FALLS AND FRACTURE RISK FACTORS AFTER DISTAL RADIUS FRACTURE

RECOVERY OF MODIFIABLE RISK FACTORS AT FOUR YEARS FOLLOWING DISTAL RADIUS FRACTURE AND THEIR ROLE AS PREDICTORS OF BONE MINERAL DENSITY, SUBSEQUENT FALLS AND OSTEOPOROTIC FRACTURES

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TITLE: **Recovery of modifiable risk factors at four years following distal radius fracture and their role as predictors of bone mineral density, subsequent falls and osteoporotic fractures**

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LAY ABSTRACT

Wrist fractures are the most common fall-related fragility fractures and often an early indicator of future falls and fractures. This thesis project described recovery patterns in various risk-factors at 4-years after wrist fracture and explored their association with bone mineral density (BMD) and subsequent falls and fractures. We found that the majority of recovery in fracture-specific pain/disability, fear of falling and health-status takes place within six months, although small changes were also noted between 6 months-4 years. People with low unaffected hand grip-strength might have low BMD. Furthermore, people with poor balance, greater fracture-specific pain/disability, osteopenia or osteoporosis and a prior history of multiple falls (≥2) had nearly 3 times higher odds of secondary falls and those with osteopenia or osteoporosis had 4 times higher odds of a secondary fracture. We believe this information will help therapists/clinicians to identify people at risk of future falls/fractures and offer preventive services.

ABSTRACT

Distal radius fracture (DRF) is one of the most common fall-related osteoporotic (OP) fracture and is an early predictor of subsequent falls and OP fractures among people with DRF. The majority of older people with DRF present with low bone mineral density (BMD) and there is often transition to reduced muscle strength, poor balance, fear of falling and physically inactive lifestyle after fall-related DRF. This thesis consists of three manuscripts which are aimed to explore the recovery patterns and the role of modifiable risk factors in predicting subsequent falls, OP fractures and BMD in patients with DRF.

The first manuscript explores the recovery patterns in modifiable risk factors for falls and OP fractures over four years in patients with DRF. Our study findings showed that patients with DRF experienced both short-term (6 months) and long-term (4 years) improvement in fracture-specific pain/disability, physical activity, fear of falling, BMD and general health status; although the majority of the recovery was achieved at six months after DRF.

The second manuscript is a cross-sectional study identifying modifiable risk factors for BMD in patients with DRF. The unaffected hand grip strength was identified as the independent predictor of BMD explaining 17% and 12% of total variability in the BMD-femoral neck and BMD-total hip, respectively. Among age-stratified women with DRF, balance and unaffected hand grip strength were identified as independent determinants of BMD explaining 10% and 32% of the total variability in BMD-femoral neck among 50-64 year and 65-80 year old, respectively.

The third manuscript is a longitudinal study identifying modifiable risk factors for subsequent falls and OP fractures at four years after DRF. The results suggest that nearly 24% of patients reported one or more subsequent falls (in the last six months) and 19% of patients experienced at least one subsequent OP fracture after DRF. Patients with poor balance, low BMD, fracture-specific pain/disability of >81 points on patient-rated wrist evaluation questionnaire and presence of a prior history of multiple falls (≥2) had three times higher odds of subsequent falls. When adjusted for BMD, age and gender, only prior falls was identified as a significant independent predictor of subsequent falls. We were not fully powered to explore association of various modifiable and non-modifiable risk factors with subsequent fractures. However, we found that patients with osteopenia or osteoporosis had clinically four times higher odds of subsequent OP fractures than patients with normal BMD.

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ABBREVIATIONS AND SYMBOLS

ANOVA	Analysis of Variance
AUC	Area under curve
BBS	Biodex Balance system
BMD	Bone mineral density
BMD-FN	Bone mineral density at femoral neck
BMD-TH	Bone mineral density at total hip
CI	Confidence interval
CIHR	Canadian Institute of Health Research
CPGs	Canadian Clinical Practice Guidelines
DEXA	Dual-Energy X-ray Absorptiometry
DRF	Distal radius fracture
ED	Emergency department
ES	Effect size
FOF	Fear of falling
FRT	Fall risk test
HS	Health status
HULC	Hand and Upper Limb Centre
ICC	Intraclass correlation coefficient
KE	Knee extensor
LE	Lower extremity
LL	Log likelihood
LS	Lumbar spine
MCS	Mental component summary
MCID	Minimal clinically important difference
MFES	Modified Fall Efficacy Scale

NA	Not Applicable
ND	Non-dominant
NICE	National Institute for Clinical Excellence
NOF	National Osteoporosis Foundation
NORA	National Osteoporosis Risk Assessment
NS	Non-significant
OP	Osteoporotic
OR	Odds Ratio
PA	Physical activity
PF	Plantar flexion
PCS	Physical component summary
PMW	Postmenopausal women
PRWE	Patient-Rated Wrist Evaluation
PST	Postural stability test
QoL	Quality of Life
RAPA	Rapid Assessment of Physical Activity
ROC	Receiver-Operator Characteristic
SD	Standard deviation
SF-12v2	12-item Short Form Health Survey
TH	Total Hip
TUG	Timed Up and Go Test
US	United States
USD	United States Dollar
VIF	Variance Inflation Ratio
WHO	World Health Organization
p	Level of significance
w.r.t.	With respect to

6m	6-month
4y	4-year
**	Significant at $p < 0.001$
*	Significant at $p < 0.05$
B	Unstandardized regression coefficient;
β	Standardized regression coefficient
r	Pearson correlation coefficient
r_p	Partial correlation coefficient
R^2	Coefficient of determination

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is a sandwich thesis consisting of 3 manuscripts prepared for peer reviewed publication. The student contribution in each manuscript is described below.

For all 3 manuscripts, Neha Dewan conceptualized the research questions, study design, data collection (where applicable as in manuscript 1 and 3), data analysis, writing and revising the drafts of the manuscripts.

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CHAPTER ONE

INTRODUCTION

Falls and Osteoporotic Fractures

Falls are very common among older adults.[1] The National Institute for Clinical Excellence (NICE) guidelines has defined falls as "an event whereby an individual comes to the ground or another lower level with or without loss of consciousness."[2,3] In North America, an older adult is admitted to the emergency department (ED) due to fall-related injuries every 11 seconds and dies from a fall every 19 minutes.[4] Approximately, 2.8 million Americans are annually treated in the ED due to fall-related injury.[5] Further, researchers predict that by 2020, nearly four million elderly Americans will have a fall every year[6] and about 12% of these falls will lead to serious injuries requiring hospital ED admission.[7,8] According to the World Health Organization (WHO) report on global burden of disease, fall-related injuries are the second leading cause of accidental deaths.[9] Furthermore, Nevitt et al. reported that nearly 57% of older adults had another fall in the year following their initial fall.[10] One in five falls may lead to serious injuries including fractures or head injury.[11,12] Nearly, 90% of all fractures result from a fall, typically from a standing height or lower.[13] The fractures which occur from such low energy trauma are considered fragility or osteoporotic (OP) fractures.[14–16]

According to the WHO, osteoporosis is defined as "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture."[17] As a consequence of bone fragility, people with osteoporosis are often at an increased risk of OP or fragility fracture after an episode of low energy trauma, such as a fall from a standing height or less.[17] In Canada, the annual risk of OP fractures is higher than breast cancer, stroke and heart attack combined.[18,19] It is estimated that one in three Canadian women and one in five men over the age of 50 years will experience at least one OP fracture in their lifetime.[18,20,21]

Economic burden due to falls and OP fractures

In 2013 alone, the direct medical cost of fall injuries for people aged 65 or older reached $34 billion in United States (US).[22,23] This creates a high economic burden on the health care system. Woolcott et al. reported that the average cost per fall leading to a visit of a patient to the ED in Canada is $11,408 and the average cost per fall requiring hospital admission due to fall-related injuries approaches $30,000.[24] The estimated cost of treating a fall is 1.85 times higher than implementing a fall prevention program.[25] A physiotherapy intervention of in-patient fall risk screening and patient education was shown to result in 2.2 lower falls per 100 patients; and a cost savings of $2,704 per 100 patients treated.[26]

Globally, OP fractures occurs every 3 seconds resulting in about 25,000 fractures daily.[27] OP fractures are so common that 1 in 2 women and 1 in 5 men over 50 years of age will suffer one in their lifetime.[28–30] Worldwide, during the year 2000, there were an estimated 9 million new fragility fractures, of which 1.6 million were at the hip, 1.7 million at the wrist, 0.7 million at the humerus and 1.4 million symptomatic vertebral fractures.[31] It is estimated that the annual osteoporotic fracture care costs nearly a sum of 20 billion USD and 32 billion EUR in the US and Europe, respectively.[27]

Distal radius fracture (DRF)

Mechanism, incidence and socioeconomic burden

A distal radius fracture (DRF), commonly referred to as a “Colles fracture”, is a fall-related low energy fracture of the distal radius seen at the cortico-cancellous junction about 2 cm above the distal articular surface.[32] It is most commonly caused by a fall on an outstretched hand from a standing height or lower among people over 50 years of age.[33] Recent data from the largest long bone fracture study done in the US on 208,094 patients reported the radius as the commonest long bone to fracture followed by tibia, humerus, multiple bones, hip and femur.[34] In United States, DRF has accounted for one sixth of ED visits and 26 to 46 % of all skeletal fractures seen in the primary health care setting.[35] The annual incidence of distal forearm fractures in males and females was reported as 1.7 and 7.3 per 1000 person-years, respectively, in European population[36] and > 39/10000 persons/year in developed countries.[30,37] The incidence of DRF is increasing, contributing to considerable medical, social and economic burden.[38] In the US, the annual cost of $ 1.1 billion is attributed to the treatment of DRF associated with osteoporosis.[39] The life time risk of DRF is estimated to be 15% and 2% in white females and males, respectively, over the age of 50 years.[34,40] In Canada, the 10-year risk of a forearm bone fracture is reported to be 6.6% among 75-84 year old females and 2.2% in males, respectively.[41] It is reported that white race, female sex over the age of 60 years and presence of osteoporosis are high risks factors for low energy fracture of the distal radius bone.[42] The risk of mortality after DRF increases with age; ranging from 12% among women aged 50-64 years to 43% for elderly women (>85 years or older).[43]

Treatment and Rehabilitation after DRF

The majority of DRFs are treated conservatively. The conservative management of DRF primarily consists of immobilization in a brace or a plaster/fiberglass cast for 3-6 weeks.[32,44] The surgical management of DRF consists of closed or open reduction, followed by internal or external fixation, with or without an associated period of immobilization.[45] The optimal bony union following DRF is ideally achieved within 4–8 weeks, substantial healing is achieved by 8–12 weeks, and full healing with remodeling of the underlying bone may take 6–12 months.[46] The patients are often considered appropriate for rehabilitation as soon as bone healing is visible on radiographs.[47] Usual referral for a postoperative rehabilitation program is recommended at 4–6 weeks.[48] Studies have shown that usually patients gain optimal strength, movement, and function within 3–6 months.[49–51] However, complications such as ongoing hand stiffness, complex regional pain syndrome, malunion, and delayed return to work often prolong the rehabilitation phase.[47,52,53]

Post-immobilization, the rehabilitation of patients with DRF is primarily aimed towards improving wrist hand pain, grip strength and hand function.[52,54,55] Bruder et al. reported findings from a survey indicating that advice and a structured home exercise are the most commonly administered physiotherapy intervention for patients with DRF.[56] Despite this, there is only one low quality trial which showed improved function with advice and a structured home exercise program when compared to a control group with no intervention after plaster cast removal.[45,57] Furthermore, a recent Cochrane review suggests that there is insufficient evidence on the best form of rehabilitation for patients with DRF.[45]

Moore et al. reported that nearly 11% of patients with DRF complained of severe pain and 63% of patients with DRF had some degree of pain at 1 year after DRF.[53] Another study has shown that over a follow-up period of 7.6 years after the DRF, nearly 15% of women present with clinically important (odds ratio 1.48, 95% confidence interval 1.04 to 2.12) functional decline.[58] The results from a recent study suggests that the majority of patients regain their function at one year after DRF but a minority of patients complain of persistent pain at rest and during activity at two years after DRF.[59] However, there are a few studies suggesting that some patients might never regain pre-fracture upper extremity functions which might have an impact on quality of life (QoL).[51,60,61] Also, it was interesting to note that patients with DRF perceive themselves as healthy and having good QoL prior to DRF.[60] In a 2-year follow-up study done on 86,128 postmenopausal women (PMW), low QoL was reported among females 50-64 years of age with wrist fractures compared to women who did not fracture.[60] This suggests the need to evaluate the QoL as an important measure post-DRF.

Overall, there is marked variability in the surgical treatment, rehabilitation and functional outcomes among patients with DRF. The clinical practice guidelines for rehabilitation of DRF also suggest weak evidence to support current conservative, surgical management and rehabilitation following DRF.[62] Under the domains of WHO International Classification of Functioning framework, the outcome assessment and rehabilitation of patients with DRF is primarily impairment based, with a focus on body structure (wrist hand pain) and function (grip strength, range of motion/wrist hand function). However, the rehabilitation framework of DRF rehabilitation needs attention towards activity, participation and bio-psychosocial domains.[47,52]

DRF as an early indicator of poor bone health, subsequent falls and OP fractures

Patients with DRF who are otherwise healthy have been reported to have a preferential bone loss at the distal forearm and generalized low bone mineral density (BMD) indicating poor bone health state.[63] Low BMD has been reported in 70-80% of patients with a wrist fracture.[64,65] It has been well documented that a history of a prior fall is a strong risk factor for subsequent falls and is often referred to as the gold standard for assessing the future fall risk in older adults.[2,10,66–68]. Considering that DRF among older adults is primarily fall-related, DRF is an early indicator for identifying those at risk of subsequent falls.[69–72] In a prospective cohort study of 52 patients with DRF, 24% of the patients had two or more new falls over a period of four months after the injury.[73]

Furthermore, first fractures are associated with an 86% increased risk of future fragility fractures.[74] Studies suggest that a prior history of fragility or non-fragility fracture is an alarming predictor for subsequent fractures within five years after the first fracture.[75] High quality evidence suggests that a DRF is an early and independent predictor of future OP fractures at other skeletal sites.[76,77] In a 3-year follow-up of 158,940 PMW, aged 50-98 years in the National Osteoporosis Risk Assessment (NORA) study, it was reported that prior wrist fracture increased future fracture risk three fold for the wrist and two fold for OP fractures at other skeletal sites. This risk was independent of BMD or other common risk factors for OP fractures.[76] Furthermore, cohort data from Rochester, Minnesota suggests that a DRF is associated with increased risk of vertebral fractures, (five-fold for women; ten-fold for men)[78] and a two fold increase in hip fracture in women >70 years of age.[79] Hodsman et al. found that although the risk of subsequent fractures at ten years after DRF was substantially lower than after OP fracture at other skeletal sites, overall risk was significantly higher than those without fracture.[37]

Socio-economic Burden

In North America, the second fracture in Medicare patients aged 50 year or older costs nearly $1.3 billion every year.[80] Future OP fractures of the hip and spine after DRF can have a marked impact on morbidity, mortality and health care costs.[17,81,82] Twenty-eight percent of women and 37% of men who suffer a hip fracture die within the following year.[83] A vertebral fracture increases the risk of death by three times in the first and second year of follow-up.[81] Long-term pain, disability and fear of falling (FOF) resulting in seclusion, isolation, institutionalization, depression and mortality are higher following hip and spine fractures.[18] Taken together, subsequent falls and OP fractures can result in high physical, emotional and socio-economic burden.

Risk factors for poor bone health, subsequent falls and OP fractures after DRF

BMD is known to be a major predictor of bone strength and shows an inverse relationship with fracture risk, such that a decrease in BMD by one standard deviation is found to increase OP fracture risk by 1.5 to 3 times.[84–87] A recent study showed that 91 % of 106 PMW who had sustained a DRF met the WHO diagnostic criteria for osteopenia or osteoporosis when assessed for BMD using dual-energy X-ray absorptiometry (DEXA) scan.[64] Another study has noted a significant decrease in BMD at six weeks of follow-up, with a mean loss of 9% ($P < 0.001$) which remained decreased at one year after DRF.[88] The current clinical practice guidelines from Canada[17] and the US[89] recommend BMD assessments among patients with prior fragility fractures. However, there is some controversial evidence regarding use of BMD for fracture risk assessment. The NORA study and meta-analysis from an international study explain that BMD is a minor risk factor given clinical risk factors such as prior fragility fracture.[76,90]

As described in previous studies, fall-related DRF places the patient at a high risk for subsequent falls[72,73,77] and fragility fractures.[76,91] This is because, after fall-related DRF, patients often transition to a physically inactive lifestyle due to pain, disability and FOF, which is theorized to increase bone loss and decrease effectiveness of protective responses through the deterioration of muscular strength, balance, coordination, and reaction time.[72,92–98]

Physical inactivity[99], muscle weakness, postural instability[100] and FOF[101] have been previously well documented as modifiable risk factors for subsequent falls and fractures among the older adults. Apart from modifiable risk factors, non-modifiable risk factors such as age[102–105], gender[99,106,107] and a prior history of multiple falls[100,101,103,105,108] have been identified as important risk factors for falls and fractures among older adults. However there are no studies describing the role of these modifiable and non-modifiable risk factors for subsequent falls and OP fracture prediction among patients with DRF.

Knowledge to practice gap

Nearly 93% of DRF are due to a fall-related injury.[109] Often, there is an interval between fall-related DRF and subsequent falls during which time, their physically inactive lifestyle, high FOF, impaired muscle strength and postural stability makes the patient prone to subsequent falls and fractures. Currently, most of the research in the rehabilitation of DRF is focused on evaluating changes in fracture-specific pain/disability, hand grip strength and function. Systematic reviews of randomized controlled trials have shown that 15% of falls can be prevented by multi-factorial fall risk screening.[110] The intervention studies have reported a reduction in falls up to 50%.[111] There is high quality evidence suggesting that exercise programs focused on improving modifiable risk factors such as physical activity (PA), muscle strength, postural balance and BMD can prevent subsequent falls and OP fractures among elderly.[112–118] Furthermore, there are reviews supporting the knowledge creation of evidence-based screening tools[70,72], clinical decision tools[119,120] for subsequent fall/fracture risk assessment and high quality trials[118,121–124] on prevention strategies specific to patients with DRF. Nonetheless, audits conducted in Ontario[125] Quebec[14] and Manitoba[126] consistently reported that nearly 80% of patients with fragility fracture did not receive appropriate screening and management for osteoporosis. Our recent survey data (abstract published) suggests that both hand and physical therapists have knowledge and skills for assessment and treatment of modifiable risk factors which can be used to identify at risk patients with DRF. [127] But, the majority of the therapists (~75%) do not identify at-risk people during the critical window between initial DRF and subsequent falls and OP fractures.[127] Despite the fact that people with DRF are at risk of subsequent falls and OP fractures and we have reliable and valid measurement tools for subsequent fall and OP fracture risk screening,[119] there are no studies evaluating the long-term expected pattern of recovery in fracture-specific pain/disability, fall risk factors such as PA, FOF, health status (HS) and BMD. The assessment of risk factors for subsequent falls and OP fractures is often missed in clinical as well as research publications evaluating outcomes among patients with DRF.[55,72] We believe that data on the description of baseline status and prospective changes in modifiable risk factors will provide a useful piece of information to therapists about the course of recovery which can be expected in patients with DRF. This would help them to guide their agreement needed to focus on subsequent fall and OP fracture prevention for patients with DRF.

The Canadian Clinical Practice Guidelines (CPGs) and National Osteoporosis Foundation (NOF) clinician's guide for prevention and treatment of osteoporosis clearly states that patients over 50 years of age with a prior history of OP fractures such as hip or vertebral fractures must be assessed for BMD using DEXA.[17,128] Furthermore, numerous studies support screening of DRF patients for BMD and intervening as required to prevent future OP fractures.[64,70,72,95] There are studies supporting that BMD testing might aid clinical decision making for reducing subsequent fractures among patients with fragility fractures including DRF.[124,129] Surprisingly, CPG from the American Academy of Orthopedic Surgeons and systematic reviews summarizing effective treatment and rehabilitation of DRF do not report this recommendation.[62,130] Also, studies from the US[131–133] Canada[125,134], Ireland[135] and many other countries[136,137] reported that only 10-20% of patients with wrist fractures were assessed and treated for osteoporosis. The cost and accessibility to DEXA could be an important concern due to lack of agreement regarding medical coverage especially among middle aged, paradoxically healthy individuals such as those with DRF.[84] Considering that it is important to identify patients with DRF who are at risk of low BMD, it could be a useful approach to investigate the modifiable factors which could influence BMD among patients with DRF. There are studies evaluating modifiable risk-factor which can predict BMD among patients with stroke[138], diabetes[139], healthy post-menopausal women[140] and older adults[141], but there are yet no studies evaluating risk factors which can predict BMD among patients with DRF.

Similarly, high quality research in the last few decades has emphasized identification[100,101,142–145] and physical therapy management[112–116,146] to mitigate multiple modifiable risk factors as a means of reducing the burden of falls and OP fractures in community-dwelling elderly[100,101,143], PMW[100,101,143,145] and people with hip fractures.[142,144] However, there is limited evidence to quantify which of these modifiable risk factors are an early and sensitive indicator of subsequent falls, OP fractures and poor bone health in the fall-related DRF population who are relatively young and potentially healthier. The most widely cited fracture risk prediction tools such as fracture risk assessment tool[147] and Garven model[148] assess 5-10 year absolute fracture risk and do not include modifiable risk factors related to physical functioning such as balance, muscle strength, PA, FOF, and self-efficacy which can be easily targeted in physical/hand therapy practice for future fall and OP fracture prevention.

A 2010 narrative review published on hand therapy management of DRF suggested that therapists have unique training skills and opportunity to screen and intervene the patients with DRF with a significant fall risk.[72] Furthermore, academic curriculum and basic training of physical therapy education includes assessment and treatment of risk factors related to falls and osteoporotic fractures.[77,149,150] However, over the course of specialization, therapists have not continued to use these skills and miss the opportunity to prevent subsequent falls and OP fractures during the rehabilitation of patients with DRF.[55,56,72,92]

Given that there is a well-established relationship between DRF and subsequent falls and OP fractures at other skeletal sites within three to four years,[76] physical therapists need clear information and understanding on the risk factors which can be used to identify those who are at risk of future falls and OP after a DRF. To the best of our knowledge, we have conducted the first long term prospective study exploring the role of common modifiable risk factors (independently or in combination with BMD and non-modifiable risk factors) on subsequent falls and OP fractures in DRF population.

An ideal time to target this research

We believe now is the ideal time to conduct this research project due to many factors. DRF is the most common low trauma fracture and is early enough in the "slippery slope" that it is an ideal time to intervene for risk factor identification for subsequent fracture prevention. Few studies have evaluated the effect of modifiable risk factors such as balance[97] and physical performance[98] in the wrist fracture population. However, most of the existing evidence is cross-sectional.[93,96,97] Our proposed study builds on a previously completed Canadian Institute of Health Research funded study that evaluated change in PA and participation at 1-year following DRF.[120] Thus, high quality baseline data collected as part of the funded study allowed us to provide a good foundation to collect follow-up reports on modifiable risk factors, new falls and incident fractures at 4 years. Furthermore, availability of baseline data collected from January 2012 to December 2013 was well aligned with the timeline of PhD training of the primary investigator to conduct a long-term follow-up study in a timely and feasible manner.

Main focus of Thesis

Our primary focus in all the manuscripts included in this thesis is to provide objective evidence on the role of modifiable risk factors which can be addressed (assessed and intervened) in patients with DRF. We believe the quantitative information/knowledge and understanding on expected recovery patterns and the role of these modifiable risk factors to predict BMD, subsequent falls and OP fractures would shift the focus of rehabilitation towards implementing subsequent fall and OP fracture prevention for patients with DRF.

Specific objectives of the thesis manuscript

Manuscript 1: The purpose of this manuscript was to describe the status of fracture-specific pain/disability, fall risk factors (PA and FOF), BMD and general health and how these change over four years following DRF; and whether they differ with respect to gender, age and incidence of subsequent falls and OP fractures.

Manuscript 2: The purpose of this manuscript was to determine the extent to which modifiable risk factors such as balance, muscle strength, PA and fracture-specific pain/disability alone or in combination explains BMD and to investigate the independent predictors of BMD among an age-stratified sample of people with DRF

Manuscript 3: The purpose of this manuscript was to determine the extent to which baseline modifiable clinical risk factors such as balance, lower-extremity muscle strength, hand grip strength, PA, FOF, fracture-specific pain/disability, BMD and general health could predict subsequent falls and osteoporotic fractures in people at four years after DRF.

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CHAPTER 2.

RECOVERY PATTERNS OVER FOUR YEARS AFTER DISTAL RADIUS FRACTURE: DESCRIPTIVE CHANGES IN FRACTURE-SPECIFIC PAIN/DISABILITY, FALL RISK FACTORS, BONE MINERAL DENSITY AND GENERAL HEALTH STATUS

Title of Manuscript:

Recovery patterns over four years after distal radius fracture: Descriptive changes in fracture-specific pain/disability, fall risk factors, bone mineral density and general health status

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Ethics Approval: This study was approved by the Health Sciences Research Ethics Board (HSREB) of the University of Western Ontario in London, Ontario, Canada.

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Abstract

Study Design: Descriptive/Longitudinal cohort

Introduction: Distal radius fracture (DRF) is a common fall-related fragility fracture that is known to be an early and independent predictor of secondary osteoporotic (OP) fractures. Changes in falls risk status, bone status and general health has not been evaluated prospectively in a population that has sustained a DRF.

Purpose of the Study: The purpose of our study was to describe the status of fracture-specific pain/disability, fall risk factors such as physical activity (PA) and fear of falling (FOF), bone mineral density (BMD) and general health status (HS) in people with a DRF and how these variables changed over four years with respect to sex, age, incidence of subsequent falls and OP fractures.

Methods: Patients (n=94) self-reported their fracture-specific pain and disability (Patient-Rated Wrist Evaluation), PA (Rapid Assessment of Physical Activity), FOF (Modified Fall Efficacy Scale), HS (12-item Short Form Health Survey) and completed dual-energy X-ray absorptiometry scan based BMD assessment (lumbar spine and total hip) at baseline (1-2 weeks post-fracture), six months and four years after DRF. Descriptive statistics and general linear models were used to describe changes in recovery patterns over four years.

Results: There was significant ($p<0.001$) improvement in fracture-specific pain/disability (60 points), FOF (1 point) and physical HS (11 points) between baseline and 4-year follow-up. There were no significant changes in PA and BMD. When stratified on age, sex, presence of subsequent falls and OP fractures, there were no significant differences in fracture-specific pain/disability, PA, FOF, and BMD at baseline, six months or four years after DRF. The physical

HS was significantly ($p<0.05$) less/poorer among those with subsequent falls (lower by 2-6 points) and fractures (lower by 5-6 points) compared to those without. Similarly, mental HS was significantly ($p<0.05$) poorer among people with subsequent falls (lower by 2-6 points) and in 50-64 year age group (lower by 3-5 points) than those without subsequent falls and in 65-80 year age group, respectively.

Conclusion: Post DRF, the majority of the improvement in fracture-specific pain/disability, FOF and HS was completed at six months and very small changes were observed between the six months and four-year follow-up.

Keywords: distal radius fracture, osteoporosis, bone density, wrist pain, health status, falls

Level of Evidence: NA

Introduction

The distal radius is one of the most commonly fractured long bones.[1] Distal radius fractures (DRF) account for one-sixth of all emergency department visits[1,2] and constitute 26-46% of all skeletal fractures observed in the primary care setting.[3–8] DRF are most commonly caused by a fall on an outstretched hand from a standing height or lower among people 50 years or older.[9] Studies suggests that elderly women are at a five times higher risk of DRF than men as a result of considerable secondary bone loss due to menopause.[10] During the recovery phase, many factors such as age, sex, injury compensation, education, pre and post-reduction radial shortening and joint involvement play an important role in predicting outcomes following DRF.[11] The overall recovery pattern after DRF is quite variable, but the majority of patients achieve optimal muscle strength, range of motion, and function within 3–6 months, regardless of whether the injury is managed conservatively or surgically.[12] However, 16 % of individuals have ongoing pain and disability at one year after DRF.[13,14] In some cases, complications such as ongoing hand stiffness, complex regional pain syndrome, mal-union and delayed return to work might prolong the rehabilitation phase.[14–16]

Among older adults, DRF is often low-energy fall-related fracture which puts the patient at risk of subsequent falls. Globally, it is estimated that nearly one in three people over 65 years of age fall every year.[17,18] Among community-dwelling older adults, 66 % of people tend to have another fall in the year following their first fall.[19] Though the etiology of subsequent falls is multifactorial, reduction in physical performance,[20] balance,[21,22] and increased fear of falling (FOF)[23] have been reported after a fall-related DRFs. Many studies have reported FOF as an independent risk factor for falls among older adults.[24–26] Another important issue after DRF is increased bone resorption.[27] Increased bone resorption or reduction in bone mineral density

(BMD) is considered an important marker of future osteoporotic (OP) fractures.[28–30] Prospective data from the National Osteoporosis Risk Assessment study reported that a previous DRF increased the relative risk of any secondary OP fracture more than two times compared with American women who did not have a prior DRF.[31]

It is estimated that nearly 21% of DRF patients retain long-term functional limitations indicating the potential that this injury may affect general physical and mental health status (HS).[12,32–34] Currently, rehabilitation of patients with DRF is primarily focused on assessment and treatment of wrist and hand function.[35–37] Similarly, the majority of the research studies have focused on evaluating changes in fracture-specific pain/disability as a measure of patient recovery and have not given much consideration to evaluate changes in fall risk factors (such as physical activity (PA) and FOF), BMD and general HS.[13,32,35,38,39] Given the fact that transition to a physically inactive lifestyle, high FOF, poor HS and reduction in BMD are important modifiable concerns which should be considered in rehabilitation of DRF, we realized the need for long-term prospective data to establish the course of recovery pattern in patients with DRF.

A few studies have prospectively evaluated the change in outcomes for fracture-specific pain/disability, function, and general HS in patients with DRF at six months,[13,38,39] one year,[13,39,40] two years,[41,42] six years[41,42] and ten years[41] of follow-up. To the date, we do not have long-term prospective evidence on the course of recovery in modifiable risk factors such as pain/disability, PA, FOF, BMD and general HS in a single dataset of patients with DRF. Furthermore, both age and sex are known to be important prognostic factors that could affect the course of recovery after DRF.[43] Studies have suggested that females and older individuals have shown poor recovery patterns in fracture-specific pain/disability and physical performance after DRF.[44–46] It might be that the DRF acts as a trigger event for a specific group of people to change their behavior because of the experience of the injury, or because of the fracture-specific pain/disability that persist after fracture healing. Therefore, it is important to understand if there are any differences in recovery patterns with sex, age, incident subsequent falls and OP fractures. The purpose of our study was threefold: i) to describe the status of fracture-specific pain/disability, fall risk factors (PA and FOF), BMD and general health; ii) to describe how these characteristics change over four years following DRF; and iii) to determine whether these characteristics differ with respect to sex, age, and incidence of subsequent falls and OP fractures.

Methods

Study Design and Study Population

This was a prospective cohort study conducted at the Roth-McFarlane Hand and Upper Limb Centre (HULC), London, Ontario. The study was approved by Research Ethics Board of University of Western Ontario. Patients (n=191) were aged 50-80 year old and diagnosed with DRF who had previously consented to baseline and 6-month (6m) follow-up assessments were invited to participate in this longer term follow-up study. The exclusion criteria were a) unable to respond to informed consent b) unable to complete assessment procedures and/or c) previous known history of neurological/cognitive impairments.

Procedure

At baseline and 6m of follow-up, a questionnaire on demographic characteristics, fracture-specific pain and disability, PA, FOF, health status and BMD assessment were completed by the patients during their hand clinic visit at HULC. For the final 4-year (4y) follow-up assessment, a package consisting of the letter of invitation, patient information sheet, consent form, self-reported questionnaires and a pre-paid envelope was mailed to the patients.

The self-reported questionnaires were used to obtain information on patient fracture-specific pain and disability, PA, FOF and general HS. A short questionnaire on the incidence of subsequent falls in the last 6m (n≥1; yes/no), the presence of a clinically diagnosed new fracture (after a first wrist fracture) at any site (n≥1; yes/no), and the nature of any fracture was also enclosed within the package. Patients were requested to return the completed questionnaires with the signed consent form in the stamped self-addressed envelope within two weeks. Up to two reminder phone calls were made by the principal investigator (ND) to all non-responders at 4-5 weeks after the first mail. Those patients who provided their informed consent and returned their mailed package were invited by a phone call to schedule an appointment for BMD evaluation at HULC. Those patients who failed to attend their scheduled appointment were phoned to reschedule the appointment at an alternate date of mutual convenience. In case of incomplete response on incidence of subsequent fall/fracture, participants were phoned to obtain their response. The patient's sex, age, occupation, body mass index, hand dominance, smoking, alcohol intake and education status were extracted from standard data record forms completed by the patients at baseline.

Outcome measures

Fracture-specific pain/disability

Fracture-specific pain and disability was assessed using the Patient-Rated Wrist Evaluation (PRWE), a standardized 15-item questionnaire.[47] The PRWE consists of 2 subscales evaluating pain and disability at the wrist and hand. The total score can range from 0-100 with a higher score indicating more pain and functional disability. The PRWE is a reliable (ICC>0.90)[47] and valid outcome measure (Standardized response mean=2.27) used to evaluate fracture-specific pain/disability in the DRF population.[48] An improvement by 11.5 points and 11 points is respectively considered as minimal clinically important difference (MCID) and minimal detectable change in PRWE scores for patients with DRF.[49]

Fall-risk factors

PA was evaluated using the 10-item Rapid Assessment of Physical Activity (RAPA) questionnaire.[50] The RAPA is a brief self-administered questionnaire used to assess a wide range of current level of physical activities ranging from sedentary to vigorous activity as well as strength and flexibility training in adults older than 50 years of age. Each question is answered as a yes/no response and a score ≥6 suggests a good level of physical activity. RAPA has good reliability and validity (when compared to Community Healthy Activities Model Program for Seniors) for physical activity assessment, particularly in the older adult with sensitivity=81%, positive predictive value=77%, and negative predictive value =75%.[50,51]

FOF was assessed using the Modified Fall Efficacy Scale (MFES), a 14-item questionnaire used to evaluate confidence in one's ability to avoid falling while performing activities of daily living. The reliability (ICC=0.93, Cronbach's alpha=0.95) and validity of the MFES have been well established in older adults. Subjects are asked to rate their confidence in performing each activity without falling on a scale ranging from 0 (not confident) – 10 (completely confident). The total score is computed as an average score across all 14 items, and a score of less than 8 indicates reduced confidence and high FOF.[52,53]

Bone mineral density

BMD was measured at the lumbar spine (L2-L4) and hip (left/non dominant) using dual-energy X-ray absorptiometry (DEXA) by a trained health professional at the HULC. DEXA is widely recognized as a gold standard method, [54,55] to measure BMD in men and postmenopausal women over the age of 50 years with acceptable accuracy errors, good precision, and reproducibility.[54] A DEXA measurement can be completed in about 5 min and involves minimal radiation exposure (about one-tenth that of a standard chest X-ray).[55] Areal BMD was expressed in grams per square centimeter. We selected BMD and T-score assessments from lumbar spine (LS) and total hip (TH). The LS is considered to be the best site to evaluate the effect of treatment or change in scores [54–56]; and some studies also reference the use of TH scans due to the larger area of bone coverage.[28,57,58] The T-scores which is "the difference between the measured BMD and the mean value of young adults, expressed in standard deviation (SD) for a normal population of the same gender and ethnicity" were recorded from the DEXA scans as given by the manufacturer.[55,59] The World Health Organization's (WHO) definition of osteoporosis was used to categorize the patients as normal with T-score of -1 or higher, osteopenia with T-score between -1 and -2.5 and osteoporosis with T-score of -2.5 or lower.[60]

For the DEXA scans available at HULC; the reference manual suggests that to ensure a significant change in T scores (LS or TH) at 95% confidence level over a period of one year, the expected precision at the T score is multiplied by 3 to account for any precision error. For actual T scores of 0 to 2.49, -2.5 to -3.5, less than -3.5, the expected precision is ± 0.010 g/cm^2, ± 0.015 g/cm^2 and ± 0.020 g/cm^2 respectively. To be 95% confident that significant change has occurred, we needed a change in BMD by ± 0.030 g/cm^2, ± 0.045 g/cm^2, ± 0.060 g/cm^2 respectively.[55]

General health status

General health was evaluated using the 12-item Short Form (SF-12v2) Health Survey, an improvised 12-item version of the 36-item Short Form Survey (SF 36). SF-12v2 is a generic self-report measure with well-established reliability and validity,[61–63] and is commonly used to measure the functional health and well-being from the patient's perspective. The 12 items of the SF-12v2 measure 8 health domains of the original 36-item questionnaire: physical functioning (2 items), role physical (2 items), bodily fracture-specific pain/disability (1 item), general health (1 item), vitality (1 item), social functioning (1 item), role emotional (2 items), and mental health (2 items).[63] The response scale for the 12 items varies across and within the scales. These domains can be categorized into two distinct concepts known as a physical component summary (PCS) and a mental component summary (MCS) score which can be calculated from SF-12v2 based on a population norm-based scoring function. Subscale and summary scores can be calculated with Quality Metric Health Outcomes Scoring Software 4.5 (copyright Quality Metric, Lincoln, Rhode Island, USA 2004–2011). The total score varies from 0 to 100, with a higher score indicating better functioning, well-being or general HS. A score of 50 or more indicates a positive perception of health and a score below 50 indicates a negative perception. It takes approximately 2-3 minutes to complete SF-12v2.[63]

Definition of fall, and incident OP fractures

A "Fall" was defined as an unintentional change in position resulting in coming to rest at a lower level such as chair or on the ground.[64] Incident OP fractures were defined as any new fracture that occurred after the baseline visit at sites which were age dependent and have shown a graded relationship with the BMD such as proximal femur, vertebral, forearm, humerus, rib, pelvis, clavicle, scapula and sternum.[65,66] Fractures of distal tibia and fibula were considered as OP fractures only in females but not in males. Fracture of any other bones such as ankle, hands, fingers, feet, toes, patella, face and skull were not considered as an OP fracture.[65,66]

Statistical Analysis:

Statistical analyses were done using Statistical Package for Social Sciences for Windows (SPSS version 23, IBM SPSS Inc., Chicago, Ill., USA). Mean ± SD and percentage (%) were used to describe the demographic characteristics of the participants. Data were tested for normality and considering central limit theorem,[67] (sample size>30) parametric tests were used for statistical analysis. The statistical significance was set at alpha < 0.05 at a 95% confidence interval. Independent t-tests were used to compare the outcomes between participants (those who completed assessment on all the outcome measures at baseline, 6m and 4y) and non-participants (those who had baseline and 6m assessment on all the outcome measures but did not participate at long-term follow-up) at baseline and 6m of follow-up. A general linear model with repeated measures of analysis of variance (ANOVA) was used with time as the within-participant factor at three levels (baseline, 6m, and 4y) to compare the change in scores over four years in the whole sample. Mauchly's test of sphericity was used to test the homogeneity of variance. In the case of significant Mauchly test results for sphericity, Greenhouse-Geisser correction was considered to adjust the tests, as recommended by Portney and Watkins.[68] Sidak's correction was considered for the multiple pairwise comparisons.

To examine if the change scores were meaningful, effect size (ES) was computed as the ratio of mean change scores ($\delta_\chi = x2 - x1$) to the standard deviation of baseline scores ($SD_{baseline}$). Mathematically, $ES = \delta_\chi / SD_{baseline}$ where δ_χ is mean change, x1 and x2 represents mean scores assessed at baseline and follow-up assessments respectively. For the purpose of clinical decision making, we used the Cohen's benchmark to indicate the magnitude of effect size i.e. trivial (ES <0.2), small (ES ≥0.2 to <0.5), moderate (ES ≥0.5 to <0.8) or large (≥0.8).[69] We used STATA 14 software to compute effect size in this study. A 3x2 general linear model (Mixed model ANOVA) with time as a repeated factor at 3 levels (baseline, 6m, and 4y) and group as the between participant factor was used to examine the recovery patterns within the subgroups and to determine if the course of recovery differs with sex (male/female), age (50-64 year/65-80 year), incidence of subsequent falls (yes/no) and fractures (yes/no).

Results

Among 191 eligible participants, 94 provided their informed consent to participate in the four-year follow-up study. The flowchart presenting the participant recruitment and retention is presented in Fig. 1. The baseline characteristics of the patients are presented in Table 1. The mean age of our participants was 63±8 years and there were more women (87%) than men (13%). The mean duration of follow-up period was 4 years (SD=1, median=4, Range= 2 to 6) or 45 months (SD=15, median=45, range= 19 to 77). Nearly 55 % of participants were followed up for a 2-4 year period, and 45 % participants were followed up for 4-6 year periods. At 4y follow-up, 20% (19/94) of people with DRF reported subsequent falls in last six months. Coincidently, 20% (19/94) of people had subsequent OP fracture after DRF. The majority of the participants in our sample were right-hand dominant, had DRF in their dominant hand, were managed conservatively, retired and had no worker compensation. There was no significant difference in the outcomes among participants and non-participants (Table 2).

Descriptive characteristics at baseline and follow-up time points

Table 3 depicts the mean and SD of the baseline and follow-up data, change scores and their respective effect size. The recovery patterns in all self-reported outcome measures and BMD over the 4y period are graphically presented in Fig. 2a and 2b respectively. The results from the repeated measures ANOVA and post hoc analysis reported for each of the measures are presented below:

Fracture-specific pain/disability (Table 3):

Fracture-specific pain/disability scores were highest at the baseline and had reduced over time. There was a significant time effect for the PRWE total scores and post hoc analysis suggested there was a significant decrease ($p<0.001$) in the scores during the follow-up period (0-6 m, 0-4y and 6m-4y). However, most of the change (49 points, ES=2.5) in PRWE scores took place during the first six months, and a moderate change (10 points, ES=0.6) had taken place during the 6m-4y period. Similar trends were reported for individual pain and function subscales on the PRWE.

Fall risk factors (Table 3):

The PA level and MFES were lower at the baseline in comparison to the follow-up assessments. Overall, there was no significant change in PA across any of the time points, and trivial to small ES were reported for change scores at all follow-up periods. There was a significant time effect for the MFES scores and post hoc analysis suggested that there was a small but significant ($p<0.001$) reduction in FOF during the 0-6m and 0-4y intervals. There was very minimal change (0.12 points) during 6m to 4y of follow-up, and most of the change in FOF took place during initial 6m of the recovery period. These results were further supported by moderate ES reported during 0-6 m after DRF.

Bone mineral density (Table 3)

Both BMD and T scores at LS and TH were comparatively better (lower) at the baseline than at the follow-up visits. There was no significant change in BMD from baseline over the period of four years at either of the LS or TH sites. This was further supported by the trivial to small effect size for the change scores reported at follow-up time points.

General health status (Table 3)

The SF-12 PCS scores were lowest at the baseline and improved at the 4y follow-up. There was a significant time effect for the SF-12 PCS scores and post hoc analysis suggested there was a significant improvement ($p<0.001$) in the health status score during the 0-6m and 0-4y periods. There was a large effect size (>0.8) for the change reported during these periods. There was a trivial change (-1.2 points, ES<0.2) during a 6m-4y period and the majority (9.4 points) of the improvement in SF-12 PCS took place during a 0-6m interval. SF-12 MCS scores were lowest at the baseline and at four years of follow-up and were highest at the 6m of follow-up. There was a significant time effect for the SF-12 MCS scores and post hoc analysis suggested there was significant ($p<0.05$, ES=0.3) improvement/increase in the MCS scores at 0-6m and significant ($p<0.05$, ES=0.5) decrease during 6m-4y period. Overall, there was no significant difference in SF-12 MCS scores from 0-4y follow-up.

Descriptive characteristics and longitudinal recovery patterns in a stratified sample: sex, age, *incidence of subsequent falls and OP fractures*

The results from mixed model ANOVA with the post-hoc analysis done on a stratified sample of people with DRF are presented in Table 4. There were no significant differences in PRWE, RAPA, MFES and BMD (LS and TH) and T-scores (LS and TH) when stratified by sex, age, the incidence of subsequent falls and fractures. There was a significant main effect of time for PRWE total, MFES, SF-12 PCS when stratified by sex, age, incidence of subsequent falls and fractures. The post hoc analysis suggests that there was a significant improvement in scores in PRWE at all 3 time periods (0-6 m, 0-4y, 6m-4y). On MFES and SF-12-PCS, there was a significant improvement in FOF and physical HS from 0-6 m as well as from 0-4y. However, the majority of the improvement was noted during the initial 6 months. There was a significant improvement in RAPA scores from 0-6m period among the subgroup of fallers and non-fallers, but no long term changes were noted over 4 years. There was a significant time effect for SF-12-MCS irrespective of age, the incidence of subsequent falls and fractures. Overall, there was a statistically significant improvement in SF-12-MCS during 0-6m followed by a significant decrease during 6m-4y of the follow-up period bringing it closer to the baseline level. However, there was no time effect for SF-12-MCS in a sex-stratified sample. We noted that there were significant differences in SF-12 PCS and SF-12 MCS among those with incidence of subsequent falls and no falls. SF-12 PCS was significantly lower/poor among those with subsequent falls/fractures than those without (Fig. 3). Similarly, SF-12 MCS was significantly lower/poor among fallers than non-fallers (Fig. 4). SF-12 MCS scores were significantly higher/good in patients aged 65-80 year old in comparison to those who were 50-64 year old (Fig. 4).

There was no significant interaction of sex, age, incidence of subsequent falls and fractures with time for any of these outcome measures except for T scores-LS and BMD-LS for which we had a significant interaction effect of age with time indicating that change in T scores-LS and BMD-LS might vary with time when stratified by age. The post hoc comparison conducted for individual age groups revealed that patients aged 65-80 year old had significant improvement in their T scores-LS from a 6m-4y period but not at other time-points. However, there was no main effect of time on T scores-LS for the 50-64 year old. Also, there was no significant main effect of time for BMD-LS in either of the age groups

Discussion

Results from this prospective cohort study indicate that patients with DRF showed both short term (6m) and long term (4y) improvement in fracture-specific pain/disability, PA, FOF, BMD and general HS with the large effects/changes in the first six months and trivial to moderate effects from six months to four years after DRF. Data from our study can inform expectations around the recovery of patients with a DRF which might be useful to hand therapists in educating patients about what recovery pattern can be expected for resuming normal activities.

The majority of the clinically important (>11.5 points)[49] and statistically significant ($p<0.05$) changes in fracture-specific pain/disability took place during the initial six months (~49 points), and only moderate changes were reported after six months (~10 points). This is consistent with other studies in which patients with DRF were followed longitudinally, and most of the recovery in pain and function was reported in the first six months[13,38,39] after DRF in comparison to the extent of recovery seen at 12 months of follow-up.[13,39] This could be because the majority of tissue and bone healing around the distal radius is completed during the initial 3-6 months.[12,15,43] However, we know that many outcome measures are not interval level scaled, including the PRWE,[70] so we are unsure whether a 10 point change seen between six months and four years represents the same change as the early recovery changes of 10 points. Since most patients would not be undergoing therapy at 6-months, this suggests that continued recovery through functional use after discharge can be expected. Furthermore, MacDermid et al. have shown a lack of worker compensation claim[11] to be one of the influential factors for the reduction in pain and disability at six months postoperative to a DRF. We must acknowledge that nearly 93% of our sample had no worker compensation claim which could be one of the factors for the favorable recovery seen in the initial six months.

In a recent study, Ydreborg et al. reported that patients with DRF (aged 58±13.3y) showed improvement in pain during initial six months after surgery which greatly worsened during six months to two years of follow-up.[71] On the contrary, our sample showed significant improvement during the 6m-4y period. However, only 27% of our patient sample was surgically treated which could partially explain the differences between our study findings and those of others.[71] Previous studies have reported that women and older adults tend to have more pain and impaired function after DRF.[43,46] In our sample, females under 65 years of age with subsequent fractures showed a trend to have higher pain and disability as reported by PRWE at all follow-up time points (except for females at baseline who had lower scores than males).[44–46] The small size of our subgroups meant we were underpowered for this analysis and this may be why we did not find any significant differences in our stratified study sample. Overall, our current data suggests that similar longitudinal recovery can be expected among people with DRF irrespective of their sex, age, incidence of subsequent falls and fractures.

With regard to PA, the participants in our study were physically under-active for light and regular activities as the average scores were suboptimal (<6 points) at baseline, 6m and 4y. At the same time, our study sample was not sedentary and had scores >1 at all three time points. Overall, we did not find any significant changes in the scores for PA among our sample with DRF. Similar to our findings, Hakestad et al. reported that there was no significant difference in self-reported PA levels as measured by the 'physical activity scale for elderly' in a sample of 50-65 year old PMW with osteopenia and healed wrist fracture in comparison to the healthy age-matched controls with no fracture.[72] The authors in this study found that there was significantly impaired physical performance as measured by the six-minute walk test in PMW with wrist fracture in comparison to their controls.[72] Our findings were contradictory to Nordell et al. who reported there was a significant reduction in PA over a period of one year for 50-84 year old women with DRF.[20] However, they used performance measure (fast walking speed) to evaluate PA in comparison to the self-reported measure used in our study.[20] In another study with two different groups of women (one with recent wrist fracture (n=41) and other with a wrist fracture one year earlier (n=20)) were compared with an age-matched control group (n=123) of women with no fracture and there was no decline in walking speed in women with wrist fracture.[22] Our study findings are consistent with an expectation that following a DRF most people will either maintain their activities or at least return to their pre-fracture activity level in the longer term. This is further informed by our FOF data which suggest that our participants were confident to perform the activities of their daily living independently without any FOF during their recovery period.

We recommend that future researchers should consider evaluating longitudinal changes in both self-reported and objectively measured PA since this will provide an external quantification that enhances the self-reported indicator. Also, most of the existing literature evaluating a change in PA after DRF is done among women.[20,72,73] To our knowledge, we could not find any study evaluating change in PA among males or a mixed sample of people with DRF which limited our ability to provide a conclusive comparison of our results with the research done in this arena. This could be another interesting aspect to consider in future research. Another reason for the nonsignificant changes observed in our study could be related to the lack of substantial responsiveness of the RAPA to evaluate a change in PA as represented by the small effect size reported in our study. Furthermore, a recent study done by Mehta et al. has described that RAPA exhibits lower reliability estimates (ICC=0.68, 95% CI: 0.34 to 0.86) to evaluate PA among patients with DRF.[74]

We did not find any significant differences in the recovery patterns for PA relative to sex, age, incidence of subsequent falls and fractures seen among our sample of people with DRF. However, overall PA levels were lower among males, younger people and those with an incidence of subsequent falls and fractures. Edward et al. have reported that elderly women with wrist fractures when followed over a period of 7.6 years, are 50% more likely to exhibit clinically important functional decline.[75] This was different from our four-year follow-up findings as our study sample consisted of both males and females and the majority of our patients were in the 50-64 year age group in comparison to ≥65 year old females only participants included in their study. FOF is an expected response after any fall-related injury among older adults,[25,76] and is known to be a salient predictor of reduced PA.[77] Our study sample scored >8 points at all follow-up time points after DRF indicating good confidence in their ability to avoid any subsequent falls and thus low FOF. Also, our participants showed a significant decrease in FOF over 4 years after the DRF. A previous longitudinal study done over a period of 4 months reported an increase in FOF among patients with DRF and nearly 24% of patients had at least two falls within the next four months.[23] Louer et al. commented that FOF was not different among those with or without DRF.[21] We did not find any significant difference in FOF among those with subsequent falls and fractures at any time point when compared to those without. We expected that FOF might increase among our sample of patients with DRF who experienced subsequent falls or fractures. But non-significant changes could be because all the participants in our study had a prior episode of fall as well as fracture (wrist fracture) at baseline due to which they did not show any further change in FOF with subsequent falls and fractures. So, it was interesting to note that subsequent falls and fractures do not have a summative effect on FOF among patients with DRF. Unlike other studies in which females and elderly tend to report higher FOF,[76,78–80] we did not find any sex or age-based differences in our sample of patients with DRF. We note that unequal distribution and a small sample of our stratified analysis could be one of the reason for the non-significant sex or age-based differences in our participants with

DRF. Future research is needed to validate these findings among a large sample of people with subsequent falls and fractures.

Regarding BMD, we did not find any significant changes in BMD or T scores during the follow-up period, and there was a very small effect size for the change reported during the recovery period following DRF. The actual LS and TH T scores for our sample at baseline were in the range of 0 to 2.49. As per the manual at HULC, in order to be 95% confident that significant change has occurred over one year, we needed a change in BMD-LS and BMD-TH by ± 0.030 g/cm2. Though not statistically significant, the change in BMD-TH reported in our study was greater than 0.030 g/cm^2 at 6m-4y and 0-4y period. Nevertheless, we recommend future research on a large sample size with yearly assessments to provide conclusive evidence on clinical significance of change in BMD in patients with DRF.

In contradiction to the nonsignificant changes in BMD and T scores observed in our study, longitudinal studies among PMW have reported substantial reductions in BMD at four months [81] and more recently at three years [82] after DRF. One case report done in a sample of PMW reported a loss of lumbar spine and hip BMD at 10, 13, 21 and 52 weeks post-fracture.[83] Mallamin et al. reported that at two months of follow-up, there was a 20% reduction in distal radius BMD and 5-8% reduction in BMD at LS and TH, in 74 patients with wrist fracture in comparison to the matched controls.[84] We did not record if our patients were taking bone forming drugs post-DRF which might have confounded our findings leading to non-significance. Also, there is a possibility that small sample could have contributed to non-significance. Nevertheless, this study provides new data showing both short and long term changes in BMD among a sample of male and females with DRF.

Despite the relatively stable BMD, nearly 20% of the patients in this study reported subsequent fractures. This supports the fact that DRF is an independent predictor of subsequent fracture irrespective of the BMD.[31,85,86] Furthermore, this also strengthens the suggestion of others[31,87] for greater attention to evaluating risk factors other than BMD which might be predictive of subsequent fractures among people with DRF. Our data suggest that hand therapists should be very concerned with secondary fracture prevention, given the potential for 1/5th of their DRF caseload to have a subsequent fracture. In previous studies, BMD is reported to be reduced in about 70-80% patients with DRF in comparison to those without fractures.[88–90] Though non-significant, females in our study scored lower on T scores and BMD in comparison to the males. This is a common finding reported in a few other studies[91,92] and is attributed to estrogen reduction following menopause.[93] Few previous studies have shown that females with wrist fracture who were <65 years of age tend to have low BMD in comparison to that of >65 years of age.[88,89] Our study participants aged 50-64 year old showed higher BMD than 65-80 year old at baseline and 6m. However at 4y follow up, people who were 50-64 year old showed lower BMD than those with who were 65-80 year old. There could be many confounders such as intake of bone forming medication, OP fracture care/prevention programs, post-fracture lifestyle that suggests to consider controlling for confounders while evaluating change in future longitudinal studies. Also, the age-stratified information reported in this study is an important finding. This information will direct the attention of therapists towards the difference in trend of improvement in BMD which can be expected among the two age groups. We did not find any difference in BMD among patients with subsequent falls and fractures when compared to those without. Future studies with large sample size would be important to detect if clinically significant long-term changes in BMD occur after DRF and comparing the findings with those without DRF.

Although DRF often occurs among functionally independent people, various studies have suggested that DRF has an impact on overall HS. Though there are no studies reporting MCID of SF-12 for patients with DRF, Hays et al. suggested that a change in scores from 3 to 5 points can be considered clinically meaningful for SF-36 measures.[94] Considering that both PCS and MCS scores of the SF-12 have shown excellent correlation, agreement and is derived from the respective component scores on SF 36,[63,95,96] the 3-10 point changes in HS observed in our study using SF-12 can be considered clinically significant. Our study results were consistent with previous studies that patients with DRF present with poor HS in the early post-fracture period show improvement over six months.[39,97] In our study, SF-12 scores for PCS improved over six months by nine points (40-49 points), and there was no further significant change during the 6m-4y interval. MacDermid et al. reported improvement in the physical component of HS scores of 10 points (37-48 points) by six months which remained constant until one year of follow-up.[39] In contrast, a recent prospective cohort study has reported a reduction in HS scores on PCS for SF-12 over a period of six months in elderly patients (>65 year old) with fall-related DRF in comparison to the non-fracture cohort.[98] Furthermore, authors reported more deterioration in HS among those with older age group (>80 years) over a period of six months.[98] We believe a fall may lead to greater health decline in frail older individuals, as their capacity for recovery may be less. In comparison, the majority (62%) of patients included in our study were <65 years old which might have resulted in difference in findings in our study. Hallberg et al. also reported significant reduction in HS as measured by SF-36 among postmenopausal women during initial six months which was then normalized at two years after wrist fracture.[99] We did not find any significant difference in physical HS in our age stratified sample at any of the time points. Brenneman et al. reported significantly less/poor physical HS on SF-12 in younger (50-64years) than older women (65-99 years) at four years of follow-up.[33] The conflicting evidence suggests the need for studies on age and sex-stratified large sample to evaluate longitudinal changes in HS of patients with DRF.

Furthermore, our non-significant study results on sex and age-stratified analysis of physical HS using SF-12 differ from that reported in previous studies using SF 36. Gruber et al. reported that women and older (>60 years) patients exhibit significantly lower physical HS as measured by SF-36 in comparison to the males and younger patients (<60 years).[42] However, these findings were from a sample of surgically-treated patients with DRF, while only 27% of our sample was surgically treated. Studies have shown that surgical management among elderly patients with DRF tend to result in poor recovery in comparison to that of conservative treatment.[100–103] The overall improvement seen in our study irrespective of age or sex could also be related to the expertise and skills of therapy provided at HULC.

The MCS for SF-12 stayed within the normal limits (51-55 points) during 4 years of the recovery period in our study participants. Our results were similar to a previous study in which MCS for SF-12 were within the normal range (51-53 points) in patients with DRF were followed at a period of six months and one year.[39] This could be because of the physical nature of injury.[97] Though, not statistically significant, older patients (>65 year old) in our study scored higher on mental component of SF-12 than the younger patients. Gruber et al. also noted that elderly (>60 year old) and females reported higher scores on mental health status at 6 years after surgically-treated DRF.[42] Some previous studies have reported that elderly females tend to have better mental HS in comparison to younger ones[104,105] which would suggest that DRF patients are similar to the normal population in this regard. This could be because older patients could have more emotional stability and thus acceptance for their bio-psycho-social state of health in comparison to the younger patients. The changes in both the domains of HS have mirrored the trend observed in other studies evaluating the impact of DRF on patients with wrist fractures. Similar to many other studies,[33,97] our data depicts that DRF had greater impact on the physical than the mental component of SF-12. This could be because pain and disability after DRF are reported to explain significant variability (33% and 28% at three months and one year respectively) in the physical component and explain a minimal amount of variability (10% and 8% at three months and one year respectively) in the mental component of SF-12.[33,97]

Overall, among all the outcome measures, there was a drastic change in PRWE scores in comparison to all other outcome measures evaluated in this study. MacDermid et al. have also reported similar findings and related it to the well-established high responsiveness of PRWE to evaluate change in outcomes among DRF population.[106]

Strengths, Limitations and Future research

Our study was a long term prospective cohort, used validated outcome measures and collected a spectrum of informative self-report and objective measures. We evaluated outcomes in both men and women at different ages. We have provided therapists with the concrete quantitative data on both short term and long term changes on various risk factors related to falls and OP fractures. This data can be used as benchmark by the clinicians as the scores of any particular patient with DRF can be compared to these average scores to determine if the patient scores are following the anticipated recovery pattern. Additionally, we provided effect size of the change reported in the outcomes at a different time point which deepens our understanding on the clinical significance of the change observed in our study. Furthermore, this parameter would be important for sample size computation needed in future intervention trials evaluating the change in outcomes after DRF. Despite this, a number of limitations should be considered when interpreting our results. Firstly, we had only 49% of the original cohort participate in the 4y follow-up which leaves the potential for selection bias. However, there were no significant differences between responders and non- responders at the baseline which suggests that this is unlikely. Secondly, we had a small sample size and unequal distribution of participants for stratified analysis which meant we were underpowered for subgroup analyses. Cohen et al.[69] recommend a minimum sample of 30 participants per cell to have 80% power, and we did not meet this target sample in the majority of our stratified analyses. We recommend future longitudinal studies use a large sample of age and sex-stratified sample comparing the outcomes with healthy controls with no fracture to provide more conclusive evidence on the natural course of recovery among patients with DRF.

Conclusions

Patients aged 50-80 years old perceive high levels of fracture-specific pain and disability, low PA, high FOF, low BMD and poor health state at post-DRF. The majority of the recovery in patients with DRF was reported during the initial six months and small changes were noted between six months and four years. People with subsequent falls and fractures after DRF present with lower physical health status compared to those without.

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Table 1 Baseline characteristics of the study population with distal radius fracture (n=94)

Variable	N/Percentage of participants
Mean Age in years	*62.6 (SD=7.7)
50-64 year old	58/61.7%
65-80 year old	36/38.3%
Sex	
Male	12/12.8%
Female	82/87.2%
Injured hand	
Left	50/53.8%
Right	42/45.2%
Hand dominance	
Left	8/8.7%
Right	84/91.3%
Dominant Hand injury	
Yes	24/34.3%
No	44/64.7%
Pain Medication	
Never	8/22.9%
Occasionally	12/34.3%
Daily	7/20.0%
Several times a day	8/22.9%
Surgical treatment	
Yes	11/27.5%
No	29/72.5%
Work Status	
Full time regular duties	15/17%

Part-time regular duties	5/5.7%
Part-time light duties	5/5.7%
Unable to work because of injury	13/14.8%
Unemployed, Inability to find a job	1/1.1%
Home maker	2/2.3%
Retired	47/53.4%
Worker Compensation involved	
No	78/92.9%
Yes	6/7.1%
Highest Education level	
Some grade school	1/1.1%
Some high school	6/6.9%
Finished high school	12/13.8%
Some college/technical/diploma program	13/14.9%
Finished college/technical/diploma program	18/20.7%
Some university	7/8.0%
Finished University	16/18.4%
Some graduate work at university	5/5.7%
Finished graduate work at university	9/10.3%
Smoker	
No	52/58.4%
Yes	29/32.6%
I quit	8/9%
Alcohol	
Never	10/11.4%
Occasionally	48/54.5%
1-6 drinks/week	19/21.6%
7-14 drinks/week	10/11.4%

15 plus drinks/week	1/1.1%
Mechanism of Fracture	
Fall on snow	23/32.9%
Other fall	37/52.9%
During sports	3/4.3%
Other than fall	7/10%

*Mean (SD)

Table 2 Comparison of outcome measures between participants and non-participants at baseline and six month follow-up

	Baseline			**6 month follow-up**		
Measure	**Participant (61)**	**Non-Participant (48)**	**p-value**	**Participant (52)**	**Non-Participant (33)**	**p-value**
PRWE-Total (0-100; 100 worst)	67.5 (20.0)	68.3 (19.7)	0.85	17.5 (13.02)	18.6 (20.3)	0.75
RAPA (0-10; 10 best)	3.6 (1.9)	3.4 (1.7)	0.54	4.4 (1.7)	4.09 (1.4)	0.42
MFES (0-10; 10 best)	8.7 (1.6)	8.9 (1.9)	0.65	9.8 (0.5)	9.7 (0.6)	0.44
BMD-TH	0.882 (0.115)	0.895 (0.146)	0.59	0.883 (0.116)	0.886 (0.148)	0.90
BMD-LS	1.092 (0.188)	1.086 (0.173)	0.88	1.094 (0.211)	1.086 (0.160)	0.86
T scores-TH (≥ -1 normal)	-1.0 (0.9)	-0.9 (1.1)	0.57	-1.03 (0.8)	-1.1 (1.1)	0.73
T scores-LS (≥ -1 normal)	-0.8 (1.5)	-0.9 (1.3)	0.64	-0.8 (1.7)	-0.9 (1.2)	0.52
SF-12 PCS (US norm=50)	39.7 (9.8)	38.7 (9.3)	0.61	49.4 (8.4)	49.2 (7.2)	0.88
SF-12 MCS (US norm=50)	50.4 (10.4)	51.5 (11.2)	0.58	55.4 (6.1)	54.9 (7.05)	0.76

PRWE, Patient Rated Wrist Evaluation; RAPA, Rapid Assessment of Physical Activity; MFES: Modified Fall Efficacy Scale; SF12-PCS, 12-item Short Form-Physical Component Summary scores; SF12-MCS, 12-item Short Form-Mental Component Summary scores; BMD, bone mineral density; LS, lumbar spine; TH, total hip; p, level of significance; US, United States

Table 3 Descriptive characteristics of outcome measures at baseline, 6 months and 4 years of follow-up: mean (SD), mean change (95% CI) and effect size (95% CI)

Measure	Absolute scores (mean ±SD)				Mean change scores (mean, 95% CI)			Effect size (95% CI)		
	Baseline	6 month	4 year	Time (p-value)	0-6 month	0-4 year	6m-4y	0-6 month	0-4 year	6m-4y
PRWE-Pain (n=69)	29.9 (11.4)	11.7 (8.9)	6.3 (9.6)	0.0001**	18.2** (14.8, 21.5)	23.6** (20.1, 27.2)	5.5** (2.9, 7.9)	1.6 (1.1,2.0)	2.1 (1.6, 2.5)	0.6 (0.3,0.9)
PRWE-Function (n=66)	38.7 (11.6)	7.6 (8.4)	3.0 (6.2)	0.0001**	31.1** (27.2, 34.8)	35.7** (31.9, 39.4)	4.6** (2.5, 6.6)	2.7 (2.1,3.3)	3.1 (2.4,3.7)	0.5 (0.2,0.9)
PRWE-Total (n=65)	68.7 (19.3)	19.4 (16.2)	9.03 (15.2)	0.0001**	49.3** (42.8, 55.7)	59.6** (53.1, 66.2)	10.4** (6.1, 14.6)	2.5 (1.9,3.1)	3.1 (2.4,3.7)	0.6 (0.3,1.0)
RAPA (n=62)	3.7 (2.02)	4.2 (1.7)	4.0 (1.8)	0.12	-0.5 (-1.2, 0.1)	-0.3 (-0.9, 0.3)	0.2 (-0.4, 0.8)	-0.2 (-0.6,0.1)	-0.2 (-0.5,0.2)	0.09 (-0.3,0.4)
MFES (n=70)	8.6 (1.8)	9.8 (0.5)	9.7 (0.9)	0.0001**	-1.1** (-1.6,-0.6)	-1.0** (-1.6, -0.5)	0.1 (-0.2,0.4)	-0.6 (-0.9,-0.3)	-0.5 (-0.9,-0.2)	0.2 (-0.1,0.6)
BMD-TH (n=31)	0.863 (0.132)	0.877 (0.132)	0.918 (0.273)	0.33	-0.015 (-0.034,-0.179)	-0.055 (-0.179,0.069)	-0.040 (-0.016,0.084)	-0.1 (-0.6,0.4)	-0.4 (-0.9,0.1)	-0.3 (-0.8,0.2)
BMD-LS (n=40)	1.059 (0.174)	1.065 (0.193)	1.063 (0.201)	0.83	0.007 (-0.030,0.017)	-0.004 (-0.036,0.028)	0.003 (-0.032, 0.037)	-0.03 (-0.5,0.4)	-0.02 (-0.5,0.4)	0.01 (-0.4,0.5)
T scores-TH (n=31)	-1.2 (1.0)	-1.1 (1.0)	-0.8 (2.3)	0.34	-0.1 (-.2,.04)	-0.4 (-1.5,0.6)	-0.3 (-1.4,0.7)	-0.1 (-0.6, 0.4)	-0.2 (-0.7,0.3)	-0.2 (-0.6,0.3)
T scores-LS	-1.08	-1.0	-.9	0.64	-0.03	-0.08	-0.05	-0.05	-0.1	-0.1

(n=40)	(1.4)	(1.6)	(1.5)		(-.2, 0.2)	(-.3, .1)	(-.3,.2)	(-0.5, 0.4)	(-0.5,0.3)	(-0.5,0.4)
SF-12 PCS (n=69)	39.5 (10.3)	48.9 (8.3)	50.1 (8.3)	0.0001**	-9.4** (-12.6,-6.3)	-10.6** (-13.9,-7.2)	-1.2 (-3.5,1.2)	-0.9 (-1.3, -0.5)	-1.0 (-1.4,-0.6)	-0.1 (-0.5,0.2)
SF-12 MCS (n=69)	51.8 (10.7)	55.2 (6.3)	51.9 (8.8)	0.007**	-3.5* (-6.7, -0.1)	-0.1 (-3.0,2.8)	3.4* (0.9,5.8)	-0.3 (-0.6,0.01)	-0.007 (-0.3,0.3)	0.5 (0.2,0.8)

PRWE, Patient Rated Wrist Evaluation; RAPA, Rapid Assessment of Physical Activity; MFES: Modified Fall Efficacy Scale; SF-12 PCS, 12-item Short Form-Physical Component Summary scores; SF-12 MCS, 12-item Short Form-Mental Component Summary scores; BMD, bone mineral density; LS, lumbar spine; TH, total hip; p, level of significance; **, p<0.001, *, p< 0.05; SD, standard deviation; CI, confidence interval; 6m-4y, 6 months to 4 years

Table 4 Within and between group differences in outcome measure based on sex, age, incidence of subsequent falls and fractures at baseline, 6 months and 4 years of follow-up

Variable		**Sex**		**Age**		**Subsequent falls**		**Subsequent Osteoporotic fractures**	
		Females	**Males**	**50-64 years**	**65-80 years**	**No**	**Yes**	**No**	**Yes**
PRWE-total	n	55	10	42	23	52	13	54	11
	Factor effect (p)	0.75		0.23		0.93		0.16	
	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.0001 [a,b,c]		0.0001 [a,b,c]		0.0001 [a,b,c]		0.0001 [a,b,c]	
	Baseline Mean (SD)	68.2 (20.4)	71.1 (11.9)	70.2 (19.0)	66.0 (19.9)	67.6 (19.6)	72.8 (18.4)	67.2 (19.6)	75.7 (16.9)
	6 month Mean (SD)	20.5 (16.6)	13.6 (13.0)	20.7 (15.8)	17.1 (16.8)	19.9 (17.1)	17.5 (12.1)	18.1 (15.3)	26.1 (19.6)
	4 year Mean (SD)	9.1 (15.6)	8.9 (13.7)	10.6 (17.4)	6.2 (10.0)	9.8 (16.5)	5.9 (8.5)	8.8 (15.4)	10.2 (15.1)
RAPA	n	52	10	39	23	51	11	52	10
	Factor effect (p)	0.40		0.63		0.29		0.14	

	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.38		0.12		0.04 [a]		0.57	
	Baseline Mean (SD)	3.8 (2.0)	3.4 (1.9)	3.7 (1.8)	3.8 (2.4)	3.9 (2.0)	2.9 (1.9)	3.8 (2.1)	3.3 (1.7)
	6 month Mean (SD)	4.4 (1.8)	3.7 (1.5)	4.1 (1.8)	4.5 (1.6)	4.2 (1.7)	4.3 (2.1)	4.4 (1.8)	3.4 (1.3)
	4 year Mean (SD)	4.1 (1.8)	3.9 (1.9)	4.1 (1.6)	4.1 (2.2)	4.2 (1.8)	3.6 (1.9)	4.2 (1.8)	3.5 (2.1)
MFES	n	60	10	42	28	56	14	58	12
	Factor effect (p)	0.56		0.81		0.52		0.71	
	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.001[a,b]		0.0001 [a,b]		0.0001 [a,b]		0.0001 [a,b]	
	Baseline Mean (SD)	8.6 (1.9)	9.0 (1.3)	8.6 (1.8)	8.7 (1.9)	8.7 (1.9)	8.6 (1.7)	8.6 (1.9)	8.8 (1.8)
	6 month Mean (SD)	9.8 (0.5)	9.9 (0.3)	9.8 (0.4)	9.9 (0.5)	9.8 (0.5)	9.7 (0.4)	9.8 (0.5)	9.8 (0.5)
	4 year Mean (SD)	9.7 (0.9)	9.7 (0.6)	9.7 (0.9)	9.7 (0.9)	9.7 (0.8)	9.5 (1.5)	9.7 (1.0)	9.8 (0.3)
BMD-TH	n	25	6	17	14	24	4	24	4

	Factor effect (p)	0.08		0.72		0.55		0.83	
	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.61		0.27		0.64		0.63	
	Baseline Mean (SD)	0.838 (0.131)	0.965 (0.082)	0.875 (0.129)	0.848 (0.138)	0.883 (0.108)	0.894 (0.111)	0.881 (0.130)	0.865 (0.128)
	6 month Mean (SD)	0.852 (0.131)	0.982 (0.077)	0.884 (0.129)	0.869 (0.140)	0.894 (0.111)	0.850 (0.220)	0.890 (0.128)	0.871 (0.138)
	4 year Mean (SD)	0.904 (0.301)	0.976 (0.079)	0,873 (0.118)	0.971 (0.386)	0.888 (0.098)	0.841 (0.212)	0.882 (0.118)	0.877 (0.122)
BMD-LS	n	34	6	20	20	33	4	31	6
	Factor effect (p)	0.08		0.93		0.96		0.20	
	Interaction effect (p)	NS		0.03*		NS		NS	
	Time effect (p)	0.42		0.16	0.18	0.22		0.73	
	Baseline Mean (SD)	1.041 (0.177)	1.159 (0.120)	1.058 (0.180)	1.060 (0.172)	1.068 (0.170)	1.084 (0.253)	1.087 (0.174)	0.976 (0.172)
	6 month Mean (SD)	1.044 (0.194)	1.84 (0.152)	1.078 (0.210)	1.053 (0.180)	1.081 (0.196)	1.047 (0.216)	1.093 (0.195)	0.995 (0.194)
	4 year	1.038	1.206	1.044	1.082	1.074	1.078	1.093	0.978

	Mean (SD)	(0.197)	(0.181)	(0.186)	(0.219)	(0.202)	(0.257)	(0.207)	(0.179)
T Scores-TH	n	25	6	17	14	24	4	24	4
	Factor effect (p)	0.64		0.76		0.73		0.76	
	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.62		0.28		0.52		0.61	
	Baseline Mean (SD)	-1.3 (1.1)	-0.9 (0.6)	-1.1 (0.9)	-1.4 (1.1)	-1.1 (0.8)	-1.2 (1.9)	-1.1 (1.03)	-1.3 (0.8)
	6 month Mean (SD)	-1.2 (1.08)	-0.8 (0.6)	-1.1 (0.9)	-1.2 (1.1)	-1.04 (0.8)	-1.2 (1.8)	-1.04 (1.01)	-1.2 (0.8)
	4 year Mean (SD)	-0.8 (2.5)	-0.9 (0.6)	-1.2 (0.8)	-0.4 (3.2)	-1.1 (0.7)	-1.3 (1.8)	-1.1 (0.9)	-1.2 (0.7)
T Scores-LS	n	34	6	20	20	33	4	31	6
	Factor effect (p)	0.22		0.98		0.88		0.19	
	Interaction effect (p)	NS		0.005*		NS		NS	
	Time effect (p)	0.28		0.22	0.01[c]	0.62		0.70	
	Baseline Mean (SD)	-1.2 (1.4)	-0.5 (0.9)	-1.05 (1.4)	-1.1 (1.4)	-1.0 (1.4)	-0.9 (2.0)	-0.8 (1.4)	-1.7 (1.4)

	6 month Mean (SD)	-1.2 (1.7)	-0.3 (1.3)	-0.9 (1.8)	-1.2 (1.5)	-0.9 (1.7)	-1.2 (1.7)	-0.8 (1.7)	-1.6 (1.6)
SF-12 PCS	n	59	10	42	27	55	14	58	11
	Factor effect (p)	0.28)		0.90		0.03*		0.02*	
	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.0001 [a,b]		0.0001 [a,b]		0.0001 [a,b]		0.0001 [a,b]	
	Baseline Mean (SD)	38.9 (10.1)	43.3 (11.3)	39.7 (10.3)	39.4 (10.4)	40.9 (10.4)	34.4 (8.1)	40.3 (9.9)	35.8 (11.8)
	6 month Mean (SD)	48.7 (18.6)	50.6 (6.8)	48.7 (8.6)	49.4 (7.9)	49.3 (8.1)	47.7 (9.3)	49.7 (7.9)	44.9 (9.5)
	4 year Mean (SD)	49.9 (8.4)	51.3 (8.3)	50.1 (9.1)	50.2 (7.1)	51.1 (7.9)	46.2 (8.9)	51.1 (7.7)	45.2 (9.8)
SF-12 MCS	n	59	10	42	27	55	14	58	11
	Factor effect (p)	0.20		0.01*		0.03*		0.38)	
	Interaction effect (p)	NS		NS		NS		NS	
	Time effect (p)	0.11		0.02[c]		0.004 [a,c]		0.06 [c]	
	Baseline Mean (SD)	51.1 (11.2)	55.8 (6.5)	50.0 (10.9)	54.6 (9.8)	53.0 (9.7)	46.9 (13.3)	51.3 (10.5)	54.4 (11.7)

	6 month Mean (SD)	54.9 (6.6)	57.1 (3.3)	54.3 (5.9)	56.7 (6.7)	55.6 (6.1)	53.8 (6.9)	54.9 (6.0)	56.9 (7.4)
	4 year Mean (SD)	51.6 (8.7)	53.50 (9.9)	49.8 (9.0)	55.1 (7.6)	52.8 (8.2)	48.1 (10.4)	51.8 (8.6)	52.5 (10.4)

PRWE, Patient Rated Wrist Evaluation; RAPA, Rapid Assessment of Physical Activity; MFES: Modified Fall Efficacy Scale; SF-12 PCS, 12-item Short Form-Physical Component Summary scores; SF-12 MCS, 12-item Short Form-Mental Component Summary scores; BMD, bone mineral density; LS, lumbar spine; TH, total hip; NS, non-significant; p, level of significance; *, p< 0.05; a: significant change from baseline to 6 months; b: significant change from 0 to 4 years; c: significant change from 6 months to 4 years

Fig. 1. Flowchart of patient recruitment and retention

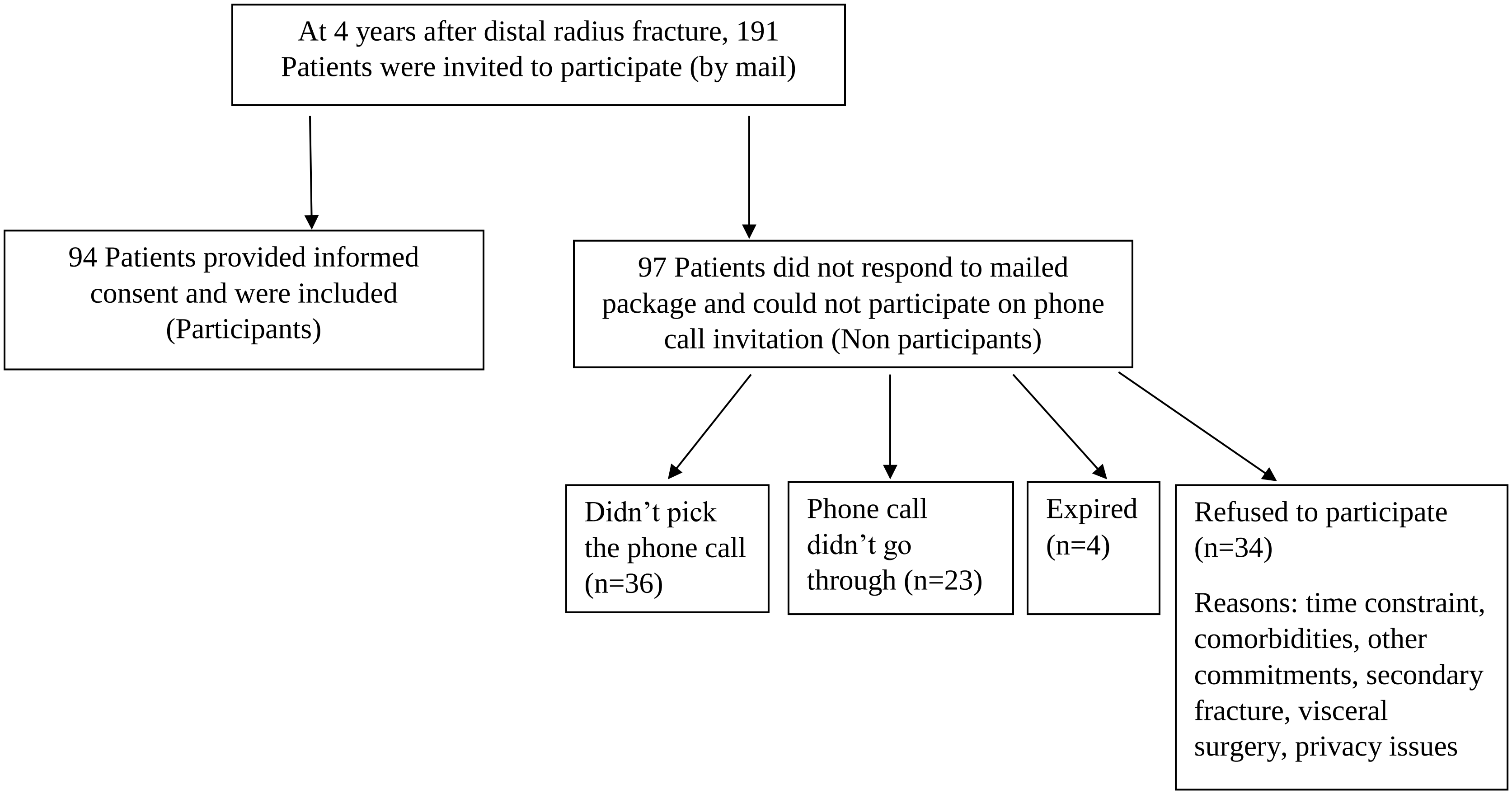
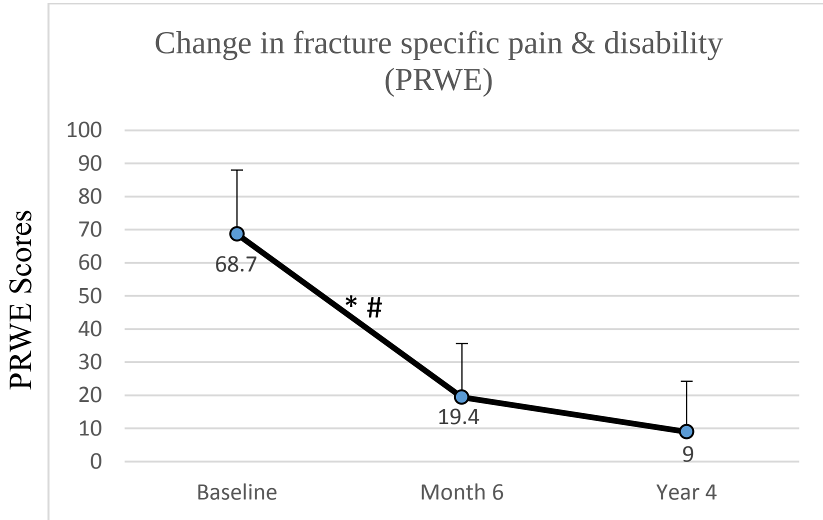
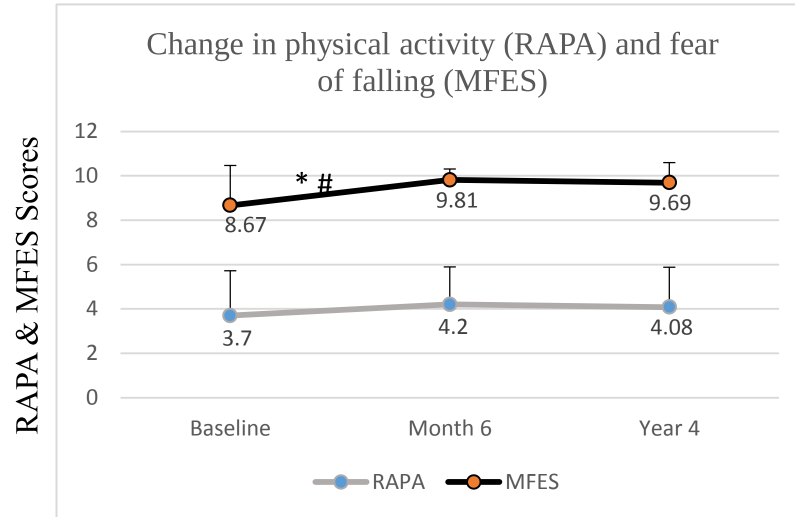
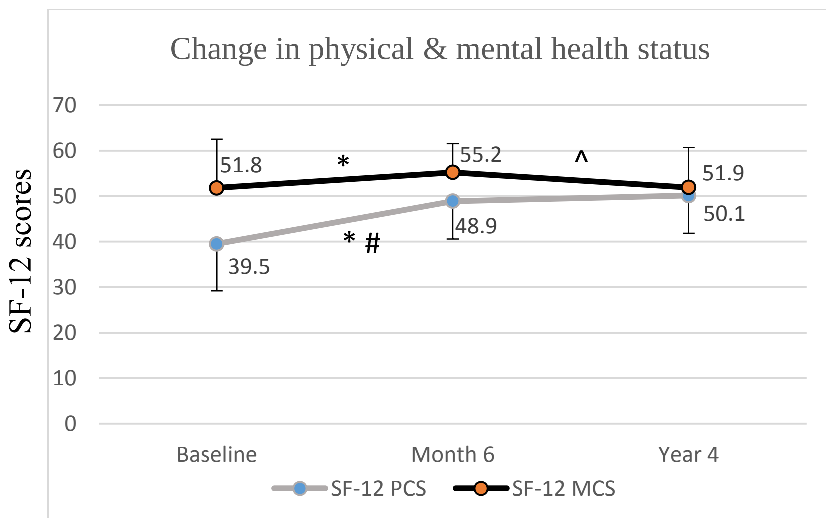


Fig. 2a. Longitudinal changes (mean±SD) in self-reported outcome measures at baseline, 6 months and at 4 years after distal radius fracture

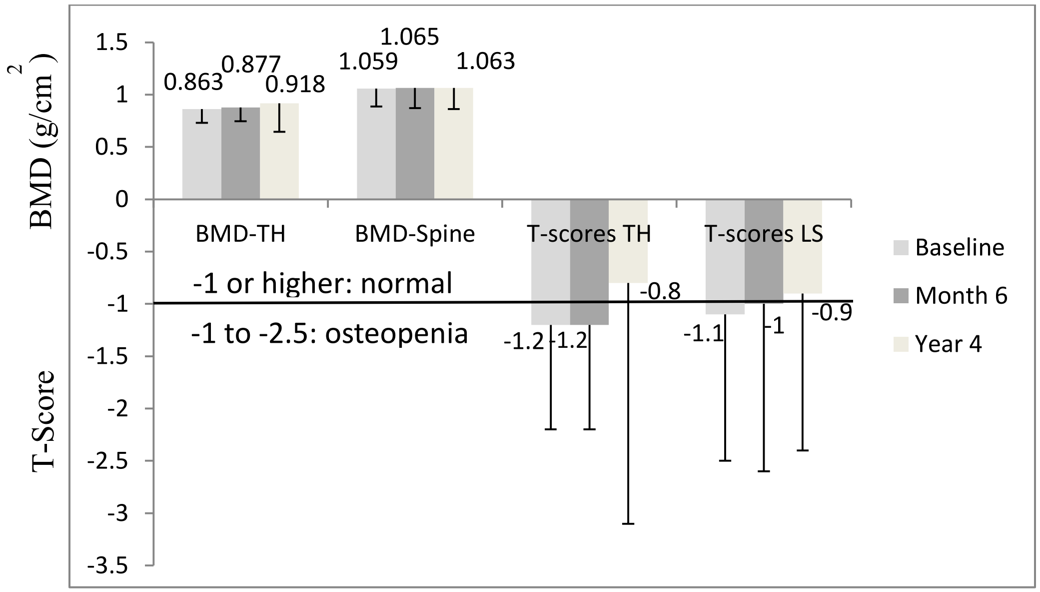






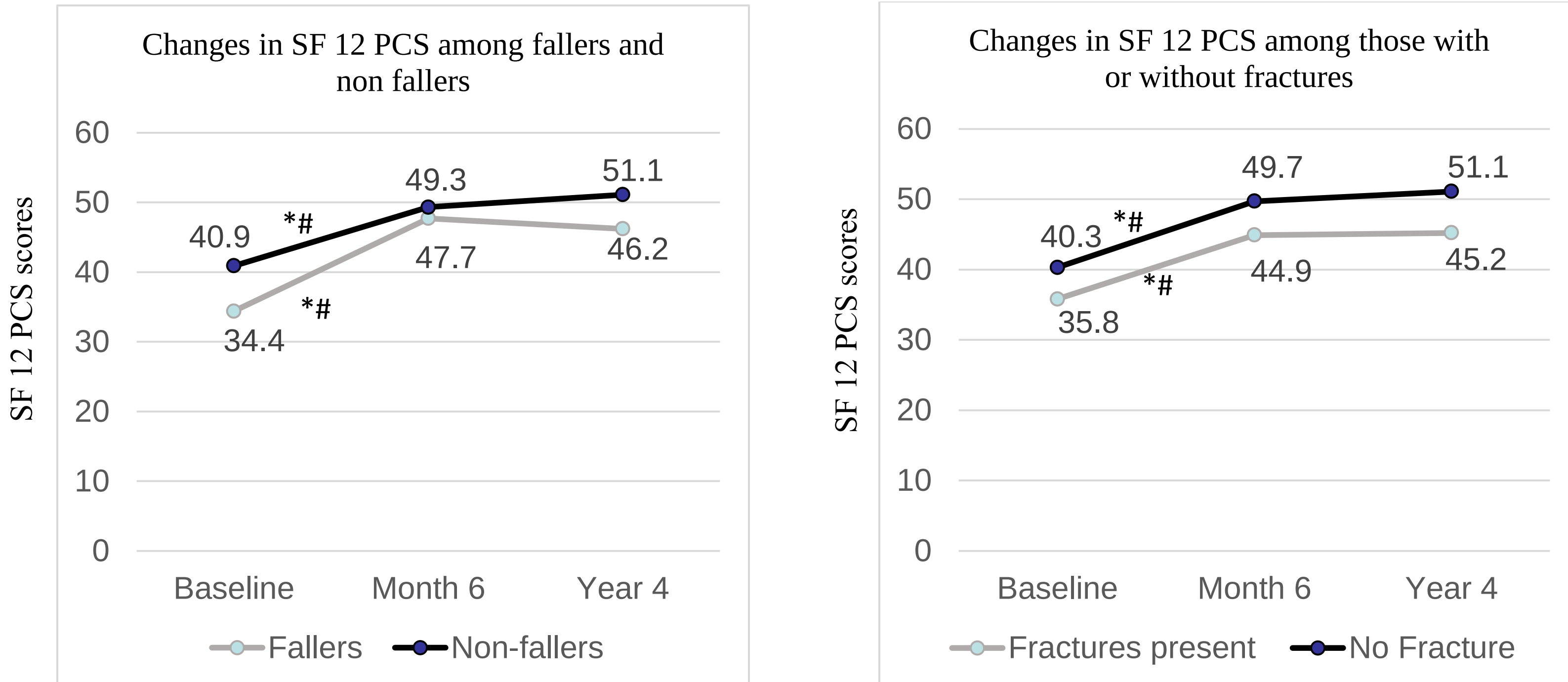
PRWE, Patient Rated Wrist Evaluation (0-100; 100 worst); RAPA, Rapid Assessment of Physical Activity (0-10; 10 best); MFES, Modified Fall Efficacy Scale (0-10; 10 best); SF-12-PCS, 12-item Short Form-Physical Component Summary scores (US norm=50 best); SF-12 MCS, 12-item Short Form-Mental component scores (US norm=50 best); *, significant change from baseline to 6m; #, significant change from baseline to 4 y; ^ significant change from 6m-4y

Fig. 2b. Longitudinal changes (mean ±SD) in bone mass at baseline, 6 months and at 4 years after distal radius fracture



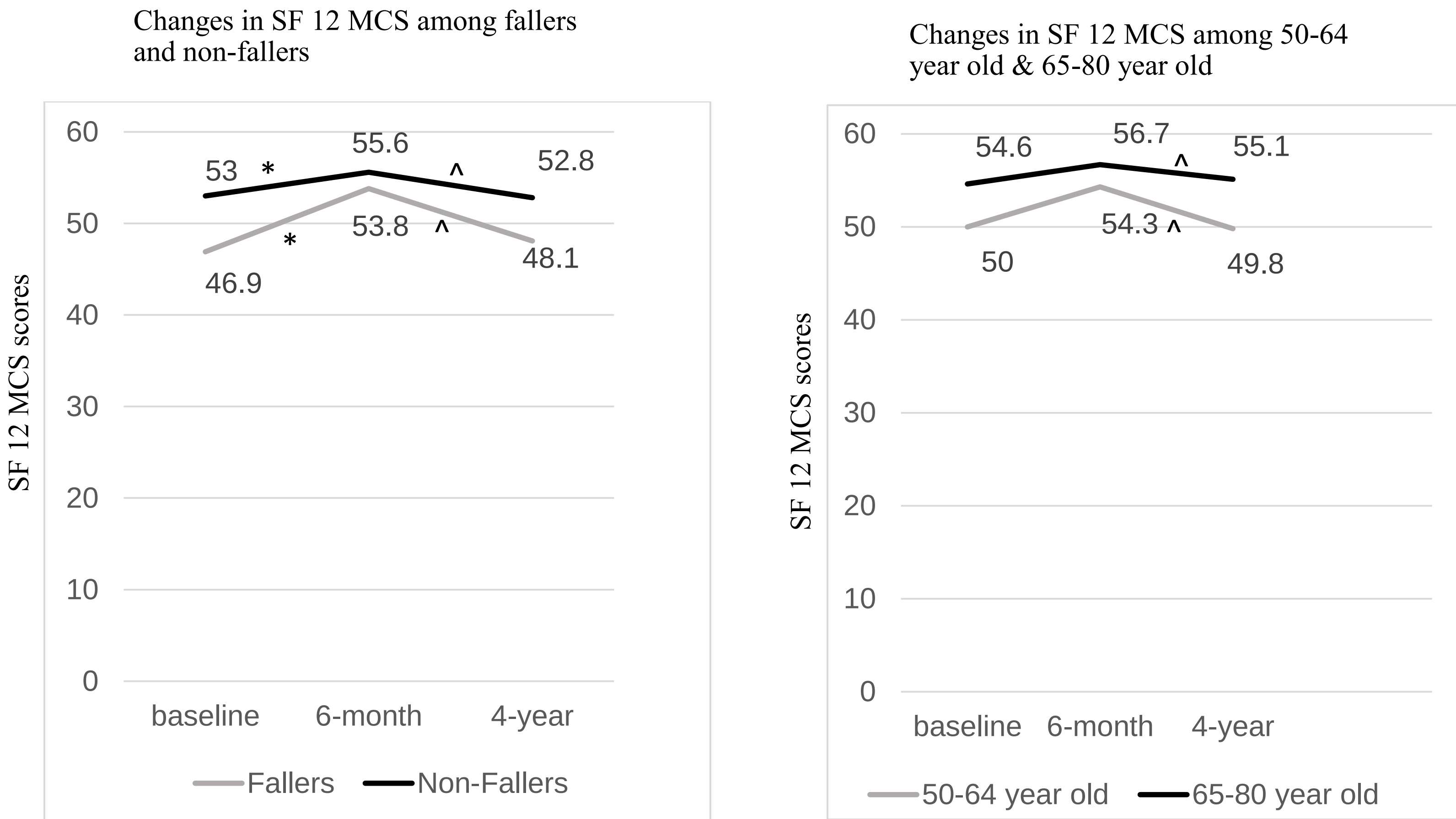
BMD, bone mineral density (≥ -1 normal); TH, total hip; LS, lumbar spine

Fig. 3. Longitudnal changes (mean ±SD) in SF12-Physical component summary scores at baseline, 6 months and at 4 years after distal radius fracture



*, significant change from baseline to 6 months; #, significant change from baseline to 4 years; SF-12, 12-item Short Form Health Survey

Fig. 4. Longitudnal changes (mean ±SD) in SF12-Mental Component Summary scores at baseline, 6 months and at 4 years after distal radius fracture



*, significant change from baseline to 6m; ^, significant change from 6 months to 4 years; SF-12, 12-item Short Form Health Survey

CHAPTER 3

ASSOCIATION OF MODIFIABLE RISK FACTORS WITH BONE MINERAL DENSITY AMONG PEOPLE WITH DISTAL RADIUS FRACTURE: A CROSS-SECTIONAL STUDY

Title: Association of modifiable risk factors with bone mineral density among people with distal radius fracture: A cross-sectional study

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ABSTRACT

Purpose: Distal radius fracture (DRF) in people >50 years is an early and independent predictor of future osteoporotic fractures. Currently, there are no studies demonstrating the extent to which modifiable risk factors explain bone mineral density (BMD) in people with DRF. Thus, the purpose of this study was to determine the extent to which modifiable risk factors such as balance, muscle strength, and physical activity can explain variability in BMD among people with DRF.

Methods: This cross-sectional study included 190 patients, 50-80 years old with a DRF. Participants were assessed for balance, muscle strength (unaffected hand grip, knee extensor, and plantar-flexor), physical activity and fracture-specific pain and disability using reliable and validated measures. Areal BMD at the femoral-neck (BMD-FN) and total-hip (BMD-TH) were assessed. Correlation and multiple linear regression was used to determine the contribution of modifiable risk factors to BMD.

Results: The mean age of the patients (163 females, 27 males) was 62±8 years. There was a weak positive correlation (r=0.25-0.40; p<0.05) between balance and muscle strength with BMD at both sites. Grip strength was an independent predictor explaining 17% ($F(1,78) = 15.19$, $p=0.0002$) and 12% ($F(1,79) = 10.80$, $p=0.001$) of total variability in BMD-FN (n=80) and BMD-TH (n=81), respectively. When stratified by age; balance ($R^2 =0.10$, $F(1,40) = 4.57$, $p=0.04$) and grip strength ($R^2 =0.32$, $F(1,23) = 10.78$, $p=0.003$) were independent significant predictors of BMD-FN among women aged 50-64 years (n=42) and 65-80 years (n=25), respectively.

Conclusions: Unaffected hand grip strength is an independent predictor of BMD in people with DRF. Since muscle strength and balance are modifiable predictors, future studies must investigate the role of muscle strength and balance in osteoporosis risk factor screening or for interventions following DRF.

Key Words: distal radius fracture, risk factor, bone density, muscle strength

INTRODUCTION

Osteoporosis, defined as a reduction in bone mineral density (BMD) and increased bone resorption, is a public health concern resulting in 8.9 million fractures per year globally.[1,2] Both the incidence and prevalence of osteoporosis is expected to increase with the rapid rise of our aging population. This raises an alarming need to identify people who are at risk of low BMD and bone fragility leading to osteoporotic (OP) fractures.

Distal radius fracture (DRF) is well documented to be an early sentinel event for secondary OP fractures.[3–5] Studies have reported that persons 50 years or older with DRF seem to have a preferential bone loss at the distal forearm and generalized low bone mass indicating a state of poor bone health.[6–8] A study by Ingel et al. demonstrated a significant decrease in BMD at 6 weeks, with a mean loss of 9% (P < 0.001); this remained decreased at one year following the DRF.[9] BMD is reported to be lower in 70-80% of patients with wrist fracture, predisposing people with DRF towards a greater risk of secondary fractures.[10–12] Cohort data from Rochester, Minnesota suggest a DRF is associated with an increased risk of vertebral fractures, five-fold for women and ten-fold for men[13] and a two-fold increase in hip fracture in women >70 years of age.[14] Future OP fractures of the hip and spine as sequelae of DRF results in a marked impact on morbidity, mortality and health care costs.[15–17] Twenty-eight percent of women and 37% of men who suffer a hip fracture die within the following year.[18] Given the substantial burden of OP fractures secondary to DRF, it is extremely important to investigate the modifiable risk factors associated with bone fragility in this population.

BMD testing using dual energy X-ray absorptiometry (DEXA) is considered the gold standard to predict the risk of OP fractures.[19] BMD is often reported to be less among seniors and females with DRF.[4,10,20] Well-known risk factors such as age[21–25] and sex[24,26] are non-modifiable, although they are important in the stratification of people who will be at higher risk of low BMD and future OP fractures after an episode of DRF. However, it might be a useful approach to investigate the modifiable factors which could influence BMD among patients with DRF. Two studies from Canada suggest that only 10-20% of patients with DRF have been assessed for BMD and treated for secondary fracture prevention.[27,28] This emphasizes an important need to determine modifiable predictors of BMD which can be targeted in routine physical therapy practice. Recently, studies have reported a transition to a physically inactive lifestyle[29–31], muscle weakness[32] and postural imbalance[31,33,34] among patients with DRF. Several studies have identified the association of modifiable risk factors with BMD among a variety of populations such as stroke[35], Parkinson[36,37], liver cirrhosis[38], Crohn's disease[39], kidney disease[40], diabetes[41], healthy post-menopausal women[42] and older adults[43] who are identified at risk of secondary OP fractures. Nevertheless, there are no studies investigating the modifiable determinants of BMD among people with DRF.

Unlike patients with spine or hip fractures, relatively healthy people with DRF have been noted to neglect preventive screening of bone health.[27,28,44–46] Also, it is not uncommon that therapists working in busy fracture clinic have often missed the opportunity to refer patients with DRF for BMD testing.[47–49] A 2010 narrative review published on hand therapy management of DRF suggests therapists hold unique training skills and opportunity to screen and intervene for modifiable risk factors related to postural balance, muscle weakness and physical inactivity among patients with DRF with a significant bone fragility.[50] However, over the course of specialization, therapists might not have continued to use these skills to identify patients at risk of secondary OP fractures.[49–51] Thus, the purposes of this study were to determine the following in people with DRF

1. whether modifiable risk factors and BMD vary by age and sex.

2. the extent to which modifiable risk factors alone or in combination explain variation in BMD and whether the strength of explanation is modified, when age and sex are controlled for.

3. the independent predictors of BMD among an age-stratified sample of women with DRF.

METHODS

Overview of the study

This study is a cross-sectional investigation of baseline data collected at 1-2 weeks post-injury as part of a larger cohort study evaluating change in activity and participation at one year following DRF.

Study Subjects

Patients (n=190) were recruited from a single tertiary hospital in London, Ontario between January 2010 and December 2013. Patients aged 50-80 years old with a DRF were eligible for inclusion. Patients with multiple fractures, previous known history of hip or vertebral fracture, neurological/cognitive impairments limiting the ability of a patient to give informed consent were excluded. All participants provided written informed consent and the study was approved by Research Ethics Board of the University of Western Ontario.

Study Variables

Outcome measure (dependent variable)

BMD: Currently, BMD assessment using DEXA is considered the gold standard for identifying individuals at risk of OP fractures.[52,19] Each standard deviation reduction in BMD is found to be associated with at least a 2-fold increase in age-adjusted fracture risk.[53] We measured areal BMD at the femoral neck (FN) and total hip (TH) (g/cm^2). We selected BMD assessment at both FN and TH as widely cited studies suggested these two sites be strong predictors of OP fractures.[53,54] As recommended by others, we expected that BMD assessment done at two sites would support the diagnostic sensitivity of our analysis.[52]

Independent Variables

Patients were assessed for balance, physical activity (PA), muscle strength of knee extensors (KE) and plantar flexors (PF), grip strength of unaffected hand, and fracture-specific pain/disability at baseline using reliable and validated measures as discussed in Table 1. The grip strength of the unaffected hand was evaluated at 3-months post-fracture. The details on assessment of these independent variables have been described in Chapter 4

Table 1 List of independent variables and outcome assessed at the baseline

	Variable	Measure
DEPENDENT VARIABLE	Bone strength - areal BMD was measured as g/cm^2 at femoral neck and total hip	# Dual energy X-ray absorptiometry (DEXA) using "Biodex System 3 Pro" Biodex Medical Systems, Inc., Shirley, NY, USA[19,52]
INDEPENDENT VARIABLE	Balance	# Biodex Balance system SD" Biodex Medical Systems, Inc., Shirley, NY, USA[55–57]
	Physical activity	*Rapid Assessment of Physical Activity (RAPA)[58]
	Hand-grip strength (unaffected hand)	#Hand-held dynamometer (Jamar hydrolic)[59]
	Knee extensor muscle strength (right)	#Biodex-Isometric peak Torque[60–62]
	Plantar flexor muscle strength (right)	#Biodex-Isometric peak Torque[60,62]
	Fracture-specific pain and disability	*Patient rated wrist evaluation (PRWE)[63,64]

* self-reported measure
\# standardized measure
BMD=bone mineral density; NY=New York; USA=United States of America
All measures were assessed at baseline except for hand grip strength which was evaluated at 3 months after distal radius fracture

Statistical Analyses

Statistical analyses were carried out using STATA/SE 12.0 software. Statistical significance was set at $p < 0.05$.

Descriptive statistics and t-test

The mean and standard deviation (SD) were used to summarize the quantitative variables stratified by age and sex. Counts and percentages were used for describing categorical data. Normality testing of dependent variables was performed using the Shapiro Wilk test. BMD at FN (BMD-FN) and BMD at TH (BMD-TH) were the primary outcomes and were treated as continuous variables. We used independent Student t-tests to investigate age and sex-based differences in modifiable risk factors and BMD.

Correlation and simple linear regression analysis

Bivariate correlations were used to look for the strength and direction of relationships between the dependent variables (BMD-FN & BMD-TH) and potential predictors (balance, PA, hand grip strength, KE and PF muscle strength) and to consider the presence of multicollinearity among the predictor variables. The correlation coefficient (r) of 0.00 to 0.19 was defined as very weak, 0.20 to 0.39 as weak, 0.40 to 0.69 as moderate, 0.70 to 0.89 as strong and 0.90 to 1.00 as very strong.[65] The partial correlation coefficient (r_p) was used to investigate the relationship between BMD and an independent variable while controlling for all other independent variables. Simple linear regression was then used to explore the strength of association between BMD and individual modifiable and non-modifiable risk factors.

Multiple regression analysis

For subsequent analyses, modifiable risk factors were simultaneously considered in a multiple linear regression model to determine the extent of variability explained in BMD while adjusted and unadjusted for age and sex. Only a significant bivariate predictors were selected for multiple linear regression to avoid model overfitting. We computed the variance inflation ratio (VIF) to look for multicollinearity among independent predictors and VIF of below 10 was considered acceptable. However, among two similar measures of lower extremity muscle strength explaining similar bivariate associations with BMD, we included only KE muscle strength in our prediction model to a) limit the number of independent variables b) reflect the use of KE muscle strength as a modifiable risk factor to predict BMD in previous literature[66] and c) to support knowledge translation, as we felt it might be easier to assess KE muscle strength in routine clinical practice. Further, we followed our analysis with formal regression diagnostics including tests for homogeneity (Breusch-Pagan/Cook-Weisberg test) and linearity of residuals (histogram, Shapiro-Wilk test, pnorm, qnorm plots) and ensured that there was no violation of the assumption of multicollinearity, homogeneity, normality, and linearity.[67] Residual versus fitted plots, leverage plots and Cook's distance were used to identify observations with high influence.

Stepwise multiple linear regression analyses were performed for the whole study sample as well as in the age-stratified female sample. The p-value for predictors to enter was ≤ 0.05 and p-value to remove was initially set at ≥ 0.06. However, p-value to remove was adjusted to 0.10 (less stringent) for BMD-TH for the age-stratified female sample to arrive at the most robust model. These prediction models generated coefficients of determination (R^2) as a measure of the extent of variability in the outcome, explained by the regression. To confirm the sensitivity of the prediction model obtained from the stepwise method, forward and backward selection regression methods were also used to determine if all methods resulted in the same set of predictors.

Power analysis: We used the G*Power software program to examine whether we were fully powered to determine a significant relationships/association for our bivariate correlation and multiple regression analysis.[68] This considers the sample size and number of predictors to correctly identify the existing relationships.

RESULTS

Participant characteristics

Our study sample consisted of 163 females and 27 males with DRF (mean age=62.11±7.68 years). About 93% of our sample was right-hand dominant; 40% injured their dominant hand. The age and sex-stratified descriptive statistics are presented as mean±standard deviation in Tables 2 and 3, respectively. As shown in Table 2, the majority were in the age group of 50-64 years, and predominantly females. While we had more female participants, the proportion of males and females within the two age groups was similar. Individuals in the 64-80 year old category with DRF had a significantly lower ($p<0.05$) BMD-FN, grip strength and PF muscle strength than 50-64 year old (see Table 2). Though not statistically a significant, we noticed BMD-TH, balance, PA, KE muscle strength, fracture specific pain/disability were comparatively poor among the small sample of 64-80 year old patients with DRF (see Table 2). Among males and females, females had a significantly ($p<0.05$) lower BMD-FN, BMD-TH, balance, grip strength, PF and KE muscle strength than males (see Table 3).

Table 2 Descriptive characteristics (age-based) of studied variables among people with distal radius fracture (n=190)

	50-64 yr old (n=121) Males: 17 (14%) Females: 104 (86%)		**65-80 yr old (n= 69)** Males: 10 (15%) Females: 59 (85%)		**p value**
Variable	**N**	**Mean (SD)**	**N**	**Mean (SD)**	
BMD-FN	79	0.870 (0.103)	51	0.821 (0.133)	0.01*
BMD-TH	80	0.906 (0.131)	51	0.879 (0.139)	0.27
Balance	103	2.1 (1.2)	55	2.3 (1.1)	0.33
Grip strength (unaffected hand)	83	26.7 (7.7)	45	23.4 (7.3)	0.02*
Plantar flexor muscle strength (right)	98	67.8 (37.5)	63	57.06 (33.2)	0.06

Knee extensor muscle strength (right)	100	90.6 (39.9)	63	74.9 (29.7)	.008*****
Physical Activity	103	4.0 (1.3)	66	3.9 (1.8)	0.74
Fracture-specific pain and disability	108	70.5 (18.4)	64	67.03 (21.8)	0.26

*****a significant at p<0.05
SD=standard deviation; BMD=bone mineral density; FN= femoral neck; TH= total hip; yr=year

Table 3 Descriptive characteristics (sex-based) of studied variables among people with DRF (n=190)

	Males (n=27) 50-64 yr old: 17 (63%) 65-80 yr old: 10 (37%)		Females (n= 163) 50-64 yr old: 104 (64%) 65-80 yr old: 59 (36%)		p value
Variable	**N**	**Mean (SD)**	**N**	**Mean (SD)**	
BMD-FN	20	0.949 (0.134)	111	0.833 (0.105)	0.0001******
BMD-TH	20	1.009 (0.142)	112	0.875 (0.122)	0.0001******
Balance	20	3.2 (0.9)	140	2.0 (1.1)	0.0001******
Grip strength (unaffected hand)	18	37.5 (9.9)	111	23.5 (5.2)	0.0001******
Plantar flexor muscle strength (right)	23	92.2 (40.6)	140	58.6 (33.1)	0.0001******
Knee extensor muscle strength (right)	24	123.6 (51.4)	141	78.0 (29.3)	0.0001******
Physical Activity	25	3.9 (1.4)	146	4.0 (1.5)	0.70

Fracture-specific pain and disability	25	74.4 (12.6)	149	68.1 (21.0)	0.14

******a significant at $p<0.001$
SD=standard deviation; BMD=bone mineral density; FN= femoral neck; TH= total hip; yr=year

Correlation and Simple linear regression

Relationship and Association between BMD and individual predictors

BMD-FN showed a moderate to weak positive correlation (r ranging from 0.25-0.40) but a significant ($p<0.05$) linear relationship with hand grip strength, PF strength, KE strength, and balance (see Table 4.) BMD-TH presented a weak but statistically a significant relationship with grip strength ($r=0.35$, $p=0.0006$) and balance ($r=0.28$, $p=0.002$) (see Table 4.) On controlled correlation analysis as represented by partial r (r_p), none of the modifiable risk factors were a significantly related with BMD-FN and BMD-TH. Simple linear regression analysis revealed that balance, grip strength, PF strength, KE strength, and age were each a significantly associated with BMD-FN. However, only balance and grip strength showed a significant ($p<0.05$) association with BMD-TH (see Table 4).

Table 4 Bivariate correlation and univariate association between individual modifiable risk factors and bone mineral density (BMD-Femoral neck and BMD-Total hip)

	BMD-FN					BMD-TH				
Variable	**N**	**r**	**r_p**	**B (p-value)**	**R^2**	**N**	**r**	**r_p**	**B (p-value)**	**R^2**
Balance	116	0.25*	0.07	0.02 (0.007) *	0.06*	118	0.28*	0.11	0.03 (0.002) *	0.08*
Grip strength	92	0.40**	0.10	0.006 (0.0001) *	0.16**	92	0.35**	0.13	0.006 (0.001) **	0.12**
PF muscle strength (rt)	119	0.26*	0.15	0.0008 (0.005) *	0.07*	120	0.13#	0.06	0.0005 (0.14)	0.02
KE muscle strength (rt)	120	0.27*	-0.01	0.0009 (0.003)*	0.07*	122	0.17#	-0.09	0.0006 (0.06)	0.03
Physical activity	122	-0.04	0.04	-0.003 (0.69)	0.001	122	-0.08	-0.04	-0.008 (0.35)	0.007
Fracture-specific pain and disability	124	-0.02	-0.03	-0.0001 (0.85)	0.0003	124	0.04	0.02	0.0003 (0.62)	0.002

p=level of significance; SD=standard deviation; BMD=bone mineral density; FN= femoral neck; TH= total hip; yr=year; rt=right; PF=plantar flexor; KE=knee extensor; R^2= coefficient of determination; B=unstandardized regression coefficient; r=Pearson correlation coefficient;
***** p <0.05, ****** p <0.001, **#** p <0.15

Multiple Regression

Variability in BMD as explained by modifiable risk factors

Regression diagnostics done to determine the appropriateness of data for multiple regression suggested the mild violation of the assumption of normality for residuals (BMD-FN p=0.04, BMD-TH p=0.02). ID 119 was identified as one of the influential observations with cooks distance of 0.22 (quite large in comparison to 4/n=0.05) and was removed, with no change in the overall fit of the model (R^2_{change} = 0.0097 for BMD-FN, R^2_{change}= 0.0154 for BMD-TH). In our final prediction model for BMD-FN and BMD-TH, there was no multicollinearity (VIF < 10), homogeneity assumption was fulfilled (p>0.05), and residuals were normally distributed (p>0.05). When adjusted for non-modifiable risk factors such as age and sex (data not shown in table), none of the risk factor independently explained variability in BMD but the modifiable risk factors collectively accounted for 20% and 16% of variability in BMD-FN (F(5,74) = 3.67, *p*=0.005, n=80) and BMD-TH (F(5,75) = 2.92, *p*=0.02, n=81) respectively. The overall fit of the regression line and beta weights are presented in Table 5a. There was no significant interaction of age and sex with any of the modifiable risk factors. We were not powered to test the interactions among the modifiable risk factors and thus these were not tested. When unadjusted for age and sex (see Table 5), grip strength of the unaffected hand explained a small but a significant amount of the variability in BMD-FN (R^2 =0.17, F(3,77) = 5.20, *p*=0.002,n=81) and BMD-TH (R^2 =0.14, F(3,78) = 4.23, *p*=0.008, n=82). The actual percent change in the regression coefficient of grip strength on the unadjusted analysis was 1.5 %.

Table 5 Unadjusted linear regression modelling of the association of modifiable risk factors on BMD

Variable	**BMD-Femoral neck (n=81)**			**BMD-TH (n=82)**		
Model summary	R^2	**Unadjusted R^2**	**Standard error**	R^2	**Unadjusted R^2**	**Standard error**
	0.17*	0.14	0.11	0.14*	0.11	0.13
Coefficients	**B (95% CI)**		**β**	**B (95% CI)**		**β**
Constant	0.69(0.60, 0.77)			0.72(0.62,0.82)		
Balance	0.007 (-0.01,0.03)		0.07	0.02 (-0.008,0.04)		0.14
Grip strength	0.005 (0.0008,0.009)*		0.34	0.006 (0.001,0.01) *		0.35
Knee extensor strength	0.0002 (-0.0007,0.001)		0.06	-0.0003 (-0.001,0.0007)		-0.08

*****p <0.05

CI=confidence interval, rt=right; BMD=bone mineral density; PF= plantar flexion muscle; R^2= coefficient of determination; B=unstandardized regression coefficient; β=standardized regression coefficient

Stepwise multiple linear regression

Independent predictor of BMD (see Table 6): The results showed that grip strength was the only independent predictor explaining 17 % and 12% of total variability in BMD-FN ($F(1,78) = 15.19$, p=0.0002) and BMD-TH ($F(1,79) = 10.80$, p=0.001), while all other modifiable risk factors were removed from the model. Mathematically, the final prediction model for full sample was presented as: BMD-femoral neck = 0.69+0.006 (grip strength) and BMD-total hip = 0.73+0.006 (grip strength)**.**

Table 6 Independent predictors of bone mineral density: Results from stepwise multiple linear regression for full sample

Variable	**BMD-Femoral neck (n=80)**			**BMD-total hip (n=81)**		
Model summary	**R^2**	**Adjusted R^2**	**Standard error**	**R^2**	**Adjusted R^2**	**Standard error**
	0.17*	0.16	0.11	0.12*	0.10	0.12
Coefficients	**B**	**95% CI**		**B**	**95% CI**	
Constant	0.69	0.003,0.008		0.73	0.64, 0.82	
Grip strength	0.006*	0.62, 0.77		0.006*	0.002, 0.009	

*p <0.05

CI=confidence interval; BMD=bone mineral density; B=unstandardized regression coefficient; R^2= coefficient of determination

BMD-femoral neck = 0.69+0.006 (grip strength)
BMD-total hip = 0.73+0.006 (grip strength)

The age-stratified stepwise regression analysis done to explore the association between BMD and modifiable risk factors among two different age groups of women with DRF is presented in Table 7. The regression analysis revealed that balance alone explained 10% (R^2 =0.10, F(1,40) = 4.57, *p*=0.04) of total variability in BMD-FN among 50-64 year old women with DRF. Hand grip strength was identified as the independent predictor explaining 32% (R^2 =0.32, F(1,23) = 10.78, *p*=0.003) of the total variability in BMD-FN among 65-80 year old postmenopausal women with DRF. However, modifiable risk factors were omitted from the regression model at pe=<0.05 and pr = >0.06 and were not able to explain variability in BMD-TH when the sample of women with DRF was stratified by age. On using pe=<0.05 and less stringent pr >0.1, we noted similar findings between the two bone testing sites; both balance (R^2 =0.07, F(1,41) = 3.48, *p*=0.069) and hand grip strength (R^2 =0.14, F(1,23) = 3.79, *p*=0.063) were revealed as independent predictors of BMD-TH in 50-64 year old and 65-80 year old women with DRF, respectively (data not presented in table). We were underpowered to conduct age-stratified stepwise regression analysis for a male-only sample.

Table 7 Independent predictors of bone mineral density at femoral-neck: Results from stepwise multiple linear regression in age-stratified female sample

BMD-FN (n=42) if age 50-64				BMD-FN (n=25) if age 65-80			
Model summary	**R^2**	**Adjusted R^2**	**Standard error**	**Model summary**	**R^2**	**Adjusted R^2**	**Standard error**
	0.10*	0.08	0.09		0.32*	0.29	0.10
Coefficient	**B**	**95% CI**		**Coefficient**	**B**	**95% CI**	
Constant	0.78	0.71, 0.84		**constant**	0.45	0.23,0.67	
Balance	0.03*	0.001, 0.06		**Grip strength**	0.02*	0.006, 0.03	

*p <0.05

CI= confidence interval, BMD-FN= BMD-femoral neck, B= unstandardized regression coefficient; R^2= coefficient of determination

Age group (50-64 year old): BMD-FN=0.78+0.03 (balance)

Age group (65-80 year old): BMD-FN=0.45+0.02 (grip strength)

The post hoc power analysis suggested that on correlation analysis, the power of our study ranged from 83-99% for all variables except for the relationship of BMD with RAPA (power =10%) and PRWE (power=7%). For multiple regression analysis, we were fully powered to provide conclusive evidence for independent predictor of BMD-FN (power=87%) but fell below the target level of 80% for BMD-TH (power= 69 %). Also, we were not fully powered to investigate independent predictor of BMD-FN for age stratified women only sample with DRF. (Power for 50-64 year old=37%, 65-80 year old=22 %). For a fully powered (0.80) study with moderate effect size (0.15), we were in need of 92 subjects for the whole sample and 77 subjects for each age-stratified women only sample.

DISCUSSION

In this study, we found that unaffected hand grip strength was an independent modifiable risk factor associated with BMD in people with DRF. Both reduced hand grip strength and poor postural balance were associated with low BMD among women with DRF. Grip strength has shown correlation with both overall muscle strength and fitness in previous studies.[69–72] Also, postural balance is seen to be related with BMD in previous studies.[42,73] Postural balance may be either a predictor or consequence of physical activity[74,75]; and weight-bearing physical activity is known to be a modifier of bone density.[76] Thus, we expect these predictors act indirectly on bone density. Our results not only support recently published papers suggesting that patients with DRF tend to have lower contra-lateral grip strength[30,31] and poor postural balance[33,34], but also add clinical implications of these findings in predicting BMD. Our study adds to the literature since we had a larger sample, and we used a stratified regression models to determine independent modifiable determinants of BMD.

In consistency with other studies,[77–79] we identified that advancing age results in reduction in muscle strength and BMD. We dichotomized our participants to 50-64 and 65-80 year age groups as the substantial bone loss usually occur at around 50 years in women and 65 years in men. When compared with males, females presented significantly lower BMD, muscle strength, and postural balance. Similar to our findings, studies have shown that bone strength, muscle strength and balance to be lower in women with DRF.[32,33] The reduction in estrogen and changes in muscle architecture (increase in non-contractile tissue such as intramuscular fat, increase muscle atrophy especially of type 2 muscle fibers) with the onset of menopause could be one of the reasons for the sex based differences.[80,81]Among all modifiable risk factors, hand grip strength, lower extremity strength and balance presented a significant relationship with the BMD. Our results were consistent with other studies confirming the importance of muscle strength to BMD.[42,82] In 117 physically active women aged 50 years or older, Marin et al. noted a high correlation of hand grip strength and BMD, irrespective of the site of BMD, while static balance exhibited a weakly positive, but a significant correlation with spinal bone density.[42] While previous studies have shown leg extensor muscle strength as a predictor of BMD among patients with Parkinson disease[36], we did not find such relationship in our study. This may be because our sample was healthier, that grip is highly correlated with leg strength, or that grip strength has less measurement error to diffuse the observable correlation.

Physical activity was not found to be associated with BMD. This was in agreement with Stewart et al. who reported no a significant relationship between routine physical activity with BMD among 55-75 year old healthy sample of men and women.[78] Our results were contradictory to the literature which suggest that skeletal loading produced during physical activities by either weight-bearing against gravity or due to the traction forces applied by the muscles on the bone results in dynamic stress on the bone tissue.[83,84] As a subsequent biologic response, the stress results in increased BMD due to osteoblastic activity.[85–89] But in most of these studies, PA levels were confined to either of adolescent girls or young adult men except the one study[88] done in elderly women. Bergstrom et al. have reported that physically active individuals have higher

BMD than those with sedentary lifestyles.[90] Similarly, a recent study has identified that 60 minutes of daily moderate to vigorous recreational physical activity results in increased BMD at femoral and spinal sites in adolescent girls but not in the older women.[91] Instead, the increased amount of sedentary time was found to be associated with the lower BMD in older women.[91] Though we did not evaluate the amount of sedentary time in our study, it might be an interesting area to consider in future research. We must acknowledge that the outcome measure used to evaluate physical activity in our study has been estimated to exhibit lower reliability estimates (ICC= 0.68)[92] and has not been validated for people with DRF. Furthermore, RAPA is a 9 item short questionnaire which might not reflect a wide range of PA engaged in by older adults with DRF which might have also biased our findings.

Similarly, it was interesting to note a lack of a significant relationship between fracture-specific pain/disability and BMD. While pain and disability are important outcomes, they do resolve within 6-months for the majority of patients with DRF[93]; this may be why they do not show an impact on BMD. Overall, we found that hand grip strength was the only risk factor which independently explained variability in BMD in a complete sample of people with DRF. This finding was similar to previous studies.[23,94,95] Interestingly, there was no difference in the modifiable determinant of BMD irrespective of whether site was at femoral neck or TH. We could not control for confounding effect exhibited by age and sex prior to the study. So, we stratified our sample to control for known confounders identified in our study.

Age and sex stratified analyses in our study revealed that balance and hand grip strength respectively explained 10% and 32% of the variability in femoral BMD in 50-64 and 65-80 year old women sample of people with DRF. The postural balance could explain variability in BMD based on the fact that postural imbalance might cause shifting of body weight away from the center of gravity which can lead to less weight bearing on the bones. Future studies must investigate if postural balance stays as an independent predictor of BMD in a body weight adjusted sample of people with DRF. Abreu et al. suggest that the aging process among elderly women with osteoporosis results in impaired sensory functions, posture and muscle imbalance which then interferes with both mediolateral and anteroposterior static balance stability.[96] Previous research has identified the association of balance impairment with low BMD among postmenopausal women suggesting the relationship between the bone disorder and balance impairment but not vice versa as noted in our study which limited our ability to compare it further with the existing literature.[73,96] Recently, Mehta et al. have established high reliability for "Timed up and go" (TUG) test for assessment of functional balance among patients with DRF (age range 62.6±7.6).[92] Based on results from our study, we advise that therapists consider evaluating postural balance using TUG to screen if their patients are at risk of low BMD and need a referral for BMD testing.

Similar to the findings seen in our study, Monaco et al. reported that hand grip strength explained 33% of the variability in distal radius BMD among 51-80 year old sample (n=102) of postmenopausal women.[94] In other studies, hand grip strength has been identified to be an independent predictor of hip,[95,97] femoral or spine BMD,[23,42,95,97,98] among women. On the contrary, Zimmerman et al. did not find any association between grip strength and BMD-TH among postmenopausal women.[98] However, they were underpowered to confirm a significant association. Although muscle forces have a positive influence on building bone[99], the size, and location of the grip muscles makes it unlikely to directly impact BMD at the hip or femoral neck. Rather grip strength may be an indicator of overall muscle strength and fitness[69–72], or confounding the relationship between activity and BMD. Conversely, better grip strength may allow people to engage in a more active lifestyle or occupational tasks that involve weight-bearing and thus indirectly could be related to better bone health. As per our understanding, due to the distant location of the site of BMD testing used in our study, this relationship is not due to the direct force of muscles on the bone as increased joint reaction force could be expected as a result of muscle contraction. Our data did not explain the mechanism or direct cause-effect relationship between wrist/hand muscle force and BMD reported at distal sites i.e. whether the relationship could be related to common genes[100] or due to some other unexplained reasons. Probably, we might explain this association as increased compensatory physical stress or muscle contraction on unaffected hand could have resulted in localized bone formation which could have improved the overall bone metabolism and had its effect on the distant skeleton.[101] Moreover, in many studies, hand grip strength is determinant of functional limitation, frailty, functional decline, and mortality among older adults.[102–105]

It was not uncommon that grip strength of the unaffected hand was evaluated in our study at 3 month of follow-up. The hand grip strength of the unaffected hand has been used previously as a reference value.[5,31,106,107] Moreover, in this study we aimed to evaluate the extent of variability explained in the BMD and not to estimate the recovery pattern of hand function.

Overall, the findings from the present study must be considered within the context of the strengths and limitations. This study has addressed a novel issue and provided an important perspective to physical therapists evaluating hand grip strength as part of the routine clinical assessment of patients with DRF. Therapists might consider evaluating grip strength of unaffected hand and comparing it with the norms to identify those who might benefit with a referral for BMD testing. However, due to the cross-sectional nature of evidence, the association between hand grip strength and BMD cannot be interpreted as causal. Future prospective research should investigate the causal relationship between wrist-hand muscle and bone interaction to determine if strengthening of hand grip strength could improve BMD among patients with DRF. Our age-stratified results are limited to females with DRF which facilitates internal validity of our findings. We strongly recommend that subsequent studies should be focused on identifying modifiable determinants of BMD among males. Also, future studies must be conducted on a large sample to validate the preliminary findings established in this study and to determine the cut off value for grip strength and actual balance scores which could identify patients at risk of secondary OP after DRF.

CONCLUSIONS

Unaffected hand grip strength (assessed at 3 months post DRF) and postural balance can be considered as modifiable factors associated with BMD among people with DRF. Since hand grip strength and balance are modifiable factors that are related to bone health, they may represent useful preventive screening approaches for secondary OP fractures.

KEY MESSAGES

What is already known on this topic

DRF is an early and independent predictor of secondary OP fractures and majority of older people with DRF present with low BMD. Modifiable risk factors such as muscle strength, balance and physical activity which can be easily evaluated in the physical therapy practice can predict BMD in a variety of patient population with musculoskeletal and neurological disorders or among healthy elderly.

What this study adds

This study adds that unaffected hand grip strength evaluated at 3-months post fracture predicts BMD at the time of DRF. Postmenopausal women with low grip strength should be considered at higher risk and may need more detailed bone health assessment and secondary OP fracture prevention.

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CHAPTER 4

RISK FACTORS PREDICTING SUBSEQUENT FALLS AND OSTEOPOROTIC FRACTURES AT FOUR YEARS AFTER DISTAL RADIUS FRACTURE – A PROSPECTIVE COHORT STUDY

Title: Risk factors predicting subsequent falls and osteoporotic fractures at four years after distal radius fracture – A prospective cohort study

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Abstract

Purpose: To determine the extent to which modifiable risk factors alone or in combination with bone mineral density (BMD) and non-modifiable risk factors could predict subsequent falls (at 6 months prior to 4-year follow-up) and osteoporotic (OP) fractures after DRF.

Methods: We assessed a cohort of patients (n=191; mean age=62±8 years; female=88.5%) shortly after DRF (baseline) and again at four years to identify subsequent falls (in last 6 months) or OP fractures. Baseline predictors collected included: age, sex and prior history of multiple (≥2) falls; and modifiable predictors such as balance, muscle strength, physical activity, fear of falling, BMD, fracture-specific pain/disability, and general health status (HS). Univariate, multivariate and stepwise logistic regression analysis was conducted to compute odds ratio (OR) with 95% CI to express the extent of association between the risk factors and outcome (subsequent falls and fracture).

Results: Among 113 respondents, 24% reported ≥1 subsequent fall and 19% reported >1 subsequent fracture at a mean four years after DRF. The significant predictors of subsequent falls included: poor balance (OR=3.3, 95% CI=1.1, 10.5), low BMD at total hip (OR=3.3, 95% CI=1.1, 10.3), high scores of fracture-specific pain/disability (OR=3.0, 95% CI=1.1, 7.8) and prior falls (OR= 3.4, 95% CI=1.3, 8.8). When adjusted for BMD, age, and sex, only prior falls (OR= 4.1, 95% CI=1.1, 15.8) remained significant. None of the modifiable or non-modifiable risk factors were significantly associated with subsequent fractures. Although the point estimate of the odds of subsequent fracture in patients with osteopenia or osteoporosis was elevated, confidence intervals were wide and nonsignificant (OR= 4.5, 95% CI=0.7, 29.3). The probability to predict subsequent falls ranged from 64% to 90% with our adjusted regression models, while the probability to predict subsequent fractures ranged from 10% to 44%. Our prediction model consisting of modifiable risk factors such as postural balance, fracture-specific pain/disability and BMD showed acceptable (AUC=0.70) discriminative ability to identify patients who might be at risk of subsequent falls and OP fractures after DRF.

Conclusion: Prior history of multiple falls (≥2) is an independent predictor of subsequent falls in patients with DRF. In clinical practice, screening of patients for balance, fracture-specific pain/disability, BMD and prior falls can be a useful strategy to identify those who might be at risk of subsequent falls after their first DRF.

Key words: wrist fracture, osteoporosis, falls, bone density, risk factors

Conflict of Interest: NA

Mini Abstract

In a prospective cohort of 113 patients followed up at 4 years after DRF, 24% of patients' experienced a subsequent fall and 19% experienced a subsequent fracture. People with poor balance, greater fracture-specific pain/disability, osteopenia or osteoporosis and a prior history of multiple falls had nearly a 3 times higher odds of subsequent falls. People diagnosed with osteopenia or osteoporosis had 4 times higher odds of a subsequent fracture.

Introduction

Distal radius fracture (DRF) is the most common low energy fracture caused by a fall on an outstretched hand from a standing height or lower [1]. In males and females over the age of 50 years, the lifetime risk of DRF is estimated to be 6% and 33%, respectively [2,3]. In the United States [US), the annual cost of 1.1 billion is attributed to the treatment of DRF associated with osteoporosis [4].

Patients with fall-related DRF have been identified to be at high risk of subsequent falls [5–7]. Reduced physical activity (PA) due to pain, disability and fear of falling (FOF) after fall-related DRF is theorized to increase the risk of future falls and osteoporotic (OP) fractures by increased bone loss and decreased effectiveness of protective responses through the deterioration of muscular strength, balance, coordination, and reaction time [6–13].

High-quality evidence suggests that DRF is an early and independent predictor of future OP fractures at other skeletal sites [14,15]. In a 3 year follow-up of 158,940 postmenopausal women (PMW), aged 50-98 years, in the National Osteoporosis Risk Assessment (NORA) study, it was reported that a prior wrist fracture increased future fracture risk three-fold for the wrist and two-fold for OP fractures at other skeletal sites [14]. In another large clinical cohort from Manitoba, Hodsman et al. showed that although the risk of subsequent fracture at ten years after DRF was substantially lower than after OP fracture at other skeletal sites but overall risk was significantly higher by 11% ($p<0.001$) than those without a prior fracture [16].

Currently, BMD assessment using dual energy X-ray absorptiometry (DEXA) is considered the gold standard for identifying individuals at risk of OP fractures [17,18]. However, the NORA study and meta-analysis of international data demonstrate that BMD is a minor risk factor given clinical risk factors such as prior fragility fracture [14,19]. In a very recent study, PMW with a wrist fracture who were followed over a period of 11.8 years experienced 1.5 fold higher risk of subsequent hip fractures in comparison to healthy controls without fracture [15]. Interestingly, this association between wrist fracture and subsequent fractures was independent of other OP risk factors and baseline BMD [15]. Considering that BMD alone could underestimate the risk of subsequent fractures, multiple studies have suggested the need to address clinical risk factors for secondary prevention of subsequent fractures among patients with DRF [6,15,20,21].

High quality studies have addressed screening [22–27] and physical therapy management [28–31] to mitigate multiple modifiable risk factors as a means of reducing the burden of falls and OP fractures in community-dwelling elderly [22,23,26], PMW women [27] and people with hip fractures [24,25]. However, there is limited evidence to quantify which of these modifiable risk factors are early and sensitive indicators of subsequent falls and OP fractures in the fall-related DRF population who are relatively young and potentially healthier than the hip or vertebral fracture population. The most widely cited fracture risk prediction tools such as the Garven model [32] and fracture risk assessment tool (FRAX) [33] assess 5-10 year absolute fracture risk but do not include modifiable risk factors related to physical functioning such as balance, muscle strength, PA and FOF which can be easily targeted in rehabilitation for future falls/fracture prevention. The non-modifiable factors such as age [34–37], sex [38–40] and prior fall history [22,23,35,37,41] are well accepted predictors of falls and fractures. Exploring and understanding the modifiable factors which can predict subsequent falls and fractures after DRF could help to address the existing knowledge to practice gap for subsequent fall/fracture prevention for people with DRF. Also, we consider it to be a crucial step in the identification of patients at risk and to design appropriate treatment strategies. The objectives of our study were to determine i) the extent to which modifiable clinical factors such as balance, lower extremity (LE) muscle strength, grip strength, PA, FOF, fracture-related pain and disability, general HS and BMD present at time of a DRF predict subsequent falls and osteoporotic fractures at 4-years after DRF ii) the association of modifiable risk factors with subsequent falls and osteoporotic fractures after controlling for BMD and non-modifiable factors (age, sex, and prior history of multiple falls).

Methods

Study design and Participants

This was a prospective cohort study conducted at Roth-McFarlane Hand and Upper Limb Centre (HULC), London, Ontario. Patients aged 50-80 years old and diagnosed with DRF who had previously consented for baseline and follow-up assessments were considered eligible to participate in this longer term follow-up study. Patients with poor English comprehension, unable to provide informed consent, unable to be scheduled for BMD assessment and those with neurological/cognitive impairments were excluded. This study was approved by Research Ethics Board of University of Western Ontario.

Study Procedure

The patient's age, sex, prior history of multiple (≥2) falls, occupation, hand dominance, mechanism of fracture, side of fractured hand, type of treatment, work status, worker compensation claim, smoking, alcohol intake, and education were recorded shortly after sustaining the DRF. These values constitute the baseline values used in the present study. Eligible patients (n=191) were invited by mail to participate in a 4-year follow-up. A package consisting of the letter of invitation, a patient information sheet, a consent form, a short questionnaire and a pre-paid envelope was mailed. The short questionnaire included a question on incidence of subsequent falls in the last 6 months (n≥1; yes/no), presence of a new fracture at any site (n≥1; yes/no), location/site of fracture and a question to rule out if fracture was caused by a fall from a standing height or by a high energy trauma such as motor vehicle accident. Patients were requested to return the completed questionnaire with the signed consent form in the stamped self-addressed envelope within two weeks. Two reminder phone calls were made to all non-responders when there was no response at 5 weeks after the first mailing. The primary investigator had phoned non-responder patients (n=99) to obtain information regarding any subsequent fall in the last 6 months (n≥1; yes/no) or fracture at any site (n≥1; yes/no).

Study Measures

Dependent/Outcome variable

Incident fall (occurred in last 6 months prior to 4-year follow up) and incident OP fractures (occurred any time after first DRF): A fall was defined as "an unintentional change in position resulting in coming to rest at a lower level such as a chair or on the ground" [42]. Incident OP fractures were defined as any new fracture at sites which are age-dependent and have shown a graded relationship with BMD such as the proximal femur, vertebral, forearm, humerus, pelvis, clavicle, scapula, sternum, ribs, and ankle [43,44].Fractures of distal tibia and fibula were considered as OP fractures only in females but not in males. Fracture of any other bones such as ankle, hands, fingers, feet, toes, patella, face and skull were not considered as OP fracture [43,44].

Potential Predictors

The predictor variables were assessed at the baseline using performance measures for balance, lower-extremity muscle strength and hand grip strength. Self-reported outcome measures were used to evaluate PA, FOF, fracture-specific pain and disability, and general HS. DEXA was used to assess BMD.

A. Performance measures

Balance was assessed using the "Biodex Balance system SD" (BBS, Biodex Medical Systems Inc., Shirley, NY, USA) a multiaxial railed perturbation device that provides the objective recording of an individual's ability to stabilize the joint to withstand dynamic stress [45,46]. A standardized procedure was followed according to the manufacturer instruction to evaluate the fall risk test (FRT) scores [47]. BBS SD program provides age specified norms for FRT which we used to categorize our participants as having an average (normal) or worse than average (above normal) scores. Recently, good and acceptable test-retest reliability (intraclass correlation coefficient (ICC)=0.69) has been established for the FRT among physically active older adults [48].

LE isometric muscle strength was measured using the "Biodex System 3 Pro dynamometer" (Biodex Medical Systems Inc., Shirley, NY, USA). Each patient was tested for knee extension (KE) and ankle plantar flexion (PF) muscle strength in both the legs using standardized procedures as described in the literature [49]. The leg dominance was determined based on the preference of leg to kick a ball. The Biodex system has shown good reliability (ICC=0.58-0.93) for assessment of knee and ankle muscle strength/peak power in the elderly population [50,51].

Hand grip strength was determined using a hand-held dynamometer (NK Digit-grip device). Hand-held dynamometer is one of the most reliable (ICC=0.95) and a valid measures for the assessment of hand grip strength [52,53]. The grip strength was assessed 3 month post-DRF for both injured and uninjured hand using standardized methods recommended by American Society of Hand Therapists [54]. The hand grip strength was reported as an average of two trials and the peak force was measured in kilograms.

To ease the clinical interpretation of muscle strength assessment done among both dominant and non-dominant (ND) extremities, we computed strength deficit for both LE muscle strength as well as hand grip strength. The strength deficit for LE muscle strength was computed as the deficit in the strength of non-dominant LE normalized to the dominant one, using the formula [55,56]:

LE muscle strength deficit = 100 - (ND/D*100)

Similarly, hand grip strength deficit was computed as the deficit in the strength of injured hand normalized to the non-injured one, using the formula [55,56]:

Hand grip strength deficit = 100 – (injured/non injured*100)

B. Self-reported measures

PA was evaluated using the 10-item Rapid Assessment of Physical Activity (RAPA) questionnaire [57]. Each question is answered as a yes/no response and a score of ≥6 suggests a good level of PA. RAPA has proven reliability and validity for PA assessment particularly in the older people [57,58].

FOF was assessed using the Modified Fall Efficacy Scale (MFES), a 14-item questionnaire that evaluates confidence in one's ability to perform activities of daily living without falling [59]. Subjects are asked to rate their confidence in performing each activity without falling, on a scale ranging from 0 (not confident) to 10 (completely confident). The total score is computed as an average score across all 14 items, and a score of less than 8 indicates a high FOF [59,60]. The reliability (ICC=0.93, Cronbach's alpha=0.95) and validity of the MFES has been well-established in the older adult population [60].

Fracture-specific pain and disability was assessed using the Patient-Rated Wrist Evaluation (PRWE), a standardized 15-item questionnaire [61]. The PRWE consist of 2 subscales evaluating pain and disability, respectively, at the wrist and hand. The total score can vary from 0-100 with a higher score indicating more pain and functional disability. The PRWE is a reliable (ICC>0.90) [61]and valid outcome measure (Standardized response mean=2.27) used to evaluate pain and disability in DRF population [62]. An improvement by 11.5 points and 11 points is respectively considered as the minimal clinically important difference (MCID) and minimal detectable change in PRWE scores for patients with DRF [63].

General health was evaluated using 12-item Short Form (SF-12v2) Health Survey, an improvised 12-item version of the 36-item Short Form (SF 36) Health Survey. SF-12v2 is a generic self-report measure with well-established reliability and validity [64–66]. The 12 items of the SF-12v2 measure 8 health domains of original 36-item questionnaire: physical functioning (2 items), role physical (2 items), bodily pain (1 item), general health (1 item), vitality (1 item), social functioning (1 item), role emotional (2 items), and mental health (2 items) [66]. These domains can be categorized into a physical component summary (PCS) score and a mental component summary (MCS) scores. The total score varies from 0 to 100, with a higher score indicating better functioning, well-being or general health. A score of 50 or more indicates a positive perception of health and a score below 50 indicates a negative perception [66].

C. Dual Energy X-ray Absorptiometry (DEXA)

BMD was measured at the lumbar spine (L2-L4) and hip (left/non dominant) using DEXA by a trained health professional at the HULC. Based on the recommendation from previous studies, we selected T-score assessments from the lumbar spine (LS) and total hip (TH) as the two sites for fracture risk prediction [18,67]. The World Health Organization (WHO) definition for osteoporosis was used to categorize the patients as normal with a T-score of -1 or higher, osteopenia with a T score between -1 and -2.5 and osteoporosis with a T-score of -2.5 or lower [68].

D. Non-modifiable predictors as control variable

The baseline data on the patient's age, sex and prior history of multiple falls (≥2) was extracted from the existing database.

For clinical interpretation, we dichotomized (2 categories) the continuous and categorical variables to represent low and high risk categories. We selected cut-off points according to the clinical normative standard for variables such as balance-FRT (36-53 year old:1.23-3.03, 54-71 year old: 1.79 to 3.35, 72 to 89 year old: 1.90 to 3.50 as normal; > normal as impaired balance) [47], general HS (>50 points as normal; ≤ 50 points as poor HS) [66,69], BMD (-1 and above as normal; -1.1 and below as osteopenia or osteoporosis) [68] or based on the pre-established optimal point suggested in the literature such as for RAPA (6 points and above as normal; <6 points as inactive) [57] and MFES (8 points and above as normal; <8 points as high FOF) [59,60]. For variables such as PRWE, we dichotomized by first grouping the scores into quartiles (25^{th}, 50^{th} and 75^{th} percentile) and selected 75^{th} percentile value as the optimal cut off point based on our clinical expertise and the point with the smallest log likelihood value (best fit) [22,70]. For muscle strength deficit, we tested 3 cut-off points as recommended in the literature [49]: 0-10% (no deficit), 11-25% (mild weakness) and >25% (marked weakness). Similar to PRWE, we had chosen optimal cut-off point for the muscle strength deficit based on the recommendations from the literature [71], our clinical expertise and the point with the smallest log likelihood value [70]. We selected >10% deficit between dominant and ND extremities as weakness for LE muscle strength [49]. However, considering that hand grip strength (both injured and uninjured hands) was assessed at three-months post-DRF, we considered >25% deficit as weak grip strength [49].

Statistical analysis

We analyzed our data using SPSS version 23 (IBM SPSS Inc., Chicago, Ill., USA) and statistical significance was set at $p < 0.05$. Mean and standard deviation were used to describe the continuous variables. Number and percentages were used to describe the categorical variables. Chi square tests were used to test if the modifiable risk factors were associated with subsequent falls and fractures; however, Fisher exact test was substituted, when the expected cell count was less than 5 [70,72]. Bivariate logistic regression analysis was conducted to compute odds ratio (OR) with 95% CI to express the extent of association between the modifiable risk factors and the outcome (subsequent falls and fracture). The significant univariate predictors with $p<0.05$ for falls and $p< 0.25$ for fractures on Wald test were used for multivariate logistic regression modeling to determine the independent predictor of subsequent falls and fractures respectively. We selected a less restrictive significance level of <0.25 for selection of independent variables for prediction of subsequent fractures [70]. This is due to the exploratory nature of this study in which we did not wish to discard potentially clinically significant risk factors. We conducted multiple logistic regression analysis for 3 models to predict subsequent falls and fractures: model 1 consisted of significant modifiable predictors unadjusted for BMD and non- modifiable risk factors; model 2 consisted of significant modifiable predictors adjusted for BMD but unadjusted for non-modifiable risk factors; model 3 consisted of significant modifiable predictors adjusted for BMD and non-modifiable risk factors. We tested for multicollinearity among dichotomous predictors using phi coefficient [73–75]. In case of high correlation (phi>0.30), [75,76] only one of the clinically important variables was selected for the regression model. We also computed the variance inflation factor (VIF) as an additional measure to look for multicollinearity among the independent predictors and a VIF below 10 was considered acceptable.

The Hosmer and Lemeshow test was used to evaluate the goodness of fit for our model. The omnibus test was used to look for the significance of the model coefficient. The deviance or -2 log likelihood (LL) statistic defines the unexplained observation, and it was used to check if there was any improvement with additional explanatory variables in our new models over the baseline model [76]. To evaluate the model fit to our sample, diagnostic statistics was performed for each of the multivariate logistic regression model using parameters such as standardized residual, cooks distance, leverage and DF Beta [70]. Due to our small sample, we were unable to analyze for potential interactions between the independent variables. The clinical significance of risk factors was reported using the effect size for a given OR. Cohen's d convention used for a small (0.2), medium (0.5) and large (0.8) effect size were considered equivalent to OR of 1.49 (weak association), 3.45 (moderate association) and 9 (strong association) respectively [74].

Furthermore, we computed probability as explained by our prediction model using the formula: P_{fall} or $P_{fracture}=e^{(\beta_0+\beta_1x_1+\beta_2x_2+\beta_nx_n)}/1+e^{(\beta_0+\beta_1x_1+\beta_2x_2+\beta_nx_n)}$ where P_{fall} or $P_{fracture}$ = probability of subsequent falls or OP fracture respectively, β0 is the constant and β1, β2 and βn represent the regression coefficients for each of the predictors x_1, x_2, x_n. The threshold used to describe the probability that a person will have subsequent falls/fractures after DRF were as follows [77]: <1% almost certainly not; <5% very unlikely; <25% unlikely; <50% possibly not;

>50% possibly; >75% likely; >95% very likely; >99% almost certain. The predicted probabilities from each model were then used to construct a Receiver-Operator Characteristic (ROC) curve, in which sensitivity is plotted against 1-specificity. The area under the ROC curve (AUC) was used to explore discriminative ability of our model (i.e., the extent to which the model will correctly discriminate among those who will have the outcome (falls/fractures) from those who will not). The AUC of 1.0 indicates that model has the perfect predictive ability [23] and SPSS produces a default cut point at 0.5 reflecting no predictive ability. We followed Hosmer and Lemeshow guidelines for interpreting AUC (≥0.9 is outstanding, 0.8≤AUC<0.9 is excellent, 0.7≤AUC<0.8 is acceptable, < 0.7 is no predictive power) [76].

Results

Descriptive characteristics

At follow-up period of 4 ± 1 years, 113 participants (mean age=62.5±7.7 years, females=100) responded to our follow-up questions on incident falls and fractures secondary to DRF. We noted that nearly 55% of participants responded between 2-4 years of follow-up and 45% participants responded between 4-6 years of follow-up. The flowchart presenting the details of participant recruitment and retention is outlined in Fig. 1. Among 113 patients, 27 (24%) patients reported incident falls (≥1) in the last 6 month period, and 21 (19%) patients reported incident OP fractures during 4 year period post-DRF. The most prevalent site of subsequent fracture was at the opposite wrist (n=6), humerus/arm (n=3), elbow (n=3), tibia (n=2), same side wrist (n=1), scaphoid (n=1), radial head (n=1), hip (n=1), ankle (n=1), foot/heel (n=1), rib (n=1) (Fig. 2) Two of the patients reported subsequent fractures at metatarsal and little finger, but fracture at these bones were not considered as OP fractures and were not counted. The details on the demographics and injury characteristics of patients are given in Table 1. The majority of participants with DRF was females, 50-64 year old, right-hand dominant, retired, non-smokers, occasional drinkers, injured their non-dominant hand and had no worker compensation. One-quarter of our patients had a prior history of multiple falls.

Univariate Association of modifiable risk factors with subsequent falls and fractures

Table 2 presents association of the modifiable risk factors with secondary incident falls. The bivariate logistic regression analysis suggests that people with poor balance, high scores on fracture-specific pain/disability, osteopenia or osteoporosis and prior falls had significantly ($p<0.05$) higher odds of falling (nearly 3 times more likely) in comparison to those with good balance, low scores on fracture-specific pain/disability, normal BMD and no prior falls (Table 2). Though, not statistically significant at $p<0.05$, people with physically inactive lifestyles (OR=5.6, 95% CI: 0.7 to 44.9) and poor physical HS (OR=6.9; 95% CI: 0.88 to 55.11) had clinically significant (medium effect size, OR>3.45) and higher odds for subsequent falls than those with an active lifestyle and good physical HS. Similarly, females had clinically significant, 4.2 times higher odds of subsequent falls than males (Table 2).

Table 3 presents the associations of modifiable risk factors to secondary incident fractures. The univariate logistic regression analysis did not suggest a significant association between the modifiable risk factors and subsequent fractures at $p<0.05$. (Table 3.) Despite $p<0.25$ for both total hip and spinal sites for T scores, we selected T scores TH for multivariate analysis to mirror our findings with the predictor of subsequent falls.

Multivariate association of modifiable risk factors with subsequent falls and fractures

The results of multivariate logistic regression and related statistics with respect to subsequent falls and fractures are presented in Table 4 and Table 5, respectively. The Hosmer-

Lemeshow goodness of fit test was not significant (p>0.05) for the 3 regression models, suggesting good fit of our models to predict subsequent falls and OP fractures.

Multiple logistic regression model predicting subsequent falls (Table 4): The unadjusted multivariate logistic regression analysis indicated fracture-specific pain/disability as an independent predictor of subsequent falls in model 1. However, on adjusting for BMD in model 2 or other non-modifiable risk factors as in model 3, none of the modifiable risk factors stayed as a significant independent predictor of subsequent falls. In model 3, the prior history of multiple falls (OR=4.1; 95% CI: 1.1 to 15.8) was found to be the independent significant predictor of subsequent falls. Though not statistically significant in our small sample, people with poor balance were reported to have a 4 times higher odds of falling (OR=4.4; 95% CI: 0.8 to 25.4) independent of BMD and other non-modifiable risk factors (Table 4). Furthermore, the OR for poor balance suggests a moderate (OR>3.45=medium effect size) clinically significant association with subsequent falls. The omnibus test of model coefficient suggests a significant (p<0.05) contribution of predictors included in the regression model 1 and 3 for predicting subsequent falls. The estimates of -2 log likelihood statistics for model 1 (-2LL=98.8) and 3 (-2LL=63.6) suggests that the addition of non-modifiable risk factors resulted in the reduction in unexplained variance and thus showed their contribution to the model. The results of the diagnostic analysis are detailed in Table 4. Despite of IDs with the high leverage and residual for model 2, there were no influential IDs (Cooks distance and DF beta were <1) for either of the models suggesting near good fit of our models to predict falls for a given sample of patients with DRF.

Multiple logistic regression model predicting subsequent fractures (Table 5): The unadjusted (model 1) and adjusted analysis (model 2 and model 3) of modifiable risk factors did not reveal any significant predictor of subsequent fractures. Though not statistically significant, people with osteopenia/osteoporosis (low BMD) presented 4 times higher odds of subsequent fractures (OR, 4.5; 95% CI, 0.7 to 29.3) independent of other non-modifiable risk factors. The OR for low BMD suggests moderate (OR>3.45=medium effect size) clinically significant association with subsequent fractures. The omnibus test of model coefficient suggests that explanatory variables did not significantly ($p<0.05$) contribute to the prediction model. However, there was a trend of significance for model 1 and 2 at $p<0.2$. Although our prediction models for subsequent fractures were not significant at $p<0.05$, the estimates of -2 LL statistics for model 1 (-2LL=85.4) and 2 (-2LL=45.9) suggests that with the addition of BMD in model 2, there was a marked reduction in unexplained variability in comparison to that in model 1. This further suggests that BMD carried a trend of contribution towards prediction of subsequent fractures. However, the non-modifiable risk factors in model 3 did not contribute much to the prediction of subsequent fractures. The results of the diagnostic analysis are detailed in Table 5 and suggest the presence of two influential cases (ID 3 and 74).

Probability and discriminative ability of our prediction models

Table 6 shows the predictive probability and discriminative ability of our prediction models to predict subsequent falls and fractures. The model 1, 2 and 3 can predict 64% (possibly), 76% (likely) and 90 % (likely) probability of subsequent falls. Fig. 3 shows the ROC curve for the prediction model 2 and 3 for predicting subsequent falls, respectively. The AUC for prediction model 2 (AUC=0.70) and 3 (AUC=0.79) were within acceptable limits. This indicates that using these models 2 and 3, 70% and 79% of people with DRF can be classified correctly for prediction of subsequent falls respectively. In comparison, the model 1, 2 and 3 can predict 10% (unlikely), 39% (possibly not) and 44% (possibly not) probability of subsequent fractures, respectively. Fig. 4 shows ROC curves for the prediction model 2 and 3 for predicting subsequent fractures. The AUC for prediction model 2 (AUC=0.70) and 3 (AUC=0.74) were within acceptable limits. This indicates that using these prediction models 2 and 3, 70% and 74% of people with DRF can be classified correctly for prediction of subsequent fractures respectively. In comparison to the prediction model 2 and 3 with AUC within the acceptable limits, the AUC for model 1 exhibited poor discriminative ability to predict subsequent falls and fractures. (Table 6)

Discussion

In this study, we found that a prior history of multiple falls (OR=4.1, p=0.03) was the only risk factor which could independently predict subsequent falls among patients with DRF. None of the modifiable risk factors could independently predict subsequent incident falls or fractures after DRF. People with poor balance (OR=4.41, p=0.09) and low BMD (OR=2.9, p=0.11) showed a trend for higher odds of subsequent falls irrespective of their age, sex and fall history. Similarly, people with low BMD (OR=4.51, p=0.11) and prior history of multiple falls (OR=3.01, p=0.19) clinically showed higher odds of subsequent fractures. At the 4 year follow-up, nearly one-quarter (24%) of our patients with DRF experienced subsequent falls during the period of the last six months. Our findings were similar to one of the cohort study of 52 patients with DRF, 24% of those patients reported two or more new falls over a period of 4 months after DRF.[5] Previous studies have shown strong association between falls, fall-related fractures and functional decline [78,79]. This suggests a strong need to consider fall-related DRF as an early sign to identify the risk factors and implementing interventions to prevent subsequent falls, fractures and functional decline after DRF.

During the four years of follow-up, about one-fifth (19%, n=21 out of 113) of patients with DRF experienced secondary OP fractures. About, 6% of the fractures were at the wrist, and 13 % were non-wrist OP fractures. In another recent study, 39.7% of subsequent non-wrist fractures were reported among patients within 11 years of prior wrist fractures [15]. It was interesting to note that the majority (15 out of 21) of secondary OP fractures in our patients with DRF were in the bones of the upper extremity. These findings were consistent with a recent study which reported the upper extremity as the commonest location of subsequent OP fracture at 11 years of wrist fracture [15]. Our findings were, however, contrary to previous studies suggesting hip and vertebral fractures as the most prevalent subsequent fracture site after DRF [14,80,81]. Studies have shown that many times, vertebral fractures are not visible clinically and require radiographic diagnosis[82,83]. There is possibility that self-reporting of subsequent fractures might have resulted in missed cases of secondary vertebral fractures in our study.

We noted that people with poor balance, PRWE scores >81 and those with the osteopenia and osteoporosis were at high risk of subsequent falls at four years after DRF. This suggests that screening of these modifiable factors can assist clinicians to identify a subgroup of people who might be at risk of subsequent falls after DRF. Few studies have shown that multiple risk factor targeted intervention strategies including balance training such as Tai Chi, muscle strengthening exercises and behavioral instructions can reduce the risk of falling by 10-25% [29,84,85]. We did not find any other studies evaluating the role of post-fracture pain on incident falls which limited our ability to compare our findings. We believe that high levels of fracture-specific pain/disability might limit the ability of a patient to perform all the functional activities of daily living or at work. This can result in functional decline which has known to be related with falls[78]. Our findings on the significant association between balance and subsequent falls were consistent with few previous studies which have identified impaired balance as a major predictor of falls [12,75] among older adults. Our results were contradictory to another study in which balance was not significantly associated with falls among patients with DRF [8]. However, the author acknowledged that one leg rise test used for balance assessment was difficult to perform by their patients with DRF and the only small sample of their patients could complete the balance assessment.

It was interesting to note that our patients with low T scores-TH (osteopenia or osteoporosis) had nearly 3 times higher odds of falling than those with normal BMD. We could not find any studies evaluating the association of BMD with falls. We believe weakness in bone strength could limit its ability to withstand weight distribution under uneven circumstances which could make the person prone to falls. Future research on evaluating the role of bone strengthening exercises on the risk of falls may validate these findings. In our study, people with a physically inactive lifestyle and poor physical HS had nearly 6-7 times higher odds of falling than those with a physically active lifestyle and good HS. Although, this was not a statistically significant finding at $p<0.05$, it was noted to be clinically significant and consistent with previous studies in which physical inactivity [77,86] and poor HS [87] have been identified with an increased risk of falls among seniors. When adjusted for BMD and other non-modifiable risk factors, only a prior history of multiple falls was identified as a significant independent predictor of subsequent falls. Likewise, longitudinal studies done among elderly have also reported that prior history of multiple falls was an independent and significant predictor of subsequent falls [22,36,88]. Other than a prior history of multiple falls, we noted a statistically nonsignificant but clinically significant association between balance and subsequent falls. This finding was in alignment with another study done among older adults [75].

In our study, none of the modifiable or non-modifiable risk factors were the significant predictor for subsequent fractures. Our findings were contradictory to a study which followed healthy PMW over five years and found that prior history of multiple falls (in last 12 months), BMD, PA and grip strength were independent predictors of subsequent fractures [37]. However, one of the reasons for non-significance of our prediction models for subsequent fractures could be because we had a small number of people with subsequent fractures. Nevertheless, we noticed that TH-BMD at total hip showed a trend of significant (p=0.08) association with subsequent fractures on multivariate analysis. Previously, a few studies have shown that ≥50 year old patients with DRF had low BMD and were at elevated risk of 10-year fracture rates [15,89–91]. Currently, BMD evaluation is recommended by the International Society for Clinical Densitometry (ISCD) for women ≥65 years of age, men ≥70 years of age and high-risk women under 65 years of age [92]. Women with low BMD are known to have seven-times and four-times increased the risk of the proximal humerus and distal forearm fracture respectively [93]. Massey et al. showed that younger patients with low BMD are at a higher lifetime risk of fractures [90]. Considering that the majority of DRF patients as reported in our study were from middle-aged and healthy, we believe early screening for BMD and appropriate treatment can have a significant impact on prevention of subsequent fractures in this group of patients. There are some studies suggesting that patients with DRF who are older than 50 years should be referred for bone densitometry [7,89,90]. One of the surprising findings of our study was that non-modifiable factors such as age and sex were not statistically significantly associated with subsequent falls or OP fractures. Smee et al. had similar findings in older adults that sex was not associated with the fall risk [77]. This was contradictory to many of the previous studies which identified older age [34–37] and female sex [22,39,40] as a significant predictor of subsequent falls and fractures among older adults.

Overall, our probability analysis suggests that modifiable risk factors such as balance, fracture-specific pain/disability and BMD together are likely (P=75%) to predict the probability of subsequent falls but possibly not (P=39%) the subsequent fractures. The addition of non-modifiable factors increased the probability of subsequent falls and fractures identification indicating the importance of evaluating both modifiable and non-modifiable risk factors to screen at-risk people. Furthermore, our prediction model of modifiable risk factors adjusted for BMD and non-modifiable risk factors showed acceptable discriminative ability indicating that the assessment of these clinical risk factors might help the therapists to correctly identify nearly 70-75% patients who might be at risk of subsequent falls and fractures after DRF.

Strength and Limitations

There were a few limitations in our study. Firstly, we had a relatively small number of people who reported subsequent falls and OP fractures. This limited our ability to conduct sufficiently powered analysis to identify all significant risk factors for secondary OP fractures. Falls are well known to the significant predictor of fractures [37,41,94]. We believe that identifying patients at risk of subsequent falls would play an important role in preventing subsequent fractures. Future studies might consider a longer follow-up period to determine the significant predictors or target multicenter clinical settings so that a large sample could be attained to conduct a fully powered analysis. Secondly, although much of our data was collected prospectively, our falls and fractures were reported based on recall of past 6 months. There is the possibility that retrospective self-reporting of falls might have resulted in recall bias and thus reporting error in our study [95–97]. To lessen recall bias, we asked our participants to inform us about the falls in last 6 months instead of over last 4 years. Similarly, we could not confirm self-reported fractures using radiographs. Moreover, the retrospective self-reporting of falls has been previously used in many other studies to report falls [77,98,99] and fractures [37,100–102] as an outcome. Also, nearly one-half of our respondents were followed at 2-4 years and another half was followed at 4-6 years after DRF. This could have further resulted in underestimation or influenced the accuracy regarding the reporting of a number of subsequent falls and OP fractures after DRF. For accuracy in reporting, future studies should consider using a weekly or monthly reporting for falls and use of medical records for reporting of fractures.

Thirdly, the response rate to participate in our study conducted at a single center clinical setting was nearly 60%. This limits our ability to generalize the findings. However, the response rate reported in our study was not uncommon to another similar study [103]. Fourthly, due to previously collected baseline data and the small sample, we were not able to control our analysis for few other risk factors such as medication intake, hormone replacement therapy, vitamin D/calcium intake, family history of falls and fracture, comorbidities, environmental hazards etc. which limited our ability to exclude the effect of residual confounding. Nevertheless, we were able to conduct our analysis adjusted for BMD and non-modifiable risk factors as proposed in the objective. Fifthly, due to the small sample size, we could not include interaction in our models.

Despite these limitations, our study had strengths. It provided prospective evidence for assessing baseline balance, fracture-specific pain/disability scores, BMD and prior falls to identify the subgroup of individuals who might be at risk of subsequent falls after DRF. We have used reliable and valid measures for assessment of measures used in this study. In cases of statistical non-significant findings related to the small sample size, we have discussed clinical significance of our results by comparing the OR statistics with respect to the ES. Furthermore, our study results provide an important preliminary data on the association of risk factors with subsequent falls and fractures which can be used for sample size calculation required to conduct fully powered future studies.

Overall our study findings have clinical implications that support subsequent fall and OP fracture prevention among people with DRF. The risk factors such as fracture-specific pain/disability, balance, and prior falls can be easily evaluated in physical therapy practice using simple measures such as PRWE for pain, Timed Up And Go Test (TUG) for balance and by asking a single question on prior history of falls. Both PRWE and TUG test have been found to be reliable and valid for assessment of fracture-specific pain/disability and balance among patients with DRF [61,62,104]. Our study findings support the recent position statement from National Bone Health Alliance working group that patients with DRF should be screened for BMD [105]. In future, the prediction models developed to identify patients with DRF who are at risk of subsequent falls or fractures require prospective validation on a large sample and cut off values for individual modifiable risk factors need to be validated to provide conclusive evidence on external validity and feasibility.

Conclusions

Based on the data studied in a 4-year prospective cohort study, the prior history of multiple falls is an independent predictor of subsequent falls in patients with DRF. Our study provided preliminary evidence that the modifiable risk factors such as fracture-specific pain/disability, balance, and BMD were associated with the subsequent falls. We suggest that modifiable risk factors such as balance, fracture-specific pain/disability, and BMD should be included in the clinical assessment of patients with DRF to identify those who might be at risk of subsequent falls and fractures. Future research is needed on a large sample of people with DRF to determine modifiable independent predictors of subsequent falls and fractures.

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Table 1 Demographics and injury characteristics of the participants (n=113)

Variable	**N/Percentage of Participants**
Mean Age in years	*62.5 (SD=7.7)
50-64 year old	69/61.1%
65-80 year old	44/38.9%
Mean follow-up period	
In months	*47 (SD=16)
In years	*4 (SD=1)
Sex	
Male	13/11.5%
Female	100/88.5%
Prior history of multiple (≥2) falls	
Yes	25/22.7%
No	85/77.3%
Injured hand	
Left	64/57.2%
Right	48/42.9%
Hand dominance	
Left	10/9%
Right	101/91%
Dominant Hand injury	
Yes	29/34.5%
No	55/65.5%
Surgical treatment	
Yes	13/23.6%

No	42/76.4%
Work Status	
Full time regular duties	16/15.1%
Part-time regular duties	5/4.7%
Full time light duties	1/0.9%
Part-time light duties	5/3.8%
Unable to work because of injury	16/15.1%
Unemployed, Inability to find a job	1/0.9%
Home maker	3/1.9%
Retired	61/57.5%
Worker Compensation involved	
No	95/93.1%
Yes	7/6.2%
Highest Education level	
Some grade school	2/1.9%
Finished grade school	1/1.0%
Some high school	7/6.7%
Finished high school	17/16.2%
Some college/technical/diploma program	15/14.3%
Finished college/technical/diploma program	22/21%
Some university	10/9.5%
Finished University	17/16.2%
Some graduate work at university	5/4.4%
Finished graduate work at university	9/8.6%
Smoker	
Yes	8/7.4%
No	65/60.2%

I quit	35/32.4%
Alcohol	
Never	16/15%
Occasionally	60/56.1%
1-6 drinks/week	20/18.7%
7-14 drinks/week	10/9.3%
15 plus drinks	1/0.9%
Mechanism of Fracture	
Fall on snow	26/30.6%
During sports	3/3.5%
Other falls	46/54.1%
Other	10/11.8%
Any falls in last 6 months prior to 4-year FU	
Yes	27/23.9%
No	86/76.1%
Any subsequent fracture after first wrist fracture	
Yes	21/18.6%
No	92/81.4%

* mean, *SD* standard deviation; FU, follow up

Table 2 Univariate association of risk factors with subsequent incident falls: Results from logistic regression modelling

	Univariate association between risk factors and Falls				
Variable	**n**	**Fallers**	**Non Fallers**	**P value**	**OR (95% CI)**
Balance-fall risk test					
Average or above	82	17	65		reference
Worse than average	15	7	8	**0.04[F]***	3.3 (1.1, 10.5)
Physical Activity					
RAPA ≥6	16	1	15		reference
RAPA <6	88	24	64	0.10[F]#	[C]5.6 (0.7, 44.9)
Fear of falling					
MFES ≥8	84	20	64		reference
MFES <8	25	6	19	0.98	1.0 (0.3,2.8)
T score-LS					
-1 and above	44	10	34		reference
-1.1 and below	39	9	30	0.97	1.0 (0.4, 2.8)
T score-TH					
-1 and above	38	5	33		reference
-1.1 and below	42	14	28	**0.03***	3.3 (1.1, 10.3)
Knee extension strength					
≤10% deficit	39	9	30		reference
>10% deficit	59	14	45	0.94	1.0 (0.4, 2.7)

Plantar flexion strength					
≤10% deficit	31	10	21		reference
>10% deficit	66	13	53	0.17	0.5 (0.2, 1.3)
Hand Grip strength					
≤25% deficit	13	2	11		reference
>25% deficit	51	16	35	0.32[F]	2.5 (0.5, 12.7)
Fracture-specific pain/disability					
≤81 points	79	14	65	**0.02***	reference
>81 points	28	11	17		3.0 (1.1, 7.8)
SF-12 Physical					
≥50=good	19	1	18		reference
<50=poor	86	24	62	0.04[F]#	[C]6.9 (0.9, 55.1)
SF 12 Mental					
≥50=good	64	12	52		reference
<50=poor	41	13	28	0.13	2.0 (0.8, 4.9)
Age					
50-64	69	18	51		reference
65-80	44	9	35	0.49	0.7 (0.3, 1.8)
Gender					
Males	13	1	12		reference
Females	100	26	74	0.18[F]	[C]4.2 (0.5, 34.0)
Prior history of multiple (≥2) falls					
No	85	16	69		reference
Yes	25	11	14	**0.01***	3.4 (1.3, 8.8)

* significant at p<0.05 on Wald test, # significant at p<0.10 on Wald test, [C] clinically significant with medium effect size of 0.5 (OR>3.45), *OR* odds ratio, *RAPA* Rapid Assessment of Physical Activity, *MFES* Modified Fall Efficacy Scale, *LS* lumbar spine, *TH* Total Hip, *PRWE* Patient Rated Wrist Evaluation, *SF 12* 12-item Short Form Health Survey, [F] Fisher exact test value

Table 3 Univariate association of risk factors with subsequent incident osteoporotic fractures: Results from logistic regression modelling

Variable	Univariate association between risk factors and subsequent fractures				
	n	**Fracture present**	**No Fracture**	**P value**	**OR (95% CI)**
Balance-fall risk test					
Average or above	82	17	65		reference
Worse than average	15	1	14	0.29[F]	0.3 (0.03, 2.2)
Physical Activity					
RAPA ≥6	16	3	13		reference
RAPA <6	88	14	74	0.72[F]	0.8 (0.2, 3.2)
Fear of falling					
MFES ≥8	84	16	68		reference
MFES <8	25	4	21	0.56[F]	0.8 (0.2, 2.7)
T score-LS					
-1 and above	44	3	41		reference
-1.1 and below	39	8	31	0.06#	[C]3.5 (0.9, 14.4)
T score-TH					
-1 and above	38	2	36		reference
-1.1 and below	42	8	34	0.09F#	[C]4.2 (0.8, 21.3)
Knee extension strength					
≤10% deficit	39	9	30		reference

>10% deficit	59	9	50	0.33	0.6 (0.2, 1.7)
Plantar flexion strength					
≤10% deficit	31	7	24		reference
>10% deficit	66	11	55	0.48	0.7 (0.2, 1.9)
Hand Grip strength					
≤25% deficit	13	2	11		reference
>25% deficit	51	10	41	1.00[F]	1.3 (0.2, 7.0)
Fracture-specific pain/disability					
PRWE ≤81 points	79	12	67		reference
PRWE >81 points	28	7	21	0.26[F]	1.9 (0.6, 5.3)
SF-12 Physical					
≥50=good	19	3	16		reference
<50=poor	86	15	71	1.00[F]	1.1 (0.3, 4.4)
SF 12 Mental					
≥50=good	64	13	51		reference
<50=poor	41	5	36	0.28	0.4 (0.1, 1.3)
Age					
50-64	69	14	55		reference
65-80	44	7	37	0.56	0.7 (0.3, 2.0)
Gender					
Males	13	1	12		reference
Females	100	20	80	0.46[F]	3.0 (0.4, 24.4)
Prior history of multiple (≥2) falls					
No	85	14	71		reference
Yes	25	7	18	0.24[F]	1.9 (0.7, 5.6)

* significant at p<0.10 on Wald test, # significant at p<0.10, [C] clinically significant with medium effect size of 0.5 (OR>3.45), *OR* odds ratio, *RAPA* Rapid Assessment of Physical Activity, *MFES* Modified Fall Efficacy Scale, *LS* lumbar spine, *TH* total hip, *PRWE* Patient Rated Wrist Evaluation, *SF 12* 12-item Short Form Health Survey, [F] Fisher exact test value

Table 4 Multivariate logistic regression model of risk factors for subsequent falls among patients with distal radius fracture

	Model 1 (N=94)			**Model 2 (N=70)**			**Model 3 (N=69)**		
	Unadjusted analysis Constant= -1.60			**Adjusted for bone mass** Constant= -2.25			**Adjusted for non-modifiable risk factors** Constant = -22.15		
Variable	**Beta**	**OR (95% CI)**	**P value**	**Beta**	**OR (95% CI)**	**P value**	**Beta**	**OR (95% CI)**	**P value**
Balance-FRT Worse than average	1.1	3.0 (0.9,9.8)	0.06#	1.2	3.5[C] (0.75, 16.13)	0.11	1.5	4.4[C] (0.8, 25.4)	0.09#
PRWE >81 points	1.1	2.9 (1.1,8.4)	**0.03***	0.9	2.5 (0.70, 8.79)	0.15	0.5	1.6 (0.4, 6.3)	0.51
T score TH -1.1 and below				1.2	3.5[C] (0.99, 12.10)	0.05#	1.0	2.9 (0.8, 10.6)	0.11
Age 65-80 year							0.1	1.1 (0.3, 3.9)	0.89
Gender Female							19.8	4138E8 (NA)	0.99
History of multiple (≥2) falls Yes							1.4	4.1[C] (1.1,15.8)	**0.03***
Diagnostic testing	No outliers or influential Ids			standardized residual of > 3 SD: ID3, ID32, ID59			No outliers or influential Ids		

		High leverage: ID36 and ID67	
-2 LL	98.8	72.3	63.6
OTMC	p=0.02 (df=2)	p=0.06 (df=3)	p=0.02 (df=6)

* significant at p<0.05, # significant at p<0.10, [C] clinically significant with medium effect size of 0.5 (OR>3.45), *FRT* Fall Risk Test, *PRWE* Patient Rated Wrist Evaluation, *TH* Total Hip, *LL* Log Likelihood, *OTMC* Omnibus Test of Model Coefficient, *df* degree of freedom

Table 5 Multivariate logistic regression model of risk factors for subsequent fractures among patients with distal radius fracture

	Model 1 (N=94)			**Model 2 (N=70)**			**Model 3 (N=69)**		
	Unadjusted analysis Constant = -1.57			**Adjusted for bone mass** Constant = -3.22			**Adjusted for non-modifiable risk factors** Constant= -2.35		
Variable	**Beta**	**OR (95% CI)**	**P value**	**Beta**	**OR (95% CI)**	**P value**	**Beta**	**OR (95% CI)**	**P value**
Balance-FRT Worse than average	-1.4	0.2 (0.03, 2.1)	0.20	0.10	1.1 (0.1, 10.9)	0.92	0.001	1.001 (0.1,10.1)	0.99
PRWE >81 points	0.7	2.11 (0.7,6.7)	0.20	1.32	3.7 [# C] (0.8, 17.2)	0.09	1.03	2.8 (0.5, 14.8)	0.22
T score TH -1.1 and below				1.35	3.9 [C] (0.7, 21.6)	0.12	1.5	4.5 [C] (0.7, 29.2)	0.11
Age 65-80 year							-0.3	0.70 (0.1, 3.7)	0.70
Gender Female							-1.2	0.3 (0.02, 3.9)	0.36
History of multiple (≥2) falls Yes							1.1	3.01 (0.6, 15.9)	0.19
Diagnostic testing	standardized residual of > 3 SD: ID 74 High leverage: ID 10, 13, 20, 36			standardized residual of > 3 SD: ID 3, 74 High leverage: ID 36, 67			standardized residual of > 3 SD: ID 3, 8, 74 Cook's distance >1: ID 3, 74		

	Cook's distance >1: ID 74	Cook's distance >1: ID 74	
-2 LL	85.4	48.5	45.9
OTMC	p=0.17 (df=2)	p=0.15 (df=3)	p=0.28 (df=6)

significant at p<0.10, [C] clinically significant with medium effect size of 0.5 (OR>3.45), *FRT* Fall Risk Test, *PRWE* Patient Rated Wrist Evaluation, *TH* Total Hip, *LL* Log Likelihood, *OTMC* Omnibus Test of Model Coefficient, *df* degree of freedom

Table 6 Probability and discriminative ability of our prediction model

Parameter	**Model 1 (N=94)** **Unadjusted analysis**	**Model 2 (N=70)** **Adjusted for bone mass**	**Model 3 (N=69)** **Adjusted for non-modifiable risk factors**
	Model contribution for prediction of subsequent falls		
Predicted probability	64.28%	75.96%	89.94%
Area under ROC Curve	0.65 (95% CI: 0.51, 0.78)	0.70 (95% CI: 0.55, 0.84)	0.79 (95% CI: 0.67, 0.90)
	Model contribution for prediction of subsequent fractures		
Predicted probability	9.9%	39.02%	44.4%
Area under ROC Curve	0.63 (95% CI: 0.48, 0.78)	0.70 (95% CI: 0.50, 0.90)	0.74 (95% CI: 0.57, 0.91)

Model 1 PRWE and Balance-fall risk test as predictors, *Model 2* PRWE, Balance-fall risk test, T-score at total hip as predictors, *Model 3* PRWE, Balance-fall risk, T-score at total hip, age, gender and prior history of multiple (≥2) falls, *ROC* Receiver-Operator Characteristic (ROC) curve

Fig. 1 Flowchart of patient recruitment and retention

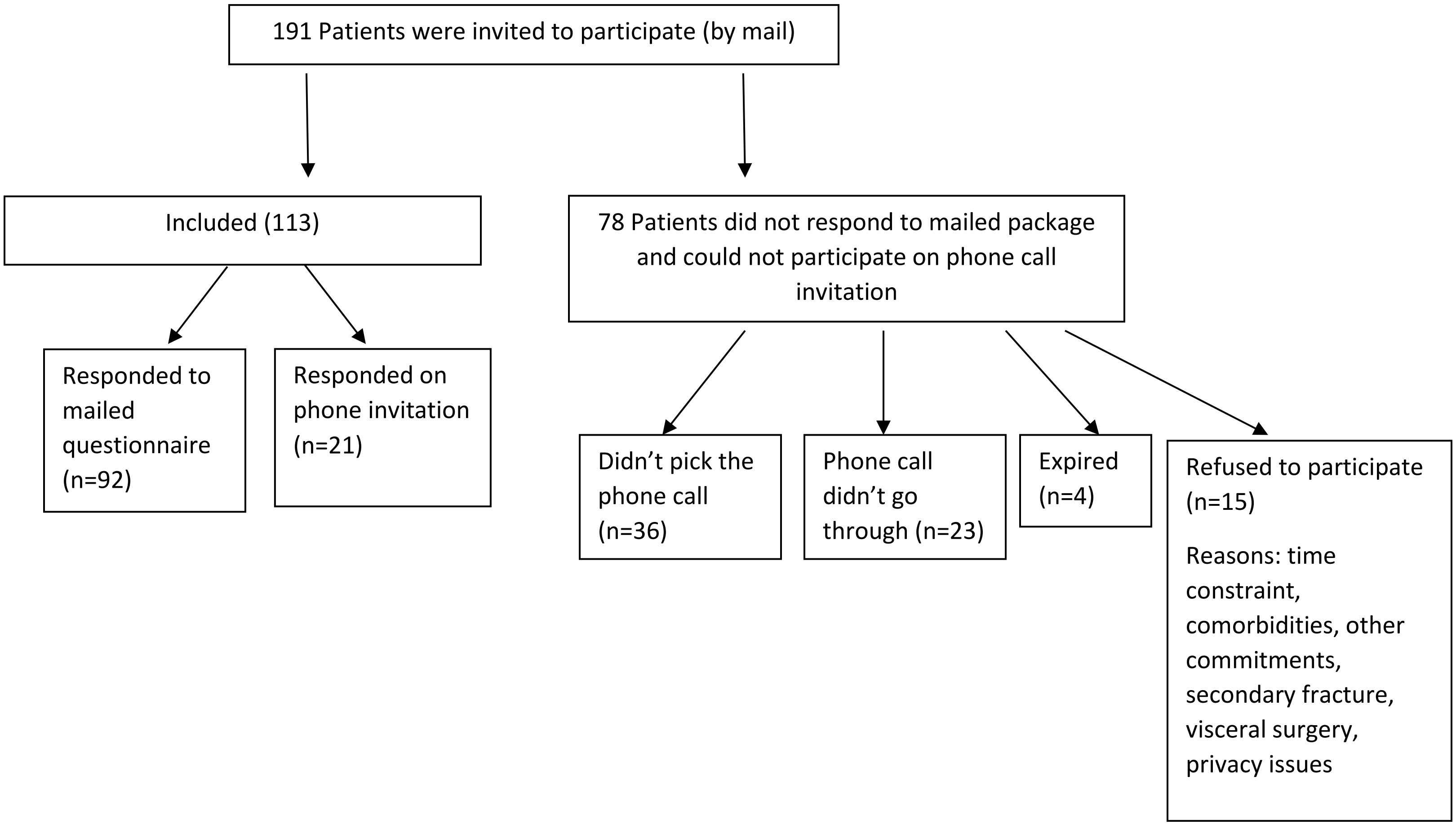


Fig. 2 Description of site of subsequent osteoporotic fracture

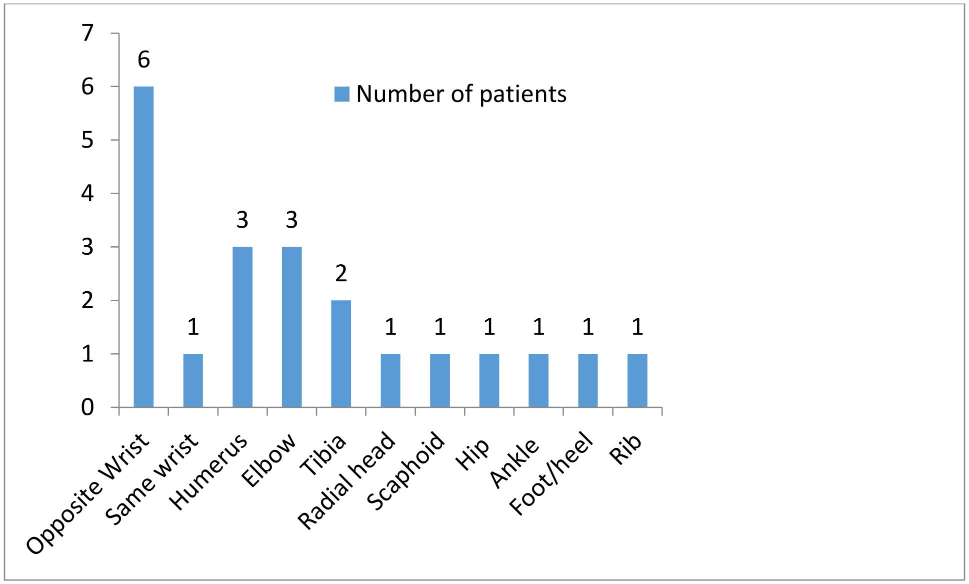
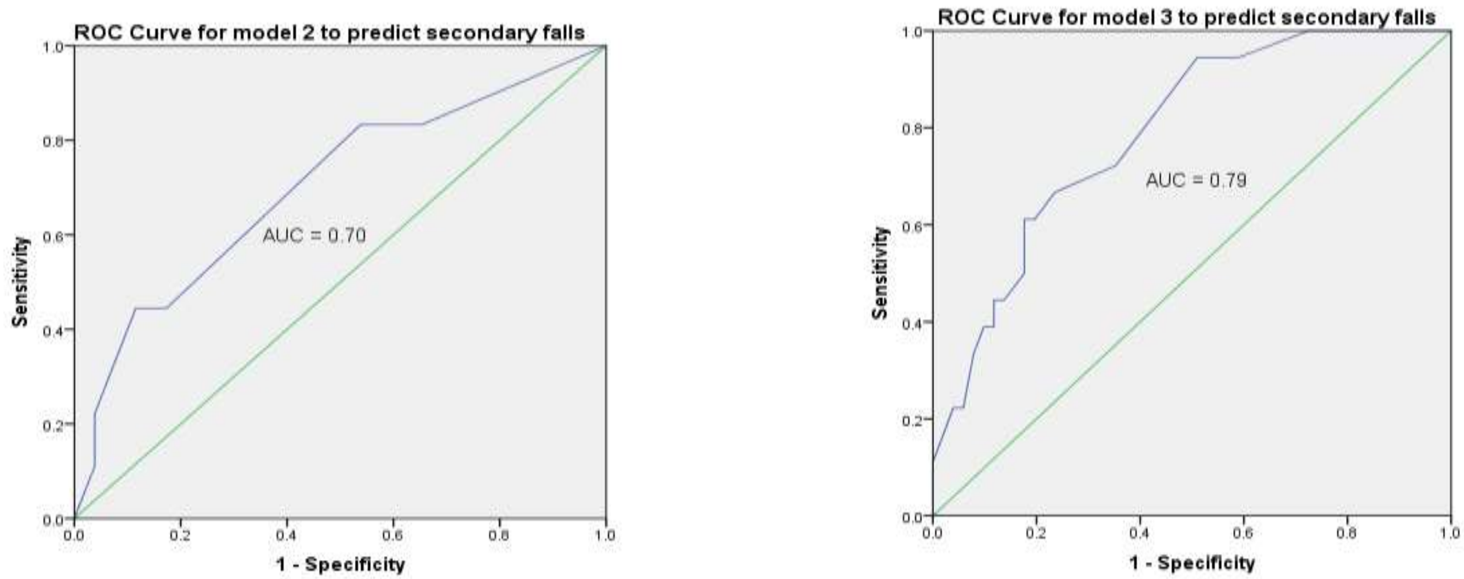
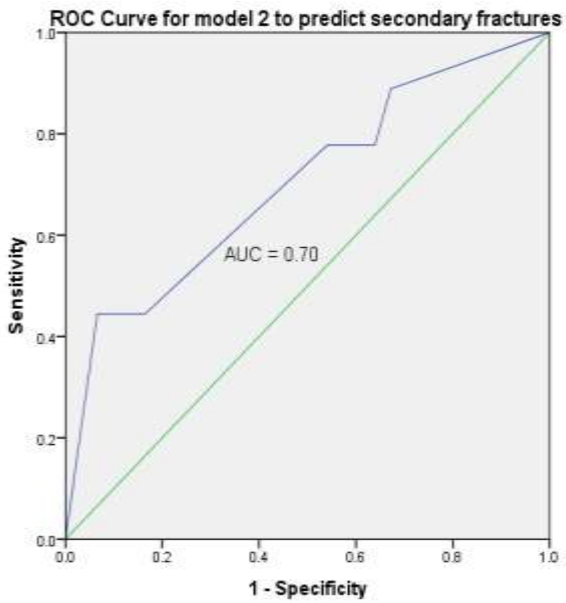


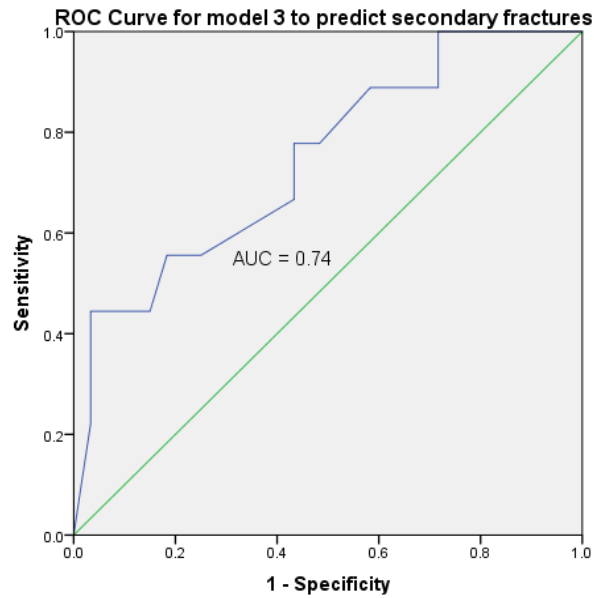
Fig. 3 ROC curve for prediction model 2 and 3 to predict subsequent incident falls in patients with distal radius fracture



Model 2 PRWE, Balance-fall risk, T-score TH as predictors, *Model 3* PRWE, Balance-fall risk, T-score TH, age, gender and prior history of multiple (≥2) falls, *ROC* Receiver-Operator Characteristic (ROC) curve

Fig. 4 ROC curve for prediction model 2 and 3 to predict subsequent incident osteoporotic fractures in patients with distal radius fracture





Model 2 PRWE, Balance-fall risk, T-score TH as predictors, *Model 3* PRWE, Balance-fall risk, T-score TH, age, gender and prior history of multiple (≥2) falls, *ROC* Receiver-Operator Characteristic (ROC) curve

CHAPTER 5.

DISCUSSION AND CONCLUSIONS

This chapter provides an overview of the content covered in the thesis and the main findings from each manuscript presented in this thesis. The specific contribution of individual study findings has been described within the manuscript chapters. In this section, the overall thesis contribution to the existing literature and clinical practice is discussed along with the potential limitations and future research recommendations.

Contextual Overview

Hip and vertebral fractures have gained marked attention for secondary fall and osteoporotic (OP) fracture prevention. However, this unique opportunity has not received priority and is noticeably missed for patients with distal radius fracture (DRF). Often, the underlying mechanism of DRF in healthy older adults is related to falls rather than osteoporosis, and the focus of assessment and treatment is primarily limited to recovery in wrist hand pain, grip strength, and hand function. There is substantial evidence stating that a history of a fall is a strong predictor of secondary falls[1–3] and OP fracture[4–6]. Furthermore, there are reliable and valid measures which can be used to assess secondary fall and osteoporotic fracture risk in DRF population.[7,8] Despite this, the majority of the patients with fall-related DRF are not assessed for fall risk factors or OP fracture risk.[9–12] This evidence to practice gap in the context of subsequent fall and osteoporotic fracture prevention in the rehabilitation of patients with a DRF formed the basis of this thesis.

In recent decades, research has focused towards a holistic assessment and treatment approach for rehabilitation of patients with DRF.[13–15] This includes early identification of clinical, fall-related risk factors such as postural balance, muscle strength, physical activity (PA), fear of falling (FOF), health status (HS) and subsequent OP fracture risk assessment such as use of fracture risk assessment tool, Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment tool and referral for bone mineral density (BMD) assessment.[8,14,16–23] Due to a lack of objective data, the extent to which clinical risk factors play a role in predicting subsequent falls and fractures in people with wrist fracture is still a mystery. This thesis provides a first attempt for in-depth insight to explore this mystery.

It is well recognized that patients with a fall-related DRF are often paradoxically healthy adults with silent osteoporosis. Yet, low trauma fractures in this patient group have not gained serious attention for a call to action as is the case with other OP fractures. Also, not all patients with DRF will suffer subsequent falls and OP fractures. So, we needed a greater depth of understanding and knowledge on the role of individual risk factors which can be reliably used to identify those patients who are at risk of subsequent falls and OP fractures. Furthermore, we were interested in exploring the role of modifiable risk factors, independent of non-modifiable risk factors, so that therapists can have an opportunity to intervene for subsequent fall and fracture prevention during the rehabilitation of patients with DRF.

Overall, this thesis provides therapists with contextual objective/quantitative data which would facilitate their understanding in the following areas during rehabilitation of patients with DRF: i. Changes which can normally be expected in wrist hand pain, PA, FOF, HS and BMD over the course of four years after DRF ii. The extent to which modifiable risk factors are associated with bone mineral density (BMD) at baseline and iii. The role of modifiable risk factors to predict subsequent falls and OP fractures at 4-years after DRF.

Overall summary of thesis results

The results presented in this thesis were derived from a prospective cohort of 191 patients who were followed over 4-years after the first episode of DRF.

The first manuscript (chapter 2) was a descriptive study and has provided longitudinal characteristics of recovery patterns in modifiable risk factors among patients with DRF over a follow-up period of 6 months (6m) and 4 years (4y). Our results demonstrated that patients with DRF showed both short-term (6m) and long-term (4y) improvement in wrist hand pain, PA, FOF, bone mass and general health status; the majority of the recovery is achieved at six months after DRF. We further compared the recovery patterns by stratifying the sample on gender, age, incidence of subsequent falls or OP fractures. When stratified, there were no significant differences in wrist hand pain/disability, PA, FOF, and bone mass at baseline, six months and 4 years after DRF. Patients with subsequent falls and fractures after DRF had significantly lower scores on physical component of HS. Patients with subsequent falls and those in the 50-64 year old age group reported significantly lower scores on the mental component of HS.

The second manuscript (chapter 3) presented cross-sectional relationships and the contribution of modifiable risk factors such as postural balance, muscle strength, PA and FOF to BMD. We found that postural balance, hand grip strength, and lower extremity muscle strength were correlated with BMD. In the whole study sample, hand grip strength was identified as an independent predictor of BMD explaining 17% and 12% of total variability in BMD at the femoral neck and total hip, respectively. However, among age-stratified women with DRF, balance and hand grip strength were identified as independent determinants of BMD explaining 10% and 32% of total variability in BMD-FN among 50-64 year and 65-80 year old, respectively.

The third manuscript (chapter 4) explored the role of various modifiable risk factors such as postural balance, muscle strength, PA, FOF, HS and BMD in predicting subsequent falls and OP fractures at four years after DRF. Our study results revealed that nearly 24% of our patients reported one or more subsequent falls (in last six months) and 19% of patients reported at least one subsequent OP fracture after DRF. The patients with poor balance (compared to age-matched normal adult), low BMD (clinically diagnosed as osteopenia and osteoporosis), fracture-related pain/disability scores of >81 points on patient rated wrist evaluation (PRWE) questionnaire and presence of prior history of multiple falls (≥2) had three times higher odds of subsequent falls. When adjusted for BMD and other non-modifiable risk factors such as age and gender, only prior history of multiple falls (≥2) was identified as a significant independent predictor of subsequent falls. We were not fully powered to explore association of various modifiable and non-modifiable risk factors with subsequent fractures. However, we found that patients with osteopenia or osteoporosis showed a trend of association (OR= 4.51, 95% CI=0.69, 29.28, p=0.11) with subsequent OP fractures. Furthermore, we have determined that using our prediction models, the probability of subsequent falls and OP fractures ranged from 64% to 90% and 10% to 44% respectively. Our prediction model, consisting of modifiable risk factors such as postural balance, fracture related pain/disability and BMD, showed acceptable (area under curve=0.70) predictive ability to identify patients who might be at risk of subsequent falls and OP fractures.

Contribution of the thesis to the literature and clinical practice

The three manuscripts included in this thesis provide deeper insight on the role of individual modifiable risk factors which can be used to identify patients who might be at risk of poor BMD, subsequent falls and OP fractures at four years after DRF. Furthermore, results presented in this thesis provided novel quantitative data which can convince therapists' to implement subsequent fall and osteoporotic fracture prevention in the rehabilitation of patients with DRF. Yet, the identification of various modifiable and non-modifiable risk factors responsible for subsequent falls and OP fractures have gained substantial attention for patients with hip fractures[24–26] but not for patients with DRF.

Indeed, our thesis work builds on previous literature and has several implications for clinical practice. Previous studies have discussed the importance of evaluating subsequent fall and osteoporotic fracture risk factors such as postural balance[20,22], PA[20,23], muscle strength[19,20,27], HS[28] or BMD[19,21] in patients with DRF. However, most of the research done on modifiable risk factors is either cross-sectional[22,23] or limited to short-term follow-up such as at 6 months to one year of follow-up.[20] The strengths of this thesis work is the long-term prospective cohort design in which patients were followed up at 6 months and 4 years (manuscript 1 and 3), age and gender stratified analysis (manuscript 1 and 2) and use of reliable and valid standardized self-reported measures (all manuscripts) to evaluate variety of important outcomes related to various modifiable fall and osteoporotic fracture risk factors in a single dataset of patients with DRF.

This thesis has provided therapists with the concrete quantitative data on both short-term and long-term changes in various fall and OP fracture risk factors. (Chapter 2, Manuscript 1) The majority of the change in the fall and OP fracture risk factor was seen during the initial six months; this must encourage therapists to evaluate fall and OP risk factors early in the phase of rehabilitation so that those at risk can be identified and timely intervention can be implemented. This data can be used as a benchmark by clinicians as the scores (for various risk factors) of any particular patient with DRF can be compared to these average scores to determine if the patient scores are following the anticipated recovery pattern or whether patient is at risk of subsequent fall or fracture. There are reviews supporting the knowledge creation of evidence-based reliable and valid screening tools,[8,14] clinical decision tools[7] for fall and fracture risk assessment and high-quality trials[29–33] on subsequent fall and osteoporotic fracture prevention strategies specific to patients with DRF. However, therapists have not consistently demonstrated their active roles and motivation to use these screening tools and interventions for subsequent fall and osteoporotic fracture prevention in clinical practice.[34,35] This could be because despite the use of reliable and valid screening tools, there are few research studies supporting the clear evidence on the role of various modifiable and non-modifiable risk factors in predicting BMD, subsequent falls and OP fractures among DRF population. In chapter 3 (Manuscript 2) of our thesis, we have addressed a novel issue on association of modifiable risk factor with BMD in DRF population and provided cross-sectional objective evidence on the contribution of modifiable risk factors to BMD in age and gender stratified sample. To explore the role of modifiable risk factors in subsequent falls and OP fractures after DRF, we prospectively followed our patients with DRF over four years (Chapter 4, Manuscript 3) and found that nearly 24% had subsequent falls and about 19% had subsequent clinical fractures. At baseline, nearly 50% of our sample had BMD-T scores of -1.1 and below suggesting osteopenia or osteoporosis. In this chapter, we have provided preliminary quantitative evidence on the extent to which each modifiable risk factor can alone or in combination with non-modifiable risk factor can predict subsequent falls and OP fractures.

In all 3 chapters of this thesis, we have directed the focus of therapists' attention towards modifiable risk factors for subsequent fall and osteoporotic fracture prevention which can be assessed and managed within the scope of routine physical therapy practice during rehabilitation of people with DRF. Given this concrete evidence, we expect that therapists might now be convinced to screen their patients with DRF to identify those subgroups who might be at risk of subsequent falls/OP fractures and can be benefited with risk reduction strategies or referral for detailed bone health assessment including BMD. Unlike patients with hip and vertebral fracture who present with significant disability post fracture, patients with DRF are often healthy, offering a unique reasonable opportunity to conduct an assessment of postural balance, muscle strength, PA, FOF, HS, and BMD, early in the phase of rehabilitation.

In North America, falls are the most common cause of hospital admission and have resulted in a direct medical cost of about $ 30 billion annually.[22,36] Furthermore, DRF are the most common fall-related OP fractures which are well recognized to be sentinel events, increasing the risk of subsequent hip and vertebral fractures by 2 to 5 times.[37–39] Given that we have high quality evidence from Cochrane systematic review suggesting the effectiveness of various exercise programs including combining balance, muscle strengthening and physical activity or tai chi programs,[40–43] it is crucial that patients with DRF be identified for subsequent fall and osteoporotic fracture risk early in the rehabilitation phase so that intervention can be started on a timely basis.

The 2009 position statement from American Academy of Orthopedic Surgeons (AAOS) encourages orthopedic surgeons to “Advise patients with fragility fractures that an osteoporosis evaluation may lead to treatment which can reduce the risk of future fractures.”[44] However, currently, clinical practice guidelines on the treatment of DRF from AAOS[45] have not stated conclusive recommendation to implement subsequent fall and osteoporotic fracture prevention (SFOFP) in routine clinical practice for treating patients with DRF. Similar findings have been mirrored in our recent survey of therapists’ clinical practice patterns in SFOFP for patients with DRF.[35] The findings suggested that majority of therapists believed that they had the knowledge and considered the evaluation of subsequent falls/OP fracture risk factors as their responsibility but often did not conduct the screening in their routine clinical practice.

Overall, our thesis work was the first of its kind to provide the causal relationship between modifiable risk factors and subsequent falls/OP fractures among DRF population. Our work builds on the previous research done by Mehta et al.[13] and Nordvall et al.[18] and has taken an important step in establishing predictive ability of various subsequent fall and osteoporotic fracture risk factors to predict BMD, subsequent falls/OP fractures in patients with DRF. Furthermore, the study finding from our thesis work support the opinion of various other authors,[22,23,39,46,47] that patients aged 50 years or older presenting with a history of fragility fracture such as DRF must be evaluated for subsequent fall and osteoporotic fracture risk and referred for detailed bone health assessment including BMD testing. Our work is also in favor of recent position statement from the National Bone Health Alliance working group that patients with DRF should be screened for BMD.[48] If our preliminary study findings can be replicated in a large fully powered multicenter sample of men and women with DRF, this might inform changes in legislation and policy frameworks that can encourage early implementation and referral for subsequent fall and osteoporotic fracture prevention in rehabilitation of patients with DRF.

Limitations

The limitations specific to individual studies have been discussed in each of the manuscript chapters. In this section, we describe the overall methodological limitation of our thesis work. One of the major limitations was the small percentage of the people who experienced subsequent falls and OP fractures at four-year follow-up. This limited our ability to conduct a fully powered analysis needed to provide the conclusive evidence on the issues discussed in this thesis. Also, our study was a single center based which further limited the sample size as well as the generalizability of our study findings. Another limitation in our overall thesis was the retrospective self-reporting of falls and OP fractures which might have resulted in recall bias, underestimation of falls and thus reporting error in our study findings. Nevertheless, the self-reporting of falls in the past one year or six months was also previously used in many other studies to report falls[49–51] and fractures[5,52,53] as an outcome. In further work, these limitations can be overcome by either collecting a large sample of patients with DRF which can be possible by targeting multi-center clinical settings or by conducting follow-up at a period longer than four years. Both the response rate and accuracy/validity of self-reporting can be improved by using a weekly or monthly reporting for falls and use of medical records for reporting of fractures.

Future Recommendation

The recommendations for future research have been noted in the individual manuscripts. In this section, we mention a few general but important research directions which can be undertaken to promote future research in the areas of knowledge creation, implementation, and translation. Firstly, future prospective studies are needed in a large sample of men and women to establish a causal relationship between modifiable risk factors and BMD. This will also guide the next step to conduct the future intervention trials to determine if a change in modifiable risk factors can improve the BMD in patients with DRF. Secondly, future researchers must replicate these findings in a large prospective sample of age and sex-stratified patients with DRF in a multicenter study to provide conclusive evidence on external validity and feasibility of these findings. Thirdly, considering that not all people with DRF present with subsequent fall and osteoporotic fractures. Thus, future prospective research must be targeted in a fully powered sample to establish validity of cut off scores for individual modifiable risk factors to identify patients who might be at risk of poor bone health, subsequent falls and fractures. Fourthly, it might also be interesting to conduct a mixed-method research study in which patient perspectives on subsequent falls, and osteoporotic fracture prevention can be evaluated to determine if we patient education program and community partnerships are needed to promote patient awareness and knowledge on this important issue raised in this thesis work. Lastly, another potential and important avenue for future long-term research could be to examine if assessing and intervening the modifiable risk factors discussed can reduce the risk of subsequent falls/OP fractures in at risk DRF population and whether it has any impact on the overall socio-economic burden.

Conclusions

This thesis work has established novel evidence on recovery patterns in modifiable risk factors and predictive ability of individual modifiable risk factors which can be used to identify patients with DRF who are at risk of low BMD, subsequent falls and OP fractures. Moreover, the modifiable risk factors discussed in this thesis can be targeted in routine physical therapy assessment and thus those patients who are at risk can be considered for intervention or referred for detailed bone health assessment including BMD testing or community-based fall and osteoporotic fracture prevention programs. Though our findings were not fully powered in this thesis work, we have provided preliminary objective evidence which has deepened our understanding on the specific risk factors which must be evaluated to promote the implementation of subsequent fall and osteoporotic fracture prevention in patients with DRF. Furthermore, the knowledge creation done in this thesis work guides the future steps and methodological design which must be undertaken to translate conclusive research in this area.

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APPENDICES

Ethics Approval from Western University

Western Research | Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice
*****REVISED*****

Principal Investigator: Dr. Joy MacDermid
Department & Institution: Schulich School of Medicine and Dentistry\Surgery,Western University

HSREB File Number: 101893
Study Title: Distal Radius Fracture prospective database 50-80 years old Overview: "Identification of Risk of Adverse Activity Transition Following a Distal Radius Fracture, 3-year prospective cohort study".
Sponsor: Canadian Institutes of Health Research

HSREB Amendment Approval Date: November 26, 2014
HSREB Expiry Date: November 01, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Other	Telephone Script	2012/03/14
Revised Letter of Information & Consent		2014/05/26

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information

✓ Erika Basile ebasile@uwo.ca	___ Grace Kelly grace.kelly@uwo.ca	___ Mina Mekhail mmekhail@uwo.ca	___ Vikki Tran vikki.tran@uwo.ca

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Covering letter

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St. Joseph's Health Centre
P.O. Box 5777
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N6A 4L6
Tel: (519) 646-6100 ext 64875
Fax : (519) 646-6049

Dated: July 16, 2015
TO:

FROM: Neha Dewan, PhD Candidate
RE: Distal Radius fracture Research

Dear XYZ

I am a graduate student writing to you with regard to the wrist-fracture study in which you have participated earlier. Your time and willingness to participate in that research study was highly appreciated by us. We are currently conducting a 3 year follow-up of all our participants and would like to know whether you would be interested to participate. We would like to follow-up with you to know your current health status. Please find enclosed questionnaires for the current study. I would really appreciate and be greatly thankful if you can complete the enclosed questionnaires and mail them back along with the signed consent form within 3 weeks in the postage-paid envelope provided.

Additionally, you will receive a phone call in the next few weeks to schedule a lab visit for your bone mineral density (BMD/bone scan) at the Hand and Upper Limb Centre (HULC). You can always decline to participate in a lab visit at HULC, but can still fill and mail the questionnaires enclosed herewith.

Your participation will not only help our research cause, but will also help you to notice any functional improvement while completing the questionnaires and BMD test reports given at HULC will help you know if your bone health is well maintained after an episode of wrist fracture

If you have any questions, please do not hesitate to call me at +1 2896983281 (anytime between 8:00am-8:00pm, at your convenience). Thank you very much for your dedication to the study.

Best Regards

Neha Dewan, PhD Candidate

Patient Information Sheet and Consent Form

Project Title: Role of modifiable clinical risk factors on future falls/fractures, bone mass and quality of life after distal radius fracture: 3-year prospective cohort study

Investigators: Dr. Joy MacDermid, PhD (Principal Investigator, HULC)

Co-investigator: Dr. Ruby Grewal, MD (Co-Investigator)
Neha Dewan MPT (Graduate Student)
Dr. Norma MacIntyre, PhD(Co-Investigator)

What is the purpose?
You are being invited to participate in a research study conducted on patients with distal radius fracture (DRF) at the Hand and Upper limb Centre (HULC). In North America, DRF are so commonly seen injuries. DRF often happens after a fall from a standing height and are often not serious injuries but do indicate a higher risk for future fractures including more serious ones such as hip fractures. After a DRF, people may change their activity and develop muscle weakness, balance problems, and fear of falling. This can lead to bone loss, higher risk of falls, future fractures, other health problems and loss of quality of life.
This study will determine the risk factors which can be used to identify who is most likely to have problems with falls, fractures, low bone mass and poor quality of life at 3 years after their first DRF.

In order to decide whether or not you want to be a part of this research study, you should understand what is involved. This letter of information gives you detailed information about the research study.

Study procedures
If you decide to be part of the study, you will be asked to answer some questions over the phone, and make a visit to the Hand and Upper limb center (HULC) for bone mineral density (BMD) testing. Your lab visits will be scheduled at a later date but within next 2 months after the phone interview.

Note: We will attempt to schedule your phone interview and lab visits on a day and time of our mutual convenience. You can decline to participate in a lab visit, but still do the phone interview.

Phone interview at 3 year follow-up will take about 15-20 minutes of your time. We will be contacting you to:

- Find out if you had any "new" falls, fracture or hospitalization since your last one. You will receive two additional similar phone calls. These two additional calls will last for about 3-4 minutes to ask you about any new injuries.
- We will ask you about your injury, physical activity, fear of falling, confidence, and general health. **For your convenience, we can also mail you questionnaires, before the phone interview.**
- We will ask your views about your opinion on fall/fracture prevention for patient with similar fracture like yours.

Lab Visit at HULC
Bone density testing is the one of the accurate method available for the diagnosis of osteoporosis. This assessment is a simple, painless, quick (5-10 min) and non-invasive procedure which will be done using dual-energy x-ray absorptiometry (DEXA) scan by highly skilled health professional at HULC. If you recently had this testing done, please inform us and we will request the result (with your permission) from your family doctor's office.

Voluntary Participation
Your participation in this study is voluntary.

Withdrawal from Study
You may refuse to answer any questions or withdraw from the study at any time with no effect on your future quality of care. You will receive a copy of the letter of information and consent form for your records. You do not waive any of your legal rights by signing the consent form.

Potential risk or discomforts associated with this study
There are no known risks associated with the study. However, you may feel a little tired or might find some questions uncomfortable to answer on a phone interview. You do not need to answer questions that make you feel uncomfortable or that you do not want to answer.

The risks involved in participating in the lab visit for bone mineral density testing are minimal. The Bone Density test involves a dual energy x-ray absorptiometry (DEXA) scan. DEXA scans use high- and low-energy x-ray beams to measure the calcium content in bone (less than the radiation received with the chest x-ray). The amount of radiation that you will be exposed to during the scan (0.5-6.0 μSv) is approximately equal to the amount of radiation acquired over one day from natural sources of background radiation if you were walking outside for a day. This amount of radiation is considered to be a negligible individual dose by the National Council on Radiation Protection and Measurements (NCRP), thus the risks are considered to be minimal. There are certain individuals who should not have DEXA scan done such as if there is possibility of pregnancy. To ensure that it is safe for you to have a DEXA scan, you will complete a brief questionnaire with me on a 2 minutes of phone conversation prior to the scheduling the date of scan. There is always a slight chance of cancer from excessive exposure to radiation. Although the risk of cancer increases with exposure to x-rays, this is less likely to occur in an older person because of the length of time required for radiation to exert the effect after the "natural radiation."

Potential benefits of participating in this study

You may not personally benefit from participation in this study. However, the results from the study will provide a better understanding about the risk to the physical therapists and hand therapists. We hope that the results from our study will result in developing better preventive strategies against secondary falls, fractures and poor bone health in patients with distal radius fracture.

How many people will be in this study

There will be 193 local participants in this study.

Other than Phone interview and lab visit
No additional testing for research purposes other than that stated above will be performed.

Will your results be kept confidential?
The overall results of the study will be available to you upon request. Your individual results will be held in strict confidence. No person, other than the study team will have access to your study related records without your permission. Your data will have no personal identifiers. Information (your age, gender weight, height) kept on a password protected hospital computer. Information collected during the study may be presented to other doctors in a presentation or paper. Your results would be part of a group of de-identified data, and would not identify you in any way. Representatives of The University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

Compensation
There is no monetary reimbursement for participating in this study. If needed, we can arrange to provide parking passes on the day of lab visit.

Whom may you contact to find out more about this study?
You will be given a copy of this letter and the signed consent form. Now or later, If you have any questions about this study or would like more information, you can contact:

Neha Dewan, IAHS 402, School of Rehabilitation Sciences,
1400, Main street west, McMaster University, Hamilton, ON L8S 1C7
Email: dewann@mcmaster.ca
Tel: +1 2896983281, 905-5259140 x 26410

Or

Dr. Joy MacDermid, Principal Investigator, can be contacted at 519-646-6000 ext 64636

Dr. Ruby Grewal, co-investigator at 519-646-6286, at the Hand and Upper Limb Centre, St. Joseph's Health Centre, Suite D0-209, 268 Grosvenor Street, London, Ontario, N6A 4L6.

CONSENT to participate in the study:

Role of modifiable clinical risk factors on future falls/fractures, bone mass and quality of life after distal radius fracture: 3-year prospective cohort study

Written consent

I have read the letter of information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction

______________________	______________________	___________
Signature of Participant	Print Name	Date

______________________	______________________	___________
Signature of person Obtaining consent	Print Name of person obtaining consent	Date

Telephone Script for Recruitment

Hi, {XYZ} this is Neha, calling from the office of Hand and Upper limb center.

May I please speak with {XYZ}.

**If the potential participant is not home ask if there is a better time to call.*

** Voice Message: Hi, This is Neha,* calling from the office of Hand and Upper limb center. *If you get time, kindly call me back at 2896983281 at your convenience.*

<u>*Do not leave a message as it may be a confidential matter you are calling about that may not be apparent to you*</u>

If they are at home, continue with the conversation

I am calling you today as you have previously participated in a wrist fracture study. We really appreciated your time and willingness for your participation.

I would like to talk to you in regard to the DRF study which would take 8-10 minutes of your time and wondering if it is the good time for you to receive my call.

Yes, Continue ahead	No Is there any convenient date and time in this week or next, you would like me to call you back

Ok…now I will **brief** you about this study.

Research studies have reported that patients with DRF are often at risk of future falls, fractures or low bone mass. We are currently conducting a 2-5 year follow-up of all our participants to know their current health status and to understand if there are any factors which may be associated with the risk of future falls, fracture and low bone mass in patients with DRF. The study is being conducted by me under supervision of my PhD supervisor, Dr. Joy MacDermid who is a co-director of HULC. This study is approved by the Research Ethics board of Western University. We notice that you can be eligible to participate in our study. Your participation in our study will allow us to identify and plan preventive intervention to reduce the risk for future falls, fractures, improve bone health and quality of life of wrist fracture patients. Recently, we have mailed you a few questionnaires along with the written consent form and the details of this study. We were just wondering if you would be interested to continue your participation by completing those questionnaires and mailing them back to us in the postage-paid envelope enclosed with the mailed package.

<table>
<tr><td colspan="3">Yes</td><td colspan="2">No</td></tr>
<tr><td rowspan="2">Category 1: Yes interested, who already mailed

Thank you for your time to complete the questionnaires. Now, as per the study procedure mentioned in the patient information form, I would like to know if you would be interested in scheduling an appointment for BMD testing at the Hand and Upper limb center (HULC). If you recently had this testing done, please inform us and we will request the result (with your permission) from your family doctor's office. or We can schedule the lab visits on a day and time of our mutual convenience. Currently, we would be happy to schedule your appointments on any of the following days: Monday, Tuesday, Wednesday, Thursdays : 10 am -</td><td colspan="2">Category 2: Yes interested but Not yet received the mail.

Would you be able to mail the completed responses to me in the next 2 weeks.</td><td colspan="2">Ok. I appreciate your honest response but wondering whether you would have some time to answer those questionnaires over this phone call which will take approximately another 15-20 minutes to complete.</td></tr>
<tr><td>Yes,

Ok…I appreciate your time and willingness to return the mail in coming 2 weeks of time. Also, we are interested to schedule your appointment for BMD testing at the Hand and Upper limb center (HULC). Once, we receive your mailed package, We can schedule the lab appointment on a day and time of our mutual convenience. Is it ok if I call you back to schedule the appointment for your BMD testing?</td><td>No, Need more time

Ask their preferred time for the return mail. Then, see yes……..</td><td>Yes
Ok. Thank you
Can you please have your package mailed by us in front of you while we go through the questions.
I will read the patient information form related to this study now
As you have heard/read the study details, Can you please give me your verbal consent whether you would like to continue your participation as Yes/No response.

Open questionnaire package,
After completion of questionnaires,

Follow category 1 instructions for a scheduling of lab appointment</td><td>No
That's alright. Thank you for your time. Have a good day….</td></tr>
</table>

3 pm, Fridays: 10 am -12 noon. Among these dates, is there any day or time which works best for you for the BMD testing at HULC? If yes…schedule and Thank them and inform them that you will receive a reminder phone call from me a day or 2 prior to your scheduled appointment. Reminder phone call: Inform them about the appointment date/timings	Yes Follow Category 1	No		
Do you have any questions? {Answer any questions they may have} ***If no, thank them for their time and say good-bye**				

In case patient says that they have NOT received the mailed package, ASK THEM:

Is it ok if will re-mail a new package of questionnaires with the study details and consent form to you. I mean whether you will be able to fill the questionnaires and return the completed package within next 2 weeks?

Yes, *Can you please inform me your current mailing address so that I can make sure that you will be able to receive it this time.*	*No* *THANK THEM FOR THEIR TIME and say goodbye…*