited to participate in an online survey asking respondents to define future research priorities in the area of osteoporosis and exercise; the response rate was 57%. Fifty-five individuals from 7 countries were invited to a half-day consensus meeting; 60% of invitees attended. The results of the online survey, knowledge synthesis activities and results of the focus group were presented. Nominal Group Technique was used to come to consensus on research priorities.

**Results:** Research priorities included the study of exercise in high risk cohorts (e.g.,  $\geq 65$  years, low BMD, moderate/high risk of fracture, history of osteoporotic vertebral fractures, hyperkyphotic posture, functional impairments or sedentary), the evaluation of multimodal interventions, research examining translation into practice, and a goal to examine fracture outcomes. The standardization of outcomes, or protocols that could be evolved into large multicentre trials was discussed.

**Conclusions:** The research priorities identified as part of the Too Fit To Fracture initiative can be used to inform the development of multicentre collaborations to evaluate and implement strategies for engaging individuals with osteoporosis in safe and effective exercise.

Key words: exercise, fracture, osteoporosis, physical activity

## INTRODUCTION

Osteoporosis-related fractures are a serious source of morbidity and mortality, and impose a substantial economic burden <sup>[1;2]</sup>. National (Osteoporosis Canada) and international (International Osteoporosis Foundation) organizations emphasize the importance of physical activity for the prevention of bone loss or fractures. However, there are research gaps that limit our ability to translate research into practice. Randomized controlled trials (RCTs) of exercise are predominantly limited to surrogate outcomes such as areal bone mineral density (aBMD). Weight-bearing exercise and/or resistance training can maintain or slow BMD loss, but may not result in large increases in BMD <sup>[3]</sup>. Exercise may have important effects on bone strength or fracture risk that are not measureable with BMD exams <sup>[4]</sup>. Population-based studies or long-term follow-up studies of RCTs examining the effect of exercise with fracture as an outcome have point estimates that suggest potential fracture risk reduction, but they are subject to bias or are underpowered, and a few suggest that the risk of certain types of fracture may be slightly increased <sup>[3;5-15]</sup>. There is good evidence that exercise can prevent falls in at-risk older adults <sup>[16;17]</sup>, which could indirectly prevent fractures; some researchers suggest that fall prevention, and not changes in BMD, should be the therapeutic target <sup>[18]</sup>. Recent meta-analyses and position papers have called for large RCTs to provide more conclusive evidence whether exercise can prevent fractures <sup>[18;19]</sup>. Others have emphasized the importance of including sophisticated measures of bone structure and strength in addition to aBMD <sup>[20]</sup>. Consensus on outcomes for future research would allow for consistency and comparability of effects to move research on osteoporosis and exercise research forward.

There are a number of key research questions that remain regarding which outcomes to use, what populations to target, what type or dose of exercise to study, and how to translate knowledge into practice. The majority of trials examining the effects of exercise on bone strength have included postmenopausal women, but few have targeted high risk individuals or older men. Evidence on the efficacy and safety of exercise is scarce for individuals with severe osteoporosis and fragility fractures <sup>[21]</sup>, posing barriers to health care providers and consumers seeking safe and effective exercise as a means to improve function and reduce fracture risk. It is only recent that meta-analyses have been able to pool studies with heterogeneous interventions to investigate efficacy specific to the type of exercise, and it is clear that the effect on BMD or fall risk depends on the characteristics of the participants, and of the type and dose (intensity,

frequency and duration) of exercise <sup>[3;22;23]</sup>. In addition, it is critical to determine what is effective when delivered in a real-world clinical or community setting. Determining future directions for research in osteoporosis and exercise can inform the design of clinical trials, but may also inform the development of exercise recommendations and facilitate enhanced patient engagement. The Too Fit To Fracture initiative was established to synthesize knowledge around exercise for individuals with osteoporosis or osteoporotic vertebral fracture, to establish practice recommendations, and to identify future research priorities. The current report outlines a process aimed at identifying clinical research priorities in the area of osteoporosis and exercise from the perspective of researchers and clinicians from multiple disciplines and countries.

## **METHODS**

The Too Fit To Fracture initiative is an international collaboration with three main aims: 1) to develop evidence-based exercise recommendations by synthesizing research on the effects of exercise on outcomes important for decision-making, using the GRADE consensus process; 2) to identify future clinical research priorities in the area of osteoporosis and exercise; 3) develop physical activity recommendations based on evidence and expert opinion by combining what we learn in our GRADE consensus with what experts recommend in a Delphi consensus process, where the latter is designed to address questions often asked by patients for which there is no research evidence to generate answers. The outcome of Aim 1 has been published previously, and the current report addresses Aim 2. For Aims 1 and 3, the expert panel came to consensus on the target populations for the knowledge synthesis process, and it was decided that the goal was to develop exercise recommendations for individuals over the age of 65 years with osteoporosis, with or without vertebral fracture. For Aim 2, we conducted a multi-step process to establish clinical research priorities: 1) Forming an expert panel; 2) Obtaining perspectives on research priorities from researchers, clinicians and stakeholders via online survey; and 3) Holding a consensus meeting to finalize research priorities.

### **Forming the expert panel**

The Too Fit To Fracture Expert Panel includes researchers and clinicians from Australia, Canada, Finland and the United States, and partners from Osteoporosis Canada. Criteria used to select panel members were previous experience with guideline development, experience in conducting clinical trials of exercise in individuals with osteoporosis or vertebral fracture, or having clinical or biomechanics expertise related to exercise prescription or nutrition in individuals with osteoporosis or spine fractures. Members of expert panel included expertise in physical therapy, geriatrics, internal medicine, endocrinology, epidemiology, dietetics, biomechanics and kinesiology.

### **Perspectives on research priorities– online survey**

The Expert Panel identified researchers and clinicians that should be invited to contribute their opinion on research priorities. Participants were identified based on a history of high-quality research on osteoporosis and exercise in older adults, or recognized clinical expertise in exercise and osteoporosis. Stakeholder groups identified included Osteoporosis Canada, the Canadian Osteoporosis Patient Network, Osteoporosis Australia, the National Osteoporosis Foundation,

and the International Osteoporosis Foundation. A list of 75 researchers, clinicians and stakeholder representatives to be invited to participate was agreed upon. We used FluidSurveys (<http://fluidsurveys.com/>) to distribute an online survey to all invitees. The survey was part of a larger modified, online RAND/UCLA Delphi method to identify appropriate exercise prescription for defined clinical indications, as was done for the 2010 Osteoporosis Clinical Practice Guidelines <sup>[24]</sup>. For the current project, we included questions on research priorities:

*What should our future research priorities be in the area of osteoporosis and exercise? What research questions, if answered, would have a large impact on the field?*

*Consider: need for knowledge, or curiosity-driven research needs or gaps in evidence to inform clinical practice impact of research on policy decisions.*

The survey participants then answered a series of questions about exercise prescription for three different clinical scenarios. At the end of the survey they were asked: *Has the survey caused you to think of any additional research questions that need to be addressed to advance the field?*

The identified research priorities were reviewed and ranked according to the frequency that they were mentioned. One panel member (LG) performed a content analysis to identify common themes and grouped responses accordingly; the frequency of responses under themes was noted <sup>[25]</sup>.

### **Identifying Patient-Centred Outcomes**

Four patient advocates with osteoporosis or vertebral fractures (1 male, 3 females) were identified by the Canadian Osteoporosis Patient Network and invited to be interviewed as a group about the outcomes that they considered important for decision-making. An interview guide was developed and included the following questions:

*Do you exercise? What types of exercise do you do? Why do you choose those types of exercise?*

*What are the most important reasons for exercising?*

*If you had to pick just one outcome, which one do you think is the most important for you?*

*Why do you think a person with osteoporosis might start an exercise program? What might make you stop exercising? What do you think will change if you stop exercising?*

*What are the risks you are willing to accept to participate in exercise?*

During the discussion, emerging themes/concepts were documented, summarized and repeated back to participants to confirm that the interpretation was correct. Additional discussion often emerged from the summaries. A final summary was agreed upon by all participants. One patient advocate reviewed this report for accuracy and relevance.

### **Research Priorities Consensus Meeting**

Fifty-five researchers, clinicians, trainees and stakeholder representatives from Canada, the United States of America, Belgium, Switzerland, Germany, Finland and Australia were invited to participate in a half-day consensus meeting, held in Minneapolis, Minnesota on October 11<sup>th</sup>, 2012, and 33 invitees were able to attend. The meeting began with a presentation of the findings of the knowledge synthesis activities completed by the Panel, which included exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fracture, and gaps in research that were identified during the knowledge synthesis process <sup>[26]</sup>. The participants were then presented with the research priorities identified in the online survey; the themes in rank order of frequency, and examples of responses under each theme were presented, as well as other responses that did not fit under themes.

Participants were placed in groups of four to six, with efforts made to diversify the groups with respect to discipline, country of origin and gender. We used Nominal Group Technique <sup>[27]</sup> to reach consensus. The technique requires independent contributions from each member and enables effective group decision-making <sup>[27]</sup>. There were three rounds of discussion, where group members were shuffled each time. At the end of each round, the groups presented their top priorities to the larger group. Participants were encouraged to word their priorities using PICO format, with emphasize on population, intervention, comparator and outcomes that should be prioritized in future research <sup>[28]</sup>. During the last round, the groups were tasked with identifying strategies to accomplish the research priorities, and barriers to research. The event culminated in a large group discussion where consensus was reached on research priorities, and strategies to build research capacity were identified. The first draft of this report was circulated to the Expert Panel and all participants for review, to ensure it accurately reflected their experience or perspectives. Additional experts who did not participate were asked to provide feedback on its utility and clarity. All contributors to the work are listed in Table 1.

## **RESULTS**

### **Online Survey**

Forty-three responses to the survey questions were recorded (57% response rate). Participants self-identified with the following profiles (some overlap): 25 (58%) academics, 7 (16%) physical therapists, 3 (7%) kinesiologists, 3 (7%) family physicians, 4 (9%) geriatricians, 3 (7%) dietitians, 1 (2%) rheumatologist, 1 endocrinologist, 1 epidemiologist and health economist, 1 biomechanist, 1 exercise specialist, 1 orthopaedic surgeon, 1 nurse practitioner, 1 patient advocate and osteoporosis counselor, and 2 academic trainees. The responses, grouped by major themes, are presented in Table 2. Additional responses are listed in Table 3.

### **Patient-centred outcomes and perspectives on exercise interventions**

Patient advocates indicated that exercise was important to them as a way to take an active role in their health. Notably, they felt that the diagnosis of osteoporosis placed restrictions on the types of exercise they could do. They were concerned about the risks associated with activities that were socially engaging and fun to do, like dancing and curling, and stated that the exercises recommended for them were boring and not inspirational. They wanted to know the safety of exercises or exercise classes, and to have instructors who had knowledge of osteoporosis. Having a diagnosis of osteoporosis was harder to deal with than having a fracture, because the fracture healed but the osteoporosis diagnosis was permanent. They identified quality of life and functional outcomes, such as mobility and activities of daily living as important. They noted that the reduction in function associated with a fracture was equally, if not more important to them as an outcome than the fracture itself. "...you're not a person anymore [when you need so much help with activities of daily living]...you are a thing that people have to look after." Measurable, concrete outcomes and estimated effects on those outcomes were identified as important for motivating people to exercise. Bone mineral density was noted as a measure of bone strength that they wanted to target with exercise, and could be measured. Fall prevention and improved balance were seen as important contributors to reduced fracture risk.

### **Consensus meeting**

The 33 attendees included (some overlap): 18 academics, 6 exercise scientists, 3 family physicians, 1 geriatrician, 2 internal medicine physicians, 6 physical therapists, 3 epidemiologists, 1 endocrinologist, 1 biomechanist, 2 dietitians, 1 medical physicist, 1 health



economist, 3 trainees, 1 National Osteoporosis Foundation representative, 1 International Osteoporosis Foundation representative, 1 advocate from the Canadian Osteoporosis Patient Network, and 4 representatives from Osteoporosis Canada.

The consensus on key research priorities was broken down into PICO elements: Population, Intervention, Comparator, Outcome. Additional questions that did not fit the PICO elements were identified.

*Population:*

A clear theme that emerged was that many previous studies of exercise had been performed in low-risk women; future research should target males and females with risk factors for fracture or impairment. Specifically, future research should prioritize studying the effects of exercise in individuals with the following characteristics: at least 65 years old, having low BMD, being at moderate or high risk of fracture, having a history of osteoporotic vertebral fractures, having hyperkyphotic posture, or having functional impairments or sedentary lifestyle. It was noted that many studies to date had excluded individuals on osteoporosis medication, and that researchers should choose to stratify based on use of osteoporosis medication to understand the interaction between medication and exercise. *Intervention:*

Two themes emerged when discussing priorities around interventions. The first theme was that interventions need to be multimodal e.g., interventions that combine weight-bearing aerobic exercise with strength training and balance training, or interventions that combine exercise with postural retraining. A second theme was to prioritize research examining implementation.

Priorities under this theme included examining how to implement exercise into primary care, how to use technology to enhance exercise prescription, testing dose-response, consideration of what patients of different genders or clinical presentations would be able and willing to do, and understanding the optimal exercise type and dose (i.e., duration, frequency, and intensity) that have the greatest effect on the outcome of interest – for example, evaluating dose-response, or the efficacy of short duration exercise versus long duration exercise (e.g., 10 min, 3x/day, 6 days/week vs. 30 min all at once, 6x/week). The latter priority arose during discussions of how to use basic science research to inform the design of clinical trials, in that basic science evidence has suggested that shorter, more frequent bouts may be more osteogenic; trials focused on examining which exercise type or dose is most effective for stimulating changes in bone in humans may allow a better understanding of mechanisms. In addition, it may be easier to engage

older adults in participating in shorter, more frequent bouts. Any exercise intervention should ensure adequate calcium, vitamin D and protein intake.

*Comparator:*

The comparator used in exercise trials was acknowledged as something that requires more careful consideration. The consensus was that comparator groups receive standard care, or standardized exercise guidelines consistent with national or international recommendations. Comparative effectiveness studies could be used to determine the effectiveness of a specific intervention relative to others, but careful attention to sample size calculations would be needed to ensure adequate power to observe between group differences if both interventions were hypothesized to have an effect on the outcome(s).

*Outcome:*

There was consensus that large trials are needed to examine the effects of exercise on the incidence of fragility fractures, including vertebral fractures, to make a strong case for the implementation of exercise programs. There was discussion around the sample size required for a trial with fracture as a primary outcome, and mention of prior estimates <sup>[19]</sup>. There was concern about the heterogeneity across outcomes used to date. There was consensus that multi-site collaboration on a large RCT would be necessary if fracture was the primary outcome. Several suggestions were made: 1) agree on a standardized protocol for intervention and outcome assessment for future trials with similar aims; 2) establish feasibility of recruitment, retention and adherence for the large trial at one or more sites, and then roll that into a larger trial by applying for funds in multiple jurisdictions with the same protocol <sup>[29]</sup>; and 3) consider evaluating multiple research questions related to exercise with one large trial. Aligned with this priority was the need to evaluate the safety of exercise (e.g., systematic monitoring of adverse events), particularly in high risk individuals, since exercise has the potential to increase the risk of fracture <sup>[6;7]</sup>. Ongoing trials evaluating the feasibility of a large trial in high-risk individuals (<http://clinicaltrials.gov/ct2/show/NCT01761084?term=vertebral+fracture&rank=11>) or with fracture as an outcome (<http://www.hta.ac.uk/project/2146.asp>) were mentioned. There was consensus that future trials still needed to consider outcomes on the causal pathway to fracture, such as falls or BMD, but that outcomes should be standardized. A novel question arose around the ability of exercise to prevent the progression from one fracture risk category to a higher level

of fracture risk. Other priority outcomes considered important for decision-making include cardiovascular risk factors, cost-benefit, resource use and function (e.g., safe functional motion, physical performance). Other outcomes of interest include cognition and muscle size, strength and quality.

*Barriers to research or implementation, other priority research questions:*

Although there was interest in a large-scale RCT with fracture as an outcome, there was concern about the strong emphasis on RCTs as the only way to address research questions of efficacy. There was concern about the feasibility of acquiring funding for a RCT with such a large sample size. Therefore, a future priority is to identify or test designs other than standard RCTs to answer questions on the effects of exercise e.g., large observational trials, stepped wedge designs, or a pragmatic design nested in a health care system <sup>[5;30;31]</sup>. Exercise interventions are costly to implement in practice because of staffing requirements, so studies examining cost-benefit or alternative methods of implementation that minimize cost are needed. Interventions aimed at increasing physical activity, or reducing sedentary behaviour, rather than specific exercise interventions, may be of interest. Adherence was identified as barrier to research and to implementation. Priority should be placed on validating self-report measures of adherence, as well as developing tools to record physical activity loading profiles. It is important to identify the type of exercise members of the target groups are willing to do prior to designing interventions, and investigating whether incorporating behaviour change strategies can improve adherence and efficacy. Prior to initiating a fracture prevention trial, there is a need to test, in a representative cohort of individuals, a battery of safe exercises that people at risk of fracture can (and are willing) to perform – and exercise to avoid.

## DISCUSSION

The perspectives of researchers, clinicians and knowledge users on research priorities related to osteoporosis and exercise were established using a formal consensus process. Future research should consider research in individuals at risk of fracture, and evaluating outcomes important to patients in addition to fracture outcomes. Research examining the optimal exercise type and dose, multimodal interventions (e.g., combined strength, aerobic and balance training) or ways to effectively implement exercise prescription in practice was emphasized. There may be a need to incorporate behaviour change strategies to enhance adherence as well as more objective methods for measuring adherence.

We acknowledge that the number of patient representatives was small, and because they were from an advocacy group, they may not be representative of patients not engaged in advocacy or self-management. Our aim was not to conduct an in-depth study of patient perceptions; their input reinforced the importance of establishing patient-centred outcomes. More work from a larger, more representative sample is needed to understand their perceived barriers to exercise participation, and the research questions that they would like to see answered. It should be noted that our knowledge synthesis activities and Delphi consensus process featured individuals with osteoporosis, with or without vertebral fracture, which may have influenced the discussion, resulting in the unintentional omission of certain important clinical populations, or greater emphasis on others; for example, there was little discussion of research in individuals with hip fractures. However, our initial question about research priorities to participants (results presented in Tables 2 and 3) was presented prior to exposure to the consensus process questions or knowledge synthesis findings. In addition, the over-arching theme of exercise and osteoporosis may have caused participants to focus on prevention-oriented research, rather than rehabilitation or therapeutic exercise for the treatment of impairments resulting from osteoporotic fracture.

## **CONCLUSIONS**

Research priorities included the study of exercise in high risk cohorts, the evaluation of multimodal interventions and a goal to examine fracture outcomes. Patient priorities were safety, improving functional outcomes, and having measurable outcomes to act as a motivator. The research priorities were identified by researchers, clinicians and stakeholders from multiple disciplines and can be used to inform the development of multicentre collaborations to evaluate and implement strategies for engaging individuals with osteoporosis in safe and effective exercise.

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**Table 1: Contributors to the Identification of Research Priorities on Osteoporosis and Exercise:** Individuals who responded to the survey or attended the meeting are listed here, and included individuals from the following disciplines: geriatrics, biomechanics, physical therapy, kinesiology, dietetics, epidemiology, basic bone biology, internal medicine, endocrinology, orthopedic surgery, medical imaging, rheumatology, occupational therapy and stakeholder groups (e.g., Osteoporosis Canada, National Osteoporosis Foundation). The patient advocates are not listed.

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**Table 2: Top Five Future Research Priorities Identified By Survey Respondents (n=42)**

<b>Response Category</b>	<b># of Related Responses (%)</b>
<b>Research to inform practice</b>	
What exercises are most effective? Dose/response, develop guidelines.	16 (38)
<b>Population-specific research</b>	
Evaluate efficacy or develop recommendations in specific populations	11 (26)
<b>How to get people to exercise</b>	
Translation of research to practice, community-based interventions, behavioural strategies	11 (26)
<b>Research with hard outcomes</b>	
Randomized trial of exercise with fracture as primary endpoint	8 (19)
<b>Evaluating harms</b>	
Adverse events, what exercises are risky	5 (12)

**Table 3: Additional Research Priorities Identified By Survey Respondents (n=42)**

<b>Response Category</b>	<b># of Related Responses (%)</b>
Evaluating cost-effectiveness of exercise interventions	3 (8)
Improving methodology or standardizing performance measures, e.g., bone quality, physical performance, QOL, axial skeleton.	3 (8)
Exercise effects on falls or balance or sarcopenia	3 (8)
What are needs and gaps in current knowledge or evidence?	3 (8)
Exercise effects on bone quality	2 (5)
What is the mechanism of reduced fracture risk (↓falls or ↑BMD)?	2 (5)
How do impairments contribute to activity and participation?	2 (5)
Interaction between exercise and nutrition or medication	2 (5)
Clarify influence of walking on fracture risk	1 (3)
Drive policy around maximizing peak BMD	1 (3)
Benefits of yoga, Tai Chi, Pilates	1 (3)
Signal transduction to cell response and how it can be amplified	1 (3)
Impact of lifestyle on bone health and fracture risk	1 (3)