MUSCULOSKELETAL STRENGTH, FALL AND FRACTURE RISK IN EARLY POSTMENOPAUSAL WOMEN

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By

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ABSTRACT

Purpose: To evaluate the course of recovery in fall-risk and functional status over the first year following a distal radius fracture (DRF), and evaluate differences in fall and fracture risk factors in women over the age of 50 years with a DRF compared to their non-fractured peers. **Methods:** Two cohorts of participants volunteered in two sub-studies of the thesis. The first was seventy-eight women recruited from a DRF Clinic within the first week after their fracture, and followed up in concert with standard clinic appointments at week three, nine, 12, 26, and 52 post-fracture. The second cohort consisted of women aged 50 years or older, with and without a recent distal radius fracture, being at least 6 months post-DRF, but no more than 2 years post-fracture. Seventy-seven women age 50-78 with (Fx, n = 32) and without (NFx = 45) a history of DRF were assessed on two occasions within 4 weeks apart using a battery of fall and fracture risk tools, including balance, mobility, gait speed, fracture risk assessment, as well as bone quality assessment using peripheral quantitative computer tomography (pQCT) and dual x-ray absorptiometry (DXA). **Results:** Fall-risk status (strength, balance, mobility) gradually improved over the first year post-fracture, with balance confidence remaining high even immediately post-fracture. In the second study, women with a recent DRF, compared to women without, demonstrated higher fall and fracture risk. Women with a recent DRF had lower bone and muscle strength in both the upper and lower extremities compared to the non-fractured controls, with no differences in DXA derived aBMD at the femoral neck or spine. **Significance of findings:** The results of these studies will help clinicians understand the normal course of functional recovery post-fracture, and assist in determining appropriate fall risk assessment and interventions for post-menopausal women at risk of fragility fracture. Results demonstrate the importance of studying women at risk of DRF as an important first indicator of bone fragility and risk of future fracture. These findings also strengthen the notion that DXA alone may not be the best predictor for fracture risk.

PREFACE AND AUTHOR CONTRIBUTIONS

I, Katie Crockett, was the primary author of all chapters within this thesis. Chapters 3 to 5 represent manuscripts that have either been submitted or have been published in peer-reviewed journals. Author contributions have been discussed and approved by the student advisory committee and were included as part of the student-supervisor agreement. Chapter 3 represents a manuscript that has been prepared and submitted to Journal of Orthopedic and Sports Physical Therapy and was co-authored by Dr. Jonathan Farthing, Dr. Jenny Basran, Dr. Vanina Dal Bello-Hass, Dr. Geoffrey Johnston, Dr. Charlene Haver, and Dr. Catherine Arnold. This portion of my thesis was a secondary study, part of a larger study where data also contributed to a previous thesis by Dr. Haver. There is no overlapping analysis as the data included in my study focused on different outcome measures over a longer time period. I developed the research questions, conducted the data analysis and interpretation, and prepared the manuscript under the supervision of Dr. Jonathan Farthing and Dr. Catherine Arnold. Dr. Basran and Dr. Dal-Bello-Haas contributed to the research design, interpretation of data and review of the manuscript; Dr. Johnston and Dr. Haver additionally contributed to data collection.

Chapter 4 represents a manuscript that has been prepared and submitted to Physical Therapy. Chapter 4 was co-authored by Dr. Saija Kontulainen, Dr. Jonathan Farthing, Dr. Philip Chilibeck, Dr. Brenna Bath, Dr. Adam Baxter-Jones, and Dr. Catherine Arnold. I contributed to components of the design, and was responsible for data collection, data entry, analysis and interpretation, and the writing of the manuscript under the primary supervision of Dr. Arnold. Dr. Kontulainen, Dr. Farthing, and Dr. Chilibeck contributed to research design, interpretation and review of the manuscript; Dr. Baxter-Jones, the primary investigator for the grant which funded this study and 2 others, contributed to research design, statistical analysis and review of the manuscript and Dr. Bath contributed to data interpretation and review of the manuscript. Chapter 5 represents a manuscript that has been submitted and accepted for publication to Osteoporosis International and utilizes the same subjects as Chapter 4, focusing on different outcome measures and research questions. Chapter 5 was co-authored by Dr.

Saija Kontulainen, Dr. Jonathan Farthing, Dr. Philip Chilibeck, Dr. James Johnston, Dr. Brenna Bath, Dr. Adam Baxter-Jones, and Dr. Catherine Arnold. I contributed to the design, and was responsible for data collection, data entry, analysis and interpretation, and the writing of the manuscript under the primary supervision of Dr. Kontulainen. The same author contributions as Chapter 4 apply to this study, Dr. Johnston provided additional advice regarding data analysis and interpretation and review of the manuscript.

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CONCEPTUAL DEFINITIONS

Bone strength: an estimate of a bone's resistance to external loading

Fall: an event which results in a person coming to rest inadvertently on the ground or floor or other lower level

Fall risk: an estimate of an individual's risk of falling, based on a variety of outcome measures which have demonstrated predictive or concurrent validity

Fragility fracture: a fracture occurring spontaneously or following minor trauma such as a fall from standing height or less

Functional status: an estimate of an individual's current ability to perform activities of daily living, such as standing from a chair, ambulating, and maintaining balance as measured from a variety of standardized functional outcome measures

Osteoporosis: a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture

Signal fracture: the first fragility fracture to occur, which should be considered a red flag for declining bone strength and future fracture risk

LIST OF COMMON ABBREVIATIONS USED

aBMD	Areal Bone Mineral Density (g/cm^2)
BBS	Berg Balance Scale
BMC	Bone Mineral Content (mg)
BMD	Volumetric Bone Mineral Density (mg/mm^3)
BSI_c	Bone Strength Index in compression (mg^2/mm^4)
CoA	Cortical Area (mm^2)
CoC	Cortical Content (mg/mm)
CoD	Cortical Density (mg/mm^3)
DRF	Distal Radius Fracture
DXA	Dual Energy X-ray Absorptiometry
MuA	Muscle Area (mm^2)
MuD	Muscle Density (mg/mm^3)
pQCT	Peripheral Quantitative Computed Tomography
SSI_p	Strength Strain Index (mm^3)
STS	Sit to stand
ToA	Total Area (mm^2)
ToD	Total Density (mg/mm^3)
TrA	Trabecular Area (mm^2)
TrC	Trabecular Content (mg/mm)
TrD	Trabecular Density (mg/mm^3)
TUG	Timed up and go test
TUGcog	Timed up and go test with cognitive task (dual-tasking)

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CHAPTER 1: INTRODUCTION, PURPOSE, AND OBJECTIVES

Early fragility fractures have recently been identified as "tremendous burden" on ageing Canadians, and our health care and social systems (Osteoporosis Canada, Fracture Liaison Services, 2013). Wrist fractures are commonly the first fracture to occur in early post-menopausal women, and are a known risk factor for a future hip fracture (Osteoporosis Canada, 2013). The reasons for this may be related to diminished bone strength in older adults with a history of fragility fracture, but may also be due to other factors such as changes in muscle properties and balance related to declining health and function following an injury. Further research is needed to determine the profile of middle-aged women at risk of sustaining an early fragility fracture, considering both fall and fracture risk factors.

Studying women with a recent distal radius fracture (DRF), and understanding the typical course of recovery over the first year post-fracture will assist in identifying key factors that may be addressed to identify those at risk of sustaining their first fracture (primary prevention). Studying women post-fracture, through intervention studies leading to rehabilitation protocol development will address secondary prevention of subsequent fractures. Although it has been established that DRFs, typically caused by a fall on the outstretched hands (Palvanen et al., 2000), are common in early post-menopausal women (Edwards et al., 2006; Orces & Martinez, 2011), there remains difficulty in predicting fall risk in this population due to the lack of standardized measurement tools and reference values for those younger than age 65. The majority of fall risk screening tools have been developed for those older than age 65. It is unknown if these same screening tools are effective in detecting fall risk in a potentially higher functioning, younger population, aged 50-64, a time period in the female lifespan when incidence of DRF increases (Orces & Martinez, 2011). The absence of reference values for this age group makes interpreting scores difficult for healthcare practitioners when attempting to determine fall risk. In addition to increased fall risk as a contributor to increased fracture risk, declining bone strength and muscle properties may also be key risk factors for fracture risk.

When determining fracture risk, there has been an apparent shift from a diagnosis of osteoporosis as defined by bone status to absolute fracture risk, with tools such as the Fracture Risk Assessment Tool (FRAX) (Sale et al., 2014). Despite this shift, the current standard protocol to screen for osteoporosis is dual energy x-ray absorptiometry (DXA)-derived areal bone mineral density (aBMD). As many fractures occur in women who are not osteoporotic when diagnosed by DXA (Jarvinen et al., 2008), assessment of bone structure and strength by more advanced technology such as peripheral quantitative computed tomography (pQCT) may enhance the identification of bone fragility and future fracture risk. This type of imaging can also measure muscle properties, such as cross-sectional area and density. By comparing these measures to traditional aBMD measures in a sample of women who have sustained a wrist fracture and those who have not, further knowledge of bone properties not detected by traditional measures can be determined. This information would enhance our understanding of bone strength in the early postmenopausal years, as well as provide a comparison sample for future research investigating changes in bone properties in early postmenopausal women over time or effects of various interventions. By combining this information with outcomes of commonly used fall and fracture assessment tools, the profile of those at risk of sustaining an early fragility fracture can be determined and ultimately lead to primary or secondary prevention.

Perceptions of fragility fracture causes in women over the age of 65 have been studied, suggesting that patients do not connect the cause of fractures to bone health (Sale et al, 2012). Patient explanations for the fracture occurring typically did not include bone health, but were reported to be due to “freak” or “fluke” events. These perceptions may be intensified in a younger population who do not perceive themselves as having a high risk of fracture. In addition to skewed patient perceptions, research indicates that practitioners may not be delivering appropriate follow-up care post-fracture as <10% of patients receive either a fall risk assessment or bone density assessment following a DRF (Myers & Briffa, 2003). Current guidelines recommend that when an older person (≥ 65) encounters a healthcare provider they should be screened for falls or risk for falling. If they present with: 1) two or more falls in the prior 12 months; 2) an

acute fall; or 3) difficulty with walking or balance, they should then be evaluated for gait and balance (Panel on Prevention of Falls in Older Persons, 2011). In addition, basic strategies for increasing bone health should be encouraged for all individuals over age 50, including regular active weight-bearing exercise, appropriate calcium and vitamin D intake, and fall-prevention strategies (Papaioannou et al., 2010). Any person over the age of 50 who sustains a fragility fracture should be referred for initial BMD testing and assessment of fracture risk (Papaioannou et al., 2010). Despite these guidelines, research indicates that appropriate follow-up is still not occurring (Myers & Briffa, 2003; Osteoporosis Canada, 2013). Osteoporosis Canada has identified a 'post-fracture osteoporosis care gap' in Canada (Osteoporosis Canada, 2013), suggesting a gap exists because: 1) the fracture is treated as an acute event by the orthopaedic surgeon or emergency physician who predominantly focus on immediate care for the fracture; and 2) the patient also treats the fracture as an isolated acute event and is unaware of the underlying contributing bone fragility. Appropriate and sensitive screening tools are needed to detect both fall and fracture risk in early postmenopausal women < 65 years of age in order to identify those at risk, but also use objective findings to enhance education on potentially declining bone health and physical function in the early stages when preventative strategies would be most effective. Without a clear understanding of the typical profile of women at risk of fragility fractures, and appropriate screening tools for this population, it may be difficult to use objective outcome measures to educate patients appropriately on their bone health and/or future fall and fracture risk.

DRF is a strong predictor of future fracture (Orces & Martinez, 2011); therefore, it is important to determine the characteristics of women who are sustaining early fragility fractures, including both fall and fracture risk factors, in order to identify those at risk of DRF and to prevent future fractures. With minimal evidence that identifies both fall and fracture risk factors in early postmenopausal women, and an aging population, the need to identify women at risk of falling and/or fracturing and intervene with the appropriate strategies to alleviate falls and fracture has become a national priority (Osteoporosis Canada, 2013). The overarching goal of this thesis is to increase the knowledge of the typical recovery period in

the first year post-fracture and to increase knowledge of the fall and fracture risk profile in this early postmenopausal population.

This thesis is comprised of three studies, which will be discussed separately in Chapters 3 to 5. The first study focused on the changes in fall risk in older women post-DRF. The typical course of recovery post-DRF specific to regional recovery at the wrist has been documented; however, the global course of recovery affecting overall physical function and fall-risk is unknown. The second and third studies compared fall and fracture risk status, as well as bone and muscle strength in postmenopausal women with a recent DRF compared to postmenopausal women without. The specific objectives and hypotheses for each study are described below.

Study 1 Title: Changes In Fall Risk In Older Women Post Distal Radius Fracture: A Prospective One-Year Follow-Up Study

The primary purpose of this study is to assess fall risk status and functional status at one, three, nine, 12, 26, and 52 weeks post-fracture in women over 50 years of age; changes in fall risk and functional status during post-fracture recovery; and if differences in fall risk and/or pattern of recovery exist in those aged 65 years and older, compared to those aged 50 to 64 years of age.

Hypotheses: Women with a recent DRF will demonstrate poorer scores in fall risk and functional status immediately following a DRF with improvement in scores over the course of the first year post-DRF. Women > age 65 will demonstrate poorer scores in fall risk and functional status as compared to women aged 50-64 years of age.

Study 2 Title: Fall And Fracture Risk Status In Postmenopausal Women With And Without A Recent Distal Radial Fracture

The primary purpose of this study is to compare fall and fracture risk status in postmenopausal women with and without a recent DRF. Secondary purposes include determining the relationship of fall risk to

fracture risk in older women and to determine the relationship of grip strength to fall and fracture risk status.

Hypotheses: The primary hypothesis is that women over the age of 50 years with a recent DRF will have higher fall and fracture risk, as compared to women with no recent history of DRF matched for a similar age, as measured by poorer performance in balance, mobility/lower body strength, grip strength, and a higher FRAX score. A secondary hypothesis is that higher fall risk will be associated with higher fracture risk in women with and without a recent DRF and lower grip strength will be associated with fall and fracture risk.

Study 3 Title: Bone Strength And Muscle Properties In Postmenopausal Women With And Without A Recent Distal Radius Fracture

The primary objective of this study is to investigate if bone and muscle strength differed in women who had experienced a recent DRF compared to women with no recent history of DRF. The secondary objective is to investigate if bone properties at the radius and tibia (measured by pQCT) or at the distal forearm, lumbar spine, and femoral neck (measured by DXA) would differ between early postmenopausal women with and without a recent history of DRF.

Hypothesis: Women with a recent DRF will have lower bone and muscle strength in the forearm, and lower aBMD in the forearm as compared to women without a history of DRF.

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1. OSTEOPOROSIS AND FRAGILITY FRACTURES

Osteoporosis is a disease affecting the skeletal system, characterized by low bone density and deterioration of bone, leading to increased bone fragility (World Health Organization (WHO), 2003). According to the WHO diagnostic criteria, women with bone density levels more than 2.5 standard deviations below the young adult reference mean are considered to have osteoporosis (WHO, 2003). Osteoporosis often remains silent until the first fragility fracture occurs; however, there has been a reported paradigm shift in the prevention and treatment of osteoporosis and fractures, with the focus of clinical guidelines now on preventing fragility fractures and associated consequences versus treating low bone mineral density (Papaioannou et al., 2010). Researchers and clinical experts report that osteoporosis and related fractures continue to be dismissed as a problem linked to aging, rather than an opportunity for prevention of future fractures (Eisman et al., 2012).

Fragility fractures have been defined as a fracture occurring spontaneously or following minor trauma such as a fall from standing height or less (Eisman et al., 2012), or at walking speed or less (Osteoporosis Canada, 2012). Fragility fractures, a consequence of osteoporosis, represent 80% of all fractures in postmenopausal women (Papaioannou et al., 2010). With 1 in 2 women and 1 in 5 men over 50 years of age suffering at least one fracture in their remaining lifetime (International Osteoporosis Foundation, 2012), the burden on patients and healthcare systems is alarming and continues to grow with the aging population (Osteoporosis Canada, 2013). The total acute care cost for all fragility fractures was about $1.2 billion, and total healthcare costs alone for osteoporosis in Canada were $2.3 billion in 2010 (Osteoporosis Canada, 2013).

2.2. DISTAL RADIUS FRACTURES

Distal radius (wrist) fractures are the most common fracture across the lifespan, accounting for one sixth

of all fractures, with a much higher incidence in women (Brogren et al., 2011; TimoBeil et al., 2011). In 2007, there were 41,606 reported wrist fractures, accounting for 22% of the total fragility fractures in Canada (Osteoporosis Canada, 2013). DRFs tend to occur at a younger age than more devastating fractures, such as hip and vertebral fractures (Akesson & Mitchell, 2012). Fractures of the distal radius have been identified and recently labeled as the 'signal fracture' for future fracture risk and osteoporosis (Osteoporosis Canada, 2013). Although it is known that fracture risk increases with age, it is unclear if DRFs in postmenopausal women are due to changes occurring in bone strength, a tendency to fall, or the combination of fall-induced loading on the outstretched arm and bone fragility (Nordvall et al., 2007). A retrospective epidemiological study from 2011 confirmed that the incidence of forearm fractures treated in hospital emergency departments among women increased with age, specifically between the ages of 50 and 59 years of age, at an annual rate of 3.9% (Orces & Martinez, 2011).

2.3. THE CARE GAP

Clearly, women between the ages of 50 and 65 are at risk of sustaining the first 'signal fracture' (Osteoporosis Canada, 2013); however, the underlying causes of falls and fractures may be different in women aged 50-64, compared to those 65 years and older (Norvall et al, 2007). The silent nature of osteoporosis, the often otherwise healthy appearance of these women, and the lack of research on fall and fracture risk in early postmenopausal women makes it more challenging to identify those at risk between the ages of 50-64.

Due to the challenge in identifying women who are at risk of sustaining a fragility fracture under the age of 65, there is a missed opportunity for implementing primary and secondary prevention strategies. Provincial audits across Canada have reported that 80% of fragility fracture patients are not receiving appropriate assessment or treatment (Akesson & Mitchell, 2012; Osteoporosis Canada, 2013). Focused preventative measures to address this care gap, described as "break the fragility fracture cycle" and "make the first break the last" have been promoted by the International Osteoporosis Foundation and Fracture

Liaison Services in Canada (Osteoporosis Canada, 2013). The report for the 2010 Clinical Practice Guidelines for the diagnosis and management of osteoporosis in Canada states that many gaps exist in our knowledge on preventing fractures. This report suggests that future research should examine the risk factors associated with fractures, including younger populations who have already sustained a fragility fracture (Papaioannou et al., 2010). Part of the challenge is that osteoporosis often goes undetected until the first fragility fracture, or 'signal fracture' occurs. Because the fracture is treated as an acute event by both the surgeon and the patient, who is typically unaware of her bone fragility/failure, the opportunity for more comprehensive post-fracture intervention, or secondary prevention, is missed (Osteoporosis Canada, 2013). In addition, diagnosis of osteoporosis and screening for risk of future falls and fracture and the associated management involves coordination of follow-up by healthcare practitioners. Although investment at this stage could prevent future higher costs, this follow-up can be costly to the health care system in the short term and the patient with a lack of clarity regarding where the clinical responsibility lies (Akesson & Mitchell, 2012). This secondary gap could be addressed if clear risk factors were identified, with definitive evidence-based guidelines developed specifically for early postmenopausal women. Healthcare professionals need to be educated on the risk factors, communicate with the health care team regarding roles for identifying and treating risk factors appropriately; effective knowledge translation needs to occur for uptake and application of the evidence based guidelines. With potential risk factors remaining unclear, it is even more difficult to target women who may seem otherwise healthy. If fracture risk is not identified early, potential outcomes include reduction in quality of life and even death, in addition to the long term economic burden and costs to the health care system and society (Osteoporosis Canada, 2013).

2.4. RISK FACTORS FOR DRF

Focusing screening and preventative measures to those early post-menopausal women at risk of osteoporotic fracture is a challenge (Rubin et al., 2013). In addition to fall risk and low areal bone mineral

density (aBMD), numerous risk factors for osteoporosis and fractures have been identified and several tools have been developed to integrate risk factors into a single estimate of fracture risk (Rubin et al., 2013).

2.4.1 Fall Risk

Circumstances of falls leading to DRF

Although the causes of falling are varied and complex, a critical factor in all age groups is the ability to respond effectively to a loss of balance (Maki & McIlroy, 2006). Balance strategies vary depending on the direction of the fall and the fracture site at risk is also dependent on the **direction of the fall**. Individuals sustaining a DRF are more likely to fall forwards or backwards, and those with a hip fracture are more likely to fall sideways (Nordvall et al., 2007). Falling forward triggers an upper extremity protective response, where the individual will attempt to break their fall with an outstretched hand, in order to protect the head, torso, or hips from impact (Sran et al., 2010). It is known that postmenopausal women have the **neuromuscular ability to rapidly move their upper extremity into position** to break a forward fall (Robinovitch et al., 2005). With increasing age, protective response time increases (Maki & McIlroy, 2006), resulting in diminishing ability for older women to effectively move their arms into a position to catch the fall. As walking speed slows, the tendency to fall sideways increases; combined with slower upper extremity lateral movement times (Robinovitch et al., 2005). Lateral perturbations are more challenging to react to with stepping reactions than anteroposterior (Maki & McIlroy, 2006) and thus the risk of humerus and hip fracture increases. Part of this challenge may be related to the profound weakening of the hip abductors and adductors and decreased rate of muscle-force production that has been observed in older adults (Rogers & Mille, 2003; Maki & McIlroy, 2006), with older women demonstrating 43% less isokinetic peak torque with abduction and 54% less with adduction compared to younger women (Rogers & Mille, 2003). Although it seems that consideration of lateral perturbations, associated reaction time to these perturbations, and stepping responses would be more appropriate for those who are at a

higher risk of sustaining a hip fracture, even early postmenopausal women may demonstrate this **weakness in the hip abductors and adductors** associated with aging. Thus, weakness of hip abductors and adductors could be considered in some of the screening tools used or developed, which require a narrowed mediolateral base of support, such as the tandem stance, tandem walk, or backward tandem walk.

The ability to arrest a fall with the upper extremities depends on how quickly the hands can be moved into a protective position prior to or during descent, but the risk of fracturing the distal radius during the protective response depends on how much energy can then be absorbed during contact (Sran et al., 2010). Women over the age of 50 may be able to break their fall with an outstretched hand, but are unable to effectively absorb energy through the arm (Sran et al., 2010). Depending on the activity being performed, the force of impact may also be increased, potentially due to faster walking speeds (O'Neill et al., 1996). If low bone mass is also a present, a fracture is more likely to result (Orces & Martinez, 2011).

Intrinsic risk factors – fall history, activity level, balance, gait speed

Falling is a risk factor for DRFs, and there are several established **risk factors specific to falling**. Some of these risk factors predict both future fall and fracture risk. In women between the ages of 40-50 years, Nitz et al. (2013) found the strongest predictor of falling was a ***history of previous falls***. Women with a fall history (defined as one or more falls in the past year) also had significantly greater odds of sustaining a fracture (OR 3.04 - CI 1.63-5.67) (Nitz et al., 2013). Another independent predictor of falls was a ***less active lifestyle*** (Nitz et al., 2013). **Poor physical condition** (D'Elia et al., 2009) and **low levels of physical activity** (Rozental et al., 2013; WHO, 2003; Peeters et al., 2009) are associated with poorer balance and increased risk of falls and fractures (Nitz et al., 2013). In the study by Nitz et al. (2013), women between the ages of 40-80 who reported multiple falls at baseline had three-times greater odds of falling once and almost five-times greater odds of falling multiple times during the 9 year follow-up

period, compared to women with no fall history. Women with a history of falls also had significantly greater odds of sustaining a fracture (Nitz et al., 2013). The majority of research studying fall risk has focused on individuals over the age of 65, where several fall risk factors have been established, including: ***age, presence of chronic diseases, history of stroke, depressive symptoms, dizziness, a history of falling, female gender, high and low levels of physical activity, limitations in daily activity, mobility problems, muscle weakness, orthostatic hypotension, use of psychotropic medication, and vision impairments*** (Peeters et al., 2009).

A history of falls is associated with ***fear of falling*** in older adults > 65 years, suggesting that fear of falling heightens after a fall. Fear of falling has also been observed to predict future falls, possibly due to a reduction in activity levels due to fear of further fall-related injury. When post-fall fear occurs, an individual may begin to question confidence in their ability to maintain balance and associates this with the recognition of being at risk of falling and further injury (Friedman et al., 2002). Although fear of falling has been reportedly low among early postmenopausal women (Ahn et al., 2009), there is less known about fear of falling in early postmenopausal women following a fall or fracture. Postmenopausal women with lower self-efficacy and poorer health perception reported a greater fear of falling, which could lead to reduced activity levels (Ahn et al., 2009).

Overall, few studies have investigated fall risk factors in women under the age of 65 years. Nitz et al. (2013) conducted a longitudinal study of 449 women aged 40 – 80 years over a nine-year period. They found that women as young as 40 displayed similar poor health characteristics that are predictive of falls and fractures as older women and that health continued to decline with advancing age. One of the limitations of this study was that fall risk predictors were limited to self-report of medical conditions and medications, with no details provided regarding what these conditions were. Regardless, this study supports the theory that middle-aged and early postmenopausal (i.e. – age 40-65) women are not immune to falls and fractures, and promotes the idea that fall prevention should target early postmenopausal women as well as the older aged population. However, it is important to understand that fall and fracture

risk factors may be different in women who are younger than age 65 years. Further research needs to be conducted in order to determine the risk factors for falling specifically among early postmenopausal women. As individuals of any age are susceptible to falls, risk factors will vary depending on the population of interest. Although research evaluating women exclusively between the ages of 40-65 is very limited, a cross-sectional study focusing solely on participants aged 45-64 with a DRF compared to an age matched control group without a fracture, found no significant difference in the incidence of previous falls, or other risk factors including previous fracture, loss of body weight, heredity, or physical inactivity (Norvall et al., 2007). They did, however, find a non-significant but clinically relevant difference in dual x-ray and laser derived T-scores in the calcaneus, suggesting that it was not necessarily fall risk alone, but possibly declining bone quality that contributed to the fracture in the group aged 45-65. The study addressed the lack of understanding on whether DRFs are due to falls or fragility, suggesting that the underlying causes of a DRF may be different in patients aged 45-64 compared to those older than age 64 and encouraged screening for both fall and fracture risk among this younger age group. However, due to the potentially higher strength, balance, and functional mobility, more challenging fall screening tools may need to be developed for this age group to detect more subtle changes that are leading to a fall.

Unexpectedly a few studies have reported that self-reported "poor health" is a protective factor against sustaining a DRF as a result from a fall, and increased physical activity in the form of **frequent walking and walking at a brisk pace** has been reported as a risk factor for forearm fractures (O'Neill et al., 1996; Kelsey et al., 1992). A study examining risk factors in those aged 45 years and older determined that indicators of poor health, such as self-reported poor or fair health, number of selected neuromuscular symptoms, and difficulty or inability to perform certain physical functions, were actually associated with a reduced risk for DRF (Kelsey et al., 2005). Other studies examining relationships of health status to other types of fractures have found similar findings where poor health is associated with increased risk for hip and proximal humeral fractures, rather than DRF (Cummings et al., 1995; Kelsey et al., 2005). The theory proposed is that poorer health is associated with decreased speed of movement and reflexes. Slower

walking velocity increases the probability of an impact on or near the greater trochanter (van den Bogert et al., 2002). This suggests that slower speed of movement decreases the ability to effectively utilize an upper extremity protective response during a fall due to slower upper extremity response times, reducing the risk for DRF (Kelsey et al., 2005). Healthy older people, moving faster, may be able to react quickly and break their fall with an outstretched hand, but with declining bone strength and inability to effectively absorb energy through the upper extremity, a fracture may result (Kelsey et al., 2005). This is supported by other lab-based research measuring neuromuscular capacity of the upper extremities during forward descent (Robinovich et al., 2005; Sran et al., 2010). In addition, more frequent walking (especially outdoors) increases the risk of falling, potentially due to extrinsic factors (i.e. tripping on curbs, obstacles, rough ground or slipping due to rain, ice, snow). If a fall occurs while walking at a brisk pace, the force that is required by the upper extremity to break the fall is also increased. If the load or force on the bone exceeds the ability of the bone to carry that load, the bone will fracture (Felsenberg & Boonen, 2005).

2.4.2 Sex

Female sex is a known risk factor for DRFs over the age of 50 (Felsenburg & Boonen, 2005; D'Elia et al, 2009). This is attributed to several reasons, the first being that women typically have smaller bones than men, and lower values of various markers of bone strength as will be discussed further in the next section (2.4.3). In addition, associated hormonal changes throughout life have an effect on bone health. High bone turnover, (Felsenburg & Boonen, 2005; D'Elia et al, 2009) has been identified as another risk factor for fractures. Bone loss in women begins to occur in early adulthood (age 20-30) after the growth of long bones ceases (Felsenberg & Boonen, 2005). The rate of bone remodeling doubles at menopause, triples thirteen years after menopause, and remains high if osteoporosis occurs (Felsenberg & Boonen, 2005). Bone loss accelerates during perimenopause, independent of chronologic age, with the rate of loss being highest in the first five years after menopause. Accelerated bone turnover leads to the irreversible loss of some trabeculae, leading to weaker bone, and increased fracture risk (Felsenberg & Boonen, 2005). An

additional risk factor, associated with the female sex, is sex hormone deficiency. The decline in estrogen production at menopause is the most important factor contributing to osteoporosis in later life (WHO, 2003). Premature menopause (before age 40) is a strong determinant of bone density and increased risk of fracture (Dawson-Hughes et al., 2013). Late menarche (Rozental et al., 2013) and endocrinopathies (D'Elia et al., 2009) have also been identified as risk factors for distal radius fractures. Sex is a clinical risk factor used in the FRAX algorithm to determine absolute fracture risk (Rubin et al., 2013).

2.4.3 Osteoporosis and Bone Strength

Low aBMD is a known risk factor for fractures in postmenopausal women (Felsenburg & Boonen, 2005). Dual x-ray absorptiometry (DXA) derived areal BMD (aBMD) is currently the "gold standard" for diagnosing osteoporosis. The World Health Organization defines osteoporosis in women as an aBMD value, or T-score, that is greater than or equal to 2.5 SDs below the mean of a young adult (WHO, 2003; Felsenburg & Boonen, 2005); however, many women who are not diagnosed as osteoporotic by DXA derived T-scores, are sustaining DRFs (Jarvinen et al., 2008), and the lifetime risk of hip fracture for a white woman over the age of 50 with normal aBMD (T-score 0 to -1.0) is still 10% to 17% (Cummings et al., 2002; Felsenberg & Boonen, 2005). At the population level, declining aBMD is associated with fracture risk; however, at the individual level, aBMD assessment is specific, but not sensitive for prediction of fractures due to the multifactorial nature of fracture risk (D'Elia et al., 2009; Downey et al., 2013). Therefore, an individual's osteoporotic status may be identified as "normal," using aBMD values, but may still fracture due to other fracture related risks not captured with DXA screening alone. Thus aBMD alone is not an effective screening tool determining fracture risk.

Although aBMD continues to be utilized as the primary method of diagnosing and monitoring osteoporosis in the clinical setting, it is insufficient to accurately predict fracture risk alone (Engelke et al., 2013; Felsenburg & Boonen, 2005). The clinical practice guidelines in Canada recommend the assessment

of aBMD at the femoral neck and spine for all men and women over the age of 50 who experience a fragility facture after age 40, or present with other clinical risk factors (Papaioannou et al., 2010), as fractures at these sites are the most costly to the individual's health and the healthcare system (Eisman et al., 2012). Even though site-specific measurements may be more predictive, as they have been shown to demonstrate higher gradients of risk for their respective sites (WHO, 2003); the discordance of aBMD in the various skeletal sites may lead to misclassification of osteoporotic status (D'Elia et al., 2009). Because the clinical protocol is to image the femoral neck and spine, those at risk of deteriorating bone in the more distal sites of the peripheral skeleton may go undetected with typical screening protocols. For example, if the individual is at risk of fracturing the distal radius, which is commonly the first fragility fracture to occur, measuring aBMD at the femoral neck and spine may be insufficient to detect deteriorating bone at the distal radius. This is important to consider in postmenopausal women. For the general elderly population, because forearm aBMD is less accurate at predicting vertebral fractures than hip or spine BMD, it is not recommended to measure unless the hip or spine cannot be measured or interpreted or in very obese patients who are over the weight limit for the DXA table (D'Elia et al., 2009). It may be appropriate to measure more than one site in women younger than 65, while in older women the probability of discordance in site-specific BMD is minimized (D'Elia et al., 2009). With age, and declining BMD, a recent study comparing postmenopausal women with a recent DRF to a control group found no significant differences in aBMD at the femoral neck, lumbar spine, and distal one-third of the radius, but a tendency to be lower in the fracture group, approaching significance, at the femoral neck and ultradistal part of the radius (Rozental et al., 2013). Clinically, DXA derived, site-specific, aBMD measures should be combined with additional clinical risk factors to assist in more accurate screening for fracture risk among early post-menopausal women.

In addition to aBMD, bone strength must also be taken into account. Bone strength depends on structural and material properties of bone. Structural properties include both geometry, referring to the size and shape of bones, as well as architecture, including trabecular architecture, cortical thickness and porosity

(Felsenberg & Boonen, 2005; Engelke et al., 2013). Material properties refer to the mineral and collagen composition, including number, size, and localization of microdamage, as well as bone turnover rate (Felsenberg & Boonen, 2005). Unlike bone structural properties, measurement of material properties of bone tissue cannot currently be done non-invasively (Dalzell et al., 2009). Micro-architectural properties, or determinates of bone strength, are not represented by aBMD (Felsenberg & Boonen, 2005), and must be evaluated with imaging tools that allow quantitative assessment of macrostructural and microstructural characteristics (D'Elia et al., 2009; Engelke et al., 2013).

Peripheral quantitative computed tomography (pQCT) is a non-invasive research imaging tool capable of capturing a cross-sectional image of bone and muscle tissues and can provide accurate measures of many cross-sectional bone features, including volumetric (v) cortical (Co), trabecular (Tr), and total (To) bone tissue mineral content (C), density (D), cross-sectional area (A), and estimates of bone strength at the distal sites and at the shaft (Schneider et al., 2001). Widespread clinical use of pQCT has been limited for diagnosis and monitoring purposes, as there is still a need to determine pQCT specific diagnostic and treatment initialization thresholds. Currently, the operational definition for diagnostic classification of osteoporosis is valid for DXA only and does not apply to any other densitometric methods, including pQCT (Engelke et al., 2008). For research purposes, pQCT has the ability to capture surrogate measures of bone strength, including BSI (bone strength index) at the distal sites, calculated as $BSI_c = ToD^2$ x ToA (the product of total density squared and total area), and SSI (strength-strain index) at the mid-shaft, calculated as $SSI_p = \Sigma [a*d^2)(CoD/ND)]/d_{max}$. Where r = distance of a voxel from center of gravity, r_{max} = maximum distance of a voxel from center of gravity, a = area of a voxel in mm^2, CoD (CD) = measured cortical density in mg/cm^3, and ND = normal physiological density of 1200 mg/cm^3) (Stratec, 2004).

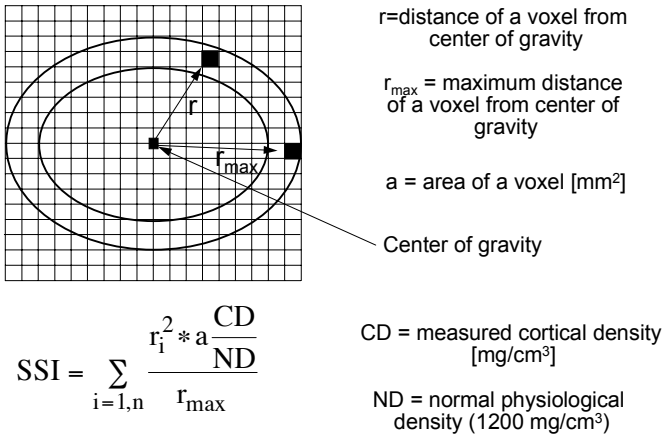

Figure 2.1. Reproduced with permission from Stratec XCT 2000 Manual, demonstrating the calculation of SSI_p.

Both BSI_c and SSI_p have been cited in the literature as having the ability to predict fracture risk, and potentially more profound predictors than that of aBMD, as measured by the "gold standard" of DXA (Sheu et al., 2011). Bone strength index (BSI_c) combining total area and the square of the total density of the distal bone cross-section, has been validated to provide a reasonable estimate of bone's resistance to compression in the tibia, integrating material and structural properties of bone (Kontulainen et al., 2008; Sui et al., 2003). The strength-strain index (SSI) incorporates both geometric properties and surrogate of material properties of cortical and trabecular bone (tissue level BMD) (Schneider et al., 2001). SSI is a valid predictive index for whole bone breaking strength in laboratory testing (Schneider et al., 2001), and has been shown to be an accurate and precise indicator of the structural properties of long bones tested in bending (Sheu et al., 2011). Poor bone strength estimated by BSI_c and SSI_p could be considered risk factors for fracture; however, these estimates have yet to be examined in a group of early postmenopausal women with a recent distal radius fracture.

Although standard pQCT is able to measure bone size, mass and volumetric density, in both cortical and trabecular bone, it is limited in evaluating the thinning cortex at the distal sites of the peripheral skeleton due to the partial volume effect. Standard pQCT can provide accurate measures of many cross-sectional

bone features, in addition to estimates of bone strength at the distal sites and shaft (Schneider et al., 2001). Standard pQCT-derived bone properties that distinguish postmenopausal women who have had a recent fracture at the distal radius, from those without fracture are not clear. However, sex differences and age-related changes have been reported. Both trabecular and cortical properties strongly influence biomechanical strength (Vico et al., 2008), but which parameters best predict fracture risk in postmenopausal women are unknown.

Trabecular density and content are important to bone strength, as trabeculae function to transfer loads across the joints and to resist compression (Felsenberg & Boonen, 2005). An intact trabecular network appears to be vital for maintaining maximum bone strength (Felsenberg & Boonen, 2005), and most of the bone mass that is lost in postmenopausal women is from the deterioration of trabecular bone (Felsenberg & Boonen, 2005). Patients with a recent vertebral fracture had four times the number of broken trabeculae than women without fracture (Aaron et al., 2000), and in the distal radius, trabecular density in the distal radius was 22% lower compared to non-fractured individuals (Vico et al., 2008). This suggests that after a recent wrist fracture, alteration of trabecular bone is predominant over the cortical shell at the distal site, and may be a stronger predictor for bone fragility. The same study found that after a wrist fracture, many trabecular parameters in the distal tibia were unaffected (except for trabecular density), but in those with a recent hip fracture, all parameters except trabecular spacing were altered in the distal tibia, suggesting limb specific changes may occur (Vico et al., 2008). Supporting this, Melton et al. (2011) determined that trabecular density had the strongest correlation with modeled ultradistal radius strength, and after accounting for trabecular density, none of the trabecular structural variables were significantly associated with bone strength. Trabecular failure occurs if there has been a reduction in trabecular elements that are perpendicular to the direction of the load (widely separated, disconnected thick trabeculae are less competent than an equivalent amount of more numerous, connected and thin trabeculae). Dalzell et al. (2009) found that females between the ages of 20-80 tended to show greater variation than males in trabecular separation and trabecular thickness in the distal radius and tibia, at all ages; however, no

trabecular bone indices were strongly associated with age. Schneider et al. (2001) found trabecular density and content in the distal radius to be the best discriminants between fractured and non-fractured women between the ages of 45-85 with a 24.7% and 29.8% difference respectively. In a group of premenopausal women with a distal radius fracture, the fracture group had lower total density, trabecular density, number and thickness, compared to a control group (Rozental et al., 2013). This supports the importance of assessing trabecular properties in fracture risk especially among women.

The size of bones, as determined by **total cross-sectional area**, appears to have an effect on whole bone strength (Felsenberg & Boonen, 2005). A study examining age related changes in determinants of bone strength in the radius in individuals aged 20-79 confirmed that women have smaller bones than men, and that changes are larger after the age of 50 (Danzell et al., 2009). Bone size is an important determinant of bone strength (Melton et al., 2011); the geometry (i.e., distribution of bone mass) defines bone size and shape. Changing the distribution changes the ability of bone to resist bending and torsion, which is not reflected in aBMD (Felsenberg & Boonern, 2005). This is represented by SSI_p, the stress-strain index in torsion. In addition, size of bones can also affect other parameters of bone and bone strength. In vertebral bones, it has been shown that 50% of the reduction in BMC is the result of a reduction in bone size (Felsenberg & Boonen, 2005). The combination of total BMD with cortical area was an accurate predictor of radius failure load determined ex vivo (Melton et al., 2011). The area of the trabecular or cortical components, relative to the total area, can provide information on changes that are occurring in the bone.

It has been shown that the largest relative effect of age is in **cortical thickness and density** at both the radius (Melton et al., 2011) and tibia (Dalzell et al., 2009). Vico et al. (2008) found that 6-8 weeks following a DRF in postmenopausal women, cortical thickness at the distal radius was less than that of a control group, but the cortical bone area was not different. The distal radius cortical density was less by 6% in those with a recent wrist fracture and 11% in those with a recent hip fracture, compared to a control group. Cortical thickness was less by 15.5% in those with a recent wrist fracture and 28.5% in those with a recent hip fracture (Vico et al., 2008). Danzell et al., 2009 studied participants aged 20-80, and reported

that parameters that declined most with aging in females were cortical density and cortical thickness in both the distal radius and tibia. More current research specific to postmenopausal women explains this finding with an observed loss of trabeculae with an increase in trabecular size at the distal radius, and a declined cortical thickness, density, and content at the distal tibia attributable to trabecularization of the cortical bone (Kawalilak et al., 2014). It appears that the changes in cortical bone tend to be greater at the distal radius, typically a non-weight bearing bone, compared to the tibia, although differences were noted in both (Vico et al., 2008). Conversely, Schneider et al. (2001) found no significant difference in cortical BMD at the distal radius in a group of women aged 45-85 years. This may be due to partial volume effects and difficulties measuring the distal cortical bone with pQCT, although the authors argue that measurements of area are more affected by the partial volume effect, and pQCT technology can assess bone geometry in this region with acceptable accuracy (Schneider et al., 2001).

2.4.4 Muscle Properties

The International Osteoporosis Foundation has published a report "Three Steps to Unbreakable Bones." (Bischoff-Ferrari, 2011). One of the primary goals of the report is to advance strategies to preserve muscle strength and mass through exercise, due to the close relationship between falls and muscle weakness, but also identify the benefits of exercise on overall bone health. The recommendations outlined in this publication are based on the identified link between muscle properties and fracture risk. Muscle mass begins to decline after the third decade; however, this becomes more noticeable around the time of menopause, with approximate declines reported to be 0.6% annually (Maltais et al., 2009; Rolland et al., 2007). The factors that contribute to the decline in muscle mass in postmenopausal years include physical inactivity, inadequate protein intake, oxidative stress, insufficient vitamin D intake, and changes in sex hormones specific to menopause (Maltais et al., 2009). Although the physiology of the effects of these factors is beyond the scope of this thesis, the association between muscle properties including muscle

cross sectional area and muscle strength, and bone strength leads to a potentially identifiable and modifiable risk factor for fracture risk.

Muscle cross-sectional area (MCSA) is another property that can be measured by pQCT, and may be associated with strength indices of the radius, as well as the muscle strength (Frank et al., 2010). This study demonstrated that MCSA in the forearm significantly contributes to predicting SSI_p in the radius shaft, but not BSI_c in the distal radius. Forearm MCSA was also a predictor of concentric, isometric, and eccentric grip torques (Frank et al., 2010). Although this is yet to be validated as a predictor of bone and muscle strength in the forearm in postmenopausal women, smaller or declining MCSA values may be identified as a risk factor for future fracture in this age group.

2.5. OTHER CLINICAL RISK FACTORS

There are several other physiological, demographic and lifestyle risk factors associated with risk of fractures in older women. This is not an exhaustive review, but each the primary factors of relevance to the studies within this thesis are summarized below:

Age

The incidence of forearm fractures increases markedly within 5 years of menopause, and reaches a peak around the age of 60 (WHO, 2003). The incidence levels off between the ages of 65-70 (WHO, 2003; Akesson & Mitchel, 2012). **Age** is strongly associated with fracture risk and has the strongest known association with BMD (Rubin et al., 2013; Peeters et al., 2009). Loss of bone density occurs with advancing age and rates of fractures increase markedly with age (WHO, 2003). It is possible that age is also associated with several other risk factors associated with both fall and fracture risk such as increased number of other medical conditions, changes in balance, muscle strength, or declining activity levels or

functional ability. In early postmenopausal women, the number of risk factors may be minimal. It is important to identify risk factors for fracture, but also important to note that the prevalence of these risk factors may be low (Rentero et al., 2008). Age is a clinical risk factor included in the FRAX to determine absolute fracture risk (Rubin et al., 2013).

Physical activity

A relationship between **poor physical condition** and **low physical activity** with balance, falls, and fractures has been identified (D'Elia et al., 2009; Rozental et al., 2013; WHO, 2003; Peeters et al., 2009; Nitz & Kahn, 2013). Exercise improves quality of life in those with osteoporosis by improving physical function, decreasing pain levels, improving muscle strength and balance (Papaioannou et al., 2010). Studies of the effects of exercise on fracture risk revealed that small increases in BMD produce exponential reduction in the relative risk of bone fractures (Borer, 2005). Specific to the distal radius, Ayalon et al. (1987) conducted an exercise program with a focus on loading the forearm bones with tensile, compressive, and bending stresses, with a duration of 5 months for 3 times per week, with 15-20 minutes of forearm loading, in addition to 50 minutes of strength, stretching, and other forms of exercise. The training produced a 3.8% increase in BMD of the distal radius, while the sedentary group continued to lose BMD (Aylon et al., 1987). Physical activity level is not currently used as a clinical risk factor in the FRAX; however, it is a therapeutic option outlined in the most recent guidelines for osteoporosis management (Papaioannou et al., 2010).

Low body weight and BMI

Low body weight and **BMI** (Felsenburg & Boonen, 2005; WHO, 2003; D'Elia et al., 2009; Peeters et al., 2009) are fracture risk factors in postmenopausal women. This is likely due to the decreased mechanical loading of the skeleton and associated metabolic influences on body composition (WHO, 2003). Although BMI is associated to fracture risk after adjusting for BMD, it is not predictive for fractures, except hip

fractures in patients with BMI of 20 kg/m^2 or less (Lewiecki et al., 2009). Therefore, it has been suggested that BMI is most useful as a clinical risk factor when BMD is not known (Lewiecki et al., 2009). Loss of body weight has been found to be a predictor of fracture risk. In a group of women aged 50-65, an observed weight loss >10% in a period of 10 years was a strong risk factor for osteoporosis and fracture (Rentero et al., 2008). An additional risk factor that has been less frequently reported is an **observed height loss**. In women aged 50-65, one of the most prevalent risk factors for osteoporosis and fracture risk was an observed height loss (Rentero et al., 2008). Body weight and height are both used in the FRAX algorithm to determine absolute fracture risk (Rubin et al., 2013).

Lifestyle factors

There are several **lifestyle factors** (Felsenburg & Boonen, 2005) that put individuals at a higher risk for fracture. As previously discussed, a **high risk of falling** and a **fall history** both increase the risk for future falls, and therefore fracture (Felsenburg & Boonen, 2005; D'Elia et al., 2009; Nitz et al., 2013; Rentero et al., 2008). A history of **smoking**, (Felsenburg & Boonen, 2005; WHO, 2003; D'Elia et al., 2009; Peeters et al., 2009; Rentero et al., 2008) has been cited multiple times as a risk factor for fractures. This is because cigarette smoking can lead to earlier menopause, reduced body weight, and enhanced metabolic breakdown of estrogen in women (WHO, 2003), all of which are risk factors in themselves for fractures. **High levels of alcohol consumption** (Felsenburg & Boonen, 2005; WHO, 2003) are detrimental to bone strength, thus increasing risk of fracture. This may be due to the effect of alcohol on protein and calcium metabolism, mobility, gonadal function, and a direct toxic effect on the osteoblast (WHO, 2003). In addition, alcohol increases the risk of falls or interferes with the protective response to injury (Dawson-Hughes et al., 2013). Although fall history and risk of falling is not accounted for in the FRAX, both smoking status and alcohol consumption are factors used in the FRAX tool to determine absolute fracture risk (Rubin et al., 2013).

Medical history

Medical history (Felsenburg & Boonen, 2005) is important to consider in predicting those at risk of distal radius fractures, as an increasing number of comorbid medical conditions has been associated with high fracture risk (Nitz et al., 2013). First and foremost, a **history of fracture** (Felsenburg & Boonen, 2005; D'Elia et al., 2009; Peeters et al., 2009) is a strong risk factor that should be a red flag independent of any other screening tool, or appearance of otherwise good health. An initial fracture in an at-risk person is sufficient grounds to require a full evaluation, including BMD measurement and fracture risk assessment and, unless contraindicated, initiation of treatment for any underlying bone fragility (Eisman et al., 2012). A study evaluating fracture prediction in early postmenopausal women found that a previous fracture and onset of menopause prior to age 40 were the only predictive variables found in women aged 50-59 (Pfister et al., 2013). This suggests that there may be instances where this is the only identifiable risk factor in early postmenopausal women. A **family history of osteoporosis**, (Felsenburg & Boonen, 2005; D'Elia et al., 2009) or **family history of hip fracture** (Peeters et al., 2009; WHO, 2003) are risk factors, as genetics may play a role in risk of fractures. Up to 50% of the variance in peak bone mass and some aspects of bone geometry that are relevant to bone strength may be determined genetically (WHO, 2003). **Medications such as corticosteroids** (Felsenburg & Boonen, 2005; Peeters et al., 2009) or **chronic glucocorticoid or anticoagulant use** (D'Elia et al., 2009) also increase one's risk for fractures. Glucocorticoid use is a predictor of fractures, primarily vertebral fractures, with risk increasing with higher doses, reported as the most common cause of drug-induced osteoporosis (Dawson-Hughes et al., 2013). There is a rapid onset of increased fracture risk with starting glucocorticoid therapy and rapid offset after discontinuation (Lewiecki et al., 2009); therefore, this is modifiable. Diabetes, rheumatoid arthritis, (Peeters et al., 2009) untreated long-standing hyperthyroidism, osteogenesis imperfect in adults, hypogonadism, or premature menopause (with onset prior to 45 years of age), chronic malnutrition, or malabsorption and chronic liver disease (Lewiecki et al., 2009) are all examples of **secondary osteoporosis**. The effects of all the disorders listed have been shown to have detrimental effects on BMD,

thus increasing risk for fracture. Previous fracture, family history of hip fracture, glucocorticoid exposure, and secondary osteoporosis are risk factors used in the FRAX algorithm for absolute fracture risk (Rubin et al., 2013).

Nutrition

Nutritional intake may be considered a risk factor, as appropriate intake of vitamin D, calcium, and protein is required for good musculoskeletal health. Low levels of **Vitamin D** (also reported as reduced sun exposure – Peeters et al., 2009) are common in elderly populations and have been shown to contribute to fractures, especially at the hip (WHO, 2003; Dawson-Hughes et al., 2013). Vitamin D supplementation prevents the BMD loss that occurs during the winter months in healthy subjects, and even relatively small amounts of supplementation in institutionalized elderly has been shown to reduce non-vertebral fracture rates (WHO, 2003). Supplementation has a direct effect on muscle and reduces the risk of falling, while assisting with calcium absorption for bone development and maintenance (Dawson-Hughes et al., 2013). There is controversy regarding the recommended dosage of Vitamin D supplementation needed to reduce fracture risk while avoiding potential adverse effects from high dosages. Canadian Clinical Practice Guidelines recommend supplementation at a range of dosage from 400 to 2000 IU daily depending on level of fracture risk (Papaionno et al., 2010). Associations between higher calcium intake and higher bone mass in premenopausal women have been made; however, older women seem to be more responsive to calcium supplementation than younger postmenopausal women (WHO, 2003). The relationship between **low calcium intake** and fracture risk remains unclear (WHO, 2003). In a recent study looking at 4960 women aged 50-65, low calcium intake was one of the most prevalent risk factors for osteoporosis and fractures (Rentero et al., 2008). Canadian Clinical Practice Guidelines recommend total daily intake of elemental calcium (through diet and supplements) for individuals over age 50 should be 1200 mg (Papaionno et al., 2010). Vitamin D and calcium intake are not currently used as clinical risk factors in currently used fracture risk assessment tools, such as the FRAX (described in Section 2.8); however,

supplementation for reducing fractures is outlined in the most recent guidelines for osteoporosis management (Papaioannou et al., 2010).

2.6 DIFFICULTIES IN SCREENING EARLY POSTMENOPAUSAL WOMEN FOR FALL AND FRACTURE RISK

Although there are several overlapping factors such as age, sex, presence of co-morbidities, the risk factors for falls and fractures are still considered to be distinct (Peeters et al., 2009). Middle-aged adults between the ages of 45-65 have been shown to represent 21% of falls recorded in adults, compared to 18% in young (age 20-45 years) and 35% in older adults (>65 years), suggesting that risk factors are present in middle-aged adults (Talbot et al., 2005). However, the majority of screening tools used to detect those at risk of falling are only validated for older adults or for specific patient populations such as those with neurological conditions. Screening and assessment tools commonly used by primary health care professionals such as physical therapists are therefore often not sensitive enough for relatively healthy postmenopausal women due to ceiling effects (Downey et al., 2013). Women in their 50s and 60s are more likely to present as low risk fallers; yet falls have been shown to be the strongest determinant of fracture (Downey et al., 2013) with 90% of all fractures in older adults resulting from falls (Peeters et al., 2009). This demonstrates the importance of understanding when an individual first begins to develop an increased susceptibility to falling.

The difficulty in screening for fracture risk in early postmenopausal women is related primarily to the silent nature of osteoporosis or declining bone health. The profile of early postmenopausal women at risk of fracturing is not well established; therefore, the screening cascade is often not implemented until the first fracture occurs. Even once the first fracture does occur, the otherwise healthy appearance of these individuals does not trigger the need to investigate bone health further from both the patient and practitioner perspectives. In addition, many women suffering DRFs are not diagnosed as osteoporotic with standard clinical imaging procedures (Jarvinen et al., 2008; Stone et al., 2003). Although clinical practice

guidelines have moved towards broader fracture risk assessment, using tools such as the FRAX, versus an osteoporosis diagnosis with aBMD derived from DXA, to our knowledge, there is no research available that uses the FRAX as a cross-sectional comparison or longitudinal outcome measure in early postmenopausal women with a recent DRF.

2.7 CLINICAL GUIDELINES FOR SCREENING FOR FALL RISK

A clinical algorithm has been developed for the decision-making process for health-care professionals to identify fall risk in their patients presenting as 65 years of age or older (Panel on Prevention of Falls in Older Persons, 2010) (Figure 2.2). If the individual screens positive for falls or risk of falling, presenting with two or more falls in the prior 12 months, presenting with an acute fall, or difficulty with walking or balance, a more detailed evaluation of gait and balance should occur. The guidelines suggest common tests of gait or balance include the Get Up and Go Test, Timed Up and Go Test (TUG), the Berg Balance Scale (BERG), and the Performance Oriented Mobility Test (Panel on Prevention of Falls in Older Persons, 2010).

There are no similar published fall risk screening guidelines for older adults at risk of falls and fracture under the age of 65 years; however recognizing the need, some community programs have adapted some of these standard tools to be used for a broader population over the age of 50 years (Albert & Shelton, 2015). The difficulty is that many of these tests appear to have a ceiling effect in community-dwelling older adults and are not sensitive to differences among individuals that may indicate risk of falling (Wrisley et al., 2010). Gait and balance tests to predict falling, appropriate for those younger than 65 years of age are not well established. Functional reach, TUG, one-leg raise, walking speed, one-leg stance have been used in this age group (Nordvall et al., 2009); however, none of the functional tests: walking forwards (15 meters with 180° turn, and 15 meters back) or backwards (20 steps tandem, timed), one-leg stance (with eyes open and closed, timed) or one-leg rise could identify persons with a DRF who were at risk of falling (Nordvall et al., 2009). Nitz et al. (2013) used the modified clinical test of sensory

interaction of balance (mCTSIB) and single-leg stance tests measured by the Neurocom Balance Master (Nitz et al., 2013). This device allows for detection of smaller changes in center of gravity (COG) during balance tests, and provides a computer output of the results including COG traces, mean COG sway velocity, and performance outside of normative data range (NeuroCom, 2013). Although this may be helpful, it is a very expensive machine that most community-based health care providers/facilities would not have access to. Nitz et al. (2013) suggest that bipedal stance on foam with eyes closed for 30 seconds, part of the mCTSIB, was the only balance measure predictive of falls in a population 40-80, with no balance measure predictive of fractures, and should be promoted as a quick and easy screening tool for falls in inactive women with poor health. Although this test challenges balance by utilizing sensory interaction for postural control (vestibular, vision and proprioception), this test does not measure dynamic transitions demanding balance control in day to day activities or reactive balance needed to prevent falls and associated injury.

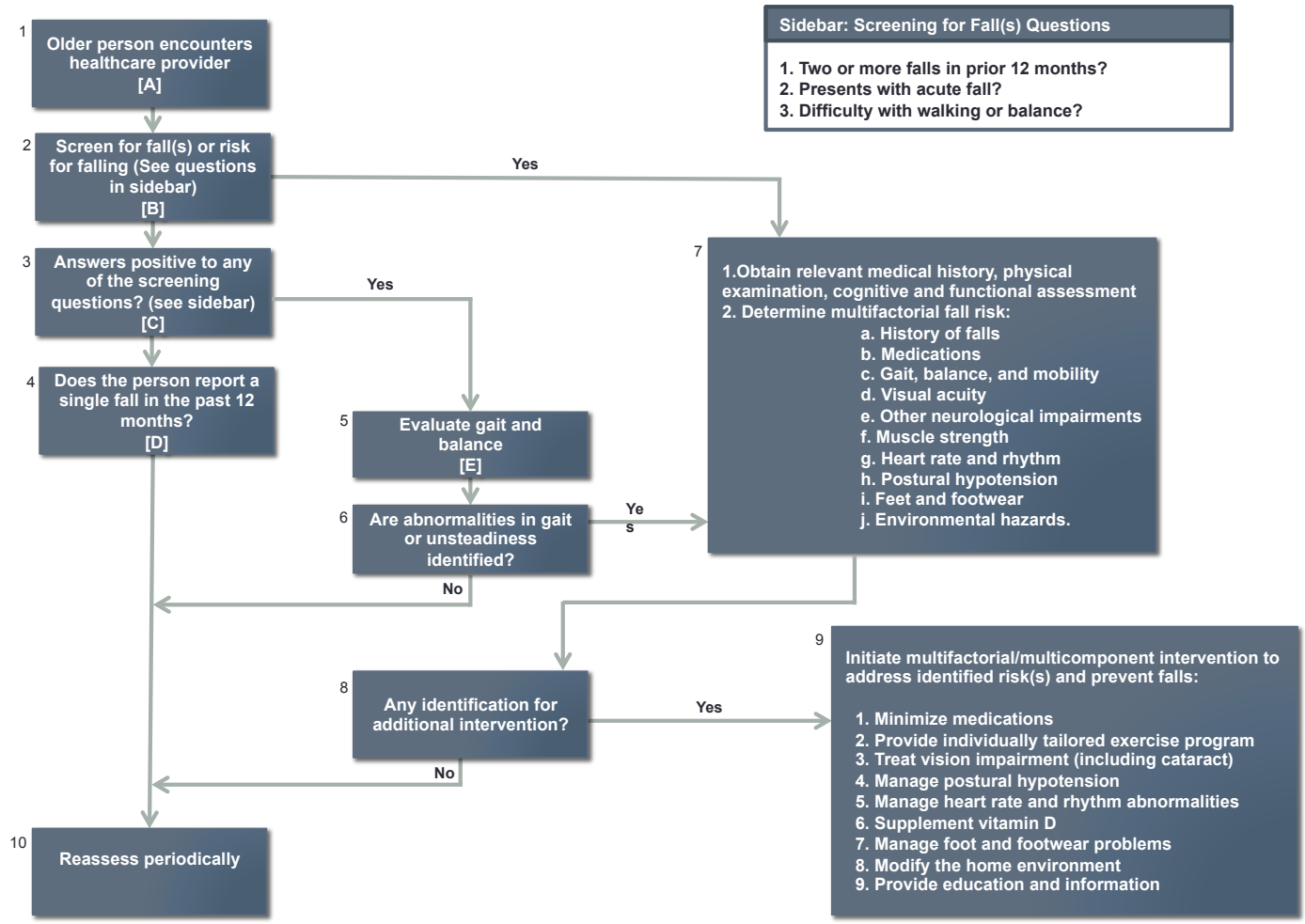

Figure 2.2. Prevention of falls in older persons living in the community: Algorithm and annotations. Adapted with permission from J Am Geriatr Soc 2010: Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons.

For busy clinicians, with limited space and time, simple, quick screening tools are more readily accepted and utilized. It has been determined that in order to distinguish fallers from non-fallers, participants or patients must be exposed to a challenging environment (Richardson et al., 2005). Ambulating backward with a tandem stance has been shown to be challenging, with more errors (stepping off the line) occurring in older women with osteoporosis with a recent fall history (Arnold et al., 2005). Altering visual input, although this is typically done by having the participant close their eyes, has been proven to make gait and

balance tasks more difficult (Walker et al., 2007; Nitz et al., 2013). Backward tandem walking narrows the medioloateral base of support, and also alters visual input or the vestibular system, depending how it is performed. Therefore the backward tandem walk may be an activity that is challenging enough to discriminate fallers from non-fallers in a high functioning group of women over age 50 years. A previous study assessing physical performance in early postmenopausal women, between the ages of 52 and 65 used the backward tandem walk score as a physical performance measure. They found that women with low BMD (> 2.0 standard deviations below the mean) had an increased time to complete the test, but this difference was not significantly different compared to a group of women with normal BMD (Palombaro et al., 2009). Of interest, there were no significant differences between the groups for gait speed (fast or habitual), number of medications or comorbidities, age, or years after menopause; however, there was a significant difference in physical activity level and BMI, with the low BMD group demonstrating lower scores for both of these measures (Palombaro et al., 2009). Another study found a positive association with the number of errors made on the test (stepping off the line), to a recent fall history in women over the age of 60 who have been diagnosed with osteoporosis (Arnold et al., 2005). This test has not been validated as a predictive measure of fall risk at this time. With further research and validation, it may have the potential to become a useful, quick screening tool for fall risk in clinical practice.

Table 2.1 summarizes available fall risk screening tools that were used in this thesis due to strong psychometric properties for assessing fall risk in older adults and potential for identifying fall risk in early postmenopausal who may not have indicated positive self-reported balance and gait difficulties as per the JAGS algorithm, but may have more subtle physical performance or confidence changes. Early evidence for use in early postmenopausal women or younger cohorts is included in the following table.

Table 2.1. Fall risk factors and associated outcome measures – Reliability and validity and evidence for use in early postmenopausal women

Fall Risk Factors	Outcome Measures	Reliability/Validity for community dwelling older adults	Studies Using These Outcome Measures in Early Postmenopausal Women or Younger Cohorts
Physical Activity Level	Physical Activity Scale for the Elderly (PASE)	PASE as a measure of physical activity suitable for use in epidemiology studies on the association of physical activity, health, and physical function in older individuals (Washburn et al, 1999)	*Hakestad et al, 2014* (Cross-sectional study in early postmenopausal women (age 51 – 65) with and without a recent distal radius fracture.
Balance	Berg Balance Scale (BBS)	BBS is a valid measure (r=0.81) with high inter-rater reliability (ICC = 0.98) as a useful predictor of risk for future falls in aging adults (Burke-Doe, 2008; Rikli & Jones, 2001).	*Edwards et al, 2006* (Retrospective cohort study, community dwelling women with prior falls and wrist fractures (age 51 – 92)
	Forward reach Single leg stance (D) Single leg stance (ND)	ICC (95% CI) = 0.89 (0.63-0.93) (Mehta, 2015)ICC (95% CI) = 0.81 (0.58-0.92) (Mehta, 2015) ICC (95% CI) = 0.96 (0.91–0.99) (Mehta, 2015)	
	Backward Tandem	Sensitive for detecting balance changes following an exercise intervention in community-dwelling older adults (Topp et al, 1993). Test-retest reliability has been examined in a pilot study of 20 older individuals (ICC = 0.92) (Arnold, 2002).	*Arnold et al, 2005* (Cross-sectional descriptive analysis investigating fall risk factors in postmenopausal women with osteoporosis: age 60-86) *Palombaro et al, 2009* (Observational cohort, comparing those with low vs normal BMD, age 51-65) *Chilibeck et al, 2013* (RCT in postmenopausal women, range of mean age for groups 55.3 – 56.7, comparing effects of exercise training and isoflavone supplementation)
Gait speed	10m walk test	Valid and reliable measure found to discriminate between older adults with and without a history of falling, OR = 1.07 (CI 1.01 – 1.13) (Morris et al, 2007).	*Edwards et al, 2006* (summarized above)
Strength	30s Chair Stand	Test-retest reliability, inter-observer reliability, and validity (ICC = 0.84-0.92, r = 0.93, r = 0.78). (VanSwearingen & Brach, 2001, Rikli & Jones, 1999).	*Ward-Ritacco et al, 2014* (Cross-sectional study of postmenopausal women age 50-65, examining contributions of body composition, physical activity, muscle capacity, and muscle quality to physical function performance.
	Grip strength	Significantly correlated to lower limb capacities; used to identify fallers from non-fallers in a healthy population of older adults (Pijnapples et al, 2008).	*Brogen et al, 2012* (Cohort, women aged 50-75 with a recent DRF between 1 and 2-4 years post-fracture) *Cho et al, 2014* (Case-control, postmenopausal women over the age of 50 with a recent DRF due to a fall and without a recent DRF with no fall history, evaluating physical performance level as a fall risk factor) *Palombaro et al, 2009* (summarized above)
Mobility	Timed Up and Go (TUG)	Sensitive (78%) and specific (86%) for predicting falls Intra-rater reliability (ICC = 0.94) ICC (95% CI) = 0.83 (0.61-0.93) (Mehta, 2015)	*Ward-Ritacco et al, 2014* (summarized above)
	Timed Up and Go Cognitive (TUGcog)	High criterion validity with high correlations to BBS (r = -0.66); excellent intra-rater reliability (ICC = 0.94). (Hofheinz, 2010)	*Coulthard et al, 2015* (Assessment of spatiotemporal and kinematic variables during the TUG and TUGcog in healthy young participants; mean age 22.5)
Balance confidence	Activities of Balance Confidence (ABC)	Test retest reliability (r=0.92) in community dwelling older adults. 84% sensitivity and 87% specificity in correctly classifying fallers and non-fallers in a cross-sectional study of community dwelling older adults. (Hill, 2005).	*Edwards et al, 2006* (summarized above)

2.8 CLINICAL TOOLS FOR SCREENING FOR FRACTURE RISK

There are several clinical tools available to predict fracture risk and low BMD. However, many of these tools have not yet found broad acceptance, and it is unknown why some prediction tools are in common use, while others are not (Rubin et al., 2013). Rubin et al (2013) identified 48 risk assessment tools for prediction of osteoporotic fractures. These clinical tools range from being very simple, with one or two risk factors, up to the most complex, including 31 risk factors (Rubin et al., 2013). Some of these tools include the Qfracture algorithm, Garvan Fracture Risk Calculator, Study of Osteoporotic Fractures, Women's Health Initiative, Fracture and Immobilization Score, in addition to the Fracture Risk Assessment tool (FRAX) and Canadian Association of Radiologist and Osteoporosis Canada (CAROC), all of which have been validated for screening of postmenopausal white/Caucasian women (Rubin et al., 2013). Clinically, it is important that these tools are accurate in their predictions, but they must also be easy to use in order for busy clinicians to utilize them. In Canada, there are 2 primary tools that are recommended in the Clinical Practice Guidelines to use for estimating the 10-year risk of a major osteoporotic fracture: the Fracture Risk Assessment tool (FRAX) of the WHO and the updated tool of the Canadian Association of Radiologist and Osteoporosis Canada (CAROC) (Papaioannou et al, 2010).

To improve fracture prediction combining aBMD with nine clinical risk factors, the WHO has developed the FRAX (Hillier et al., 2011). Because using aBMD alone in the estimation of fracture risk will miss many patients who will later fracture, the combination of aBMD with clinical risk factors provides a better estimation of fracture risk than either would alone (Lewiecki et al., 2009). The FRAX is a computer-based algorithm for the assessment of fracture probability in men and women, specific to their region of residence/geographic distribution (McCloskey et al., 2011). The tool is available at no cost online, is easy to use and readily accessible. The Canadian version of this tool has been validated in a sample of 36,730 women and 2873 men providing estimates of 10-yr probability of hip fracture (+/- BMD) (Leslie et al., 2011). Risk of fracture can be calculated in men or women using the following risk factors in the equation: age, BMI, prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term use

of oral glucocorticoids, presence of rheumatoid arthritis or secondary osteoporosis, and daily alcohol consumption of 3+ units daily. Femoral neck aBMD can be entered to enhance prediction scores, but a FRAX score can also been determined without aBMD values. Research has shown that the FRAX accurately predicts hip fractures in women with normal and low bone mass, performing best with overall prediction of sensitivity and specificity of fracture risk in those identified as low risk by aBMD alone (Hillier et al., 2011). The article states that FRAX can be helpful in stratifying risk among women who have not yet experienced a fracture and in women with low bone mass (osteopenia), representing the majority of all postmenopausal women (Hillier et al., 2011). Although these results are promising for an appropriate clinical prediction tool for fracture in postmenopausal women, this study was conducted with participants aged 65 years and older only, so results cannot necessarily be generalized to postmenopausal women under the age of 65. FRAX has the ability to estimate the 10-year absolute probability of fracture at a major site such as hip or spine, but no prediction values exist for minor fracture sites such as the radius (Pfister et al., 2013).

The CAROC is a 10-year absolute fracture risk assessment tool. It stratifies women and men over age 50 into 3 zones of risk: low (<10% risk), moderate (10-20% risk), and high (>20% risk) (Papaioannou et al., 2010). Risk categorization is obtained from age, sex, and T-score from the femoral neck. The presence of additional risk factors including a prior fragility fracture after age 40 and recent prolonged use of systemic glucocorticoids changes the risk classification; if both are present, the patient is considered to have a high risk regardless of BMD (Papaioannou et al., 2010). The most recent Canadian Clinical Practice Guidelines provide an integrated approach to manage patients at risk of fracture, using these risk categories (Figure 2.3). The new CAROC system is well calibrated to the Canadian population, and provides a simple alternative when it is not feasible to use the full Canadian FRAX tool (Leslie et al., 2011). In addition,

there is now an online version and an app available for mobile devices for improved convenience.

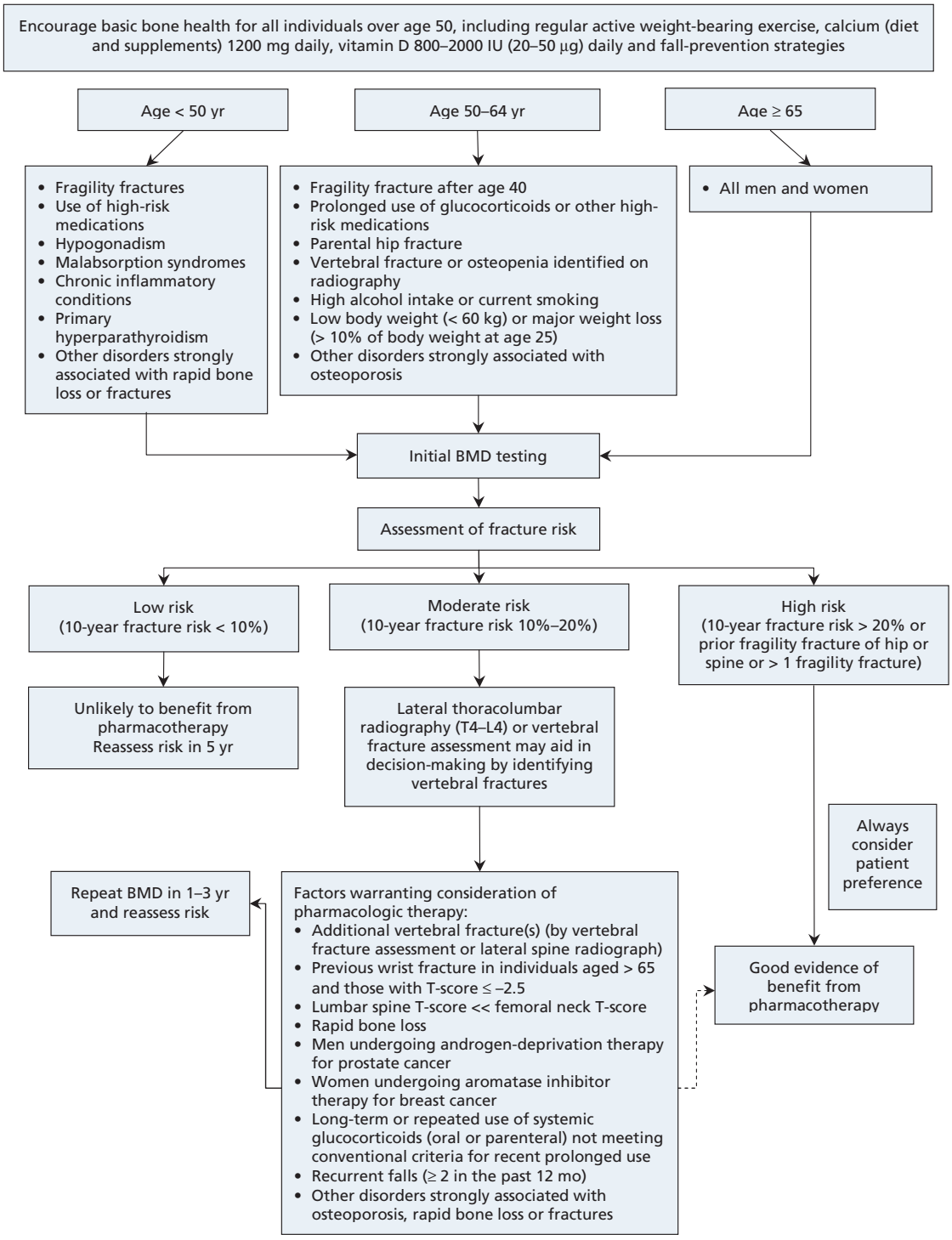

Figure 2.3. Integrated approach to management of patients who are at risk for fracture. Reproduced with permission from the CMAJ 2010 Clinical Practice Guidelines for the diagnosis and management of osteoporosis in Canada: Summary.

Both tools have advantages and disadvantages, and there is high concordance (90%) between the two tools in individuals over age 65 (Papaioannou et al., 2010). Significantly different risk estimates have been found between the two tools for adults <65 years, with the FRAX being more conservative in selecting individuals for pharmacotherapy, suggesting that the FRAX tool may be the preferred tool (Beattie et al., 2015). There is some criticism of the FRAX in recent literature, suggesting that the FRAX is overestimating bone fragility, resulting in higher rates of pharmacological interventions and has led to inappropriate overdiagnosis and overtreatment (Jarvinen et al., 2015). In response to this criticism, others fear that individuals currently treated for osteoporosis may stop therapy and suffer preventable osteoporotic fracture (BMJ Rapid Responses, 2015). Jarvinen et al. (2015) maintain that the focus of the FRAX is on drug treatment, leaving widely feasible non-pharmacological interventions overlooked. This is the concern with fracture risk assessment tools that have a threshold for pharmacological treatment, but not for any non-pharmacological treatment. There have been no thresholds determined that identify those in early stages of fracture risk that may benefit from fall prevention, exercise management, and reducing modifiable risk factors such as smoking and alcohol intake. In addition, the FRAX risk factors are not dose dependent, and it does not take some important risk factors into consideration, such as fall risk. However, at this time, the FRAX is the most commonly used tool and has become a standard for clinical practice (Jarvinen et al., 2015) as it offers a more complete assessment of risk factors, compared to the CAROC (Leslie et al., 2011). Acknowledging the limitations of FRAX, this tool provides health care providers and patients a strong basis to assess and discuss the individuals' risk of future fracture, with the outcome being complimentary to clinical judgment (Dawson-Hughes et al., 2013). In addition, the FRAX report is preferred by family physicians and results in better post-fracture follow-up and treatment that agreed more closely with a specialist (Beattie et al., 2014). For these reasons, the FRAX was used as a fracture risk assessment tool for the purposes of this thesis.

2.9 FUNCTIONAL RECOVERY FOLLOWING A DISTAL RADIUS FRACTURE

Understanding the fall and fracture risk factors and developing a profile of middle-aged women at risk of sustaining a fragility fracture before it occurs is important for primary prevention strategies; however, understanding the normal recovery following a DRF is also important, as post-fracture is where secondary preventative strategies can be implemented.

The timing, extent and nature of recovery at the wrist and upper extremity are variable. DRFs are usually treated on an outpatient basis with around 20% of patients, mostly patients older than 65 years, requiring hospital admission (Handoll & Madhok, 2003). Typically, a DRF is managed non-operatively, involving reduction under anaesthesia if the fracture is displaced, and wrist immobilization for approximately six-weeks (Handoll & Madhok, 2003). In some cases, surgery is required involving internal or external fixation and immobilization.

In the literature, recovery has been focused on regional recovery of the upper extremity, and not recovery of the individual in a more holistic approach including assessment of a broader scope of fall risk factors including balance, overall strength and lower extremity functional mobility, fall history, and cognitive changes including a fear of falling. The most common outcome measures used for assessment of pain and disability are range of motion (ROM) (MacDermid et al., 2003), grip strength, and patient surveys including the Patient-Rated Wrist Evaluation (PRWE) (MacDermid et al., 2003), DASH, and SF-36 (Michlovitz et al., 2001). These are often reported at initial assessment and at time periods throughout an intervention to detect the effectiveness of the intervention used. Pre-fracture baseline values are often difficult or impossible to measure unless the patient was seen previously at the facility prior to the occurrence of the fracture. Pain and disability in the year following a DRF has been studied to describe how impairments changed, with evaluations at baseline, 2, 3, 6, and 12 months, with 129 patients receiving reduction or fixation as determined by individual physicians, as well as post-fracture treatment ranging from home programs to intensive therapy depending on the patient's needs (MacDermid et al.,

2003). Total pain and disability scores to summarize trends of pain, specific activities, patients' "usual role", and functional difficulties, were reported. At baseline 81% of patients experienced severe or very severe pain and disability, improving dramatically in the first 3 months, with a slower improvement from 3 months to 1 year. At 1 year post-fracture, 79% of patients had no/minimal pain and disability, with 3% continuing to report moderate, 4% severe, and 1% very severe pain and disability at this "late stage." This study concluded that most patients should experience the majority of improvement within six-months post-fracture, but a minority of patients will have lasting difficulties that persist for one year. The normal course of recovery is for symptoms to become mild within three months. Atypical responses may indicate the need for further evaluations, changes in treatment programs, or modification of plans for return to work. Atypical responses or persisting impairments may be due to secondary compensation, more severe fracture displacement, patient education level. These factors have been reported as determinants of higher reported pain and disability six months after a DRF (MacDermid et al., 2002). It has also been found that DRF symptoms may persist beyond a year, and often result in permanent disability, particularly in the elderly (Wakefield & McQueen, 2000). Baseline pain intensity, established by scores greater than 35/50 on the PRWE pain subscale, may be used to screen individuals at risk of developing chronic pain, with symptoms lasting up to a year or longer post-DRF (Mehta et al., 2015).

Table 2.2 summarizes the evidence investigating functional recovery and fall risk factors following a DRF without a planned intervention as part of the study objective. Further research is required to determine how DRFs affect lower extremity function, fall-risk, and fear of falling over the first year following a DRF.

Table 2.2. Evidence Investigating Normal Functional Recovery and Fall Risk After a Recent Fracture

Study	Population Measured	Outcome Measures	Findings	Limitations
MacDermid et al., 2003	Patients with a recent DRF (Age range 18-78), (n=129)	PRWE at baseline, 2, 3, 6, and 12 months post-fracture	Normal course of recovery following DRF: severe symptoms subside within the first 2 months and majority of patients can be expected to have minimal pain and disability by 6 months post-fracture	Outcomes measures were regionally specific to the wrist. Global function and bone strength were not evaluated. This study was not specific to early postmenopausal women.
Brogen et al., 2012	Women with a DRF treated with cast or external fixation, examined 1 and 3 years post- DRF (Age range 50-75), (n=49)	Pain score, disability (DASH), grip strength, range of motion	Pain scores, grip strength, and ROM improved significantly; mean improvement was moderate or small. Patients with moderate or severe malunion demonstrated a significantly worse DASH score at 1 yr vs the remaining patients. After DRF pain, grip strength, and ROM continued to improve beyond 1 year, up to 2-4 years.	Outcomes measures were regionally specific to the wrist. Global function and bone strength were not evaluated.

* To our knowledge, there have been no previous studies investigating fall risk over a period of time post-distal radius fracture.

2.10 REHABILITATION FOLLOWING A DISTAL RADIUS FRACTURE

Due to the variability on the timing, extent, and nature of recovery at the wrist and upper extremity, rehabilitation during the post-immobilization phase can also be variable, with more extensive rehabilitation generally being provided in response to complications, pain, stiffness, and functional disability (Handoll et al., 2009). Inconclusive evidence exists throughout the literature regarding best practice guidelines and ideal therapeutic management following a DRF during the mobilization phase. Because of the complexity of the nature of these fractures, including fall-risk status, osteopenia or osteoporosis, inability to work or remain independent, in addition to secondary complications, it is difficult to establish concrete guidelines. Access to physical therapy and other rehabilitation services and variations on health care benefits in Canada, makes the delivery of effective rehabilitation even more complex. In preparation for this thesis, a detailed review of the literature was conducted to summarize physical therapy interventions post-DRF. The focus of DRF rehabilitation is on managing pain and enabling the patient to regain motion, strength, and function. Interventions evaluated in the literature included heat/cold modalities, active ROM exercises, joint mobilizations, strengthening/resistive exercises, soft-tissue mobilization, retrograde massage, dexterity exercises, education, home modifications, balance training, and postural education, as well as a comprehensive program addressing improvement of bone health and fall risk. In agreement with a recent Cochrane Review "Rehabilitation for distal radial fractures in adults," (Handoll et al., 2009) I concluded that insufficient and often inadequate evidence of effectiveness of commonly applied interventions exists. There is a strong need to advance the knowledge base and literature in the rehabilitation management of these common osteoporotic fractures.

It has been suggested that post-fracture rehabilitation is an integral part of successful recovery, due to the increased risk of long-term impairment with involvement of the wrist joint. Functional restoration has a direct influence on quality of life, as well as the duration of sick leave and laborer compensation, and therefore is of social economic interest, in addition to personal value (Krishak et al., 2009). The average number of weeks lost from work following a DRF has been reported to be 9.2 weeks, ranging from zero to

52, with self-reported disability and occupational demands being the strongest predictors of time lost (MacDermid et al., 2007). This provides parameters for expected time loss from work, but also identifies factors associated with work loss, suggesting that monitoring patients by self-report may assist with a more proactive approach to disability management (MacDermid et al., 2007). Variations on the type of therapy required ranges from early active finger motion in both conservatively and operatively treated wrist fractures to encourage resumption of normal hand function and decrease complications (Oren & Wolf, 2009), to an appropriate comprehensive program for osteoporotic patients at risk of falling, suggesting that patients at risk of falling should receive appropriate balance training and risk factor prevention with minimization or elimination of fall risk (Lin & Lane, 2006). However, some studies have found that one session to receive a home exercise program is just as beneficial as receiving a course of physical therapy interventions (Kay et al., 2008). Some studies have found that a home exercise program is beneficial following a DRF (Krischak et al., 2009; Maciel et al., 2005). The home exercise program should be progressed in phases, during the mobilization phase, starting with a phase dedicated to pain reduction and reduction of postoperative edema, progressing to passive exercises to stretch soft tissue, and early active movements without resistance to increase muscle activity, to proprioceptive neuromuscular techniques for range of motion and strength and pull/push techniques, followed by dynamic muscle exercises against resistance (Krischak et al., 2009). It remains unclear if a home exercise program is sufficient enough to replace other types of physical therapy interventions (Watt et al., 2000; Wakefield & McQueen, 2000; Kay et al., 2008; Maciel et al., 2005; Handoll et al., 2009). Michlovitz et al. (2001) reported that there appears to be moderate support for the use of joint mobilization in patients whose loss of motion can be attributed to joint stiffness. Joint mobilization and soft tissue mobilization are commonly used treatment techniques reported by 80% of therapists who responded to a survey on treatment techniques following DRF (Michlovitz et al., 2001). Joint mobilization techniques refer to the passive accessory movements applied to a joint, with a 5-grade (I-V) classification system. Grades I and II mobilizations are most often used for pain reduction, while grade III-IV are most often considered to be techniques used to restore biomechanical faults and improve ROM, and grade V mobilizations involve a

high-velocity thrust beyond the available end ROM (Mangus et al., 2002). Passive joint mobilizations are rarely used in isolation throughout the course of treatment, and most often combined with soft tissue mobilization, education, and exercise instruction. Therefore, it is difficult to report the effectiveness of passive mobilizations in isolation. The evidence of the benefits of including a home exercise program following a DRF (Krischak et al., 2009; Maciel et al., 2005) suggest that passive therapies should always been combined with instruction on appropriate home exercise program.

Typically in clinical practice, physical therapy treatment is primarily focused on upper limb exercises, with a minority receiving lower limb exercises, and very few having a fall risk assessment (Myers & Briffa, 2003). It is not clear what the reasons for this are, but it is in keeping with the similar lack of follow-up post DRF regarding future fracture risk and measured of bone strength (Osteoporosis Canada, 2013). Possibly, there is a shortage of rehabilitation resources for post-DRF patients to access unless they seek private services for a fee, or they do not perceive any future risk when there may be minimal dysfunction due to minor pain or lack of range of motion in their wrist. Other factors such as declining bone and muscle strength and fall-risk may be subtle and not as obvious. Therefore, in most cases, the fall and resulting fracture are often regarded as an "accident" or normal consequence of aging, and the patient is left unaware of their overall declining musculoskeletal health (Osteoporosis Canada, 2013). It is up to the healthcare practitioner to take an individual approach to the management in care based on the resulting deficits at the wrist, but also looking beyond the wrist to also consider other identifiable and modifiable fall and fracture risk factors. Basic bone health should be encouraged for all individuals over age 50, including regular active weight bearing exercise, calcium and vitamin D supplementation, and fall-prevention strategies (Papaioannou et al., 2010).

2.11 GAPS IN THE LITERATURE

It is well recognized that DRF is a strong predictor of future fracture (Orces & Martinez, 2011); however appropriate fracture preventative strategies are not being implemented (Osteoporosis Canada, 2013). This

may be related to the lack of knowledge regarding the profile of women who are sustaining early fragility fractures, including both fall and fracture risk factors, the ability for existing tools to evaluate fall and fracture risk in this population, and the changes that occur in fall and fracture risk over the first year following a DRF. It is crucial to determine the profile of early postmenopausal women at risk of fracturing, in order to identify those at highest risk for future fractures. With minimal research available on identifying both fall and fracture risk factors in early postmenopausal women, and an aging population, the need to identify postmenopausal women at risk of falling and/or fracturing and intervene with the appropriate strategies to alleviate falls and fracture has become a national priority (Osteoporosis Canada, 2013).

Overall, there is very little research on functional recovery following a DRF and changes in fall risk status following a DRF, as summarized previously in Table 2.2. The evidence investigating bone and fall-risk factors specifically comparing women with a recent DRF to women who have not fractured their wrist is also limited. The available evidence for bone and fall-risk factors in early postmenopausal women with and without a recent DRF, and the associated limitations are summarized in Table 2.3. In summary, these studies have found that there are differences in musculoskeletal outcomes in those with a recent distal radius fracture or fragility fracture, compared to those without. There is one study that has evaluated bone measurements with pQCT. This study reported that pQCT outcomes were able to discriminate well between fractured and non-fractured individuals; however, the assessment of bone strength in early postmenopausal women was limited to bone resistance in bending and torsion (Schneider et al., 2001). Risk factors identified in those with a previous fragility fracture included age > 65, history of falls, poor hip aBMD, maternal history of a fracture, low physical activity, and prior fragility fracture; however, these studies included all fragility fractures, not specific to DRF (Albrand et al., 2002). Those with a prior DRF were found to have poorer balance, gait, lower extremity strength, lower grip strength and reduced quality of life, compared to non-fractured peers (Edwards et al., 2006; Hakestad et al., 2014; Cho et al., 2014); however, inclusion criteria for both of these studies included a diagnosis of osteopenia or measured poor

bone mass with calcaneal ultrasound, potentially introducing bias and limiting these findings to those with poor bone density and mass. Three studies relied of self-reports to identify risk factors for fracture, concluding that those with a recent DRF were more likely to walk at a brisk pace, reported lower physical activity levels at home or work, had fewer fertile years and were less likely to have used oral contraceptives; patients older than 64 years of age had a history of falling more often (O'Neil et al., 1996; Kelsey et al., 2005; Nodvall et al., 2007). The gaps in the research comparing women with and without DRF specific to early postmenopausal women include the need for a more comprehensive understanding of musculoskeletal status, combining measurement of both fall and fracture risk factors to assist in determining a more comprehensive profile of early postmenopausal women at risk of fracturing.

Table 2.3. Evidence Investigating Bone and Fall-Risk Factors Comparing Women with DRF vs non-fractured peers. (Evidence specific to objective bone measures includes studies utilizing DXA or pQCT only.)

Study	Population Measured	Outcome Measures	Findings	Limitations
Schneider et al., 2001	Women aged 45-85 with Colles' fracture from 1 month-3 years post-fracture (n=107) vs. women who have not (n=214)	BMC, BMD, area (To, Tr, Co) xCSMI, pCSMI	These tomographic indicators discriminate well between fractured and non-fractured individuals.	Assessment of bone strength was limited to bone resistance in bending and torsion.
Albrand et al., 2002	Postmenopausal women (mean age = 59.1 +/- 9.8, over a 5 year period (n=672). Women who sustained a fragility fracture within the timeframe: n = 75, with 16 of these fragility fractures occurring at the wrist	Questionnaire: Information on social and professional conditions, demographic data, current and past medical history, fracture history, medication use, alcohol consumption, caffeine consumption, daily calcium intake, cigarette smoking, family history of fracture, and past and recent physical activity, incident falls and fractures. Physical exam: anthropometric and BMD measurements; grip strength, walking speed, tandem walk, tandem balance, chair stand	Independent predictors of osteoporotic fractures: age >/= 65, past falls, total hip BMD, left grip strength, maternal history of fracture, low physical activity, personal history of fragility fracture.	Fragility fractures were not isolated to the wrist.
Cho et al., 2014	Postmenopausal women over fifty years of age with a recent DRF due to a fall and age-matched controls	Short Physical Performance Battery; questionnaire for other clinical risk factors	Women with recent DRF had significantly lower scores on the chair stand and grip strength	Assessment was limited to fall risk and physical performance; no data regarding bone strength
Edwards et al., 2006	Community dwelling women over age 50, with prior falls and low bone mass (With DRF, n=26; without DRF, n=24)	Berg Balance Scale, Dynamic Gait Index, timed 10m walk, Activities of Balance Confidence, Falls Risk Assessment (vision, somatic sensory, reaction time, and quadriceps strength)	Fracture group demonstrated a trend towards poorer balance and gait. ABC scores were in a low fall risk range, but fracture group demonstrated trend towards lower ABC scores. Fracture participants with high balance scores walked faster.	Inclusion criteria included those with low bone mass, determined by calcaneal ultrasound. Included women up to age 92, with a mean age range of 70 in the fracture group and 71 in the control group.
Hakestad et al., 2014	Postmenopausal women, aged 54-65, with a recent DRF and osteopenia, matched to healthy controls, aged 51-65.	Quadriceps strength, dynamic balance, six-minute walk test, Quality of Life, aBMD (lumbar spine, total hip, femoral neck, femoral trochanter), PASE	Women with a recent DRF scored lower on quad strength, dynamic balance, 6 min walk, quality of life compared to matched controls	Inclusion criteria included a diagnosis of osteopenia, potentially introducing bias

O'Neil et al., 1996	Women (45-82 y) with a recent DRF (n=62); Control Group 1 (n=50) fall on the outstretched hand/no fracture; Control Group 2 (n=116) no history of fall or fracture	Questionnaire: self-reported walking pace, physical activity, calcium intake, smoking, alcohol consumption, gynaecological and hormonal factors	Those with a fracture: are more likely to walk at a brisk pace, with lower self-reported physical activity at home or work, had fewer fertile years and less likely to have used oral contraceptives.	Data collected was self-reported; no physical examination, no data regarding bone strength
Kelsey et al., 2005	1150 female and males with a DRF; 2331 controls age 45 years and older	Standardized questionnaire on clinical risk factors	DRFs tend to occur in people with low bone mass who are otherwise in relatively good health, are physically active, but somewhat prone to falling and whose movements are not slowed by lower extremity problems and other disabilities.	Data collected was self-reported; no physical examination, no data regarding bone strength
Nordvall et al., 2007	93 women and 5 men with a recent DRF; 98 controls (45 years of age and older)	aBMD measured by Heel-DXL, questionnaire of quality of life, questionnaire on risk factors	Patients >age 64 had a history of falling more often, but no difference in T-score. Patients aged 45-64 showed a non-significant lower T-score but no difference in history of falling. No significant differences between groups for all other risk factors.	Data collected relied on self-reports. Bone measurements were specific to the calcaneous only.

SUMMARY OF THE LITERATURE

In conclusion, DRFs are most prevalent in early postmenopausal women compared to women over the age of 65 years, and are often the first 'signal fracture' to occur. This first fracture provides an opportunity to implement preventative strategies for future fragility fractures known to result in more significant disability or death such as at the hip or spine. There are a number of factors that have been established as DRF risk factors including fall risk, previous fall and fracture history, and changes in bone and muscle strength. However, additional clinical risk factors and appropriate tools to determine subtle changes in known risk factors have not been studied as thoroughly in early postmenopausal women. Although some important additional clinical risk factors such as fear of falling, being over age 65, increased number of comorbidities and/or medications have been identified in a wider age range, the prevalence of these risk factors in women aged 50-59 is low. Clinical tools for screening for future risk have been developed for 10-year fracture risk; however, these may not be sensitive enough to detect early post-menopausal women at risk for 'minor' fracture sites. Current guidelines suggest the use of screening tools, in addition to other clinical risk factors to determine fracture risk. Due to the lack of inclusion of fall risk in the screening tools, and the high association of falls with fracture, current fall prevention guidelines recommend that a gait and balance assessment should be done with any individual in a clinical setting presenting with recurrent falls, difficulty with walking or balance, or after an acute fall. Given the association of falls to DRF risk, further investigation of screening tools and fall risk during the post-fracture recovery period will help to inform clinical practice for earlier screening, post DRF rehabilitation and fall risk assessment.

Rehabilitation following a DRF has been focused on regional recovery of the upper extremity (i.e. pain, range of motion, strength). Previous studies have concluded that symptoms improve dramatically in the first three months, with majority of improvement within six-months post-fracture. A minority of patients will present with residual difficulties persisting at one year post-fracture. There is no evidence to our knowledge of the typical course of recovery for the lower extremities, fall-risk status, or fear of falling. It has been suggested that rehabilitation is an integral part of the complete concept for DRF, due to the

increased risk of long-term impairment with involvement of the wrist joint (Krishak et al., 2009). Functional restoration has a direct influence on the quality of life, as well as the duration of sick leave and laborer compensation, and therefore is of social economic interest, in addition to the personal interest of restoring ROM and strength deficits, and restoring pain-free, functional status returning to activities of daily living. Recommendations for clinical practice guidelines from professional organizations regarding the type, intensity, and duration of postoperative treatment do not exist; nor are there recommendations supported by studies regarding which patients might possibly benefit more or less from physical therapy (Krishak et al., 2009). Insufficient and often inadequate evidence of effectiveness of commonly applied interventions exists (Handoll et al., 2009). The most recent Cochrane Review concludes that "It is not possible to establish exactly what rehabilitation intervention is necessary for acceptable functional recovery, or what type of rehabilitation specialists should provide this care, or when or for how long this care should be provided, or in what circumstances it should be provided" (Handoll et al., 2009, p.21). Given that this is the most common osteoporotic fracture with rising incidence expected in the coming years (Osteoporosis Canada, 2013), there is a compelling need to advance the knowledge base and literature in the rehabilitation management of DRF. Because of the lack of evidence regarding evidence-based management of DRFs, particularly in postmenopausal women at an increased risk of falling and future fracture, future research in this area is warranted and necessary.

The current literature investigating functional recovery and fall risk following a DRF, as well as bone and fall-risk factors specifically in women with a DRF comparing those without, summarized previously in Tables 2.2 and 2.3, outlines the limitations in the current available literature. There is an obvious lack of knowledge in functional recovery following a DRF, although there is some evidence on the regional recovery specific to the wrist and upper extremity. There are very few studies that combine both fall and fracture risk factors, and the few studies available have limitations including those with known low bone mass only, including a wide age range not focusing on early postmenopausal women, and reliance on self-reported measures of clinical risk factors. Literature investigating musculoskeletal changes using pQCT

technology, specific to early postmenopausal women is extremely limited. However, there is evidence that this technology is able to discriminate well between fractured and non-fractured women between the ages of 45 and 85. The purpose of the three studies described in the following three chapters were designed to address these gaps identified in the literature.

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CHAPTER 3: STUDY 1 - CHANGES IN FALL RISK IN OLDER WOMEN POST DISTAL RADIUS FRACTURE: A PROSPECTIVE ONE-YEAR FOLLOW-UP STUDY

INTRODUCTION

Distal radius (wrist) fractures are the most common fracture across the lifespan, accounting for one sixth of all fractures, with a much higher incidence in women (Brogren et al., 2012; TimoBeil et al., 2011). In caucasian women, the lifetime risk of a fractured wrist is about 16% (versus 2.5% for men). Falling is the leading cause of low-energy or fragility fractures with 10-15% of falls in the elderly resulting in fracture (Burke-Doe et al., 2008; Nordvall et al., 2007). Falling is the most important risk factor for those who experience an upper extremity fragility fracture (Palvanen et al., 2000). The primary mechanism of injury for a wrist (distal radius) fracture is falling forward while walking, often occurring due to landing onto one or both outstretched hands (Orces & Martinez, 2011). Wrist fractures occur more often in relatively healthy women with low bone mass as compared to older women with lower functional status. Compared to women older than 65 years, post-menopausal women in their 50s and early 60s are less likely to have compounding comorbid conditions, which are known to increase with age and can contribute to risk of falling (WHO, 2003). In addition, pre-retirement women tend to be more active with careers (Osteoporosis Canada, 2013) and demonstrate maintained physical activity levels from early adulthood (Cho et al., 2014). Although the incidence of falling increases with age and declining physical activity levels, the largest patient group with wrist fractures includes early post-menopausal women with higher levels of activity in work or leisure (Brogren et al., 2011). A recent study confirmed that the incidence of wrist fractures treated in hospital emergency departments among women increased dramatically between age 45 and 64 years, (Orces & Martinez, 2011) at an annual fracture rate of 3.9% among women aged 50-59 years of age.

Few studies have evaluated fall and fracture risk status in women aged 50-59 (Pfister et al., 2013) or the functional changes that occur in the first year of recovery post-wrist fracture that may increase future fall risk. Cho et al. (2014) suggest the increased risk of wrist fractures in this age group may be the combination of maintained levels of physical activity and subtle declines in physical performance thus exposing individuals to higher "risk". This is supported by findings that women who walk regularly have a higher risk of wrist fractures, compared to those who did not walk regularly (Silman et al., 2003). With potentially faster walking speeds, moving more quickly, or more active lifestyles, women may frequently put themselves in riskier situations where they are more likely to fall. This brings to question the utility of commonly used fall risk screening tools such as walking velocity, activity levels and balance (Burke-Doe et al., 2008; Rikli & Jones, 2001; Washburn et al., 1999) in identifying women at risk of fractures and falls in the early post-menopausal years.

Experiencing a wrist fracture is known to significantly increase the risk of a future hip fracture, or other osteoporotic fracture. The risk of any subsequent fracture increases steadily with time, reaching 55% by 10 years and 84% by 20 years post-wrist fracture (Orces & Martinez, 2011). Fall history is an important predictor of future falls (Burke-Doe et al., 2008). Falls and fractures often share common risk factors, including prior history of falls or fracture, muscle weakness, gait and balance deficits, and increased age (Burke-Doe et al., 2008). Identifying fall risk in post-menopausal women < 65 years of age can be missed due to their otherwise normal healthy status. Fall risk screening tools have not been examined in this population. In addition, the changes that occur relative to these risk factors over the first year post-fracture are not known and may assist in determining why risk of future falls and fracture increases post-fracture.

Several long-term studies suggest the majority of individuals who experience a wrist fracture will recover full upper extremity motion and strength within 6 months post-fracture, although a minority experience functional disability up to a decade after the fracture (Brogren et al., 2011). Range of motion at the wrist and grip strength have been shown to be diminished at one year post-fracture with mean grip strength demonstrating 88% strength of the uninjured hand adjusted for hand dominance (Brogren et al., 2011).

About 8% continue to demonstrate increased pain scores (moderate to very severe) and disability outcome measures (Brogren et al., 2011; MacDermid et al., 2003). Despite this evidence specific to regional recovery at the upper extremity, there is little knowledge of the natural course of fall risk status during the first year following a wrist fracture and the differences that may exist between age cohorts.

The purpose of this study was to determine: 1) fall risk status and functional status at one, three, nine, 12, 26, and 52 weeks post-fracture in older women; 2) changes in fall risk and functional status during post-fracture recovery; and, 3) if differences in fall risk and/or pattern of recovery exist in those aged 65 years and older, compared to those aged 50 to 64 years of age.

METHODS

Participants

Seventy-eight women age 50 years or older with a recent wrist fracture were recruited from an orthopedic distal radial fracture clinic. These women were part of another randomized controlled clinical trial, which involved targeted grip strength training of the unaffected hand compared to a standard rehabilitation protocol (Magnus et al., 2013). Given no difference between intervention and control groups for fall risk measures, all participants regardless of rehabilitation protocol were included in this study. Participants were recruited within the first week after fracture, and were followed at weeks 3, 9, 12, 26, and 52 post-fracture, in concert with the time of their orthopaedic follow-up visit. Sixty-three of the 78 participants who were assessed at baseline (81%) completed testing up to the full year post-fracture. Participants included women who sustained a wrist fracture with either surgical or non-surgical repair. Exclusion criteria included: 1) Participants who sustained a prior wrist fracture in their adult years; 2) significant neurological or medical conditions that affected daily living (i.e. stroke, Parkinson's disease or other systemic neurological conditions affecting balance); 3) inability to walk independently with or without a walking aid; 4) any history of upper extremity neurological problems including conditions such as reflex sympathetic dystrophy; 5) a current severe painful hand or wrist problem (e.g. systemic polyarthropathy in the wrist or hands); or cognitive impairment.

Procedures

All participants signed informed consent and ethics approval was obtained from the University of Saskatchewan's biomedical ethical review board.

Baseline Descriptive Measures: Handedness was assessed by the Waterloo Handedness questionnaire (Steenhuis et al., 1990), and cognitive functional status assessed by the Mini-Cognitive Screening test (Borson & Scanlan, 2003). A detailed falls history questionnaire and a medical and demographic questionnaire were completed at baseline.

Outcome Measures

***Fall Risk and Functional Status**:* The modified BERG Balance Scale (BBS) (Rose, 2010), BBS single leg stance and standing forward reach items, the 30-second chair stand test (Rikli & Jones, 1999), and the 50 foot walk test (Hinman, 2002) were used to assess general fall risk status.

The BBS includes 14 items assessing functional balance and consists of day to day tasks such as picking up an object from the floor, turning in a circle, reaching, and balancing on one leg. The BBS is a valid measure (r = 0.81) with high inter-rater reliability (0.98 ICC) as a useful predictor of risk for future falls in aging adults (Burke-Doe et al., 2008). The modified BBS, using the more challenging 9 tasks, with a maximum score of 36 was used, due to the higher functioning status of this population (Rose, 2010). Single leg stance and forward reach (two of the items in BBS) were also reported as independent measures.

For the 30-second chair stand test, the participants were instructed to fully stand up and fully sit down as many times as possible in 30 seconds. One full stand and sit was considered one repetition. The number of repetitions was recorded for each participant. This test has established test-retest reliability, inter-observer reliability, and validity (ICC = 0.84-0.92, r = 0.93, r = 0.78) (Rikli & Jones, 1999; VanSwearingen & Brach, 2001).

The timed 50-foot walk test has been incorporated into the physical performance test (PPT), a performance based measure used to identify individuals who are at risk of recurrent falls (VanSwearingen & Brach, 2001), with documented normative values for community dwelling older adults (Reuben & Siu, 1990). The 50-foot walk test has been used to validate other functional and health status instruments and as an outcome measure for comparison of balance intervention programs in community dwelling older adults (Hinman, 2002).

Testing adhered to the published standard protocols for each measure. All testers were trained in using the standard protocol. A fall history questionnaire developed by the researchers provided details of falls prior to the fracture and during each visit post-fracture.

***Physical Activity Status and Balance Confidence**:* The Physical Activity Scale for the Elderly (PASE) is a self-report questionnaire designed to assess current level of activity (occupational, household and leisure) of community-dwelling older persons, based on the one week period previous to the date of administration. Construct validity has been established by correlating PASE scores with physiologic and performance characteristics: peak oxygen uptake, resting heart rate and blood pressure, percent body fat, and balance; this has provided evidence for the validity of the PASE as a measure of physical activity suitable for use in epidemiology studies on the association of physical activity, health, and physical function in older individuals (Washburn et al., 1999).

The Activities-specific and Balance Confidence (ABC) Scale is self-report questionnaire designed to measure the psychological impact of balance impairment and/or falls (Hill, 2005). Test retest reliability has been established (r=0.92) in community dwelling older adults, as well as 84% sensitivity and 87% specificity in correctly classifying fallers and non-fallers in a cross-sectional study of community dwelling older adults (Hill, 2005).

***Self-Reported Pain and Function of the Upper Extremity**:* A patient rated wrist evaluation (PRWE) was used to evaluate functional ability of the affected upper extremity. The PRWE was developed as a reliable

and valid tool for quantifying patient-rated wrist pain and disability, and has been validated in patients with a distal radius fracture (MacDermid et al, 1998). A simple score can be computed on a scale of 100; the PRWE allows patients to rate their status from 0 to 10 for subsections of pain, activities of daily life, and work as indicators of subjective outcome (MacDermid et al, 1998).

Statistical Analyses

Descriptive data were generated for all variables, as well as relevant medical and demographic information (Table 3.1). Analyses of fall-risk data revealed no effects of the grip strength training intervention, so data was pooled for analyses of fall risk measures. Missing data were replaced using group series mean, as data were determined to be missing completely at random (Little's MCAR test) (Tabachnick & Fidell, 2007) (See Table 3.1 for a description of missing data). Due to a ceiling effect, ABC data was negatively skewed across weeks 1, 9, 26, and 52; therefore data were reflected and transformed using log10 transformation to achieve a normal distribution (Tabachnick & Fidell, 2007). A three-way mixed ANOVA with repeated measures with a 2×2×4 design (group x age category x time) was used to rule out main effects of the grip strength training intervention as well as any interaction effects, and to determine differences between groups of those aged 50-65 versus those > 65 years of age at different time points, as well as changes over the year for the following measures: PASE, log transformed ABC, PRWE, BBS single leg stance item, BBS forward reach item, 30-second chair stand test, and 50 foot walk test at fast and usual speeds. SPSS 22.0 was used for all statistical analyses with $p < 0.05$ used for determining statistical significance, with a Bonferroni correction used for multiple comparisons testing.

Table 3.1. Number of missing data points

	Week 1	Week 3	Week 9	Week 12	Week 26	Week 52
30sChairStand	-	10	-	14	15	21
BBS - reach	-	10	-	14	15	20
BBS – single leg balance	-	12		15	15	21
50 ft walk (usual speed)	-	11	-	14	15	11
50 ft walk (fast speed)	-	11	-	14	15	11
PASE	0	-	14	-	14	20
ABC	0	-	4	-	14	20
PRWE	25	-	7	-	13	16

Note: 30sChairStand, BBS and 50 ft walk were not tested at week 1 and week 9. PASE, ABC, and PRWE were not tested at week 3 or week 12. Our data were missing completely at random, as indicated by a non-significant Little's MCAR test: 30s Chair Stand, $\chi 2= 21.65$, $p= .600$; BBS, $\chi 2= 117.08$, $p= .180$; PASE, $\chi 2= 76.07$, $p= .793$; ABC, $\chi 2= 13.83$, $p= .462$; PRWE, $\chi 2= 46.90$, $p= .352$.

RESULTS

Descriptive Characteristics

All participants included in the study demonstrated a negative screen for cognitive impairment using the Mini-Cognitive Screening Test (Borson & Scanlan, 2003). Of the 63 participants followed over the first year, the mean age was 63 (SD = 8.4) years, with age ranging from 50 to 84 years (Table 3.2). Thirty-six subjects (57%) were under the age of 65, and 27 (42.9%) were 65 or older. Eighteen percent of the sample required surgical repair, 59% fractured their dominant wrist, with 91% being right-hand dominant. All participants received a standard written home exercise protocol to maintain mobility and strength of their fractured limb after cast removal. Twenty participants (26%) reported receiving additional physical therapy intervention. Details regarding frequency and type of intervention received was not reported, although standard physical therapy intervention focused on enhanced mobility and strengthening for the affected extremity when progress was limited.

Table 3.2. Baseline descriptive characteristics

Characteristics	Overall Group (N=63)		Age < 65 (n=36)		Age > 65 (n=27)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	63 (8.4)	50-84	57.4 (4.3)	50-64	70.9 (5.8)	65-84
Height (cm)	161.5 (6.6)	147.5-175.8	162.9 (6.3)	151.0-175.8	159.6 (6.6)	147.5-172.5
Weight (kg)	67.9 (13.3)	44-111.8	69.3 (12.3)	45.6-111.8	66.0 (14.7)	44 – 97.9
Number of Medical conditions	1.7 (2.1)	0 -8	1.14 (1.7)	0-7	2.5 (2.3)	0-8
Number of medications	1.8 (1.8)	0-6	1.1 (1.3)	0-4	2.4 (1.9)	0-6

Medical and Demographic History

This questionnaire was used to confirm exclusion criteria and to determine other medical conditions and health status that may affect fall and fracture risk. The number of medical conditions reported ranged from 0 to 8, with 58% reporting 0 or 1 medical condition; only 9% reported greater than 4 medical conditions. The number of medications ranged from 0 to 6 (mean = 2). Seventeen percent reported taking calcium supplementation, 22% reported using Vitamin D supplementation, and 11% reported being on a bone altering medication.

Falls History Reported at Baseline

All participants reported at least one fall at week 1 post-wrist fracture. There were two (3%) participants that reported two falls, five (8%) participants that reported three falls, and four (6%) participants that reported > 3 falls.

Fall risk and functional status (Week 3, 12, 26, 52): Means and standard deviation for the following outcome measures are summarized in Table 3.3 and mean scores for age categories in Table 3.4.

30s Chair Stand:

Mauchly's test revealed a violation of sphericity (W=0.746, $p<0.05$), indicating significant differences between the variance and covariance across repeated measures and a need for Greenhouse-Geisser correction. Repeated-measures ANOVA with Greenhouse-Geisser correction determined a significant main effect of time, F (2.6,151.4) =4.279, p=0.015, and no between subjects effect of age category for 30s Chair Stand, although this approached significance, F (1,59) =3.411, p=0.07.
Pairwise comparisons with Bonferroni correction revealed an increase in chair stand repetitions from week 3 to week 52 (p=0.044).

Berg Balance Scale:

Total scores on the modified BBS demonstrated ceiling effects, leading to non-normal distributions in data. Therefore, BBS single leg stance item (timed up to one minute) and BBS standing forward reach item (measured in inches) were used in the analysis.

Single Leg Stance:

The repeated-measures ANOVA revealed no significant main effect of time, F (3,177) =0.157, p=0.157; however, there was a significant between subjects effect of age category F (1,59)=15.410, $p<0.001$, with the younger age category demonstrating better performance.

Forward Reach:

The repeated-measures ANOVA revealed a significant main effect of time, F (3,177) =4.153, p=0.007, and between subjects effect of age category F(1,59)=8.511, p=0.005. Pairwise comparisons with Bonferroni correction revealed a significant difference in reach scores from week 12 to week 52 (p=0.002), with performance declining at week 52.

50 Ft Walk Test, Usual Speed:

Mauchly's test revealed a violation of sphericity (W=0.616, $p<0.001$), with significant differences between the variance and covariance across repeated measures. Repeated-measures ANOVA with Greenhouse-Geisser correction found a significant main effect of time, F (2.2, 132.1) =7.003, p=0.001, and a between subjects effect of age group $F(1,59)=6.231$, p=0.015, with the younger group demonstrating faster gait speeds. Gait speed increased significantly from week 3 to 26 (p=0.008) and week 3 to 52 (p=0.009), approaching significance from week 3 to week 12 (p=0.075) using pairwise comparisons with Bonferroni correction.

50 Ft Walk Test, Fast Speed:

Mauchly's test revealed a violation of sphericity (W=0.485, $p<0.001$), with significant differences between the variance and covariance across repeated measures. Repeated-measures ANOVA with Greenhouse-Geisser correction revealed a significant main effect of time, F (2.0, 119.6) =3.765, p = 0.025) and between-subjects effect of age group F (1,59) =9.488, p=0.003, with the younger group demonstrating faster gait speeds. Pairwise comparisons with Bonferroni correction revealed no significant differences across time.

Physical activity, balance confidence, and self-reported pain/function (Week 1, 9, 26, 52):

Physical Activity Scale for the Elderly:

Mauchly's test revealed a violation of sphericity (W=0.741, $p<0.05$), with significant differences between the variance and covariance across repeated measures. Repeated-measures ANOVA with Greenhouse-Geisser correction revealed a significant main effect of time, F (2.5,146.0) = 4.279, p=0.01, and between subjects effect of age group $F(1,59)=10.052$, p=0.002 for PASE scores. Scores increased significantly from week 9 to 26 (p=0.019) and week 9 to 52 (p=0.009).

Activities of Balance Confidence (ABC):

ABC data were not normally distributed due to ceiling effects; therefore transformed scores were used for the repeated measures ANOVA. Raw data scores revealed that 60 subjects (92%) scored greater than 67% on the ABC and were therefore considered "not at risk of falling" (Lajoie & Gallagher, 2004) at weeks 1 and 9. There were 63 subjects (97%) who scored greater than 67% on the test and were therefore considered "not at risk of falling" at weeks 26 and 52.

Repeated-measures ANOVA, sphericity assumed, revealed a significant main effect of time, F (3,177) =4.110, p=0.008 and no between subjects effect of age group F(1,59)=1.925, p=0.172. Pairwise comparisons with Bonferroni correction revealed a decrease in ABC score from week 1 to week 9 (lower confidence), although this was not significant. Scores increased significantly from week 9 to 26 (p =0.019) and week 9 to 52 (p = 0.009).

Raw mean ABC scores at week 1 were the same for those aged ≥ 65 years and those aged 50 to 65 years ($\bar{x}$ = 89%, SD =12%, 17% respectively). However, at week 9, the older group demonstrated a decrease in ABC score ($\bar{x}$ = 86%, SD=14%), while the younger group score increased slightly at week 9 ($\bar{x}$ = 90%, SD=13%), and reached a ceiling effect by week 26 ($\bar{x}$ = 93%, SD=10%). The group aged ≥ 65 consistently demonstrated lower ABC scores at week 9 ($\bar{x}$ = 86%, SD=14%), 26 ($\bar{x}$ = 90%, SD=11%), and 52 ($\bar{x}$ = 89%, SD=14%) compared to the group aged 50 to 64. Independent samples t-tests were used to determine age group differences with the log transformed data. No significant differences existed between groups at any time point.

Self-reported pain and function of the upper extremity (PRWE):

Mauchly's test revealed a violation of sphericity (W=0.560, p<0.001), indicating significant differences between the variance and covariance across repeated measures. Repeated-measures ANOVA with Greenhouse-Geisser correction revealed a significant main effect of time, F(2.3, 133.0)=62.265, p<0.001)

and no between subjects effect of age group $F(1,59)=0.138$, $p=0.712$. Pairwise comparisons with Bonferroni correction revealed an increase in PRWE score from week 1 to week 9 ($p < 0.001$). Scores decreased significantly from week 9 to 26 ($p < 0.001$) and week 26 to 52 ($p = 0.002$).

Table 3.3. Mean (SD) scores for all primary outcome measures

	Week 1	Week 3	Week 9	Week 12	Week 26	Week 52
30sChairStand (reps)	-	13.6 (4.7)**	-	14.5 (4.5)	15.1 (4.4)	15.1 (4.6)
BBS – reach (inches)	-	12.6 (2.3)	-	13.4 (2.5)**	13.1 (2.5)	12.3 (2.5)
BBS – single leg balance (sec)	-	29.5 (19.7)	-	30.8 (20.35)	34.9 (19.9)	33.4 (19.9)
50 ft walk (usual speed) (sec)	-	13.8 (2.5)*	-	13.2 (2.4)	12.8 (2.0)	12.5 (2.4)
50 ft walk (fast speed) (sec)	-	10.7 (1.7)	-	10.4 (1.7)	10.3 (1.8)	9.9 (2.0)
PASE (item scale)	121.4 (84.0)	-	115.0 (67.2)*	-	140.2 (59.0)	141.3 (56.1)
ABC (percent)	88.6 (14.5) †	-	88.0 (13.2)*	-	91.8 (10.3)	91.0 (11.5)
PRWE* (item scale, /100)	1.2 (1.4) †	-	43.2 (26.9)	-	23.1 (22.9)	14.2 (16.2)

Note: 30sChairStand, BBS, and 50 ft walk were not tested at week 1 and week 9. PASE, ABC, PRWE were not tested at week 3 or week 12. † Significantly different than Week 9. * Significantly different than Week 26 and 52, ** Significantly different than Week 52 only.

Table 3.4. Mean (SD) scores for age categories: age 50 to 64 and age 65 and older

	Single leg balance (seconds)		Forward Reach (cm)		50 foot walk (Usual speed) (seconds)		50 foot walk (Fast speed) (seconds)		PASE (Item scale)	
	Age 50-64	Age 65+	Age 50-64	Age 65+	Age 50-64	Age 65+	Age 50-64	Age 65+	Age 50-64	Age 65+
Week 1	-	-	-	-	-	-	-	-	141.6 (96.9)	94.5 (53.6)
Week 3	34.8 (20.1)	22.3 (15.4)	13.2 (2.0)	11.8 (2.4)	13.3 (2.3)	14.4 (2.6)	10.2 (1.3)	11.3 (2.1)	-	-
Week 9	-	-	-	-	-	-	-	-	134.7 (71.8)	88.6 (50.7)
Week 12	37.9 (20.3)	21.3 (16.4)	14.0 (2.3)	12.6 (2.5)	12.6 (2.0)	14.0 (2.7)	9.9 (1.3)	11.1 (2.0)	-	-
Week 26	42.5 (17.5)	24.9 (22.6)	13.8 (1.7)	12.3 (3.1)	12.3 (1.8)	13.4 (2.1)	9.8 (1.5)	11.0 (1.9)	134.7 (71.8)	88.6 (50.7)
Week 52	39.3 (18.1)	25.9 (22.6)	12.7 (2.5)	11.8 (2.5)	12.0 (2.6)	13.2 (1.8)	9.5 (2.0)	10.5 (1.7)	158.9 (52.2)	117.8 (53.2)

Note: Only variables where there was a between subjects effect of age category are reported here. ($p<0.05$). Single leg balance, forward reach, and 50 ft walk were not tested at week 1 and week 9. PASE was not tested at week 3 or week 12.

DISCUSSION

With the increased incidence in wrist fractures in women aged 45 – 64 (Orces & Martinez, 2011), and the resultant escalation of future fracture risk following this first 'signal' fracture, determining the potential risk factors in the recovery period is clinically important. This study included individuals aged 50 to 84 years who were followed over the first year following a wrist fracture to allow for the analysis of the fall-risk and functional status changes over the first year, as well as to compare differences in age categories of those aged 65 and older, to those between the ages of 50 and 65 years.

Current guidelines to screen for fall risk, focused on older adults age 65 years and older, recommend an evaluation of gait and balance, suggesting common tests such as the BBS, timed up and go (TUG), and Performance Oriented Mobility scale(Panel on Prevention of Falls in Older Persons, 2011). Screening guidelines recommend that an evaluation of gait and balance should be performed for any older adult reporting a fall in the past 12 months (Panel on Prevention of Falls in Older Persons, 2011). Despite evidence that declines in balance begin by the fourth and fifth decade of life (Isles et al., 2004), there are currently no guidelines specific for those younger than age 65 years. The use of standardized fall risk measures designed for an older population may identify balance deficiencies in a younger cohort particularly if utilizing more challenging items as opposed to composite scores. We attempted to address the potential ceiling effect by utilizing tests deemed more challenging such as single leg stance, and a modified version of the BBS. There was a significant improvement in the majority of scores for the fall-risk and functional measures indicating a likely decline in function immediately following fracture, followed by functional recovery throughout the first year. Exceptions were the single leg stance time and an unexpected decrease in forward reach performance. The decline of forward reach (distance reached forward while maintaining feet stable on the ground) may be attributed to a subtle decline in postural stability in the forward direction (LowChoy et al., 2008), which became more evident post-cast removal. The change in dynamic balance in a forward direction may related to fear avoidance or lack of confidence when pushing the limits of stability in the forward direction. This situation may be similar to the balance

disturbance experienced with the fall that caused the wrist fracture and may better represent a possible fear component when pushing the center of gravity to the limits of stability, especially post-cast removal, assuming the cast provided a sense of protection. It was also possible that participants were reaching well beyond the fall-risk threshold of 7 inches (LowChoy et al., 2008), possibly with a decreased motivation to reach any further. The mediolateral stability, tested by decreasing the mediolateral base of support with single leg stance was not significantly affected post-fracture; however, there was a significant difference between the age categories for both single leg stance and forward reach with older women demonstrating lower balance capabilities.

In order to identify fallers from non-fallers among older adults, it is necessary to present them with age appropriate and challenging fall risk measures, including balance tests. Determining cut-off scores to identify fall-risk particularly for the higher functioning older adult population is difficult and more research is needed. This study found that more challenging isolated tests may be required to discriminate fall risk in this population. Adding other parameters such as sensory interaction tests: balancing on an unstable surface, with and without eyes open for single leg stance, may also demonstrate greater variance with age (LowChoy et al., 2008). The finding of a decline in forward reach scores closer to one year post-fracture, after the cast has been removed may be an important factor to consider during rehabilitation and fall risk education for older women during the recovery phase and may be a useful clinical measurement tool to identify risk for future forward falls.

Cho et al. (2014) suggest that there may early subtle declines in physical performance in women over the age of 50 with a recent wrist fracture, as identified with a chair stand test and grip strength. They also found that total scores on a Physical Performance Battery or physical activity level, estimated by time per week spent walking, did not differ from the control group. In our study, the 30s Chair Stand test demonstrated a significant improvement between week 3 and week 52. Scores ranged from 6 to 32 repetitions in the younger group and 0 to 36 repetitions in the older group; however, mean scores ranged from 14 to 16 in the younger age category and 13 to 14 in the older age category, above the threshold for

fall-risk and within norms established for women over the age of 60 (Rikli & Jones, 1999). Although this may not be an ideal test to determine fall-risk in women between the ages of 50 and 64, it is interesting that there may have been an effect on lower extremity strength following an upper extremity fracture. Although we do not know pre-fracture scores or normative values for women younger than 60 years of age, there was a significant improvement in scores over the first year, suggesting a decline may have occurred immediately post-fracture. This may be associated with the observed decline in physical activity status or possibly a change in participation in activities that were not assessed in this study, such as changes in leisure activities, or activities related to employment status. In turn these may have been impacted by the influence of wearing a cast and declines in function of the hand and wrist immediately following the removal of the cast. It has been suggested that chair stand ability not only relates to strength, but also balance, particularly weight shifting forward (Benson, 2014) and leg power (Crockett et al., 2013). A poorer performance of chair stand testing post-wrist fracture, compared to age-matched controls is consistent with previous research (Cho et al., 2014). This could reflect changes in physical activity level resulting in leg strength deterioration or possibly diminished forward balance or diminished confidence in weight shifting forward. Further research could help explain the factors to explain this.

Similarly, the 50-foot walk test, at both usual and fast speeds, was faster between baseline and 6 months post-fracture with continued increases up to 1 year. The younger age category consistently demonstrated faster gait speeds with both their usual and fast speeds. The literature indicates a non-linear relationship in gait speed and falls with participants with faster (1.3 m/s) and slower (<0.6 m/s) gait speeds at higher risk of falling (Quach et al., 2011). Because we used a 50-foot walk test that included a turn-around mid-way, we were unable to calculate gait velocity; however, speed changes can likely be assumed with progressively faster times to complete the 50-ft walk test throughout the recovery phase. This study found slower gait speeds immediately following the fracture (first measured at week 3 post-fracture), potentially related to decreased physical activity levels, lower extremity strength or fear of falling. Since baseline pre-fracture values could not be established, the scores were compared to normative values and/or the change

from the previous time point where possible. Scores on the functional measures including the BBS, 30s Chair Stand test, and 50-foot walk test changed over the first year, but mean values consistently remained above fall-risk levels (Table 3.3).

Low physical activity levels have been associated with poor balance, falls, and fractures (Peeters et al., 2009; Rozental, et al., 2013; WHO, 2003). In this study, physical activity levels (PASE scores) were lower immediately post-fracture, and further reduced at 9 weeks, which coincided with the time post-cast removal. Scores then increased at week 26 and further increased at week 52, close to baseline values. Because of the nature of the PASE, subjects were asked to estimate their physical activity levels the week prior to their fracture, providing us with an estimate of physical activity levels prior to the fracture and the ability to compare scores at 52 weeks post-fracture to their usual activity levels. Therefore, the period of casting immobilization post-fracture may contribute to the initial declines in physical activity levels as the cast interferes with typical activities especially if the dominant hand is fractured, which could in turn contribute to other-health related aspects of life (Nitz et al., 2013). This would have to be further evaluated in future research, as specific changes in health status were not documented throughout the year in this study and the sample size was not large enough to compare those who fractured their dominant hand versus non-dominant. The decreased physical activity levels post-cast removal could be explained by a reduced level of confidence, where ABC scores at 9 weeks were also lower compared to Week 52, as the protection from the cast is no longer present. This could also be associated with coinciding symptoms such as loss of range of motion and weakness. Self-reported pain and dysfunction (PRWE) specific to the upper extremity increased from Week 1 to Week 9, which would be expected due to the fracture and the limitations caused by the cast, as Week 1 was reported as participants could best recall pre-fracture pain and function. Scores then decreased significantly after week 9, continuing to decrease to week 52, but pain and dysfunction still remained higher than baseline values (Table 3.3). This is consistent with previous literature reporting the typical recovery of pain and function at the wrist over the first year post-fracture, with the majority of individuals expected to have minimal pain and disability by six months post-fracture,

and a minority still reporting pain and disability at one-year (MacDermid et al., 2003). Importantly, physical activity levels, as measured by the PASE followed similar trends as the 30-second chair stand test, 50 foot walk test (usual speed), and balance confidence as measured by the ABC, suggesting that physical activity levels may be related to functional ability during post-fracture recovery (Figure 3.1).

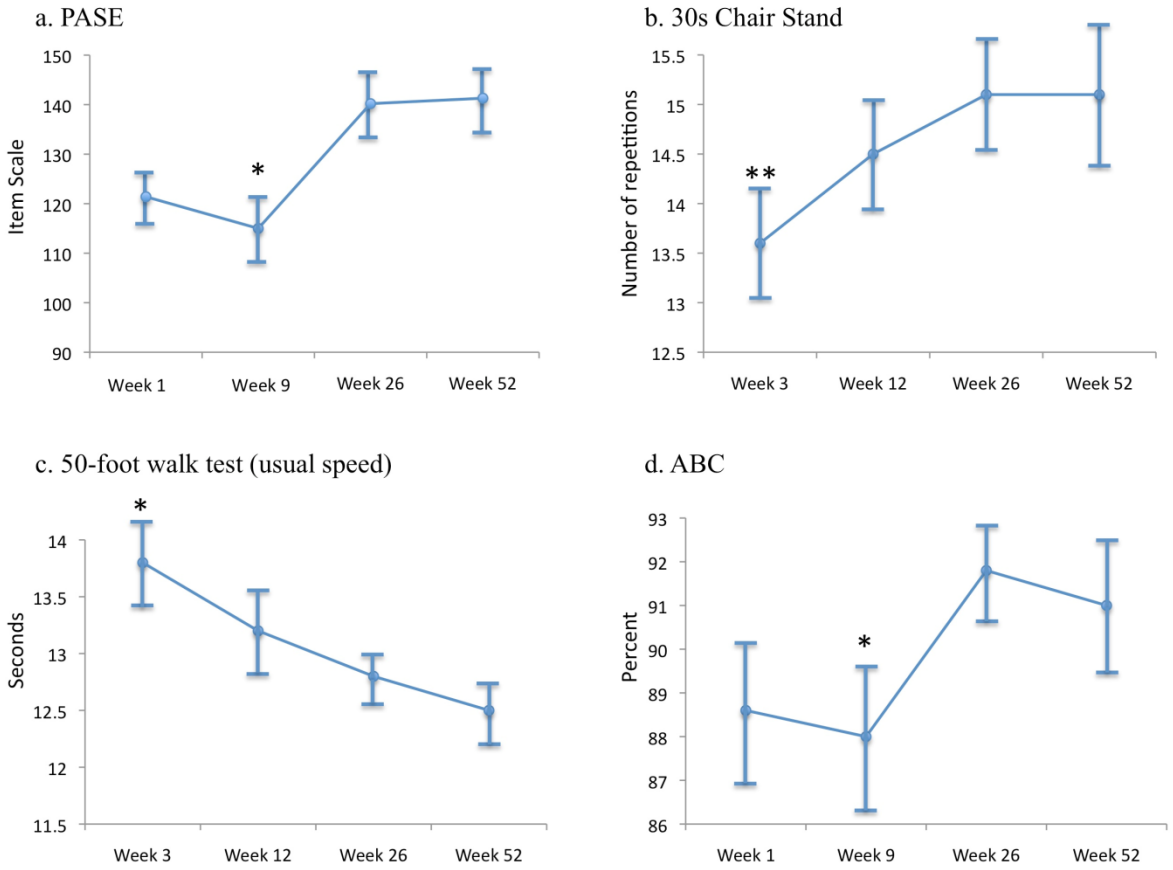

Figure 3.1. Changes in a) physical activity levels (PASE), b) lower extremity function (30s Chair Stand), c) gait speed (50-ft walk test), and d) balance confidence (ABC) across the first year post-fracture. Mean values at each time point represent the mean for all participants (N=63). Note: 30sChairStand and 50 ft walk were not tested at week 1 and week 9. PASE and ABC were not tested at week 3 or week 12. * Significantly different than Week 26 and 52, ** Significantly different than Week 52 only.

Interestingly, balance confidence remained high, even immediately post-fracture, with the majority (92%) of participants scoring greater than 67%, thus being considered 'not at risk of falling' (Lajoie & Gallagher, 2004). Although there was a decrease in mean scores between week 1 and week 9, coinciding with

decreased physical activity levels, this was not significant and mean values remained in the low fall risk range. There was no significant difference between the younger and older age categories for balance confidence. These results suggest that there may be a lack of sensitivity with this scale or that confidence was not influenced by a wrist fracture within this study sample. The nature of multiple contact visits with a variety of health professionals, specialists and research assistants during the 1-year recovery period may have contributed to higher confidence scores. However, other studies report high scores in balance confidence in women over age 45 with a recent wrist fracture, with a mean score of 92% (+/- 10.2%) (Mehta et al., 2014). It is possible that a fall resulting in a wrist fracture does not substantially impact balance confidence in this population.

We recognize the limitations of this study. First, participants included in the study were those attending routine follow-up visits with their orthopaedic surgeon, which may create a biased sample of women committed to attend medical appointments regularly. While data were collected prospectively, this was a subsample, from a larger study where there is significantly more contact and intervention provided than the typical post-wrist fracture follow-up. In addition, we were unable to collect pre-morbid data to allow for comparison of recovery to true baseline values. In order to allow participants to manage the large number of outcome measures, and reduce the number of dropouts over the data collection period of one year, not all data was collected at each time point. The sample size was small, which did not allow for further sub-analyses, such as comparing those with a dominant arm fracture versus non-dominant arm fracture.

CONCLUSION

In conclusion, women aged 50 and older with a recent wrist fracture demonstrated poorer performance in functional and fall risk outcomes immediately post-fracture, regardless of age category. These functional declines could indicate potential for increased risk of future falls and fracture, especially within the first 6

months post-fracture and even at 1-year post-fracture. This is significant and prompts a need to intervene in this early phase post-fracture. Differences in fall risk between older adults 65 years and those younger than 65 years is not well known, as few studies have measured fall risk for individuals between the ages 50 and 64 years. With current evidence directed towards fall prevention programs for older adults who are at very high risk for falling, addressing fall risk in the younger, higher functioning female population with a recent history of fracture may still require screening but with a less intensive approach (Mehta et al., 2014). Promoting basic screening with the appropriate screening tools as part of routine fall prevention practices for all wrist fracture patients, may be the first step in reducing the fragility fracture cycle. The findings may also direct future research regarding the need to develop sensitive screening tools and rehabilitation protocols to reduce future fall risk by addressing factors such as lower extremity function, gait speed, and balance. The development of tests to detect subtle, early changes in fall risk status could assist in identifying and implementing appropriate preventative strategies for women at risk of sustaining their first fragility fracture.

KEY POINTS

Findings: Functional declines in women over the age of 50 with a recent wrist fracture could indicate potential for increased risk of future falls and fracture, prompting a need to intervene in this early phase post-fracture.

Implications: Promoting basic screening with the appropriate screening tools as part of routine fall prevention practices for all wrist fracture patients may be the first step in reducing the fragility fracture cycle. Findings may direct future research regarding the need to develop sensitive screening tools and rehabilitation protocols to reduce future fall risk by addressing factors such as lower extremity function, gait speed, and balance.

Caution: Participants included in the study may be a biased sample of women committed to attend medical appointments regularly, with significantly more contact and intervention provided than the typical post-wrist fracture follow-up.

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RELATIONSHIP OF STUDY 1 TO THESIS:

This study evaluated the recovery of fall-risk and functional status over the first year following a DRF in women age 50 years and older. Previous risk factors for falling have been identified and include speed of walking, low or high levels of physical activity, history of falling, female sex, mobility or balance problems, and muscle weakness. The significance of these risk factors to women age 50 – 65 is not well established. Previous research has determined regional recovery of the upper extremity, such as changes in pain and disability in the upper extremity; however, recovery or changes in lower extremity function, fall-risk, and cognitive changes including a fear of falling are not well known. A pilot study examining test-retest reliability of selected measures associated with increased fall risk in females over the age of 45 with a recent DRF has recently been published (Mehta et al., 2014), offering valuable information on screening measures used in this thesis. Mehta et al. (2014) report that the results of the pilot study were based on a small number of patients, and promote concentrated research efforts to create further evidence in determining appropriate fall risk assessment approaches in DRF patients. This study established the typical course of recovery of these factors in a sample of women included in a larger intervention study post DRF (Magnus et al., 2013). This established longitudinal data set presented an excellent opportunity to first evaluate typical recovery for a number of regional functional and fall risk factors post DRF. Because the baseline scores pre-fracture could not be determined in this study, further cross-sectional and longitudinal research is needed to determine the normative values for this population as well as predictive values for fall and fracture risk. Knowing the typical trend in recovery, but not comparable to baseline or normative values, leads to the next questions, explored in Study 2 and 3.

CHAPTER 4: STUDY 2 - FALL AND FRACTURE RISK STATUS IN POSTMENOPAUSAL WOMEN WITH AND WITHOUT A RECENT DISTAL RADIUS FRACTURE

INTRODUCTION

Fractures of the distal radius (DRF) are the most common fractures in women over age 50 years (Edwards et al., 2006; Mulhall et al., 2002; Handoll et al., 2009), with the incidence increasing with age from 9% at age 50-59 to 38% after age 80 (Barrett-Conner et al., 2009). The incidence of wrist fractures in women attending hospital emergency departments increases between ages 45 and 64 years, with an annual rate increase of 3.9 % (Orces & Martinez, 2011). Low energy or fragility fractures have been defined as a fracture occurring spontaneously or following minor trauma such as a fall from standing height or less (Nordvall et al., 2007). In 2007, there were 41,606 reported wrist fractures and 188,128 total fragility fractures in Canada at an average annual total acute care cost of $1.2 billion (Osteoporosis Canada, 2013). A history of fracture in the adult years (45 years and older) has been identified as a marker of osteoporosis, and a strong predictor of future fracture (OR 1.48 - CI 1.20-1.84) (Osteoporosis Canada, 2013; Kelsey et al., 2005). With women at a greater risk of sustaining a wrist fracture than men (Edwards et al., 2006; Nguyen et al., 2001) and growing numbers of postmenopausal women in Canada diagnosed with osteoporosis, identifying risk factors for fragility fractures is crucial for both primary and secondary prevention. Fractures have been identified as a tremendous burden on aging Canadians, our healthcare and social system, and the national economy as a whole; therefore, determining risk factors has become a high national priority (Osteoporosis Canada, 2013).

Falling, the most important risk factor predicting low energy fractures, is the leading cause of unintentional injury in older adults (Palvanen et al., 2000) and the single strongest predictor of future falls (Barrett-Conner et al., 2009). Additionally, 95% of upper extremity fractures are the result of a fall (Palvanen et al., 2000). Fall risk assessment tools have been developed primarily for adults older than age

65 years, with limited normative data for older women between the ages of 50-65 years. Falls may be underreported in this younger age group, as falls without injury are quickly forgotten (Guesens et al., 2003). If the fall results in a fracture, the fracture is often treated as an acute event and the patient is left unaware of his or her bone fragility (Osteoporosis Canada, 2013). Previous reports indicate that less than10% of patients receive any form of fall risk assessment or bone density assessment following a DRF creating a substantial proportion of women not being identified, assessed, or treated for their elevated risk of subsequent osteoporotic fracture (Myers & Briffa, 2003).

Fracture risk in postmenopausal women is usually assessed by dual energy x-ray absorptiometry (DXA) derived areal bone mineral density (aBMD) measurements (Nguyen et al., 2001; Norvall et al., 2007; Jarvinen et al., 2008); however, low aBMD is only one of the prognostic variables for wrist fracture risk (Nguyen et al., 2001; Kelsey et al., 2008). In fact, VanHelden et al (2008) found that most patients with a recent DRF did not have osteoporosis as diagnosed by aBMD. Instead they had a combination of fall and fracture related risk factors that differed from low aBMD (van Helden et al., 2008). Fall-related risk factors included: having more than one fall in the previous 12 months, use of psychoactive drugs, low levels of activities of daily living, articular symptoms, impaired vision, urinary incontinence, and Parkinson's disease. Fracture-related risk factors identified included: a fracture after the age of 50 or a clinical vertebral fracture, mother with a fracture history, body weight < 60 kg, severe immobility, and use of glucocorticoids (van Helden et al., 2008).

The World Health Organization has developed a Fracture Risk Assessment (FRAX) tool using an algorithm providing a 10-year probability of fracture (Hillier et al, 2011). The algorithm takes into consideration several risk factors impacting bone strength and associated fracture risk including aBMD. Fall risk factors are not included in the FRAX algorithm (Geusens, 2009); therefore, FRAX alone may underestimate fracture risk in patients with a history of one or more falls. Falls and fractures often share risk factors, such as: prior history, muscle weakness, gait, and balance deficits, and increased age (Burke-

Doe, et al, 2008). The contributing factors predicting wrist fracture risk are not clear, especially for those aged 50-65 years.

Soft tissue properties such as forearm muscle strength may also be important predictors of future fractures (Albrand et al., 2003). Grip strength is an independent predictor of osteoporotic fractures (OR 2.05 - CI 1.00 – 3.09) (Albrand et al., 2003), and is also a good marker of overall physical performance in community-dwelling older people (Stevens et al, 2012). Cho et al (2014) suggest that it may be the combination of maintained physical activity with subtle declines in physical performance, including grip strength and chair stands, that increase risk of DRFs. Grip strength has been considered to be a strong determinant of radius bone strength, as assessed by peripheral quantitative computed tomography (pQCT), due to the considerable strain isometric gripping places on the forearm bones (Hasegawa et al, 2001). We recently reported 16% lower bone strength at the distal radius (measured from pQCT imaging) accompanied by 20% lower grip strength (Crockett et al, 2015). Grip strength may be a simple measurement tool to identify fall and fracture risk in women over the age of 50 years, but further research is needed to determine its relationship between fall and fracture risk status (van Helden et al, 2008).

The primary purpose of this study is to compare fall and fracture risk status in postmenopausal women with and without a recent DRF. Secondary purposes include determining the relationship of fall risk to fracture risk in older women and to determine the relationship of grip strength to fall and fracture risk status. The primary hypothesis is that women over the age of 50 years with a recent DRF will have higher fall and fracture risk, as compared to women with no recent history of DRF matched for a similar age, as measured by poorer performance in balance, mobility/lower body strength, grip strength, and a higher FRAX score. It is hypothesized that higher fall risk will be associated with higher fracture risk in women with and without a recent distal radial fracture and lower grip strength will be associated with fall and fracture risk.

METHODS

Participants and Procedures

Women aged 50 years or older with a history of wrist fracture (minimum 6 months and maximum 24 months post fracture) were recruited from local orthopaedic surgical clinics and within the community through newspaper and poster advertisement. The control group, women over the age of 50 without a recent history of wrist fracture since 35 years of age, was recruited through newspaper and poster advertisement. Exclusion criteria included: 1) taking high dose corticosteroid treatment or bone altering medications such as bisphosphonates or hormone replacement therapy in the past year; 2) presence of significant neurological or medical conditions that affect daily living (i.e. stroke, Parkinson's disease or other systemic neurological conditions affecting balance); 3) inability to walk independently; 4) any history of upper extremity neurological problems including conditions such as reflex sympathetic dystrophy; or 5) currently presenting with a severe painful hand or wrist problem (e.g. systemic polyarthropathy in the wrist or hands). All participants signed informed consent prior to testing. Ethics approval was obtained from the University of Saskatchewan's ethical review board.

A total of 166 women were screened by telephone, and 89 did not meet eligibility criteria or chose not to participate. Seventy-seven women age 50-78 with (Fx, n=32) and without (NFx, n=45) a recent history of DRF were assessed on two occasions within four weeks using a battery of fall and fracture risk tools. This was part of a larger study that also investigated bone and muscle properties in this cohort, reported in another manuscript (Crockett et al., 2015). All functional testing used standardized protocols and was carried out by two trained individuals, a physical therapist (KC) and an athletic therapist. DXA (QDR Discovery Wi)[a] technology was used with QDR software for Windows XP (QDR Discovery, Hologic, Inc.) with a single operator obtaining aBMD (g/cm^2) of the femoral neck, following the Hologic protocol (Hologic, 2004), to be used in the calculation of the FRAX score.

Demographic and Descriptive Measures

Handedness was determined by the Waterloo Handedness questionnaire (Steenhuis et al, 1990). Physical activity in the past seven days was assessed using the Physical Activity Scale for the Elderly (PASE) (Washburn et al. 1999), cognitive functional status by the the Mini-Cognitive Screening test (Borson & Scanlan, 2003), and a medical and demographic questionnaire documented associated confounding factors including: current medications, menopausal status, and vitamin and supplement intake.

Height was measured using a wall-mounted stadiometer and weight was measured using a standardized scale. A fall history questionnaire was used to collect self-reported data on the number and details of previous falls, including location and reason for the fall.

Primary Outcome Measures

Fall Risk Status

Fall risk status was determined using: 1) the timed up and go (TUG) (Podsiadlo & Richardson, 1991) and timed up and go cognitive (TUGcog) tests (Shumway-Cook et al., 2000), 2) the 30 second sit to stand test (30sSTS) (Rikli & Jones, 2001), 3) the timed gait (normal and fast speeds) test (Bohannon et al., 1996), 4) the backward tandem walk (Rinne et al, 2001), 5) the BERG balance scale (BBS) (Berg et al., 1989), and 6) the self-report of activities of balance confidence (ABC) test (Hill, 2005).

1) The TUG is a performance-based functional test that measures how quickly an individual can stand from an armless chair, walk around a marker 3-meters away, and return to the original position. The TUG is a valid and reliable (r=0.95) measure for quantifying functional mobility in older adults with a high sensitivity (78%) and specificity (86%) for predicting falls for individuals with a score of 8.5 seconds or higher (Burke-Doe, et al., 2008; Rikli & Jones, 2001). The TUGcog is a dual-tasking version of the TUG associated with fall risk, (Hofheinz & Schusterschitz, 2010), completing the TUG with the addition of counting backwards by threes during the test. The TUGcog is has demonstrated high criterion validity with high correlations to the Berg Balance

Scale (BBS) (r = -0.66), with excellent intra-rater reliability (ICC = 0.94) (Hofheinz & Schusterschitz, 2010).

2) The 30sSTS, a test of lower extremity function, strength, and power, has established test-retest reliability, inter-observer reliability, and validity (ICC = 0.84-0.92, r = 0.93, r = 0.78) (van Swearington & Brach, 2001; Rikli & Jones, 1999). Participants were instructed to fully stand up and fully sit down as many times as possible in 30 seconds, with one full stand and sit considered one repetition. The number of repetitions was recorded for each participant.
3) The 10-meter timed gait test was used to determine the time to walk over a 10-meter walkway, with 2 meters on either end of the walk-way to allow for acceleration and deceleration prior to and after the timed portion of the test. Three trials of walking at the usual speed and the fast speed were performed, with the average score calculated for analyses. The 10 meter walk test is a valid and reliable measure found to discriminate between older adults with and without a history of falling, OR = 1.07 (CI 1.01 – 1.13) (Morris et al., 2007) with excellent intra- and inter-rater reliability (r = 0.95, 0.97) and strong correlations to the BBS, and TUG (Scivoletto et al., 2001).
4) The backward tandem walk over an 8 foot long beam was scored by taking the number of errors and categorizing into 3 groups, no errors, 1-5 errors, more than 5 errors. This test has been found to be sensitive for detecting balance changes following an exercise intervention in community-dwelling older adults (Topp et al., 1993), and test-retest reliability has been examined in a pilot study of 20 older individuals (ICC = 0.92) (Arnold et al., 2002). Arnold et al (2005) found a positive association with the number of errors made on the test (stepping off the line), to a recent fall history in women over the age of 60 who have been diagnosed with osteoporosis.
5) The BBS includes 14 items assessing functional balance, and consists of day to day tasks such as picking up an object from the floor, turning in a circle, reaching, and balancing on one leg. The BBS is a valid measure (r=0.81) with high inter-rater reliability (0.98 ICC) as a useful predictor of risk for future falls in aging adults (Burke-Doe et al., 2008; Rikli & Jones, 2001). Given the ceiling effect that occurs with the BBS in community-dwelling younger-older adults, we also

included one of the more challenging tasks, the forward functional reach test, as an independent measure in our analyses. The Functional Reach test measures forward reach ability from a standing position. The test has shown inter-rater reliability (ICC = 0.98) and retest reliability in a sample of healthy subjects (Isles et al., 2004). Although results vary as to the ability of this test to discriminate between fallers and non-fallers, normative values have been published for individuals aged 20-80 (Isles et al., 2004).

6) The Activities-specific and Balance Confidence (ABC) Scale is self-report questionnaire designed to measure the psychological impact of balance impairment and/or falls (Hill, 2005). Test retest reliability has been established (r=0.92) in community dwelling older adults, as well as 84% sensitivity and 87% specificity in correctly classifying fallers and non-fallers in a cross-sectional study of community dwelling older adults (Hill, 2005).

Fracture Risk and Fragility Status

The 10-year probability of a major osteoporotic fracture was calculated using the FRAX® (Fracture Risk Assessment Tool), which included DXA-derived aBMD at the femoral neck in the algorithm. The FRAX, developed and validated by the World Health Organization (Leslie et al., 2011), provides a single score for fracture risk. This score includes the predictors age, sex, weight and height (from which BMI is computed), prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and daily consumption of more than two units of alcohol, with increased predictive validity of the model further improved by including aBMD (Peeters et al., 2009).

Grip strength was evaluated with a JAMAR hand-held dynamometer (Patterson Medical Holdings, Inc, Bolingbrook, Ill.)[b] to assess isometric strength of forearm muscles, measured on both sides, with 3 trials of each. The highest measure of the three trials on each hand was used to calculate the mean score between the right and left hand (Crockett et al., 2015).

Statistical Analysis

Descriptive data including age, height, weight, number of prescriptions, physical activity level, age of onset of menopause, and total calcium and vitamin D supplementation were compared between women with and without DRF using independent t-tests. Variables demonstrating significant correlations ($p < .05$) to fracture risk or a difference between groups with an independent t-test (exploratory analysis, p-value < .10) were included as covariates in the primary analysis. The BBS and ABC demonstrated a ceiling effect, with data negatively skewed violating the assumption of normality; therefore, data was reflected and transformed using log10 transformation to achieve a normal distribution (Tabachnick & Fidell, 2007).

Multivariate analysis of covariance (MANCOVA) was performed to compare the Fx and NFx groups for the primary fall and fracture risk factors: 30sSTS, BBS, gait velocity (normal and fast speeds), TUG, TUG cog, ABC, mean grip strength, and FRAX allowing the statistical adjustment of the data with physical activity level as a confounder due to the strong relationship of physical activity levels to fall and fracture risk (Heesch et al., 2008; Moayyer et al., 2010). Significance was set at $\alpha = 0.05$. The backward tandem walk was analyzed using a chi-square table to determine if there was a relationship between the number of errors made (no errors, 1-5 errors, or > 5 errors) and the 2 groups (fracture and control). Correlations between grip strength and the primary fall and fracture risk factors were examined in both Fx and NFx. Correlations between fracture risk (FRAX) and the primary fall risk factors were explored in both the Fx and NFx. Data was analyzed using SPSS version 22.0 (IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp).

RESULTS

There were no significant differences in age, height, weight, PASE scores, number of medications, age of onset of menopause, or total calcium or vitamin D supplementation between groups ($p>0.05$) (Table 4.1). Demographic data was reported previously as part of another study that also investigated bone and muscle

properties (Crockett et al., 2015). Fracture risk (FRAX) and physical activity (PASE) demonstrated a significant negative correlation (r=-0.244, p=0.032). Because of this significant correlation and lower physical activity scores in the NFx compared to Fx group ($p < .10$), PASE was used as a covariate. There was a significant MANCOVA group difference, controlling for physical activity level (Pillai's Trace = 0.241, $p < 0.05$), with the Fx group demonstrating poorer outcomes on the 30sSTS, TUG, TUGcog, fast gait velocity, and FRAX (p=0.003, 0.007, 0.009, 0.018, 0.022), with differences in normal gait speed approaching significance (p=0.052). Between group differences (21% poorer 30sSTS performance and 20% lower grip strength in the Fx group) were reported in our previous comparison focused on bone and muscle properties (Crockett et al., 2015).

Table 4.1. Descriptive characteristics

		Mean (SD)	p-value
Age (y)	*Fracture*	64.0 (8.4)	0.791
	Control	62.5 (8.7)	
Height (cm)	*Fracture*	160.5 (8.3)	0.107
	Control	161.9 (5.7)	
Weight (kg)	*Fracture*	71.1 (13.4)	0.706
	Control	72.8 (14.8)	
PASE	*Fracture*	161.9 (84.5)	0.081
	Control	166.1 (71.4)	
Number of medications	*Fracture*	1.9 (2)	0.927
	Control	1.7 (2)	
Age of onset of menopause (y)	*Fracture*	47.4 (4.1)	0.159
	Control	47.95 (8.7)	
Total calcium supplementation (mg)	*Fracture*	1287.6 (574.9)	0.597
	Control	1319.2 (544.6)	
Total vitamin D supplementation (IU)	*Fracture*	394.7 (216.7)	0.969
	Control	426.9 (237.2)	

PASE = Physical Activity Scale for the Elderly

The backward tandem was not used in the MANCOVA due to the variation in the number of errors made, and three subjects from the fracture group who refused to attempt the test; therefore, scores were categorized for non-parametric analysis. Chi-square analysis for the number of errors made in the backward tandem walk demonstrated no significant association between the group category and the category for number of errors made, Phi (0.086) and Cramer's V (0.086), $p = 0.761$. In the fracture group 15 (46.9%) had no errors, 8 (25%) had 1-5 errors, 6 (18.8%) had > 5 errors, 3 (9.4%) refused to attempt. In the control group, 27 (60%) had 1-5 errors, 11 (24.4%) had 1-5 errors, and 7 (15.6%) had > 5 errors. In the fracture group, significant moderate to strong Pearson r correlations (Cohen, 1988) were present between grip strength and the following measures: 30sSTS (0.37, $p = 0.039$); BBS (-0.61, $p < 0.001$); Forward reach (0.39, $p = 0.033$); gait velocity (normal speed) (0.37, $p = 0.036$); gait velocity (fast speed) (0.40, $p = 0.024$); TUG (-0.51, $p = 0.003$); TUGcog (-0.48, $p = 0.010$); ABC (-0.43, $p = 0.014$); FRAX (-0.49, $p = 0.005$); PASE (0.39, $p = 0.029$) (Table 4.2). In the control group, significant moderate correlations of grip strength were only present with the BBS (-0.30, $p = 0.046$); forward reach (0.50, $p < 0.001$); gait velocity (normal speed) (0.35, $p = 0.020$); gait velocity (fast speed) (0.47, $p = 0.001$); TUG (-0.35, $p = 0.019$); TUGcog (-0.43, $p = 0.003$); and FRAX (-0.34, $p = 0.023$) (Table 4.2).

Table 4.2. Correlations between grip strength and FRAX with primary fall and fracture risk factors

		30sChair Stand (reps)	BBS (item score)	Forward Reach (cm)	Single leg stance (sec)	PASE (item score)	Gait Velocity *Normal* (m/s)	Gait Velocity *Fast* (m/s)	TUG (sec)	TUGcog (sec)	ABC (%)	Grip strength (kg)	FRAX (%)
Grip strength	*Fracture*	.37*	-.61**	0.39*	0.25	.39*	.37*	.40*	-.51**	-.48**	-.43*	1	-.49**
	Control	.12	-.30*	0.50	-0.07	-.05	.35*	.47**	-.35*	-.43**	-.27	1	-.34*
FRAX	*Fracture*	-.33	.67**	-0.47*	-0.25	-.34	-.41*	-.40*	.59**	.51**	.28	-0.49**	1
	Control	-.05	.11	-0.47*	-0.12	-.17	-.11	-.23	.37*	.31*	.33*	-0.34*	1

$p < 0.05$ *
$p < 0.01$**

In the fracture group, significant moderate to strong Pearson r correlations (Cohen, 1988) were present between FRAX and the following fall risk measures: BBS (0.669, $p < 0.001$); forward reach (-0.47, $p = 0.007$); gait velocity (normal speed) (-0.41, $p = 0.021$); gait velocity (fast speed) (-0.40, $p = 0.025$); TUG (0.59, $p < 0.001$); TUGcog (0.51, $p = 0.006$) and grip strength (-0.49, $p = 0.005$). In the control group, significant moderate correlations to FRAX were present with the forward reach (-0.47, $p = 0.001$); TUG (0.37, $p = 0.012$); TUGcog (0.305, $p = 0.044$); and ABC (0.33, $p = 0.029$).

DISCUSSION

The primary purpose of this study was to compare fall and fracture risk status in postmenopausal women with and without a recent DRF, with a secondary purpose to determine the relationship of grip strength to fall and fracture risk status, as well as the relationship of fall risk to fracture risk.

Although falls and fractures often share risk factors, such as prior history, muscle weakness, gait, and balance deficits, and increased age (Burke-Doe et al, 2008), the risk factors associated with wrist fracture are not clear, especially for those age 50-65. The FRAX tool captures fracture-specific risk factors, but fails to include any fall risk measures. Fall risk measures that are currently available are often lacking normative data in those younger than age 60. The strength of this study is combining both fall and fracture risk measures in a population that includes those aged 50-78, comparing a group with a recent DRF to a control group with no recent DRF.

The World Health Organization FRAX tool uses validated clinical risk factors and femoral neck aBMD to estimate the 10-year probability of major osteoporotic fracture. This includes fractures of the spine, hip, proximal humerus, and distal radius (Lewiecki, 2010). If the FRAX calculation demonstrates a 10-year probability of major osteoporotic fracture of 20% or more, then pharmacological therapy is advised (Lewiecki, 2010). In our study, the mean FRAX score of both groups remained under the threshold for

pharmacological therapy (20%), with a mean of 13% in the fracture group and 9% in the control group. It is not clear if the FRAX may underestimate the threshold for treatment given the potential limitations in not including other fall and fracture risk factors. FRAX is also not designed to identify those individuals who may benefit from other treatment measures such as fall prevention. Although the FRAX is a fairly simple and widely available online tool, it does have limitations. The FRAX requires clinical judgment to determine whether a patient who reports a diagnosis of rheumatoid arthritis actually has a clinical diagnosis of this disease, what level exposure to glucocorticoids is sufficient to enter this as a clinical risk factor, or when a previous fracture is appropriate for entry as a FRAX risk factor. The input for most of the FRAX clinical risk factors is dichotomous, therefore the dose response to the associated risk cannot be accounted for. This may lead to under- or over- estimating the actual fracture risk in some patients. For example, the risk associated with alcohol consumption and glucocorticoid therapy increases with dose, but the risk calculation with FRAX assumes an average dose or exposure, without allowing for specification. Some important risk factors are not included in FRAX, such a frailty, falling, rate of bone loss, and vitamin D deficiency (Lewiecki, 2010). Since aBMD input for FRAX is limited to the femoral neck, fracture risk will be underestimated in patients with low lumbar spine BMD and relatively preserved BMD at the femoral neck, or in women under the age of 60, where site-specific measurement (i.e., forearm) may be indicated (D'Elia et al., 2009). It is important that clinicians are educated on the availability of the FRAX and the ease of its use. However, clinicians should also be aware of the limitations in order to best interpret the outcome score, while still considering the whole relevant clinical picture. Based on this study, a 20% cut-off may underrepresent those at risk of future fracture. It may be useful to determine different cut-off or threshold scores to address women at risk who do not meet criteria for pharmacologic treatment due to specific factors addressed through the FRAX, but who could benefit from alternate therapies.

With the fall risk measures, the fracture group consistently demonstrated a poorer performance (Table 4.1), although interpretation of the scores to identify future fall risk is difficult due to the lack of normative data for women under the age of 60. For example, with the 30s chair stand test, normative data

is available in 5-10 year age increments, starting at age 60. The threshold for fall risk age 60-64 is 12 repetitions or less (CDC, 2014). As the age increases, the threshold is lower, (ie – age 65-69, 11 repetitions, age 70-79, 10 repetitions). The cut off score for those aged 50-59 is not known; however, in this sample, the Fx group completed a mean of 12 repetitions, versus the mean of 16 repetitions for the NFx group (Table 4.3). Due to the lack of normative data in the 50-59 age group, it is difficult to interpret scores with respect to fall risk. However, the poorer performance in the fracture group is suggestive of reduced function, perhaps leading to fall risk. The success on this test is related to lower extremity function, specifically knee extensor strength and power. Knee extensor strength and rate of torque development has been shown to be a strong predictor of success on the 30s chair stand test (Crockett et al., 2013) and decreased quadriceps power or rate of torque development has been linked to an increased risk of falling (Laroche et al., 2011). This test may detect the more subtle functional declines that occur in the lower extremities and has potential to be a good predictor of fall and fracture risk for this population. Normative data should be determined for age groups younger than age 60 to more accurately estimate fall risk in early post-menopausal women at risk of sustaining a DRF. Further research is required to better understand this relationship and allow clinical use and interpretation in a wider age range.

Table 4.3. Fall and fracture risk means (SD) for each group / normative values
(Age 50-59: Fx, n=14; Ctl, n=18 Age 60-69: Fx, n=10; Ctl, n=16 Age 70-79: Fx, n=6, Ctl, n=10)

	Fracture	Control	*p* value	Normative Data	Fall risk threshold
30sChair Stand (repetitions)	Age 50-59 = 12.0 (4.1) Age 60-69 = 12.0 (3.3) Age 70-79 = 12.5 (2.6) Overall = 11.9 (3.6)	Age 50-59 = 16.0 (3.6) Age 60-69 = 13.8 (4.1) Age 70-79 =11.2 (1.6) Overall = 14.3 (4.1)	0.003	Age 60-64: 12-17 Age 65- 69: 11-16 Age 70-79: 10-15 [a]	Age 60-64: <12 Age 65- 69: < 11 Age 70-79 = < 10 [b]
BBS (item score)	Age 50-59 = 54.77 (2.01) Age 60-69 =55.5 (0.5) Age 70-79 = 54.5 (2.0) Overall = 53.9 (5.8)	Age 50-59 = 55.6 (1.7) Age 60-69 = 55.4 (0.6) Age 70-79 = 55.0 (0.9) Overall = 55.4 (1.2)	0.046	Age 60-69: 55(2) Age 70-79: 53(4) [c]	41-56 = low fall risk 21-40 = medium fall risk 0-20 = high fall risk [d]
Forward reach (cm)	Age 50-59 = 30.0 (8.3) Age 60-69 = 30.7 (6.7) Age 70-79 = 29.83 (7.3) Overall = 29.6 (7.7)	Age 50-59 = 36.1 (4.8) Age 60-69 = 32.94 (5.1) Age 70-79 = 29.0 (6.2) Overall = 33.4 (5.8)	Not included in MANCOVA	Age 50-59: 38.1 (0.5) cm Age 60-69: 36.8 (0.5) cm Age 70-79: 34.1 (0.5) cm [e]	< 7 inches (or 17.8 cm) [f]
Gait Velocity (normal speed, m/s)	Age 50-59 = 1.3 (0.3) Age 60-69 = 1.4 (0.2) Age 70-79 = 1.3 (1.9) Overall = 1.3 (0.3)	Age 50-59 = 1.4 (0.3) Age 60-69 = 1.5 (0.2) Age 70-79 = 1.3 (0.1) Overall = 1.4 (0.2)	0.052	Age 50-59: 1.4 m/s Age 60-69: 1.3 m/s Age 70-79: 1.27 m/s [g]	< 1.8 ft/sec (or < 0.54 m/s) = risk for recurrent falls [h] < 0.6 m/s or > 1.3 m/s [i]
Gait Velocity (fast speed, m/s)	Age 50-59 = 1.8 (0.4) Age 60-69 = 1.8 (0.3) Age 70-79 = 1.7 (0.2) Overall = 1.7 (0.4)	Age 50-59 = 2.0 (0.4) Age 60-69 = 1.9 (0.3) Age 70-79 = 1.6 (0.2) Overall = 1.9 (0.4)	0.018	Age 50-59: 2.0 m/s Age 60-69: 1.8 m/s Age 70-79: 1.7 m/s [g]	Not determined
TUG (seconds)	Age 50-59 = 6.8 (1.2) Age 60-69 = 6.4 (1.64) Age 70-79 = 8.9 (1.77) Overall = 7.3 (2.9)	Age 50-59 = 5.5 (0.8) Age 60-69 =5.9 (1.4) Age 70-79 = 9.4 (1.4) Overall = 6.1 (1.3)	0.007	Age 50-59: 6.4 (0.2) sec Age 60-69: 7.2 (0.2) sec Age 70-79: 8.5 (0.2) sec [f]	>13.5 sec [j]
TUGcog (seconds)	Age 50-59 = 8.3 (2.5) Age 60-69 =7.6 (2.9) Age 70-79 = 8.9 (1.8) Overall = 9.0 (4.5)	Age 50-59 = 6.4 (1.4) Age 60-69 = 6.7 (2.1) Age 70-79 = 9.4 (1.4) Overall = 7.2 (2.0)	0.009	Age 60-87 = 9.8 (2.4) sec [k]	> 15 sec [j]
ABC (%)	Age 50-59 = 91.0 (6.9) Age 60-69 = 93.1 (11.3) Age 70-79 = 86.2 (11.9) Overall = 88.0 (12.3)	Age 50-59 = 93.7 (14.3) Age 60-69 =91.5 (9.1) Age 70-79 = 84.9 (21.3) Overall = 91.1 (14.6)	0.028	80% - high level of physical functional [l]	< 67% [m]
Grip strength (kg)	Age 50-59 = 21.1 (6.3) Age 60-69 = 20.9 (4.6) Age 70-79 = 21.8 (3.3) Overall = 20.4 (5.9)	Age 50-59 = 26.1 (4.5) Age 60-69 =25.1 (5.0) Age 70-79 = 22.5 (4.9) Overall = 24.8 (4.9)	0.001	Age 50-59 = 25.8 Age 60-69 = 21.7 Age 70-79 = 19.4 [n]	Not available
FRAX (%)	Age 50-59 = 11.9 (4.7) Age 60-69 = 11.2 (2.3) Age 70-79 = 11.8 (1.6) Overall = 13.0 (6.2)	Age 50-59 = 5.7 (2.4) Age 60-69 = 9.2 (4.2) Age 70-79 = 14.9 (9.5) Overall = 9.1 (6.3)	0.022	Not available	Not available

a.Rikli & Jones, 1999
b. CDC, 2014
c. Steffen et al, 2002
d. Shumway-Cook, 1997
e. Isles et al 2004
f. Weiner et al, 1992
g. Bohannon, 1997
h. VanSwearington & Branch, 1998
i. Quach et al, 2011
j. Shumway-Cook & Brauer, 2000
k. Hofheinz et al, 2010
l. Myers 1998
m. Lajoie & Gallagher, 2004
n. Calculated from Mathiowatz et al, 1985

Mean BBS scores were very high in both groups (Fx = 53.9/56, NFx = 55.4/56), although ranges in scores were much larger in the fracture group (24-56) compared to very high scores in all participants in the control group (49-56). The BBS has demonstrated a strong link to fall risk, but also has a ceiling effect in this younger, higher functioning population (Downs et al., 2013). Some of the more difficult individual components in this test may be better at detecting the early, more subtle changes in function, such as the single leg balance or forward reach task. The forward reach test measures forward reach ability from a standing position. In individuals aged 50 to 80, normative values range from 34 – 38 cm (Isles et al., 2004). The mean value of the fracture group was 29.5 cm, below the normal range, and in the control group was 34 cm, just within the normal range, possibly indicating an early sign of decreased ability to control the center of gravity within the limits of stability for the fracture group. Normative values of single leg balance up to 30 seconds has also been published in individuals aged 20-80 (Bohannon et al., 1984). Mean values range from 14.2 seconds up to 29.4 seconds in the ages of 50-59, 60-69, and 70-79, with the mean for all ages 50-79 being 22 seconds. With the BBS, maximum points are awarded for 10 seconds or more; therefore, in our study, the test was discontinued after 10 seconds. Data is not available beyond that for this specific subcategory; however, this may be investigated further in future studies.

The TUG and TUGcog were both significantly different between groups, with the fracture group performing poorer on both tests. However, mean scores remained well below the 'fall risk' threshold of 14 seconds (Shumway-Cook et al., 2000) in the control and the fracture group. This is therefore likely not a good indicator of fall risk in this younger, higher functioning group.

Gait velocity was well above the cut-off scores available for fall risk, although gait velocity was significantly different between the groups, with the fracture group demonstrating lower speeds overall. Normative values for gait velocity to discriminate between fallers and non-fallers is not available; however, there are cut-off values provided to identify functional ability and risk for adverse events in the older adult population > age 65 (Abellan et al., 2009). The fracture group was significantly slower than the

control group; therefore, we suggest normative values in this younger population, and the relationship to fall risk should be investigated further. Quach et al. (2011) found a U-shaped relationship between gait speed and falls in community dwelling older adults, with faster and slower gait speeds at higher risk than those with normal speeds (1 m/s to < 1.3 m/s). When we looked at age groups age 50-59 and 60-60, gait velocity in the Fx group was slower; however, in the age group age 70+, gait velocity in the Fx group was faster. A larger sample size would be required to further investigate this relationship, specifically in the age group age 50-59 where research is lacking.

Grip strength is associated with many aspects of health and whole body strength, as well as fall risk (Pijnapples et al., 2008). Normative data is available for individuals aged 50 to 78 years, although it is reported for the right or left hand, and has a different expected range every 5 years of age. The mean between the right and left extremities for each age category was calculated, and the mean across age categories from age 50 to 79 years was calculated to be 23.8 kg (Mathiowetz et al., 1985); therefore, the control group mean was above the expected value at 24.8 kg and fracture group mean was below at 20.4 kg. This is consistent with previous literature which has reported the relationship of grip strength to fracture risk, as a predictor of bone strength at the forearm (Frank et al., 2010). Grip strength has been significantly correlated to lower limb capacities and used to identify fallers from non-fallers in a relatively fit and healthy population of older adults (Pijnapples et al., 2008). In our study, grip strength in the fractured population was strongly correlated with several of the fall risk and functional outcomes measures, including strong positive correlations with the BBS, FRAX, TUG, and TUGcog. In the control group, the only strong correlation was a positive relationship of grip strength with gait velocity at the fast speed, and with forward reach. The relationship of grip strength and fast gait speed is consistent with the Pijnapples study (2007), where participants with greater grip strength had a higher risk of falling after a trip, explained by higher walking velocity increasing the demands for adequate balance recovery. Further, women in their fifties who were classified as unstable with various balance measures, were also found to be weaker with lower extremity strength and demonstrated greater errors in joint position sense (Low

Choy et al., 2008). We found grip strength to be one of the strongest associations to fall risk measures, easy to measure clinically, and related to whole body strength (Rantanen et al., 2003); therefore, the clinical utility as an indicator for fall risk warrants further investigation.

The FRAX does not include any functional or balance assessment; however, we found strong correlations with the BBS, TUG, and TUGcog in the Fx group. In addition, there were moderate correlations with the forward reach, and gait velocity at both the usual and fast speeds (Table 4.2). This is interesting, as DRFs as a risk factor for future fractures have been suggested to be related to diminished bone strength (Eastell et al., 2001) in older adults with a history of fragility fracture (Nordvall et al., 2007), but may also be due to other factors such as decreased muscle strength (Oyen et al., 2011) and balance (Graagmans et al., 1996) related to declining health and function following an injury (Edwards et al., 2006; Jarvinen et al., 2008). Given the cross-sectional nature of this study, it is difficult to know if the Fx group performance was poorer prior to the DRF or as a consequence of the recent fracture. Future prospective research could track functional performance and changes in fall risk prior to and/or following a recent fracture in order to determine the value of these measures in predicting those at risk of fracture

Balance confidence discriminates fallers from non-fallers, with a cut off score of 67% and below indicating fall risk (Lajoie et al., 2004); however, in the population studied here, balance confidence remained high in the fracture group, despite the recent wrist fracture attributable to a fall. The balance confidence was significantly lower in the fracture group (88%) compared to the control (91%), but the mean score remained above the 'fall risk' threshold. Consistent with the literature (Edwards et al., 2006), this suggests that balance confidence may be affected following a wrist fracture associated with a fall, but the ABC may not be sensitive enough to identify subtle declines in confidence that may have an impact on curtailing activity and increasing fall risk in this younger, healthier population, age 50 years and older.

There were several strengths to this study. The time period women were assessed post-DRF fracture (6-24 months) was in keeping with typical recovery and rehabilitation protocol time frames, allowing for

measurement techniques such as grip strength, but still allowing assessments to be performed as close to the time of fracture as possible. In addition, the inclusion of individuals younger than age 60 provided data from those in the age group where there is a significant increase in incidence of wrist fractures. This may help identify those at risk of falling and fracturing before the first 'signal' fracture (Osteoporosis Canada, 2013) occurs, or further evaluate and educate those who have sustained their first fragility fracture to demonstrate their risk of future fracture and guide appropriate rehabilitation assessment, intervention, and secondary prevention efforts.

Study Limitations

It is important to consider the limitations of the small sample size. Although sufficient for the analyses provided here, the small sample size did not allow for further sub-categorization and analysis between those younger than age 65, versus those older than age 65. Based on the effect size calculated for FRAX (0.30) and grip strength (0.37), we would require a sample size of 62 subjects to achieve power of 0.80; therefore, to further reduce the number of participants per group by subdividing into age categories, a larger sample size would be required. In addition, the cross-sectional design does not allow for determination of factors which predict fracture risk. Further prospective research will be required to determine the predictive nature of the variables examined to distal radius fractures. In terms of the testing procedures, there was some variability in the timing of obtaining scans post-fracture, as this ranged from six months post-fracture up to two years post-fracture. Further research should be focused on developing normative data in the younger population, as well as the predictive ability for these tests to assist in identifying those at risk of early fragility fractures.

Conclusion

Women with a recent DRF demonstrate higher fall and fracture risk compared to women without as measured by the TUG, fast gait velocity, 30sSTS and the FRAX. Current clinical tools with established cut-off values for identifying fall and fracture risk in older adults may not be sensitive enough for this

younger cohort, specifically those aged 50-65. Grip strength is associated with several fall risk performance measures and fracture risk. With DRF occurring approximately 15 years earlier than hip fractures, determining appropriate fall risk screening tools may help to identify future risk factors and interventions. Further prospective research is needed to determine the best screening tools for fall and fracture risk status in women over the age of 50.

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RELATIONSHIP OF STUDY 2 TO THESIS:

This study identified the differences in fall and fracture risk status in a group of women with a recent DRF, compared to those without. Although some risk factors for fractures have been established, the causes of wrist fracture are not clear, especially for those aged 50-65. Normative values for fall and fracture risk screening tools in this age group have not been established. This study provided data for several fall-risk and functional outcome measures in older women across three decades of older adulthood, identifying differences between those with a recent DRF compared to those without. This information will assist in developing the profile of those at risk of an early fragility fracture and direct relevant future research on determining appropriate fall risk screening tools for this middle-aged to older population and further establish normative values in early post-menopausal women for fall-risk outcome measures currently used for older adults beyond 65 years of age. Further knowledge to identify differences in bone strength and muscle properties will also assist to determine subtle fracture risk differences that may not be apparent with traditional clinical fracture risk assessment tools. The third study in this thesis addresses this screening gap and together with the results from study 2 will provide comprehensive information comparing both fracture and fall risk factors in women with and without DRF to guide clinical practice and future research.

CHAPTER 5: STUDY 3 - BONE STRENGTH AND MUSCLE PROPERTIES IN POSTMENOPAUSAL WOMEN WITH AND WITHOUT A RECENT DISTAL RADIUS FRACTURE

INTRODUCTION

The increasing incidence of distal radius (wrist) fracture in women over the age of 50 is a growing public health concern, as this is often the first sign of osteoporosis and bone fragility (Åkesson & Mitchell, 2012; Eisman et al., 2012; Osteoporosis Canada, 2013). Direct costs for wrist fractures have been reported to range from $104-170 million per year in Canada and the USA, with these costs predicted to rise with an aging population (Åkesson & Mitchell, 2012; Osteoporosis Canada, 2013; Nellans et al., 2012). There are many additional societal effects further increasing personal and health care costs, including lost work hours, loss of independence, and lasting disability (Nellans et al., 2012). This highlights the importance of identifying risk factors to optimize preventative efforts for distal radius fracture (DRF) in early postmenopausal women.

Clinically, dual energy x-ray absorptiometry (DXA) is the current standard method used for diagnosis of osteoporosis and estimated fracture risk (Kanis, 2002; Papaioannou et al., 2010); however, many fractures occur in women who are not osteoporotic when diagnosed by low areal bone mineral density (aBMD) (Jarvinen et al., 2008; Peeters et al., 2009; Stone et al., 2003). Although osteoporosis diagnosis and fracture risk assessment is based on femoral neck aBMD derived T-scores (Papaioannou et al., 2010), site-specific aBMD measurement from the distal radius has provided the strongest prediction of wrist fracture risk (Stone et al., 2003). It has been suggested that prediction of fracture risk in women younger than 65 should include information of bone properties at the wrist and forearm, such as volumetric bone density and distribution of material (i.e., geometry) to estimate bone strength (D'Elia et al., 2009; Petit et al., 2005). Peripheral quantitative computed tomography (pQCT) scanning provides information of these bone properties and surrounding soft tissues. Strength indices derived from pQCT have been shown to be

associated with fracture risk in men (Sheu et al., 2011), but whether these measures are comparable to distal forearm aBMD remains unclear, especially in women younger than 60 years of age. In the work of Schneider et al. (Schneider et al., 2001), pQCT-based measures of distal radius bone content (a measure of bone's axial compressive strength), cross-sectional moment of inertia (a measure of bone's bending resistance) and polar moment of inertia (a measure of bone's torsional resistance) discriminated between fractured and non-fractured bones in individuals aged 45-85 years, leading to speculations that the mechanism of DRF was due to combined compressive, bending and torsional stresses in different proportions. Importantly, bone content measures were the strongest predictors of the fracture condition, indicating that bone's resistance to fracture likely depends predominately on its compressive strength. The pQCT-based bone strength index (BSI_c) is a compressive strength metric combining volumetric bone density and geometry (i.e. total area) to estimate the compressive failure load of bone (Kontulainen et al., 2008). One validation study found that BSI_c explains 85% of the variance in experimentally-derived compressive failure load at the distal tibia (Kontulainen et al., 2008); however, it is not known whether BSI_c at the distal radius differs between those with a recent DRF fracture compared to those without.

In addition to bone strength measures, the capability of muscle size, quality, and strength to discriminate between those with and without previous fracture is poorly understood. Previous studies evaluating the course of recovery after DRF have indicated that in some individuals, pain and disability remains higher at the injured site, even at one year post-fracture (MacDermid et al., 2003). Further, it has been shown that grip strength remains up to 12% lower at the injured site (Brogren et al., 2011). Thus, the muscle-bone interaction in the upper extremity may play an important role in determining bone strength (Brogren et al., 2011; MacDermid et al., 2003), while also contributing to the ability of the upper extremity to absorb impact forces from fall impact (Kawalilak et al., 2014; Sran et al., 2010).

With limited evidence comparing bone and muscle strength in early post-menopausal women who have and have not experienced a recent DRF, the primary objective of this study was to investigate if bone and muscle strength differed in women who had experienced a recent DRF compared to women with no recent

history of DRF. Our secondary objective was to investigate if bone properties at the radius and tibia (measured by pQCT) or at the distal forearm, lumbar spine, and femoral neck (measured by DXA) would differ between women with and without a recent history of DRF. We hypothesized that women with a recent DRF would have lower bone and muscle strength in the forearm, and lower aBMD in the forearm as compared to women without a history of DRF.

METHODS

Participants

Women with a history of recent DRF were recruited from local orthopaedic surgical clinics and within the community through newspaper and poster advertisement. Women with no history of DRF fracture were recruited from the community via newspaper advertisement.

Inclusion criteria consisted of: (i) women aged 50 years or older; (ii) postmenopausal (defined as no menses for one year); (iii) 6-24 months post-fracture; or (iv) having never sustained a previous DRF fracture or any other fragility fracture. Exclusion criteria included: (i) having been on high dose corticosteroid treatment or exposure to bone altering medications such as bisphosphonates or hormone replacement therapy in the past six months; (ii) significant neurological or medical conditions that affect daily living (i.e. stroke, Parkinson's disease or other systemic neurological conditions affecting balance); (iii) inability to walk independently; (iv) a history of upper extremity neurological problems including conditions such as reflex sympathetic dystrophy; or (v) a current severe painful hand or wrist problem (e.g. systemic polyarthropathy in the wrist or hands). All participants signed informed consent prior to testing. Ethics approval was obtained from the institution's ethical review board.

A total of 166 women were screened by telephone interview for eligibility to participate in this cross-sectional case control study. Sixty-nine participants were ineligible; 20 women chose not to participate.

Seventy-seven women (46% of those screened) were able to and willing to participate in this study (Fracture [Fx], n=32; non-fracture [NFx], n=45) (Figure 5.1).

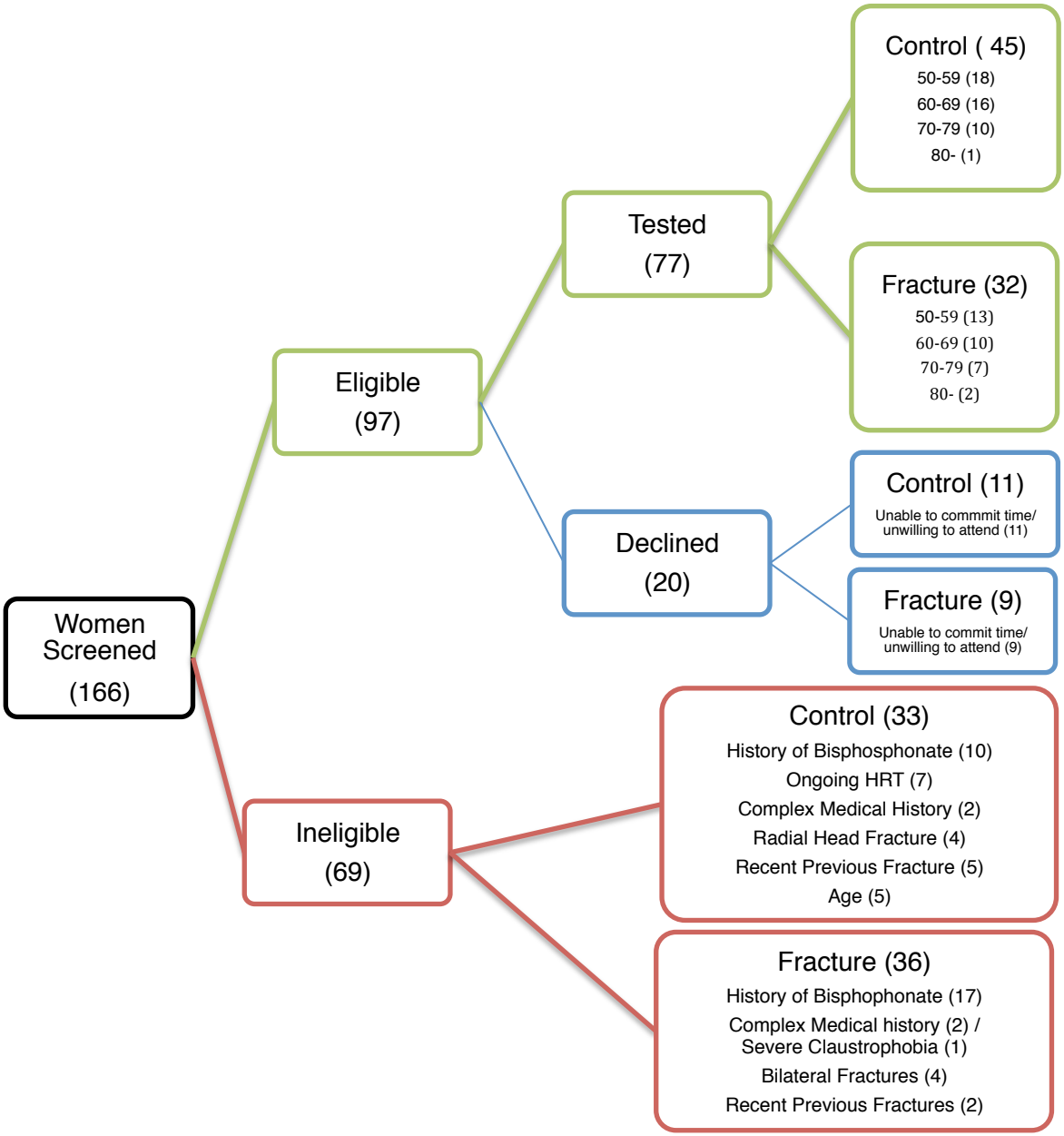

Figure 5.1. Recruitment flow chart

Measurements

Background characteristics

Handedness was assessed using the Waterloo Handedness questionnaire (Steenhuis et al., 1990) and physical activity using the Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1999). The Mini-Cognitive Screening test was used to determine the presence of a cognitive impairment that may impact self-report accuracy (Borson et al., 2000). Medical and demographic questionnaires (which included self-reported age at onset of menopause) were completed at the time of testing. Height (cm) was measured using a standard wall-mounted stadiometer and weight (kg) was measured using a standard scale. Handgrip strength (kg) was measured using a JAMAR hand-held dynamometer (Patterson Medical Holdings, Inc, Bolingbrook, Ill.) using both the right and left upper extremities; 3 maximal repetitions, with a minimum of 30 seconds rest between attempts, were assessed (Lafayette Instrument Company, 2004). The average score achieved was recorded, and the mean value between the right and left extremities was used for analyses. Grip strength was chosen as a clinically relevant measure of forearm and hand muscle strength, due to its relationship to fracture risk (Karkkainen et al., 2008) and bone strength at the distal radius shaft (Lorbergs et al., 2011). Grip strength also represents an important predictor of frailty and functional decline in older adults (McLean et al., 2014). The 30-second chair stand test has been referred to as a functionally relevant measure of lower extremity strength in older adults (Jones et al., 1999), with the individual performing as many repetitions of a full stand and return to the sitting position in 30 seconds, without the assistance of the upper extremities (Rikli & Jones, 2001). Rapid sit to stand performance provided a combined measure of strength and power; both of which have been associated with estimated bone strength in the lower limb (Cousins et al., 2010; Crockett et al., 2013; Lang et al., 2010). The 30-second chair stand test is also associated with fall risk and functional ability in older adults (Jones et al., 1999), and thus clinically is used to assist prediction of future fracture risk. Calcium (mg) and Vitamin D (IU) intakes were measured using the Food Frequency Questionnaire (Nutrition Quest, Berkeley, CA, USA; www.nutritionquest.com) combined with self-reported use of

supplementation.

Peripheral quantitative computed tomography (pQCT)

A single operator scanned the non-fractured or non-dominant forearm, as determined by the Waterloo Handedness Questionnaire (Steenhuis et al., 1990), and left lower leg at the distal and shaft sites using pQCT (Stratec XCT2000) with our standard data acquisition protocols and a voxel size of 0.4x0.4x2.4mm (Duckham et al., 2013). A scout scan was obtained over the joint line with the reference line positioned at the medial tip of the distal endplate of both the radius and the tibia (Duckham et al., 2013). Cross-sectional slices were obtained at 4% and 65% of the radius length and at 4% and 66% of the tibia length, proximal from the reference line. In the forearm, these sites corresponded with radius length between the point at the proximal and lateral border of the head of the radius and most distal point of the lateral margin of the styloid process of the radius; in the lower leg, these sites corresponded with the tibia length from the base of the medial malleolus to the superior margin of the medial epicondyle (Marfell-Jones, 2001). One investigator (KC) analyzed all scans using the manufacturer's software package (Stratec Medical, version 6.0). Scans of the 4% site radius and tibia were analyzed using contour mode 1, with density threshold of 280 mg/cm^3 to separate bone from surrounding soft tissue. Peel mode 2 with the inner threshold of 480 mg/cm^3 was used to obtain trabecular bone. Scans from the 65% site of the radius and 66% site of the tibia were analyzed using separation mode 4 with inner and outer threshold of 480 mg/cm^3. Muscle tissue was differentiated from subcutaneous tissue and bone using contour mode 1 and by selecting voxels with a density greater than 40 mg/mm^3 and less than 280mg/mm^3. Muscle density was then calculated by dividing the total muscle content by muscle area.

Measured bone properties at the distal sites (4% of limb length) were total and trabecular bone areas (ToA and TrA, mm^2) and densities (ToD and TrD, mg/cm^3). Bone strength index (BSI_c, mg^2/cm^4) was calculated as ToD^2 x ToA to estimate bone's resistance in compression at the distal sites (Kontulainen et al., 2008). This BSI_c equation represents compressive failure load (F) of bone, and is based upon the

classic experimental work of Carter and Hayes (1977), which found bone to have an ultimate compressive stress (F/ToA) directly proportional to apparent density squared. Reorganizing this relationship yields $BSI_c = F \approx ToA_t \times ToD^2$. The key requirement using this equation is that the bone is primarily loaded in compression. Bone properties including cortical area (CoA, mm^2) and density (CoD, mg/cm^3) were measured at the radius (65%) and tibia shaft (66%) sites. To estimate bone's resistance in torsion (i.e., torsional bone strength), we analyzed polar density weighed section modulus (SSI_p, mm^3) at the shaft sites (Kontulainen et al., 2008). Muscle density (mg/cm^3) and area (mm^2) were measured at the forearm and lower leg shaft sites as indicators of muscle quality and cross-sectional area (Frank et al., 2015). Precision errors in our lab across reported bone parameters ranged from 1.7 – 6.1% at the radius sites and 0.7 – 2.1% at the tibia sites in postmenopausal women (Duckham et al., 2013). Our lab precision for muscle area and density at the forearm and lower leg in postmenopausal women ranged varied between 1.2- 3.7% (Frank et al., 2015).

Dual energy x-ray absoptiometry (DXA)

Areal bone mineral density (aBMD; g/cm^2) at the ultradistal forearm of the non-fractured or non-dominant forearm, lumbar vertebrae L2-4, and left femoral neck was measured by DXA in array mode (QDR Discovery Wi; Hologic, Inc., Bedford, MD, USA) using QDR software for Windows XP (QDR Discovery, Hologic, Inc.). Coefficients of variation for these measures in our lab were 0.7% for the lumbar spine and 1.0% for the proximal femur (Chilibeck et al., 2013). Precision of aBMD has been reported as 1.9% at the distal forearm (Sievanen et al., 1992).

STATISTICAL ANALYSIS

Independent t-tests were used to assess Fx and NFx group differences for demographic, anthropometric and lifestyle characteristics including: physical activity levels, age at onset of menopause, vitamin D and calcium intakes, height and weight, and DXA-derived aBMD at the femoral neck and lumbar spine. Site-

specific (upper and lower extremity) multivariate analysis of variance (MANOVA) was used to compare between-group difference for five primary outcomes at the forearm (BSI_c at distal radius, SSI_p at shaft, forearm muscle area and density, grip strength) and lower extremity ($BSI_c$the distal tibia, SSI_p at shaft, lower leg muscle area and density, sit to stand performance) between groups. Univariate between-groups ANOVA was used to explore differences in secondary outcomes (ToD, ToA, TrD, TrA, CoD and CoA) at both extremities as well as ultradistal forearm aBMD. Significance was set at $\alpha = 0.05$ with Bonferroni adjustment applied for multiple comparisons. Data was analyzed using SPSS version 22.0 (IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp).

RESULTS

Demographic, Anthropometric and Lifestyle Characteristics

There were no significant differences ($p>0.05$) between the Fx and NFx groups for age, height, weight, physical activity levels, age at onset of menopause, vitamin D and calcium intake, or aBMD at the femoral neck and lumbar spine (Table 5.1). There were no indications of any cognitive impairment as measured with the Mini-Cognitive Screening Test (Borson et al., 2000).

Table 5.1. Descriptive data

	Fracture (n=32)	Non-Fracture (n=45)	Significance (*p* value)
	Mean (SD)	Mean (SD)	
Age (y)	64 (8.4)	63 (8.7)	0.460
Height (cm)	160.6 (8.4)	161.9 (5.7)	0.414
Weight (kg)	71.1 (13.4)	72.8 (14.8)	0.611
PASE	161.9 (84.5)	166.1 (71.4)	0.814
Age of Menopause (y)	47.4 (4.1)	47.9 (8.7)	0.822
Dietary calcium intake and supplementation (mg)	1288 (574.9)	1319 (544.6)	0.807
Dietary Vitamin D intake and supplementation (IU)	395 (216.7)	427 (237.2)	0.544
aBMD at the femoral neck (g/cm^2)	0.69 (0.1)	0.71 (0.1)	0.582
aBMD at the lumbar spine (g/cm^2)	0.89 (0.2)	0.93 (0.2)	0.338

PASE = Physical Activity Scale for the Elderly, aBMD = areal bone mineral density

Primary outcomes

One participant's pQCT forearm scan was excluded from the analysis due to measurement error. Three participants did not have their lower leg scanned due to large leg girth and limited size of the gantry. Two DXA-scans were excluded: one from a participant with bilateral hip replacement and another one had a non-removable bracelet on her wrist.

Bone Strength Indices, Muscle Area, Density and Strength

There was a significant multivariate effect indicating a group difference (Pillai's Trace = 0.20, $F(3.41,69) = 5$, $p = 0.008$). The Fx group had 16% lower BSI_c at the distal radius ($p = 0.033$), 3% lower forearm muscle density at the radius shaft site ($p = 0.016$), and 20% lower grip strength ($p = 0.001$) than the NFx

group (Table 5.2, Figure 5.2). There were no significant differences in SSI_p at the radius shaft or forearm muscle area (Table 5.2, Figure 5.2). Similarly at the lower leg, there was a multivariate group difference (Pillai's Trace = 0.28, $F(5,68)$, $p < 0.001$), with the Fx group demonstrating 19% lower BSI_c at the distal tibia ($p = 0.010$), 6% lower muscle density at the tibia shaft site ($p = 0.001$), and 21% lower repetitions on the 30s chair stand test ($p = 0.003$). There were no significant differences in SSI at the tibia shaft or lower leg muscle area (Table 5.3, Figure 5.2).

Table 5.2. Group means (SD) for primary outcomes in the forearm.

		Fracture (n=30)	Non-Fracture (n=45)	Mean Difference (CI)	Significance (*p* value)
		Mean (SD)	Mean (SD)		
pQCT					
Distal radius	BSI_c (mg^2/mm^4)	20.9 (6.2)	24.3 (6.99)	-3.4 (-6.6 to -0.3)	0.033
Radius shaft	SSI_p (mm^3)	248.7 (52.7)	272.0 (57.6)	-23.3 (-49.4 to 2.9)	0.080
Muscle	Area (mm^2)	2779.5 (289.8)	2811.4(367.0)	-31.9 (-190.9 to 127.1)	0.690
	Density (mm/cm^3)	72.8 (3.5)	74.6 (2.7)	-1.8 (-3.2 to -0.4)	0.016
MUSCLE STRENGTH					
Grip strength	(kg)	20.5 (6.1)	25.0 (4.9)	-4.3 (-6.8 to -1.8)	0.001

BSI_c = bone strength index in compression , SSI_p = stress-strain index, bone strength in torsion

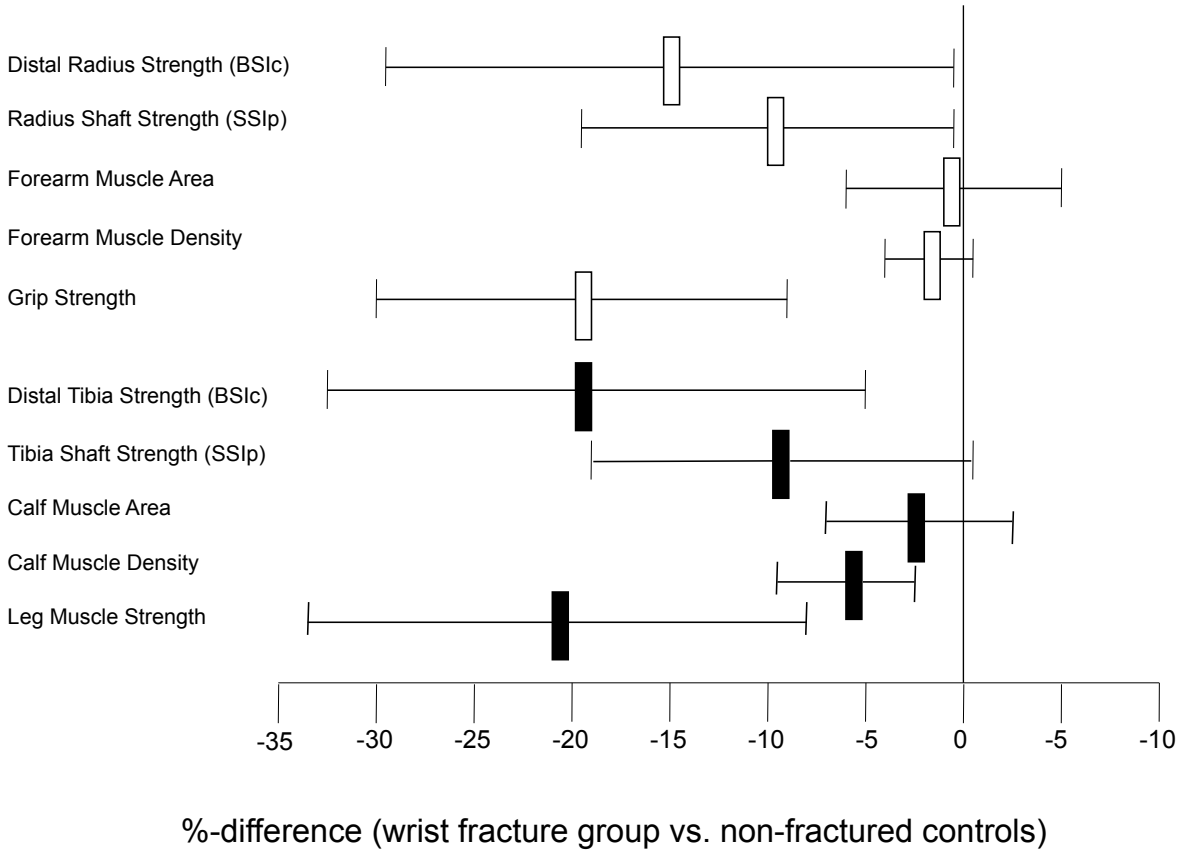

Figure 5.2. Percent mean differences between the fracture and non-fracture groups in bone strength, muscle properties, and muscle strength

Table 5.3. Group means (SD) between group comparisons of primary outcomes in the lower leg.

		Fracture (n=32)	Non-Fracture (n=42)	Difference (CI)	Significance (*p* value)
		Mean (SD)	Mean (SD)		
pQCT					
Distal tibia	BSI_c (mg^2/mm^4)	66.0 (21.6)	79.8 (22.9)	-13.8 (-24.3 to -3.3)	0.010
Tibia shaft	SSI_p (mm^3)	1969.4 (380.1)	2159.4 (480.5)	-190 (-395.8 to 15.9)	0.070
Muscle	Area (mm^2)	5890.1 (846.1)	6086.3 (872.6)	-196.2 (-599.1 to 206.7)	0.335
	Density (mm/cm^3)	66.5 (6.2)	70.6 (3.5)	-4.0 (-6.3 to -1.8)	0.001
MUSCLE STRENGTH					
30s Chair Stand	(repetitions)	11.9 (3.5)	14.7 (4.1)	-2.8 (-4.6 to -1.0)	0.003

BSI_c = bone strength index in compression , SSI_p = stress-strain index, bone strength in torsion

Secondary outcomes

pQCT-derived bone properties and forearm DXA

Univariate ANOVA revealed significant differences between groups at the distal site with 7.9% lower TrD ($p = 0.009$) in the Fx group, but no differences for ToD, ToA, or TrA. At the shaft site, the Fx group had 4.3% lower CoD ($p = 0.021$) but no differences in CoA (Table 5.4). At the tibia distal site, the Fx group had 11.7% lower ToD ($p = 0.004$), and 10.7% lower TrD ($p = 0.006$), but there were no significant differences between groups for ToA or TrA (Table 5.4). At the shaft site, there was no significant difference in CoD or CoA (Table 5.4). There was no difference in the ultradistal forearm aBMD between the groups (Table 5.4).

Table 5.4. Group means (SD) and between group comparison of secondary outcomes in the upper and lower extremities

Upper extremity		Fracture (n=30)	Non-Fracture (n=45)	Mean Difference (CI)	Significance (*p* value)
		Mean (SD)	Mean (SD)		
pQCT					
Distal radius	ToD (mm/cm^3)	225.0 (34.0)	242.7 (39.3)	-17.6 (-34.9 to -0.4)	0.056
	TrD (mg/cm^3)	193.1 (24.1)	209.0 (26.6)	-16.0 (-27.9 to -4.0)	0.009
	ToA (mm^2)	408.8 (48.8)	410.2 (60.9)	-1.5 (-27.7 to 24.7)	0.831
	TrA (mm^2)	381.8 (52.2)	381.5 (66.7)	0.3 (-28.1 to 28.8)	0.981
Radius shaft	CoD (mm/cm^3)	999.1 (98.9)	1043.2 (68.0)	-44.0 (-81.9 to -6.2)	0.021
	CoA (mm^2)	82.4 (10.5)	83.9 (12.0)	-1.5 (-6.7 to 2.7)	0.567
DXA					
Ultradistal forearm	aBMD (g/cm^2)	0.38 (0.1)	0.41 (0.1)	-0.03 (-0.1 to 0.01)	0.080
Lower extremity		Fracture (n=32)	Non-Fracture (n=42)	Mean Difference (CI)	Significance (*p* value)
Distal tibia	ToD (mm/cm^3)	235.6 (41.0)	264.8 (42.0)	-29.2 (-48.6 to -9.8)	0.004
	TrD (mg/cm^3)	218.3 (38.0)	243.0 (36.7)	-24.6 (-42.0 to -7.3)	0.006
	ToA (mm^2)	1164.0 (112.2)	1122.0 (135.4)	42.1 (-16.8 to 101.0)	0.159
	TrA (mm^2)	1114.2 (111.3)	1063.1 (144.2)	51.1 (-10.2 to 112.4)	0.101
Tibia shaft	CoD (mm/cm^3)	1038.0 (52.3)	1056.7 (51.2)	-18.7 (-42.7 to 5.36)	0.123
	CoA (mm^2)	284.0 (43.2)	300.8 (44.8)	-16.8 (-37.3 to 3.7)	0.118

ToD = total density, TrD = trabecular density, ToA = total area, TrA = trabecular area, CoD = cortical density, CoA = cortical area, aBMD = area bone mineral density

DISCUSSION

The most important finding of this study was that postmenopausal women over the age of 50 with a recent DRF, (when compared with women without a recent DRF) had 16% lower bone strength at the distal radius and 19% lower bone strength at the distal tibia. These findings, combined with the observed differences in muscle density and strength, provide insight to the possible etiology behind DRF in postmenopausal women. The additional analysis of the trabecular and cortical bone properties suggest that trabecular bone deterioration in early postmenopausal years may contribute to the observed lower bone strength in women with fractures. Because research in this area has been heavily focused on the older postmenopausal women, information of both bone and muscle strength deficits in early postmenopausal years is important knowledge for clinical practice; although, further research is warranted to determine causal effects and develop clinical guidelines specifically for early postmenopausal women.

The finding of lower total and trabecular bone densities at the distal radius and tibia sites agree with previous pQCT findings reporting 12-25% lower trabecular density in the distal radius and tibia in previously fractured women when compared to their non-fractured peers (Schneider et al., 2001). These findings suggest that deterioration in trabecular bone may play a role in declining bone strength, predisposing to DRF in early menopausal years. Despite a 4.3% lower CoD at the radius shaft in the fracture group, the estimated torsional bone strength or other cortical bone properties did not differ at the tibia or radius shafts. Lower cortical density at the radius shaft in the fracture group may reflect greater overall cortical porosity; however, this interpretation warrants caution since the observed CoD difference did not exceed the least significant change (4.6%) reported for CoD at the radius shaft in postmenopausal women (Duckham et al., 2013) and may reflect measurement error (Duckham et al., 2013; Uusi-Rasi et al., 2007).

To our knowledge, there are no previous studies that have examined differences in muscle density comparing postmenopausal women with a recent DRF to those without. There were no significant

differences in muscle area, but there were differences in muscle density in both the upper and lower extremity; therefore, although muscle quality seems to be affected, muscle quantity appeared not to be affected. This is highlighted by the fact that the women with a recent DRF demonstrated poorer performance on functional strength measures of grip strength and number of repetitions on the 30s chair stand test. This may also suggest early postmenopausal changes that are occurring in muscle quality and strength, despite no differences in the size of the muscle. This is consistent with observations that muscle strength declines to a greater degree than total muscle mass or cross-sectional area (Marcell, 2003), since muscle quality reduces with age (Lang et al., 2010; Narici & Maffulli, 2010). This relationship may be enhanced in those at greater risk of fracture. The negative relationship between grip strength and fracture risk has been reported in a prospective study assessing postmenopausal women (Karkkainen et al., 2008). In addition, grip strength has been demonstrated as a strong predictor of bone strength at the distal radius shaft (Lorbergs et al., 2011). Although the 30s chair stand test has not been used to assess the relationship between lower extremity strength to bone strength, a positive association between peak leg extensor power and estimated bone strength at the shaft and distal sites in the lower leg has been demonstrated in older individuals (Ashe et al., 2008; Cousins et al., 2010). While this research used seated knee extension equipment versus the sit to stand motion, the techniques have been correlated significantly to chair rises in elderly subjects (Hardy et al., 2010) and knee extensor strength and power are associated with improved performance on the 30s chair stand test (Crockett et al., 2013). Considering that exercise interventions can maintain bone strength in postmenopausal women (Nikander et al., 2010), future research should evaluate the role of the muscle-bone interaction and muscle function for maintaining bone strength. Despite the evidence in bone and muscle strength differences, there were no significant differences in aBMD at the femoral neck or spine. DXA derived aBMD at the ultradistal forearm site was also not significantly different; however, this did approach significance, with the fracture group demonstrating lower aBMD compared to the control group (Table 5.4). Similar to this study, Rozental et al. (2013) compared fracture and non-fracture groups in premenopausal women, and reported no differences in aBMD at the femoral neck, lumbar spine, and distal end of the forearm but significant differences in bone microarchitecture

were observed, independent of aBMD. Although aBMD continues to be a primary bone assessment tool used in the clinical setting, aBMD alone appears insufficient to accurately predict fracture risk (Engelke et al., 2013; Felsenberg & Boonen, 2005), especially in women younger than age 65. Therefore, the findings from the current study are clinically relevant by providing insight into potential use of bone and muscle strength profiles when assessing risk of DRF in early postmenopausal women.

A rigorous aspect of this study lies in the stringent exclusion criteria with a focus on assessment of both bone and muscle properties in the upper and lower extremities in women under the age of 60. The time period post-fracture (6 months to 2 years) was in keeping with typical expectations of recovery at the wrist, allowing for functional measurement techniques such as grip strength but still allowing bone imaging to be performed as close to the time of fracture as possible. Most patients should experience the majority of improvement in grip strength, pain, and disability within six-months post-fracture (MacDermid et al., 2003). We also recognize the limitations in our small sample cross-sectional study design. Further longitudinal research with a larger sample size is warranted to determine the predictive nature of bone and muscle properties for DRF risk.

This study does have some limitations. The range in timing of obtaining scans post-fracture (from 6 months to 2 years) might have some influence on our comparisons. Importantly, the non-fractured extremity was used for comparisons, which was unlikely to have undergone any significant changes in bone outcomes due to disuse. Although we did not control for limb dominance in the analysis due to the small sample size, previous studies suggest there is little difference in post-fracture bone strength between the dominant and non-dominant limb at this site (Vico et al., 2008). Further, our effect sizes (5-10%) appeared larger than unilateral differences (1-5%) reported for individuals in the control group of unilateral loading comparisons (Kontulainen et al., 2002). Finally, the BSI_c measure has been only validated at the distal tibia (Kontulainen et al., 2008). This index warrants further validation work with distal radius specimens.

In conclusion, post-menopausal women age 50 years and older with a recent DRF have lower bone and muscle strength in both the upper and lower extremities compared to the women without a recent DRF, despite no differences in DXA derived aBMD at the femoral neck or spine and no difference in bone strength at the tibia shaft. Although DXA is clinically used for diagnosing osteoporosis in individual patients, this study provides further support for the notion that aBMD alone may not provide a sufficient predictor for DRF risk.

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RELATIONSHIP OF STUDY 3 TO THESIS:

Declining aBMD, as derived from DXA, is a known risk factor for fracture risk, specifically if the T-scores are low enough to classify one's skeletal health as "osteoporotic." Although aBMD of the femoral neck and lumbar spine is currently the standard protocol used for diagnosis of osteoporosis and often used to estimate fracture risk clinically, many fractures occur in women who are not diagnosed as "osteoporotic" using this method. pQCT derived estimates of bone strength, as well as bone and muscle properties can provide a better understanding of early musculoskeletal-specific fracture risk factors that occur in early post-menopausal women. Although pQCT technology provides valuable information, it is not yet developed for widespread clinical use. Further research is required to develop application to clinical screening tools. This study provides information on the differences in bone and muscle strength in a group of women over the age of 50 with a recent DRF, compared to their non-fractured peers. This information will assist in developing the profile of those at risk of an early fragility fracture and direct relevant future research on the fracture risk and possible clinical assessment tools.

CHAPTER 6: GENERAL DISCUSSION AND CONCLUSIONS

The rationale for this dissertation was to compare fall and fracture risk in early postmenopausal women who sustained a DRF verses women who did not and to determine the longitudinal recovery of these factors post DRF. With the identification of the national burden of fractures on Canadians who suffer a fragility fracture, as well as the burden on the economy, secondary prevention of future fragility fractures has recently become a national priority, targeting patients with a new and/or prior fracture. Primary prevention, although recognized as important, has not received the same immediate attention in Canada (Osteoporosis Canada, 2013). Primary prevention will target those at high risk of a first fragility fracture and individuals age 50 years and older (Figure 6.1).

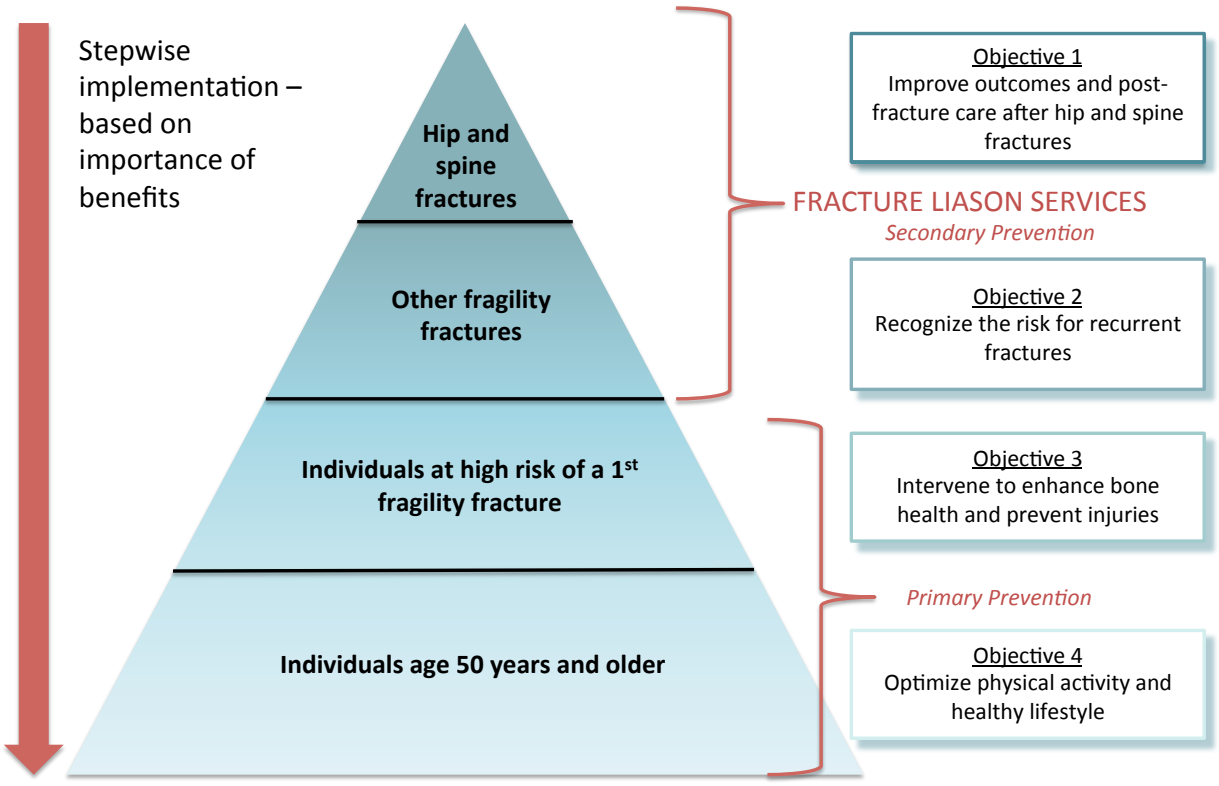

Figure 6.1. A systematic approach to fragility fracture in Canada. Adapted from Osteoporosis Canada, Fracture Liason Services, 2013.

This thesis focuses on both secondary and primary prevention by identifying fall and fracture risk markers in women over age 50 with a recent DRF as well as providing longitudinal follow-up data of these factors. Although the "gold standard" study would be longitudinally following middle aged women to their first fragility fracture and beyond, a study of this type is beyond the scope of this dissertation. In order to implement primary and secondary preventative strategies, it is important to first develop the profile of those who have sustained an initial fragility fracture, in order to develop screening protocols to prevent this initial fracture in women at risk and to recommend assessment and treatment to prevent a second fracture. Because osteoporosis is a silent disease, and often goes unrecognized until the first fracture occurs, identifying women at early risk of first fracture can be a challenge.

Fracture risk tools and advanced technology for obtaining volumetric values of bone and muscle properties through musculoskeletal imaging have been developed (Rubin et al., 2013; Engelke et al., 2008). In addition, there are several commonly used fall risk screening tools available; however, with both fall and fracture risk screening, the ability for existing assessment tools to accurately predict fall and fracture risk in early post-menopausal women is not known.

The three studies outlined in this dissertation were designed to increase the knowledge of the typical recovery period in the first year post-fracture and to increase knowledge of the fall and fracture risk profile in this early postmenopausal population. The strengths of the first study were the timelines of follow up post-fracture, including the first week of fracturing, and multiple follow-up time points throughout the first year using a longitudinal study design. This study also included women under the age of 65 years, where literature in fall and fracture risk is limited. The strengths of the second and third studies included stringent exclusion criteria, with no bone altering medications in the past year, a two-year window of time since the fracture, and the inclusion of women as young as age 50. With the standard practice of prescribing pharmaceutical agents following an early fragility fracture or with moderate to high fracture risk combined with recurring falls, data comparing bone strength in a sample where there is no confounding effect of current pharmaceutical bone altering influence is limited.

The findings from Study 1 demonstrated declines in fall-risk and functional status that occurred post-fracture. Importantly, mean scores always remained below fall-risk levels as defined by cut-offs for older adults 65 year and older using the current tools available. Even though there were significant differences between the age groups, with the older group (65 and years and older) consistently demonstrating poorer scores on functional and fall-risk measures, mean scores remained below the fall-risk threshold identified in the literature for older adult cohorts for both age groups. These results suggest the tools designed for fall risk assessment may need to be modified or new tools developed in order to effectively identify risk for future fracture and falls for women recovering from a DRF. In turn, this may direct future research to develop more appropriate rehabilitation protocols, which may address some of the changes occurring in lower extremity function, gait speed, and balance.

The findings from Study 2 and 3 contribute to the knowledge on the profile of early post-menopausal women, in terms of both fall and fracture risk status. Results demonstrated that women with a recent DRF compared to women without, demonstrated higher fall and fracture risk. Similar to the results in Study 1, cut-off measures developed for adults age 65 and older did not apply to this younger cohort. Women with a recent DRF, compared to women without, demonstrated lower bone and muscle strength in both the upper and lower extremities. Both studies confirmed the importance of studying fall and fracture risk differences in women susceptible to DRF as this is the earliest fragility fracture to occur. These results, in combination with previous studies, will assist ongoing efforts to break the cycle of future fractures (Åkesson & Mitchell, 2012; Osteoporosis Canada, 2013) and develop the profile of those at risk of fragility fractures, in order to better inform primary prevention strategies.

The following questions arose from this study that may direct future research in this area:

1) Is grip strength a valid and reliable measure to determine fall or fracture risk in early postmenopausal women? Are there other physical screening tests for fall risk that may be more sensitive to determine fall risk in this younger middle-aged population?

2) What are the normative values of current commonly used fall risk screening tools for women younger than age 65? Once normative values have been established, can the same tools be used to predict fall-risk in this younger cohort?

3) Are there other risk factors yet to be documented that can measure fall or fracture risk in this population?

4) What preventative measures can be taken in the cohort of women aged 50-65 to optimize physical activity/lifestyle health to decrease fall and fracture risk?

5) What are healthcare professionals' opinions on where the responsibility lies in educating patients on their risk of future fracture? And what preventative strategies are currently being implemented? (i.e., What interventions, including educating patients, are occurring from the perspective of the orthopaedic surgeon, family physician, occupational or physical therapist, nurse or nurse practitioners, nutritionist, and from the perspective of the patient?)

6) What are the patient perspectives of those aged 50-65 on the underlying reasons for their fracture, and do they link their distal radius fracture with poor bone health and future fracture risk?

7) Within the use of DXA, is site-specific measurement occurring in early post-menopausal women? Should scores outside of the "normal" range be used to initiate non-pharmaceutical interventions to enhance bone health and prevent injuries? If so, at what DXA score is this appropriate?

8) If DXA does not have the required sensitivity to delineate those aged 50-65 at risk of fracturing, is it warranted to develop pQCT analyses to a level appropriate for general practice usage? Using pQCT, what

measurable changes can be achieved with a primary prevention program for individuals both pre and post distal radius fracture?

9) Are there similar results and differences in bone strength, muscle properties and fall risk in men who are at risk for or sustain a DRF?

10) What is the effect of a post-DRF rehabilitation protocol, which incorporates lower extremity strength and balance, in addition to the typical rehabilitation protocols, which are directed at regional recovery at the wrist? What are the barriers to implementing such protocols? How can these barriers be minimized?

CHAPTER 7: CLINICAL IMPLICATIONS

Fragility fractures are currently a national, and even a global problem, with Fracture Liason Services (Osteoporisis Canada, 2013) implementing secondary fracture prevention care gaps in many areas of the world. This has been a recent national effort to ensure that fragility fracture sufferers are receiving appropriate assessment and intervention to reduce future fracture risk. The information provided in this dissertation will contribute to the knowledge base to identify secondary preventative efforts, and potentially primary prevention efforts. Understanding the profile for early post-menopausal women at risk of their first fragility fracture and following recovery after a DRF is an important step in developing preventative strategies. Health care professionals need to know where to target efforts in fall and fracture prevention within their scope of practice. If all health care professionals are aware of the clinical risk factors and the profile of early postmenopausal women at risk of sustaining a fracture before it occurs, it may be possible to prevent the first fracture. If the first fracture occurs before an individual can be identified as at risk and primary prevention can be implemented, secondary prevention of future fractures should then occur.

Understanding the typical course of recovery during the first year following a distal radius fracture demonstrates the need for various rehabilitation strategies throughout the first year, targeting fall and fracture risk. These results may help clinicians to understand the normal course of recovery post-fracture to determine when patients are deviating from the norm, but also to direct future research to develop more appropriate rehabilitation protocols which may address some of the changes that are occurring in lower extremity function, gait speed, and balance. Due to the increase of reported falls and DRFs peaking between ages 50 and 65, more sensitive tests for women aged 50-65 should be developed to detect early signs of fall or fracture risk, in order to implement early intervention strategies. The development of tests to detect the subtle changes in physical declines that may be contributing to fall and fracture risk could assist in identifying women at risk of sustaining their first fragility fracture to implement appropriate preventative strategies.

Developing the profile of those at risk of suffering early fragility fractures is required to target primary prevention strategies. The results obtained from this dissertation are clinically relevant, as they assist in developing this profile and direct relevant future research on musculoskeletal properties, possible clinical assessment tools, and appropriate rehabilitation protocols. These studies demonstrate the importance of studying DRF as the earlier fracture to occur, providing further data for ongoing efforts to break the cycle of future fractures (Åkesson & Mitchell, 2012; Osteoporisis Canada, 2013) and strengthen the notion that DXA alone may not be the best predictor for fracture risk. Further evaluation of the bone and muscle strength relationships should be pursued, which may include the exploration of specific exercises and training protocols capable of strengthening the radius at the wrist and forearm.

Based on the results of this thesis combined with current clinical guidelines and literature review, the following clinical recommendations are suggested, within the limitations of the findings previously presented.

1) All healthcare practitioners who come into contact with a postmenopausal women with a recent DRF should educate these patients on basic bone health: regular active weight-bearing exercise, calcium (diet and supplements) 1200 mg daily, vitamin D 800-2000 IU daily and fall-prevention strategies (Papaiouanno et al., 2010). Consistent education through all healthcare disciplines may result in better patient comprehension, understanding, and potentially better adherence to recommendations.
2) Education should be patient-specific by supplementing general information with objective outcome measures, such as scores on available screening tools for both fall and fracture risk.
3) Based on the results of this thesis, screening measures that may show promise in early postmenopausal women include grip strength, TUG, gait velocity, 30sSTS and the FRAX. Although there are limitations with these clinical tools with the established cut-off values for identifying fall and fracture risk in older adults not being sensitive enough for this early

postmenopausal women, scores may be used to determine baseline measures and monitoring of functional status overtime. Grip strength may be one of the most promising measures, as there are established normative values for this age group and this measure has been associated with several fall risk performance measures and fracture risk as well as many aspects of health and whole body strength.

4) Patients should be educated on their recent fracture as an indicator of declining bone quality and future fracture risk, regardless of osteoporosis diagnosis from DXA derived diagnoses of osteoporosis status. This is in line with previous recommendations in replacing the diagnosis of osteoporosis and osteopenia with the concept of fracture risk (Sale et al., 2014). Promoting basic screening with the appropriate screening tools as part of routine fall prevention practices for all wrist fracture patients may be the first step in reducing the fragility fracture cycle.

Although there are limitations, the FRAX could be used as a simple, time and cost effective screening tool easily utilized in a clinical setting to determine fracture risk in this cohort. Based on the results of this thesis, it is likely that early postmenopausal women will not demonstrate a 10-year probability of major osteoporotic fracture of 20% or more, where pharmacological therapy would be advised; however, this tool could also be used educate patients on the clinical risk factors that they do demonstrate, establishing their 10-year probability of a major osteoporotic fracture. Non-pharmacological management should still be implemented when risk is <20%, especially as risk approaches this threshold. It may be useful to determine different cut-off or threshold scores to address women at risk who do not meet criteria for pharmacologic treatment due to specific factors addressed through the FRAX, but who could benefit from alternate therapies.

The results obtained from this dissertation are clinically relevant, as they assist in developing the profile of those at risk of suffering an early fragility fracture and direct relevant future research on musculoskeletal properties, possible clinical assessment tools, and appropriate rehabilitation protocols. The importance of studying DRF as the earlier fracture to occur is strengthened, and results may assist in highlighting the

non-pharmacological aspects of the current fracture risk guidelines in the management for early post-menopausal women with an early fragility fracture.

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APPENDICES

APPENDIX A. Telephone Screening Questionnaire

Screen: #_____

Initials:_____

TELEPHONE SCREEN

Script in italics is only a guideline for the telephone screener.
Intro: Thank-you for your interest in participating in this study. In order to find out if you are eligible, there are several questions that I need to ask you. Is it all right if I ask you some questions over the phone?

1. First, I need to get some contact information.

   Name:_____
   Address:_____
   Postal Code:_____
   Telephone:_____
   Email:_____(if applicable)

2. What is your age?_____
   If < 50, not eligible
   If matching for age ranges, use key below

50 – 60	*60-70*	*70-80*	*80-90*	*90+*

3. Have you had any fractures of your wrist/lower forearm?
   NO *If **no**, and recruiting for **no fracture**, go to **question 4***
   *If **no**, and recruiting for **just fracture**, **not eligible***

   YES *If **yes**,* When did the fracture occur? _____

   ***If less than 6 months, finish the survey**, but they cannot be booked until 6 months post,*

   ***If less than 2 years**, and recruiting for **fracture** group ask:*

   - How did it happen? _____
   - Did you receive surgery? NO YES (L / R pins / plate / rod)
     If yes, record which arm (L / R), indicate if pins/plate/rod and document in file for testing

   - Were you in a cast? *if **yes**,* For how long? NO YES: _____
   - Are you currently receiving any therapy treatment for your forearm? Describe.
     _____

Screen: #_____

Initials:_____

4. Have you had any other fractures in your lower legs? NO YES
   *If **yes,***
   - Can you describe where and when: _____
     _____

5. Do you have metal implants (pins, joint replacements) anywhere in your wrists/forearms/lower legs? NO YES
   *If **yes**,*
   - Can you describe? _____
     _____

   If they have any metal implants, document which arm/leg and record in file for testing (see above).

6. Can you walk independently, either with or without a cane or other walking aid?
   YES NO ***If no, excludes***

7. Do you have any medical or neurological conditions that affect your day to day activities? i.e. difficulty walking to and from the bathroom, unable to shower or bathe, prepare meals, etc. YES NO
   *If **yes**,*
   - Can you describe?_____

   ***If answer is Yes**, and the condition limits daily activities such that assistance is needed, check with PI regarding need for further follow-up or exclusion*

8. Are you currently taking, or have you ever taken any medications for osteoporosis?
   YES NO
   *If **yes**,*
   - What were/are they? _____

   *If they have been **on hormone replacement therapy**, a bisphosphonate (i.e. Fosamax, Didracal), exclude; if unsure check with researchers*

9. Have you taken any oral corticosteroids in the past year? YES NO
   *If **yes**,* _____

   *If **yes**, get more details, if it is higher dose corticosteroid treatment, i.e. for rheumatoid arthritis, etc. then exclude, if it is a low dose such as an inhaler for asthma, continue with questions*

10. Do you have any difficulties with balance? YES NO
    *If **yes**,*
    - Can you describe?_____

Screen: #_____

Initials:_____

*If **yes**, and it appears significant especially in combination with next question, check with PI regarding need for further follow-up or exclusion*

11. Have you had a fall or falls in the past year? (Described as any body part landing on the ground or other lower surface (i.e. chair or stairs) YES NO
    *If **yes,***

    - How many? *(circle one)* 1 2 3

12. Do you have any of the following conditions?
    - Uncontrolled hypertension YES NO
    - Recent heart attack YES NO Describe_____
    - Recent stroke YES NO Describe_____
    - Parkinson's, multiple sclerosis or other YES NO
    - Neurological condition YES NO Describe_____
    - Congestive heart failure YES NO
    - Recent lung or blood clot YES NO Describe_____
    - Respiratory infection, i.e. pneumonia YES NO Describe_____
    - Osteoporosis YES NO Describe_____
    - Recent fracture (other than forearm) YES NO Describe_____
    - Chest pain/angina YES NO Describe_____
    - Vision or Hearing Problems YES NO Describe_____
    - Reflex sympathetic dystrophy or other neurological conditions
        - Affecting the arm? YES NO Describe_____
        - Severe arthritis in either wrist or hand? YES NO Describe_____
    - Any other health problems YES NO Describe_____

    If they present with a recent significant medical or neurological concern (i.e. stroke, heart attack, chest pain), inform PI for further follow-up/ and possible exclusion

13. Do you have any other questions about the study?
14. *If eligible, explain the protocol of coming for two testing sessions, and will complete a consent form at the first appointment. Book 1st testing session if they meet eligibility, and send out information package:*

DATE:	
TIME:	

15. *If not eligible, thank them for their interest and inform them that the information from this telephone interview will be destroyed.*

APPENDIX B. Ethics approval certificate 1

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval
Study Amendment

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Jonathan P. Farthing	Kinesiology	11-28

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
College of Kinesiology
87 Campus Drive
Saskatoon SK S7N 5B2

STUDENT RESEARCHER(S)
Charlene Magnus

FUNDER(S)
NATURAL SCIENCES & ENGINEERING RESEARCH COUNCIL OF CANADA (NSERC)

TITLE
: Does Strength Training the Non-Injured Limb Improve Rehabilitation for the Injured Limb After Shoulder Injury?

APPROVAL OF	APPROVED ON	CURRENT EXPIRY DATE
Amendment to Study: -Addition of non-surgical, non-strength training control group -Removing objective functional tests -Modifying the strength training program's number of contractions -Decreasing the number of strength tests and range of motion tests Subject Information and Consent Form (19-May-2011)	23-May-2011	21-Mar-2012

Delegated Review ☒ Full Board Meeting ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing.

Michel Desautels, Ph.D., Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607-110 Gymnasium Place
Saskatoon SK S7N 4J8

APPENDIX C. Ethics approval certificate 2

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval
Study Amendment

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Cathy Arnold	School of Physical Therapy	11-119

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
College of Kinesiology
87 Campus Drive
Saskatoon SK S7N 5B2

SUB-INVESTIGATOR(S)
Jonathan P. Farthing, Saija Kontulainen, Philip D. Chilibeck, Joel Lanovaz, Geoff Johnston, James (J.D.) Johnston

STUDENT RESEARCHER(S)
Katie Crockett

FUNDER(S)
SASKATCHEWAN HEALTH RESEARCH FOUNDATION (SHRF)

TITLE
: The Relationship of Bone Architecture and Strength at the Forearm to Other Indices of Fall and Fracture Risk in Older Women With and Without a History of Wrist Fracture

APPROVAL OF	APPROVED ON	CURRENT EXPIRY DATE
Sharing of questionnaire data between BIO 10-17 (CAST - Cross-training of Arm Strength Training Trial: Does cross-training improve function and reduce risk of future falls and fracture in the first year following a distal radial fracture?) and BIO 11-119 (The Relationship of Bone Architecture and Strength at the Forearm to Other Indices of Fall and Fracture Risk in Older Women With and Without a History of Wrist Fracture)	13-Mar-2014	24-Nov-2014

Delegated Review ☒ Full Board Meeting ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing.

Ildiko Badea

Ildiko Badea, PhD., Acting Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607-110 Gymnasium Place
Saskatoon SK S7N 4J8

APPENDIX D. Consent form 1

CAST-Cross-training Arm Strength Training Trial: Does cross-training improve function and reduce risk of future falls and fracture in the first year following a distal radial fracture?

INFORMATION FOR PARTICIPANTS

Investigators:

Principal Investigator: Dr. Jon Farthing (Ph.D., M.Sc., B.Sc.Kin), College Kinesiology
Co-investigators: Dr. Cathy Arnold (Ph.D., M.Sc., BSc.P.T.), Associate Professor, School of Physical Therapy; Dr. Geoff Johnston (M.D., MBA, B.Sc., FRCSC), Professor, Department of Surgery, Division of Orthopedics, College of Medicine; Dr. Vanina dal-Bello Haas (Ph.D., M.Ed., B.Sc.P.T.), Associate Professor, School of Physical Therapy; Dr. Jenny Basran (M.D., B.Sc. Biological Sciences), Assistant Professor, Department of Medicine, Division of Geriatrics; Ms. Charlene Magnus (M.Sc., B.Sc.Kin.), Ph.D. Student, College of Kinesiology

Study Phone Line: 966-1068

Address: College of Kinesiology, 87 Campus Drive, Saskatoon, Saskatchewan, S7N 5B2

Sponsor: RUH Foundation Research Grant; U of S President's NSERC

Information about the Study:
You are invited to participate in this study because you are age 50 years or older, female and have recently fractured your wrist. Women who have fractured their wrist may be at risk of future fracture and this study will investigate fall and fracture risk up to one year post-fracture as well as the effect of a rehabilitation program designed to improve function, strength and mobility during the recovery period.

Voluntary Participation: It is up to you to decide whether or not to take part in this study. This information sheet and consent form will tell you about all parts of the study, why it is being done and the possible benefits, risks and discomforts. If at anytime reading this, you have questions or you do not understand what is written, please ask the research assistant or the orthopedic surgeon who is with you or call the study phone line if questions arise when you are at home. If you would like to participate you will be asked to sign the consent form on the last page. If you do decide to participate, you are still free to withdraw from the study at any time without giving any reasons for your decision.

Purpose and Objectives of the Study:
The objectives of this study are to evaluate: (1) the effects of two types of home exercise programs on recovery, strength and mobility following a wrist fracture and (2) determine future fall and fracture risk in the first year following a wrist fracture.

Description of the Study:
If you agree to be in this study, the following will happen: 1) you will be asked to fill out

questionnaires regarding your medical history, handedness, fracture and fall history and a short test on memory and thinking skills. These questionnaires will determine if you are eligible for the study. 2) if eligible, you will be randomly assigned (i.e. assigned by chance, as determined by a random numbers table) to one of two groups. There is a 50/50 chance of being assigned to either group. Group 1 will focus on improving mobility and function using the current standard protocol at the fracture clinic. Group 2 will use the standard protocol at the fracture clinic and will also strength train their healthy (uninjured) limb while wearing their cast and for the remainder of the follow-up period of the study. The strength training will be conducted at home, and will train your finger strength and hand grip strength. You will be given a hand-grip trainer to take home to conduct the exercise training. The training will start with 2 sets of 8 grip contractions (approximately 5 minutes to complete exercise), and will work up to 5 sets of 8 grip contractions (approximately 15 minutes to complete exercise). The exercise will be conducted 3 times per week and will be taught to you at your first visit to the clinic if you are in the strength training group. It will take approximately 10 minutes to teach the exercise. Once you are assigned to a group, a research assistant will measure the strength and motion of your unaffected arm and will instruct you on home exercises to continue. You will be asked to record in a log how often you do these exercises. Any exercise equipment that you need will be provided free of charge. You will also fill out a questionnaire about hand function, physical activity and fear of falls. The research assistant will arrange subsequent visits to see you, preferably at the same time that you come back for reviews with the orthopedic surgeon at the Distal Radial Fracture Clinic. 3) On the second visit, approximately 3 weeks after the fracture, the research assistant will test your balance, walking, and some general day to day tasks such as getting up and down from a chair, putting on a jacket and picking up objects. You will continue to have strength and motion testing for the unaffected arm, and for the affected arm once the cast is removed. In total, you will be assessed 6 times – right after your fracture, 3 weeks later, 6 weeks later, 9 weeks later, 12 weeks later and 26 weeks later. These are timed to coincide with regular reviews. One year after your fracture, you will receive a package of 4 short questionnaires to complete and return in a self-addressed envelope. (See below for a timeline of events and estimated time for each visit).

Timeline of Events

Fracture occurs

- cast applied (after surgery if it was required)

1st Clinic Visit (5-10 days after fracture) – Estimated time for visit: 1 hour 45 minutes

- Strength and motion of unaffected arm assessed
- History of prescriptions and medications
- X-ray
- Questionnaires (assessing hand function, handedness, falls history, memory, thinking, and demographics)
- Learn at-home exercises

3 Weeks – Estimated time for visit: ~ 2 hours
- Strength and motion of unaffected arm assessed
- X-ray
- Questionnaires (assessing hand function, falls history and physical activity)
- Balance, walking, and day-to-day tasks assessed

6 Weeks – Estimated time for visit: ~ 2 hours
- cast removed (approximately at 6 weeks)
- Strength and motion on both limbs assessed
- X-ray
- Questionnaires (assessing hand function, falls history and physical activity)

9 Weeks – Estimated time for visit: 1 hour, 30 minutes
- Strength and motion on both limbs assessed
- X-ray
- Questionnaires (assessing hand function, falls history and physical activity)

12 Weeks – Estimated time for visit: 2 hours
- Strength and motion on both limbs assessed
- X-ray
- Questionnaires (assessing hand function, falls history and physical activity)
- Balance, walking, and day-to-day tasks assessed

26 Weeks - Estimated time for visit: 2 hours
- Strength and motion on both limbs assessed
- X-ray
- Questionnaires (assessing hand function, falls history and physical activity)
- Balance, walking, and day-to-day tasks assessed

52 Weeks - Estimated time for visit: 1 hour, 30 minutes
- Strength and motion on both limbs assessed
- X-ray
- Questionnaires (assessing hand function, falls history, and physical activity) received and mailed to researchers

Specific Testing Procedures:
A trained graduate student with experience in testing and exercise interventions (i.e. College of Kinesiology with Certified Exercise Physiologist designation CEP) will conduct all physical tests and will assess you prior to testing to ensure that the tests are appropriate for you. The tests are designed for adults aged 50 years and older and most include everyday tasks that you would do at home, such as getting up from a chair, walking, shifting

weight onto one leg. There will be rest breaks during the testing. All testing will be conducted at a Royal University Hospital, either in the Outpatient Department or Physical Therapy Department. The testing procedures are described below;

Grip Strength: Isometric (a type of muscle contraction where the joint angle and muscle length do not change throughout the contraction) grip strength assessment using a hand-held calibrated handgrip dynamometer (a measuring instrument used to assess your grip strength) will be conducted as follows: you will be seated with the arm flexed at a 90º angle. The average and peak values obtained from three maximal voluntary efforts will be used for comparison. The contractions will be 2-3 seconds in duration and each separated by 1 minute of rest. Your unaffected extremity will always be tested first. You will be asked to complete a practice repetition to become familiar with the testing protocol. You will also complete sub-maximal contractions of each strength task to minimize the learning effect associated with each testing procedure.

Balance and functional task testing: You will be asked to perform several tasks such as looking over your shoulder, turning in a circle, balancing on one leg, picking up objects and standing with one foot in front of the other (Berg Balance Scale), walking a set distance (walking 10 m at a usual and quick pace). You will also be asked to move from sitting to standing as many times as you can in 30 seconds (30 s Chair Stand). Other functional testing would include the Physical Performance Test which includes some activities of daily living such as picking up small objects and putting on a coat. For the balance testing, you will be wearing a safety belt around your waist, so that if at any time you feel that you are losing your balance, the research assistant will assist you.

Questionnaires: There are 4 questionnaires you will be asked to complete. One questionnaire will ask you questions about how confident you feel doing a variety of day to day tasks in the home and out in the community, two questionnaires will ask about hand and arm function for daily tasks, one questionnaire will ask about physical activity you have engaged in during the last 7 days.

Participant Responsibilities:
You will be responsible to inform the primary investigator or research personnel about any new health concerns you have during the course of the study. As well, you may be asked to visit your family physician or give permission to contact your physician if the investigators have any concerns about your health during the study.

Risks and Discomforts:
Side effects that may occur as a result of involvement in this study include: joint discomfort after exercising or testing, or some fatigue following testing. Testing and exercise have been carefully designed to avoid any of these side effects from occurring. The exercise program is designed to be gentle exercise that will be progressed slowly based on your own individual presentation. If joint discomfort occurs, the exercises will be modified

based on individual concerns. There are no other unforeseeable risks associated with this study.

Research Related Injury or Cost:
There will be no costs to you for participating in this study. You will not be charged for the exercise program, equipment or any testing procedures. You are expected to transport yourself to and from the testing site, reimbursement for parking will be provided. In the event that you become ill or injured as a result of participating in this study, necessary medical treatment will be made available at no additional cost to you. You should seek immediate medical attention if you have an adverse event. By signing this document you do not waive any of your legal rights.

Confidentiality:
The researchers will protect your privacy, and safeguard the confidentiality of information collected about you during the course of this study. Absolute confidentiality cannot be guaranteed. Identification will only be by your initials and an assigned study number. A representative of the sponsor may require access to your health records during the study to verify the accuracy and completeness of study-related information. Government regulatory agencies in Canada (Health Canada, Therapeutic Products Directorate) and the Research Ethics Board may inspect study records to ensure compliance with their standards for approving the study. Access to your personal health information may include copying and taking copies away. However, in this case, all personal identifiers would first be removed and substituted by your assigned study number and initials. Rarely, your study documents may be obtained by courts of law. Reports based on results of this study may be presented for medical and scientific publication, but your identity will not be disclosed. With your permission, your physician may be informed of your study participation and, if required, consulted regarding your health and treatment.

Benefits to the Participant:
The following, although not guaranteed, are benefits of being involved in this study:

Individual Benefits: You will be provided with home exercises designed to enhance recovery following your wrist fracture. At the end of the study, you will receive an individualized summary of your test results in the mail.

General Benefits: Involvement in this study will be an important contribution to scientific knowledge of rehabilitation and exercise management after a wrist fracture and may help to improve quality of life and prevent falls for other women who fracture their wrist in the future.

Voluntary Participation and Withdrawal:
Your participation in this study is entirely voluntary. You may withdraw from the study at any time with no loss of benefits or penalty and your future medical care will not be

affected. If you choose to enter the study and then decide to withdraw at a later time, all data collected will be retained for analysis. By law, this data cannot be destroyed.

If you choose to not participate in this study or decide to withdraw, the investigator will discuss alternative programs that you might choose to participate in. These could include other exercise programs for individuals with wrist fracture, or individual treatment by a physical therapist. Your orthopedic surgeon will follow your progress and will discuss these options with you.

On receiving new information about the treatment or your condition, the investigators might consider it to be in your best interests to withdraw you from the study without your consent if they judge that it would be better for your health.

If you have any questions about your rights as a research subject or concerns about the study, you should contact the Chair of the Biomedical Research Ethics Board, c/o the Office of Research Services, University of Saskatchewan at (306) 966-4053

CONSENT FORM

CAST-Cross-training Arm Strength Training Trial: Does cross-training improve function and reduce risk of future falls and fracture in the first year following a distal radial fracture?

The purpose of this study is to examine (1) the effects of two types of home exercise programs on recovery, strength and mobility following a wrist fracture and (2) determine future fall and fracture risk in the first year following a wrist fracture.

Please read the following carefully before signing the consent form:

- I have read the study information or have had it read to me and understand the information
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions
- I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive
- I understand that I am not waiving any of my legal rights as a result of signing this consent form
- I have read this form and I freely consent to participate in this study.
- I have been told that I will receive a dated and signed copy of this form
- I agree that my family physician can be informed of my participation in this study and, if required, contacted regarding my health _____YES _____NO

Signature of Participant: _____Date: _____

Signature of Individual Conducting Consent: _____Date:_____

Signature of Witness: _____Date:_____

APPENDIX E. Consent form 2

UNIVERSITY OF SASKATCHEWAN

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: **The Relationship of Bone Architecture and Strength to Fall and Fracture Risk in Women with and without a History of Wrist Fracture**

PRINCIPAL INVESTIGATOR: Dr. Cathy Arnold, Ph.D, Professor[1]

SUB-INVESTIGATORS AND STUDENT RESEARCHERS:
Co-investigators: Dr. Jon Farthing,Ph.D., Associate Professor[2]; Dr Saija Kontulainen, Ph.D., Associate Professor, [2] Dr. Phil Chilibeck, Ph.D., Professor[2]; Dr. Geoff Johnston, M.D., FRCSC, Professor[3]; Dr. Joel Lanovaz, Ph.D. Assistant Professor[2]; Dr. J.D. Johnston, Ph.D., Assistant Professor[4];
Student Investigator: Ms. Katie Crockett, MSc. Student[1].

[1] School of Physical Therapy, 210 – 1121 College Drive, Saskatoon, Saskatchewan S7N 0W7, College of Medicine, [2] College of Kinesiology [3]Department of Surgery, Division of Orthopedics, College of Medicine; [4] Department of Mechanical Engineering, College of Engineering.

SPONSOR (FUNDING AGENCY): Saskatchewan Health Research Foundation

CONTACT PHONE NUMBER: 966-8619

INTRODUCTION:
You are invited to participate in this study because you are age 50 years or older and female. You may or may not have fractured your wrist in the past 2 years. Women who have fractured their wrist may be at risk of future fracture and this study will investigate bone architecture and fall and fracture risk compared to women who have never fractured their wrist. This study will provide the researchers with information about bone strength and risk of future fracture in women. It is up to you to decide whether or not to take part in this study. This information sheet and consent form will tell you about all parts of the study, why it is being done and the possible benefits, risks and discomforts. If at any time reading this, you have questions or you do not understand what is written, please ask the researcher who is with you or call the contact phone number if questions arise when you are at home. If you would like to participate you will be asked to sign the consent form on the last page. If you do decide to participate, you are still free to withdraw from the study at any time without giving any reasons for your decision.

WHO IS CONDUCTING THE RESEARCH?
This research project is being conducted by the Bone and Joint Imaging Group, funded by the Saskatchewan Health Research Foundation.

WHY IS THIS STUDY BEING DONE?
The objective of this study is to evaluate the relationship of bone strength and architecture as evaluated by state of the art bone measurement tools to other fall and fracture risk measures in women with and without a history of wrist fracture.

WHO CAN PARTICIPATE IN THE STUDY?
If you are female, age 50 years or older, with no neurological or medical conditions that affect day to day living, no neurological conditions in the upper extremity, and have not taken any bone altering medications, you are eligible to participate. We will be recruiting an equal number of women who have sustained a wrist fracture in the past 2 years and women who have not. A total of 100 women will be participating in this study.

WHAT DOES THE STUDY INVOLVE?
If you are eligible and agree to be in this study, the following will happen: You will attend two testing sessions at the University of Saskatchewan. During the first session you will have bone properties measured in the non-fractured or non-dominant wrist by two different computed tomography tests: peripheral Quantitative Computed Tomography (pQCT) and High Resolution-peripheral Quantitative Computed Tomography (HR-pQCT). You will also be asked to fill out questionnaires regarding your medical history, confidence in doing day to day tasks, handedness, fracture and fall history and a short test on memory and thinking skills. There will be a short walking test, a strength test of your gripping ability in both hands and a general test of day to day tasks such as putting on a jacket and picking up objects. This first testing session will last approximately 2 and ½ hours. At the second visit you will have a dual energy X-ray absorptiometry (DXA) scan of your bones at the hip, whole body, spine and both forearms. The researcher will also test your balance, walking, and day to day tasks such as getting up and down from a chair. There will be a questionnaire to fill out regarding your physical activity level and food intake. This second test session will take approximately 2 hours. We may ask if you are willing to let us take photographs for research presentations or teaching purposes (see consent form last page). You are not obligated to consent to this, and you can still participate in the study. Any photographs would remove identifiers.

Specific Testing Procedures:
There will be trained graduate students and a medical imaging technician with experience in 1) bone testing and 2) function and balance testing who will conduct all physical tests. Prior to the testing, you will complete a medical and demographic questionnaire and if the testers have any concerns about any conditions that you have and the potential safety of the tests, we may need to consult with your family physician prior to testing. The physical tests are designed for adults aged 50 years and older and most include everyday tasks that you would do at home, such as getting up from a chair, walking, shifting weight onto one leg. There will be rest breaks during the testing. All testing will be conducted on two occasions at either at the Physical Activity Centre or the RJ Williams Building at the University of Saskatchewan. You can wear your regular street clothing, but we will ask you to wear either loose fitting pants or shorts and a short sleeved shirt for ease of movement and

measurement. The technician will ask you if you have any metal in your limbs, and the scan will not be done on that limb if metal is present. The testing procedures are described below:

First we will measure your height and weight along with the lengths of your non-dominant or non-fractured forearm (if you've experienced a fracture) and lower leg according to our standard procedures.

pQCT: Your non fractured or non-dominant forearm will be scanned with pQCT at one site at the forearm. Both upper arms will be scanned at one site. You will be sitting on a chair during the scanning. Then your lower leg will be scanned at two sites: one scan of the ankle and another one at the site that corresponds 2/3 of the leg length. A total of 7 scans will be performed. This will take approximately 30 - 40 minutes.

HR-pQCT: We will also scan your non fractured or non-dominant forearm at the wrist and lower leg at your ankle with our new high resolution pQCT. You will be sitting on a chair during the scanning. A total of 2 scans will be performed, taking approximately 30 minutes to complete

DXA: a dual energy X-ray absorptiometry scan of your bones for the hip, spine and both forearms will be performed. We will also do a whole body DXA scan to assess fat and lean (i.e. muscle) mass. All of these tests take approximately 20 minutes in total. This machine is standard for measuring bone density. This involves lying still on a padded table in your street clothes (any metal or jewelry removed) while a measurement arm on the machine scans you from above.

Grip Strength: Grip strength will be assessed by having you squeeze a hand-held dynamometer (a measuring instrument used to assess your grip strength). You will be required to make three maximal grip contractions. The contractions will be 2-3 seconds in duration and each separated by 1 minute of rest. If you have had a wrist fracture, your non-fractured arm will always be tested first. You will be asked to complete a practice repetition to become familiar with the testing protocol. You will also complete sub-maximal contractions of each strength task to minimize the learning effect associated with each testing procedure.

Balance and functional task testing: You will be asked to perform several tasks such as standing with eyes open and closed on a foam block, looking over your shoulder, turning in a circle, balancing on one leg, picking up objects and standing with one foot in front of the other (Berg Balance Scale), walking a set distance (walking 10 m at a usual and quick pace) and standing up from a chair and walking 3 meters, turning around and sitting down again (Timed Up and Go Test), and walking backwards along a line or beam anchored on the floor. You will also be asked to move from sitting to standing as many times as you can in 30 seconds (30 s Chair Stand). Other functional tests will include the Physical Performance Test which includes some activities of daily living such as picking up small objects and putting on a coat. For the balance testing, you will be wearing a safety belt around your

waist, so that if at any time you feel that you are losing your balance, the research assistant will assist you.

Questionnaires: There are 7 questionnaires you will be asked to complete. These questionnaires include information about your medical history, how confident you feel doing a variety of day to day tasks in the home and out in the community, hand and arm function for daily tasks, food eaten in the past 7 days, and physical activity involvement.

The balance, function, strength tests and the questionnaires will take approximately 2 hours in total.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?
Although you may not personally benefit from the study, involvement in this study will be an important contribution to scientific knowledge of bone properties and fall risk in women 50 years of age and older.

ARE THERE POTENTIAL RISKS AND DISCOMFORTS?
Side effects that may occur as a result of involvement in this study include: mild joint discomfort after testing, or some fatigue following testing. This will be minimized by having you perform a gentle warm-up (i.e. stretching) before exercise testing. When doing balance testing, there is a remote possibility of losing your balance and stumbling or falling. The tester will be close to you at all times and you do not have to perform any tasks that you feel uncomfortable doing. Testing has been spread over two days and has been carefully designed to avoid any of these risks or discomforts from occurring. There is a certain amount of radiation exposure from the peripheral computed tomography scans and the dual energy X-ray scans. However, this radiation exposure is small due to minimal presence of radiosensitive tissues at peripheral sites. The total amount of radiation from the study is low (less than 14microSv). This amount is approximately 28% of the amount of radiation you would receive from taking a trans-Atlantic flight from North America to Europe (50 microSv), or approximately 10% from what you would receive from a routine full-mouth dental X-ray (80-150 microSv).

There may be other unforeseeable risks associated with this study. You will be responsible to inform the primary investigator or research personnel about any new health concerns you have during the course of the study. As well, you may be asked to visit your family physician or give permission to contact your physician if the investigators have any concerns about your health during the study.

WHAT HAPPENS IF I DECIDE TO WITHDRAW?
Your participation in this study is entirely voluntary. You may withdraw from the study at any time with no loss of benefits or penalty and your future medical care will not be affected. If you choose to enter the study and then decide to withdraw at a later time, all data collected will be retained for analysis. If you choose to not participate in this study or decide to withdraw, the investigator will discuss alternative ways of obtaining bone and fall

risk assessments. If you are part of the Distal Radial Fracture Clinic, your orthopedic surgeon will follow your progress and will discuss these options with you.

WILL I BE INFORMED ABOUT THE RESULTS OF THE STUDY?
Following the conclusion of the study (anticipated by December, 2013), you will receive a report in the mail summarizing the results of the study. Group results may also be disseminated in presentations at research conferences and through publication. In the event that any individual test scores might present as a health concern (i.e. DXA scores), we will notify your physician.

WHAT WILL THE STUDY COST ME?
You will not be charged for any research related procedures. You will not be paid for participating in this study. You are expected to transport yourself to and from the testing site, but an honorarium will be provided to partially cover your parking or transportation expenses.

WHAT IF SOMETHING GOES WRONG?
In the event that you become ill or injured as a result of participating in this study, necessary medical treatment will be made available at no additional cost to you. You should seek immediate medical attention if you have any medical concerns. By signing this document you do not waive any of your legal rights.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
The researchers will protect your privacy, and safeguard the confidentiality of information collected about you during the course of this study. Absolute confidentiality cannot be guaranteed. Identification will only be by your initials and an assigned study number. Reports based on results of this study may be presented for medical and scientific publication, but your identity will not be disclosed. With your permission, your physician may be informed of your study participation and, if required, consulted regarding your health and treatment.

WHO DO I CONTACT IF I HAVE ANY QUESTIONS?
If you have any questions about the study, you can contact: Dr. Cathy Arnold @ 966-6588.

If you have any questions about your rights as a research subject or concerns about the study, you should contact the Chair of the Biomedical Research Ethics Board, c/o the Office of Research Services, University of Saskatchewan at (306) 966-4053

UNIVERSITY OF SASKATCHEWAN

CONSENT TO PARTICIPATE

STUDY TITLE: The Relationship of Bone Architecture and Strength to Fall and Fracture Risk in Women with and without a History of Wrist Fracture

Please read the following carefully before signing the consent form:

- I have read (or someone has read to me) the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I understand that I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future relationships.
- I give permission to the use and disclosure of my de-identified information collected for the research purposes described in this form.
- I understand that by signing this document I do not waive any of my legal rights.
- I will be given a signed copy of this consent form.
- I would be willing to be contacted at a future date for follow-up, or a subsequent study that I may be eligible for _____YES _____NO
- I agree that my family physician can be informed of my participation in this study and, if required, contacted regarding my health__YES _____NO
- I do not have a family physician (put a check mark if applicable) _____.
- I agree that photo images of myself (with no identifiers) can be used for research presentations and/or teaching purposes. No image data that identifies me would be used in any publications related to this study. _____YES _____NO

I agree to participate in this study:

Printed name of participant: Signature: Date

_____ _____ _____

Printed name of person obtaining consent: Signature Date

_____ _____ _____

APPENDIX E. Falls Questionnaire

Subject ID: _____
Date: _____ /_____ /_____
Initials_____

FALL HISTORY QUESTIONNAIRE

- Have you had any falls (*refer to definition*) in the past YEAR?

  A fall is defined as coming to rest on the ground or at another lower level with or without loss of consciousness or injury.

  NO ____ YES ____ How many? _____ (*if **yes**, complete rest of page)*

- **MOST RECENT (First Fall):**
  What time? _____ AM / PM
  What were you wearing on your feet? _____

- **SECOND FALL:**
  What time? _____ AM / PM
  What were you wearing on your feet? _____

- **THIRD FALL:**
  What time? _____ AM / PM
  What were you wearing on your feet? _____

• **Where did you Fall?**	**1st fall**	**2nd fall**	**3rd fall**
Getting in/out of bed	_____	_____	_____
Getting on/off a chair	_____	_____	_____
Getting in/out of shower or bath	_____	_____	_____
Getting on/off toilet	_____	_____	_____
Walking in my house	_____	_____	_____
Going up or down stairs in my house	_____	_____	_____
Going up/down steps or stairs to get in or out of my house	_____	_____	_____
On level ground outside (*where*_____*)*	_____	_____	_____
On uneven ground outside (*where*_____)	_____	_____	_____
Walking outside	_____	_____	_____
At a curb	_____	_____	_____
In a public building	_____	_____	_____
Getting in or out of a vehicle	_____	_____	_____
Other (please state): _____	_____	_____	_____

- **What symptoms did you have before or when you were falling?**
  1st fall: _____

  2nd fall: _____

  3rd fall: _____

• **Why did you fall?** (*Check all that apply)*	**1st fall**	**2nd fall**	**3rd fall**
Tripped			
Slipped			
Not paying attention			
Doing more than one thing (eg: talk & walk)			
Lost balance			
Legs gave out			
Felt frail/weak			
Felt dizzy			
Unsure			
Weather (rain, ice, snow)			
Being careless			
Rushing			
Not using my walker/cane			
Other:			

• **Injuries** (*check all that apply for each fall*)	**1st fall**	**2nd fall**	**3rd fall**
Bruises (*in general*)			
Cuts/Scrapes			
Wrist: Bruised ___Broken ___(*check which apply*)			
Hip: Bruised ___ Broken ___(*check which apply*)			
Ribs: Bruised ___Broken ___(*check which apply*)			
Back Pain			
Bumped Head			
Other:			

APPENDIX G. Demographic and Medical History Questionnaire

Subject ID: _____
Date: _____ /_____ /_____
Initials_____

DEMOGRAPHIC AND MEDICAL HISTORY QUESTIONNAIRE

Name of Family Physician: (if known) _____
Clinic: _____

Which of the following best describes your place of residence? (Check off all that apply)

☐ House ☐ Apartment or condo ☐ Senior residence ☐ Other

☐ Live alone ☐ Live with another adult

For the following questions,
Please fill in the blanks, circle or check your response

1. Are you experiencing any of the following symptoms today or have experienced them within the last few days?

Symptoms		
1. Dizziness when getting up from a chair or bed?	YES	NO
2. Any Light-headedness	YES	NO
3. Chest pain	YES	NO
4. Shortness of breath	YES	NO
5. Nausea or vomiting	YES	NO
6. Fainting	YES	NO
7. Blurring of vision	YES	NO
8. Extreme fatigue	YES	NO
9. Muscle weakness	YES	NO
10. Muscle Cramping	YES	NO
11. Unusual or severe pain of any kind	YES	NO
12. Any other symptoms or concerns you are worried about (please explain to staff present)	YES	NO

2. Have you ever been diagnosed as having any of the following conditions? (check off all that apply)

Conditions	✓	**Approximate year of onset**
• Heart Attack		
• Transient Ischemic Attack		
• Angina (chest pain)		
• High blood pressure		
• Stroke		
• Peripheral Vascular Disease		
• Diabetes		
• Neuropathies (problems with sensation)		
• Respiratory Disease		
• Parkinson's Disease		
• Multiple Sclerosis		
• Polio/Post Polio Syndrome		
• Epilepsy/Seizure		
• Other neurological conditions		Describe:
• Any other balance disorders		Describe:
• Osteoporosis		
• Rheumatoid Arthritis		
• Other arthritic conditions		Describe:
• Uncorrected Visual problems		
• Inner ear problems/ear infections		
• Cancer		
• Joint Replacement		
• Cognitive condition		
• Any other health problems		

3. Do you require eyeglasses? *(Circle one)* YES NO

4. Do you require a hearing aid? (*Circle one)* YES NO

5. Do you currently smoke? *(Circle one)* YES NO

6. If you consume alcohol, how much do you typically consume per day? _____
per week? _____

7. Have you required emergency medical care or hospitalization in the past 2 years? *(Check one)*

   YES ☐ NO ☐ NOT SURE ☐

   If YES, explain why_____

8. List all prescription medications that you currently take (include any hormonal replacement therapy (HRT), birth control pills, glucocorticoids (cortisol or hydrocortisone) and any medications for osteoporosis or other health conditions

Name	Dosage	For what reason

9. List all over-the-counter medications that you currently take. (Pain killers, antacids, allergy pills and hydrocortisone creams or supplements (vitamins) are all examples of over-the-counter medications)

Name	Dosage	For what reason

10. Have you ever had a wrist fracture? *(Check one)*

    YES ☐ NO ☐ NOT SURE ☐

If yes, please indicate the body site and date:

Left or Right *(Circle one)* Date: (mm/yy) _____/_____

If yes, did you require surgery:

If yes, please indicate if you have had physiotherapy:

Where: _____

Number of treatment sessions: _____

What type of therapy: exercise instruction, stretching, hands on "mobilizations", other (describe) _____

_____

11. Have you ever had any other broken bones or stress fracture? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

If yes, please indicate the bone and date:

Bone _____

Left or Right (Circle one) Date: (mm/yy) _____/_____

12. Has your father or mother fractured his/her hip? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

13. Have you ever been treated for or diagnosed with arthritis or other joint or bone disease? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

If yes, please explain: _____

14. Have you menstruated in the past 12 months? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

If yes, have you menstruated in the past 3 months? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

15. If yes, has the length of your cycle become less predictable in the past year? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

If no, when did you stop menstruating? Date: (mm/yy) _____/_____

16. Have you used any female hormones in the preceding 3 months? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

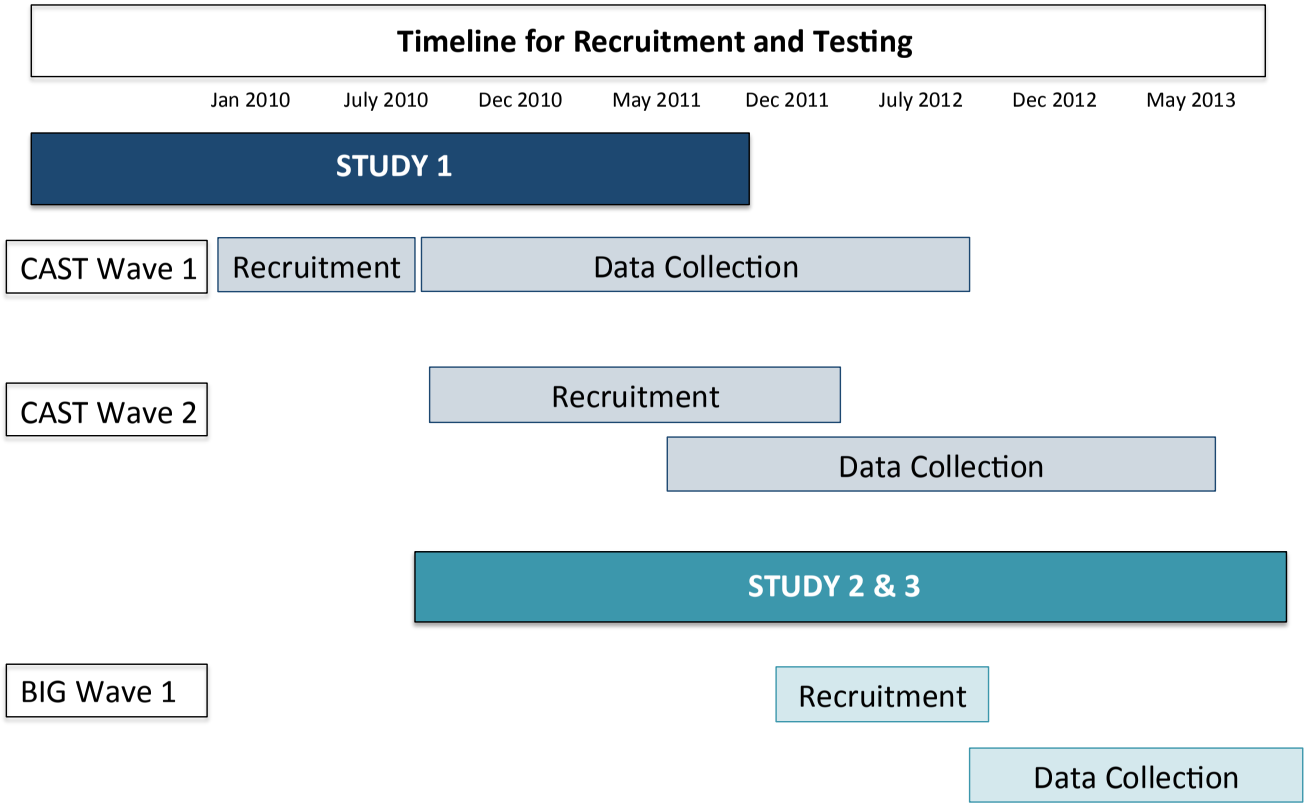
If yes, please fill in the question #9.

17. Have you had your uterus (hysterectomy) or both ovaries removed**?** ? *(Check one)*

YES ☐ NO ☐ NOT SURE ☐

Thank-you for completing this questionnaire!

APPENDIX H. Timeline for Recruitment and Testing


Timeline for Recruitment and Testing
Jan 2010
July 2010
Dec 2010
May 2011
Dec 2011
July 2012
Dec 2012
May 2013
STUDY 1
CAST Wave 1
Recruitment
Data Collection
CAST Wave 2
Recruitment
Data Collection
STUDY 2 & 3
BIG Wave 1
Recruitment
Data Collection

APPENDIX I. Publications Arising from this Thesis

Crockett, K., Arnold, C.M., Farthing, J.P., Chilibeck, P.D., Johnston, J.D., Bath, B., Baxter-Jones, A.D.G., Kontulainen, S.A. (2015) Bone strength and muscle properties in postmenopausal women with and without a recent distal radius fracture. *Osteoporosis Int*. DOI: 10.1007/s00198-015-3160-8

APPENDIX J. Copyright Permission Documents

Permission Request Letter to Stratec-Med

To whom it may concern:

I am currently writing my PhD thesis entitled Musculoskeletal Strength, Fall and Fracture Risk in Early Postmenopausal Women, which is scheduled to be published September 2015. I am writing to request permission to include the following material in my thesis publication:

Figure 17 – 8.2.5 Calculation of stability index SSI, page 55 of the XCT 2000 Manual

Title of the document: XCT 2000 Manual, Software Version 5.50

Publisher: Stratec Medizintechnik GmbH

Date of publication: 23.02.04

I would like to receive permission to use the above-mentioned material for this thesis, in all media and formats (both print and electronic publication) in English language. Please note that use in electronic format will be for versions which are equivalent to or substitute for the print version. By way of example, distribution in electronic form would be inclusion in a digital research collection.

I will make full acknowledgement to the XCT 2000 Manual in the usual manner, but please do provide any specific acknowledgement wording you would like me to use.

If you do not control the appropriate rights to this material, please advise to whom I should apply.

I would be most grateful if you would send me a signed copy of this letter to indicate that you will grant permission for this use on the terms requested by August 2015.

Many thanks for your assistance.

Yours sincerely,

Katie Crockett, PhD candidate
University of Saskatchewan

As the authorized rights-holder of the above-mentioned material I hereby grant permission to re-use such material in accordance with the terms stated above.

Signature: Date: 16.6.2015

Name: Johannes Willnecker

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