Determinants of fracture risk among individuals with spinal cord injury: a case control study.

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background/Objectives: Low areal bone mineral density (aBMD) of the hip and knee region has been associated with fracture risk in individuals with SCI; however the contribution of bone micro-architecture to fracture risk has not been evaluated. The primary objective of this study was to determine whether a relationship exists between indices of bone strength (aBMD at the distal femur and proximal tibia; trabecular vBMD; average hole size, H_A; cortical thickness, CTh; buckling ratio, BR; cross-sectional moment of inertia, CSMI; and polar moment of inertia, PMI) and potential fracture risk factors (gender, age, bisphosphonate use, time post-injury, fractures, and completeness of injury). The secondary objectives were to 1) determine whether indices of bone strength can discriminate between SCI patients with and without fragility fractures; 2) determine if these indices of bone strength correlate with the number of fractures sustained; and 3) determine the proportion of individuals with SCI who have a trabecular vBMD at the ultra-distal tibia that is below 72mg/cm^3.

Materials and Methods: A nested case-control study was performed. Forty seven men (n=33) and women (n=14) with chronic SCI (C2-T12 AIS A-D) with a duration of paralysis of at least two years were included in this study. Subjects with SCI were questioned about the cause, location, and time of the lower extremity fragility fractures. Fracture presence was verified by x-rays. aBMD of the distal femur and proximal tibia were determined using dual energy x-ray absorptiometry (DXA). Trabecular volumetric bone mineral density (vBMD) and H_A were measured at 4% of the tibia length, and CTh, BR, CSMI, and PMI were measured at 66% of the tibia length of individuals with chronic SCI using peripheral quantitative computed tomography (pQCT). Linear and multiple regression models were used to determine significant correlates (age, gender, completeness of injury, duration of injury,

bisphosphonate use, and fractures) of indices of bone strength, while logistic regression was used to assess the relationship between indices of bone strength and fragility fractures. To assess the relationship between multiple fragility fractures and indices of bone strength, a poisson regression analysis was performed.

Results: Risk factors found to be related to the indices of bone strength include gender, completeness of injury, duration of injury, bisphosponate use, and prior fractures. An increase in H_A (OR=1.081, 95% CI=1.001-1.166, p=0.0470), a decrease in aBMD in the distal femur (OR=0.988, 95% CI=0.978-0.998, p=0.0226), and a decrease in CSMI (OR=0.098, 95% CI=0.012-0.838), p=0.0338) were associated with fractures. Fractures were not associated with aBMD at the proximal tibia, trabecular vBMD, CTh, or BR. The poisson regression model predicting the number of fragility fractures sustained among individuals with chronic SCI from aBMD, vBMD, H_A, CTh, CSMI, PMI, and BR were each statistically significant. Finally, only 7.7% of our population had a trabecular vBMD fracture threshold of less than or equal to 72mg/cm^3. We found a trabecular vBMD fracture breaking point of approximately 126mg/cm^3 and 115mg/cm^3 at the ultra distal tibia in individuals with complete and incomplete SCI, respectively.

Conclusion: Specific bone strength measures, specifically aBMD at the distal femur, H_A, and CSMI are associated with fracture risk and may improve our ability to identify individuals with SCI at high risk of fracture. Larger population based studies are needed to determine the most appropriate risk factors that contribute to bone loss and understand the role and importance of these and other indices of bone strength on skeletal fragility in individuals with SCI.

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List of Abbreviations

aBMD	Areal Bone Mineral Density
AIS	American Spinal Injury Association
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index (kg/m^2)
BR	Buckling Ratio
CaMos	Canadian Multicentre Osteoporosis Study
CI	Connectivity Index
CoA	Cortical Area (mm^2)
CP	Cerebral Palsy
CSA	Cross Sectional Area (mm^2)
CSMI	Cross Sectional Moment of Inertia
CTh	Cortical Thickness (mm)
DOI	Duration of Injury
DXA	Dual Energy X-ray Absorptiometry
FFQ	Food Frequency Questionnaire
H_A	Average Hole Size (mm)
HR-pQCT	High-resolution peripheral quantitative computed tomography
IL-6	Interleukin-6
LEMS	Lower Extremity Motor Score
LOI	Level of Injury
OB	Osteoblast
OC	Osteoclast
ORIF	Open Reduction Internal Fixation
PARA SCI	Physical Activity Recall Assessment for People with Spinal Cord Injury
pQCT	Peripheral Quantitative Computer Tomography
PMI	Polar Moment of Inertia
pSSI	Polar Stress Strain Index
PVE	Partial Volume Effect
ROM	Range of Motion
SCI	Spinal Cord Injury
vBMD	Volumetric Bone Mineral Density
WHO	World Health Organization

1.0 CHAPTER 1: INTRODUCTION

1.1 Rationale

Individuals with a spinal cord injury (SCI) experience substantial declines in bone mass in the lower extremities [1-6], thereby increasing the risk of fragility fractures. Individuals with SCI are susceptible to low-energy fractures known as fragility fractures. Fragility fractures have been reported to most commonly occur among individuals with SCI during normal daily activities such as transferring from a chair to a bed, rolling in bed, or bumping into unseen objects [7-12]. The majority of fragility fractures in individuals with SCI occur around the knee at the distal femur and proximal tibia [1,6-8,11-13]. An individual with SCI has approximately twice the risk of suffering from a lower extremity fracture for each unit decline in hip and femoral neck t-score than age and gender matched individuals without SCI in their lifetime [7]. Fracture prevalence rates among individuals with SCI are reported to range from 1% to 34% [7-9,12,14]. Fragility fractures result in increased healthcare costs, long term hospitalization, and increased disability [14]; consequently, quality of life is reduced. Therefore, establishing strategies to improve the identification of individuals at high risk of fracture would facilitate fracture prevention/reduction strategies.

Currently, areal bone mineral density (aBMD) assessed by dual-energy x-ray absorptiometry (DXA) is the gold standard for diagnosing osteoporosis and fracture risk in postmenopausal women and men over the age of 50 [15,16]. However, it is becoming increasingly apparent that aBMD alone is insufficient to predict fracture risk. New Canadian osteoporosis guidelines have proposed that clinical risk factors such as age, sex, prior fragility fractures, and glucocorticoid use be incorporated with aBMD to assess fracture risk [15,17]. Bone properties such as a bone's structure and architecture also play a role in bone strength,

thus contributing to fragility fractures. Peripheral quantitative computed tomography (pQCT) is a new non-invasive technique that provides a measurement of volumetric bone mineral density (vBMD). pQCT can also characterize a bone's geometry, and generate an index of bone strength that reflects the ability of bone to resist torsion or bending [18]. A few previous investigations of bone health among individuals with SCI have been performed using pQCT; in addition most of these studies were conducted in males. They report a decrease in total aBMD, trabecular vBMD, cortical thickness, and stress strain index by 45-47% [4,19], 15-49% [19,20], 17-47% [4,19],17-19% [4], respectively, in the tibia compared to controls. Although SCI is uncommon in women, with a male-to-female ratio of approximately four to one [21], women in general are at high-risk of osteoporosis [17]. Therefore, we need to determine if women with SCI face greater deterioration of bone mass than men with SCI.

pQCT has previously been used to determine bone structure in other fracture-prone populations such as post-menopausal women, dialysis patients, and children with cerebral palsy. Cortical and trabecular micro-architecture have been found to be strong correlates of bone strength and fracture risk in *in vivo* and in *ex vivo* studies [22,23]. For example, cortical thickness defined as the difference between the outer and inner radius of cortical bone, provides an index of the degree of endosteal resorption, and, in addition to cortical density and area, has been associated with fractures among individuals on dialysis [24]. Thinning of cortical bone leads to a distinct increase in the buckling ratio [25] among dialysis patients. Buckling ratio expresses the likelihood that bone will fail due to extreme cortical thinning. Another cross-sectional study demonstrated that the mean values for intertrabecular spacing within the bone marrow at the radius can distinguish between women with and without fractures [26]. Sornay-Rendu et al [27] reported that vBMD and changes in cortical and

trabecular structure are associated with fractures in postmenopausal women. In children with cerebral palsy (CP), stress-strain index of bone, a surrogate measure of bending strength that takes into account material properties of bone, was reduced by approximately 64% compared to healthy controls as a result of smaller and thinner cortical bone, and not because of a reduction in cortical bone density [28]. These studies confirm the importance of bone geometry, in addition to BMD, as indicators of bone strength. Review of lower extremity pQCT data may enhance our ability to predict fractures among people with SCI and low bone mass.

Fracture threshold and fracture breaking point have recently been proposed in predicting fracture risk among individuals with SCI. Fracture threshold is defined as aBMD value in a specific skeletal site, below which osteoporotic-related fracture begin to occur, whereas fracture breaking point is defined as a point in which the majority of fractures occur [29]. Low BMD of the distal femur and proximal tibia has been found to be different among individuals with SCI with and without a history of fragility fracture. A study conducted by Garland et al [29] reported a DXA-based aBMD fracture threshold of 0.78mg/cm^2 at the knee and a fracture breaking point of 0.49mg/cm^2 in males with SCI. Recently, fracture threshold for vBMD were identified with a femoral distal epiphysis trabecular vBMD of less than 114mg/cm^3 and a tibia epiphysis trabecular vBMD of less than 72mg/cm^3 among individuals with complete SCI [30]. Fracture threshold values may be a useful technique in assessing fracture risk among the SCI population, but further validation of its positive predictive value is required.

Despite the high rates of fracture occurrence, there are no consensus-based guidelines for the determination of fracture risk and optimal treatment for individuals with SCI, which

has resulted in variation of diagnostic protocols between SCI clinicians [31]. However, a protocol has been proposed in which fracture risk can be ascertained with aBMD measurements of the knee region and fracture risk factors [32]. The current practice of using DXA-based aBMD to predict fractures in men and women over the age 50 years cannot be applied to predict fracture risk in individuals with SCI because different risk factors apply [30]. Studies need to explore potential correlates associated with fractures among individuals with SCI to determine those at high risk of fracturing. Newer technology such as the pQCT allow for the analysis of bone structure and indices of bone strength. The current pQCT literature has small sample sizes, and focuses on men with motor complete paraplegia. Little is known about the changes in bone architecture that occur in females, tetraplegics, and individuals with an incomplete SCI. Therefore, characterizing changes in bone structure in a broad spectrum of individuals with SCI will improve our understanding about the physiological changes that occur in bone post-injury and will enhance our ability to assess fracture risk among individuals with different levels of neurological impairments. Fracture threshold values established by the pQCT may also be a useful diagnostic technique in fracture risk assessment; however there is no evidence that applies the vBMD fracture thresholds among individuals with SCI.

In conclusion, this study will determine potential correlates of fracture risk, increase our understanding of fractures and bone structure among individuals with SCI, and potentially explain why some individuals with SCI experience multiple fractures while others experience only one or none. Therefore, this study will ascertain which individuals with SCI are at highest risk of fragility fractures.

2.0 CHAPTER 2: BACKGROUND

2.1 Spinal Cord Injury

According to the Rick Hansen Institute approximately 4000 Canadians sustain a SCI each year [33]. SCI can occur as a result of trauma (car accidents, gunshot wounds, falls, etc.) or disease (transverse myelitis, aneurysm repair, etc). Thirty five percent of traumatic spinal cord injuries occur as a result of car collisions, while 16.5% and 6.2% occur as a result of falls and other motor vehicle accidents, respectively [34]. SCI primarily affects young adults. The average age of injury is 37.6 years; the majority of injuries occur between the ages of 16 and 30 [35], in which 80% of the SCIs occur in males [36]. However, the average age of injury is steadily rising due to an increased proportion of older adults experiencing SCI [21]. Individuals with SCI have a life expectancy of 25 to 30 years beyond their injury; the contributing causes of death most often are cardiac and respiratory dysfunction. Individuals with SCI are expected to reach normal life expectancy [37]. SCI is a multifaceted issue; it can occur in men or women, at any age, and at any segment with varying severities along the spinal cord.

SCI can be classified using the International Standards for Classification of SCI as either an incomplete injury or a complete injury. If sensory and/or motor functions are preserved below the neurological level, including the lower sacral segment, the injury is known as incomplete. With an incomplete injury, individuals will experience sensations at the anal mucocutaneous junction as well as deep anal sensation, and can voluntarily contract their external anal sphincter. A complete injury has no preservation of sensory and motor function in the lowest sacral segment, S4 and S5. However, when sensory and motor function below the neurological level and above S5 remains partially innervated with a complete injury this is

termed zone of partial preservation (ZPP). Tetraplegia (a preferred term to quadriplegia) refers to damage or impairment of motor and/or sensory function in the cervical segment resulting in loss of function in the arms, trunks, legs and pelvic organs. Paraplegia is the damage or impairment to neural elements in the thoracic, lumbar or sacral segments of the spinal cord. The neurological level of injury determines the degree of trunk, legs, and pelvic organ function preserved. However, since the cervical segment of the spinal cord has not been affected, the functions of the arms are spared in paraplegics [38].

The majority of individuals with SCI have damage to both the upper and lower motor neurons. However, sometimes individuals with SCI can have damage to just the upper motor neuron or just the lower motor neuron. The upper motor neuron injury refers to injuries above the level of the anterior horn cell, resulting in a spastic type of paralysis. Conversely, damage to the lower motor neuron causes injury at or below the level of the anterior horn cell, which results in flaccid paralysis [36].

The severity and extent of the SCI is assessed by the American Spinal Injury Association (ASIA) impairment scale (AIS) (Table 1). Understanding the impairment scale is important because it is a single label describing the person's functional impairment and anticipated abilities as a result of their SCI. AIS is a five-level standard grading system; one level for complete (AIS A), and three for incomplete (AIS B-D). The AIS is based on a systematic two-component neurological examination: 1) sensory examination, and 2) motor examination. The sensory level is examined by extensive testing of skins' sensitivity to pin prick and to light touch. Dermatomes, areas of the skin that provide sensory input [39], are each scored as either normal, impaired or absent sensation. Likewise, the motor level is

determined by a manual muscle exam to test the strength of 10 key muscle groups on a six-point scale (0 to 5).

Table 1: AIS Impairment Scale

AIS Grade	Description
A	Complete; no sensory or motor function preserved in the sacral segments S4-S5
B	Incomplete; sensory but no motor function preserved below the neurological level and extending through the sacral segments S4-S5
C	Incomplete; motor function preserved below the neurological level; most key muscles have a grade < 3
D	Incomplete; motor function preserved below the neurological level; most key muscles have grade ≥3
E	Normal motor and sensory function

2.2 Osteoporosis

2.2.1 Bone

Bone is a complex connective tissue characterized by its unique hardness and rigidity. At a macroscopic level, bones are composed of cortical and trabecular compartments. Cortical (or compact) bone represents approximately 80% of the skeleton [40]. Cortical bone is very dense; 80-90% of its volume is calcified tissue [41]. The shaft or diaphysis of the bone is primarily comprised of cortical bone. However, the metaphysis, the region below the growth plate, and the epiphysis, the area above the growth plate is composed mainly of trabecular (or cancellous) bone. Trabecular bone consists of thin interconnected trabecular struts, and represents approximately 20% of the skeleton [40]. Only 15-25% of the volume of trabecular bone is calcified. The function of trabecular bone is primarily metabolic, while cortical bone has primarily a mechanical function [41]. Bones also consist of an outer fibrous connective tissue called the periosteum and an inner membranous sheath called the endosteum. The periosteum contains an inner cambrium layer comprised of undifferentiated cells that become

bone forming cells, called osteoblasts, during osteogenesis. The endosteum contains surface cells called osteoblasts and osteoclasts that line the medullary cavity [41].

Bone is comprised of functionally distinct cells called osteoblasts, osteoclasts, and osteocytes that are required to support the structural, biomechanical, and mechanical integrity of bone. Osteoblasts are bone forming cells which are responsible for the synthesis of osteoids, unmineralized bone matrix [41]. Once the bone matrix has been synthesized, the osteoblasts become embedded inside the calcified matrix and are converted to osteocytes [42]. Osteoclasts are large multinucleated bone lining cells up to 100μm in diameter and are responsible for bone resorption.

To maintain their regulatory functions, bone must respond to mechanical forces by undergoing bone remodelling and modeling. Bone remodelling and modeling are the processes by which bone is being turned over, allowing for the maintenance of the shape, size, and quality of the skeleton. This process is characterized by the coordinated actions of osteoblasts and osteoclasts. Bone is modeled and remodelled by the interactions of these cells to regulate mineral homeostasis, repair micro-fractures, and modify the bone's structure in response to daily stresses imposed on the bone [42,43]. Understanding the basics of the bone remodelling cycle is critical, particularly when abnormalities occur in the cycle in common diseases that affect humans such as osteoporosis. Furthermore, understanding how bone remodelling is regulated is a key first step in the prevention and treatment of osteoporosis.

There are four distinct stages in the remodelling cycle: activation, resorption, reversal, and formation (Figure 1). Activation involves the recruitment of osteoclasts. During the resorption phase, osteoclasts attach to the bone surface and begin to erode the matrix and minerals by acids and lysosomal enzymes. After the completion of osteoclastic resorption, a

reversal phase begins in which osteoblasts are employed to begin filling in the eroded cavities by laying down new bone. Once new bone has completely filled the resorbed cavities, a protective layer of lining cells are placed and a prolonged resting period begins until a new remodelling cycle is initiated [40]. Complete mineralization of a bone segment may take up to 3 months [41]. During growth, the balance between bone formation and bone resorption is positive, resulting in an increase in bone mass. Bone formation and bone resorption are coupled until approximately 35 to 40 years, and then an increase in bone resorption relative to bone formation occurs, leading to bone loss [42]. Bone remodelling and modeling affect the external size and shape of bone as well as its internal micro-architecture by removing or depositing material from the surface of the bone. As a result, cortical and trabecular bone become thicker during growth and thinner during aging.

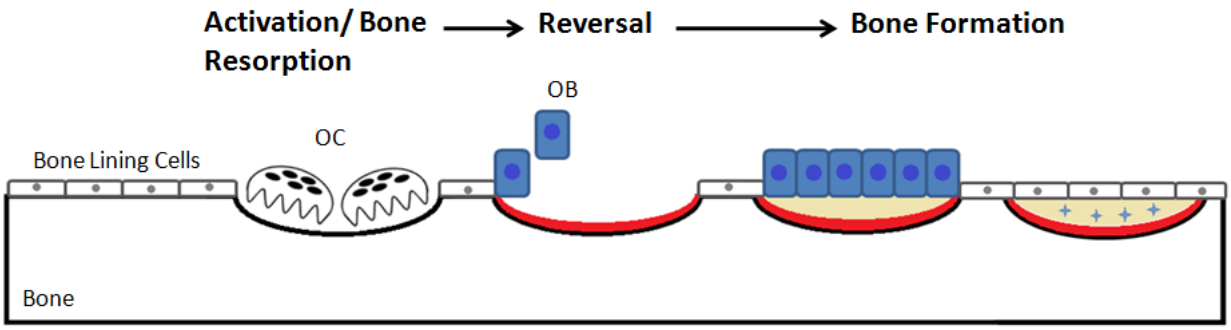


Figure 1: Bone remodelling cycle (OC: osteoclasts; OB: osteoblasts)

2.2.2 Changes in Bone with Aging

During adulthood, the first change in the remodelling cycle that leads to bone loss is a decrease in bone deposition at the cellular level. When bone formation is less than bone resorption, a small amount of bone from the skeleton is removed with each remodelling cycle, resulting in bone loss and architectural deterioration in cortical and trabecular bone. The changes that occur in cortical bone are generally related to the size and diameter of the bone.

As long bones increase in length before either sex reaches puberty, the formation of bone on the periosteal surface widens the shaft of the bone, while a small volume of bone is concurrently removed on the endocortical surface. Since periosteal apposition exceeds endocortical resorption, the cortex of the long bone becomes thicker and farther from the axis [44]. Girls will achieve a smaller diameter because estrogen in girls inhibits periosteal apposition while promoting net bone formation on the endocortical surface, leading to a narrower inner diameter. In boys, androgen production increases bone formation on the periosteal surface, resulting in a larger diameter and thicker cortex (Figure 2) [44,45]. However, during aging, the amount of bone within the periosteal envelope is reduced by bone resorption on the endocortical, intracortical, and trabecular surfaces. Periosteal apposition offsets endosteal resorption more in men than in women which leads to a net loss of bone that is greater in women than in men [46-48]. In both genders, cortices become thin and porous

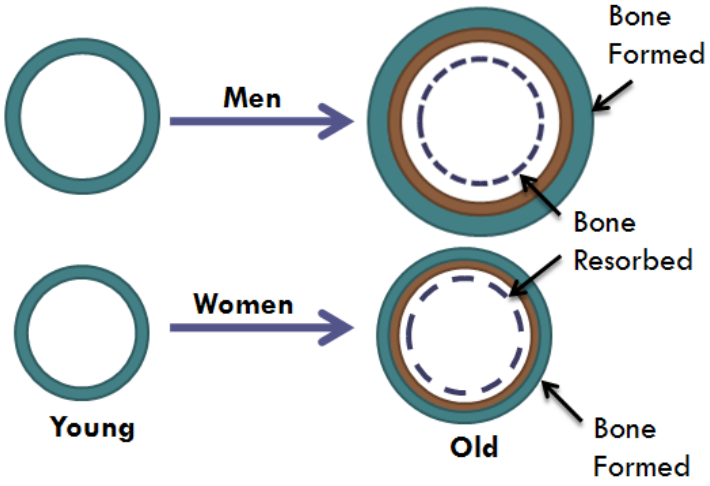


Figure 2: Changes in cortical thickness in men and women during aging. Adapted from Seeman [45]

while trabeculae thin and begin to disappear with aging [45,49]. The trabecularization of the cortex caused by the increase in cortical porosity, increases the surface to volume ratio so that

remodelling occurs vigorously, predisposing the bone to buckling, microdamage, and ultimately fractures [43,50].

Age-related changes can also be seen in trabecular bone. These include a decrease in bone volume, bone surface density, trabecular thickness, trabecular number, and connectivity [49,51]. Trabecular bone has more surface than cortical bone; there are more remodelling sites per volume, resulting in a greater proportion of trabecular bone turn over [52]. In men, trabecular bone loss occurs mainly by thinning rather than loss of connectivity (fewer number of trabeculae), while in women, trabecular bone loss occurs mainly by loss of connectivity [43,48,53]. Loss of connectivity is a result of rapid bone loss that occurs in midlife in women due to estrogen deficiency. Estrogen deficiency increases bone resorption by osteoclasts and reduces bone deposition by osteoblasts, producing a high bone turnover rate [43]. Trabecular struts are thinned and many begin to disappear, particularly horizontal struts, causing the loss of connectivity [49], which in turn reduces bone strength and increases the risk of fracture.

2.2.3 Osteoporosis

Osteoporosis is a skeletal disorder characterized by a reduction in bone mass and a deterioration in bone micro-architecture, which clinically results in increased bone fragility and fracture risk [54]. Osteoporosis mainly affects post-menopausal women; however both younger men and women may also be affected [55]. In Canada, two million Canadians suffer from osteoporosis; 1 in 4 women and 1 in 8 men [56].

Currently, the diagnosis of osteoporosis and fracture risk is primarily based on assessing areal bone mineral density (aBMD) by dual energy x-ray absorptiometry (DXA) [15,16]. Osteoporosis is defined as having an aBMD at the femoral neck of 2.5 or more standard deviations (SD) (T-score $\leq$ 2.5 SD) below the peak bone mass for young adults.

Recent 2010 guidelines for the diagnosis and management of osteoporosis [17] in Canada have suggested that certain clinical factors increase the risk of fracture independent of aBMD and proposed that managing osteoporosis should focus on preventing fragility fractures and their harmful effects rather than treating low aBMD. Currently, two tools are available in Canada for estimating 10-year risk of a major osteoporotic fracture and both tools incorporate clinical risk factors. The Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool stratifies men and women over the age of 50 into low (<10%), moderate (10-20%), or high (>20%) risk for major osteoporotic fracture within 10 years. An initial risk category is provided based on age, sex, and femoral neck T-score. However, certain clinical factors such as the presence of a prior fragility fracture after age 40 and prolonged glucocorticoid use raises the individual's fracture risk to the next higher risk category. The World Health Organization (WHO) Fracture Risk Assessment tool (FRAX) varies from the CAROC tool because it is based on a more complete set of clinical risk factors: sex, age, BMI, prior fracture, parental hip fracture, prolonged rheumatoid arthritis, smoking, alcohol intake, and aBMD at the femoral neck. These diagnostic criteria are used in predicting fracture in post-menopausal women and men over the age of 50 [15,16]; therefore, it is not clear how to apply these diagnostic criteria in individuals with SCI. The majority of individuals with SCI fall into the osteoporotic group. Therefore, there is ambiguity over an appropriate diagnostic criteria and intervention protocol for individuals with low bone density such as individuals with SCI.

2.3 SCI and Osteoporosis

SCI is a condition known to be associated with a substantial amount of bone loss following the injury, predisposing individuals with SCI to an increased fracture risk. Various

cross-sectional studies and prospective studies have reported a significant reduction in BMD in the lower limbs among individuals with SCI compared to controls (Table 2). However, there is immense variability between studies in the amount of bone loss that occurs following a SCI. For example, prospective studies have reported that BMD at the knee decreases between the ranges of 1.1% to 47% per year [2,3,20,57-60], suggesting individual variability in the amount of bone loss following a traumatic SCI. Among individuals with SCI, the most common site of bone loss is at the distal femur and proximal tibia [61]. Studies have demonstrated that individuals with SCI can lose up to 70% and 52% of BMC in the distal femur and proximal tibia, respectively [1,2,30,61].

Bone loss generally involves the lower extremities in individuals with paraplegia, although, bone loss has been noted in the upper extremities in addition to the lower extremities among individuals with tetraplegia [2,59,62]. Bone demineralization in the upper extremity has been found to be significantly different when comparing paraplegic and tetraplegic individuals [60,63]. A 12-month prospective cohort study demonstrated that tetraplegics had a trabecular BMD loss of 28% and 15% and cortical BMD loss of 3% and 4% at the radius and ulna, respectively. No significant changes were reported in trabecular or cortical BMD of the radius and ulna in paraplegics [20]. Contradictory results have been reported regarding the changes that occur in the lumbar spine. Changes in the lumbar spine have been found to increase, decrease, and remain unchanged in individuals with SCI [6,59-61,64,65].

The rate of bone loss after SCI varies over time. Initially, during the acute phase of SCI, BMD in the lower extremity decreases at a rate of 1-2% per week [1,2,57,66]. The rapid bone loss is attributed to an increase in osteoclastic activity [2,67,68]. Following 1-2 years

post-injury, bone resorption markers begin to return to normal [67] and bone loss in the lower extremity decreases to a rate of 1% per month [57,66]. Approximately 2 to 3 years after SCI, a steady state between bone resorption and bone formation is established [3,58,69]. In a prospective study, Biering-Sorensen et al demonstrated that after a SCI, new steady state for bone mineral content (BMC) in the femoral neck and proximal tibia were achieved after decreasing by 30-40% and 50-60%, respectively [60]. Although this study had a longitudinal design, the sample size was very small and included only six men and two women. In contrast, a few cross-sectional studies have reported that BMD in the lower extremity may continue to decline at a rate of 1% per year [57,66]. Whether bone remodelling re-establishes at a new steady state after SCI remain controversial.

Table 2: Changes in BMD and Bone Structure Following a Spinal Cord Injury

Reference	Study Design	Number of Participants Mean Age ± SD	Years Post Injury Mean ± SD	Complete/ Incomplete	Skeletal Sites Measured	Results (compare to control or other interpretation)
Biering-Sorensen, et al, 1990 [60]	PS	6 men; 2 women; 18-49 years	9 days-53 months	8 Complete 1 Incomplete	FN, PT	FN: 30-40% ↓/30-53 months PT: 50-60% ↓/30-53 months
Dauty et al, 2000 [61]	CS	31 males 36 ± 12.3	> 1 year	26 Complete 5 Incomplete	DF, PT, FN, FT	DF: 70% ↓ in BMD PT: 52% ↓ in BMD FN: 30% ↓ in BMD FT: 39% ↓ in BMD
De Bruin et al, 2005 [3]	PS	9 men; 1 woman 40.9 ± 19.7	5 weeks	4 Complete 6 Incomplete	DT, DR	Trabecular and Cortical of Radius: no change <u>DT</u> Trabecular: 40% ↓ in 3 years Cortical: 11% ↓ in 3 years
De Bruin et al, 2000 [58]	PS	9 men 32.4 ± 9	5 weeks	4 Complete 5 Incomplete	DT, TS	Trabecular: 35.5% ↓ within 2 years Cortical: 12.9% ↓ within 2 years
Demirel et al,1998 [62]	CS	32 men; 9 women 35.8 ± 12.7	2-30 months 9.5 ± 4.5 months	21 Complete 20 Incomplete	LE	Paraplegics: ↓ 2.19 ± 3.5 Tetraplegics: ↓ 2.50 ± 0.55
Dionyssiotis et al, 2006 [4]	CS	39 men, 2 groups: A: 38.22 ± 15.6 B: 39.47 ± 13.81	A: 5.97 ± 5.9 years B: 5.65 ± 5.8 years	Complete	TS, DT	BMD_{trab}: 58% ↓ in A; 49% ↓ in B BMD_{tot}: 47% ↓ in A; 45% ↓ in B THI_{cort}: 20% ↓ in A; 17% ↓ in B
Eser et al, 2004 [19]	CS	89 men 41.5 ± 14.2	12.0 ± 11.3 years	Complete	DT, DF, TS, FS, PT	BMD_{tot}: 45% ↓ tibia; 57% ↓ femur CSA_{cort}: 30% ↓ tibia and femur THI_{cort}: 35% ↓ tibia; 33% ↓ femur
Eser et al, 2005 [30]	CS	89 men; 10 women 41.5 ± 13.7	2 months – 24.5 years 12.3 ± 11.6 years	Complete	DT, DF, TS, FS, PT	DF: 54% ↓ BMD in first 5 years DT: 73% ↓ BMD in first 7 years vBMD of epiphysis in LE best predicts fracture threshold

Reference	Study Design	Number of Participants Mean Age ± SD	Years Post Injury Mean ± SD	Complete/ Incomplete	Skeletal Sites Measured	Results (compare to control or other interpretation)
Finsen et al, 1992 [70]	CS	19 men 15-64 years	7 months- 33 years		DT	DT diaphysis: ↓ 26 % in BMD DT epiphysis: ↓ 45% in BMD
Frey-Rindova et al, 2000 [20]	PS	27 men; 2 women 19-59 years	Undefined	10 Complete 19 Incomplete	TS, DT	BMD_{trab}: 15%↓ in 12 months BMD_{cort}: 7% ↓ in 12 months
Frotzler et al, 2008 [71]	CS	39 men 42 ± 10.8	0.9 – 34 years 12.0 ± 10.8 years	Complete	FS, DF, TS, DT	In 30 months DF: BMD_{trab}: 1.30%↓ FS: BMD_{cort}: 0.17% ↑ pSSI: 1.72% ↓ DT: BMD_{trab}: 1.67% ↓ DS: BMD_{cort}: 0.48% ↓ CTh: 0.73% ↓ pSSI: 0.55% ↓
Garland et al, 2001 [1]	CS	45 men < 40 years	Acute: 114 days Chronic: 10 years	Complete	DF, PT	DF: 37% ↓ 10 years after PT: 36% ↓ 10 years after
	CS	31 women, 3 groups: ≤ 30 years 30-50 years > 50years	18 months	Complete	Knee	≤ 30 years: 38%↓ 30-50 years: 41% ↓ > 50years: 47% ↓
Garland et al, 1992 [2]	CS	20 men 28.1 ± 0.78	5 years 3649.6 ± 326.6 days	Complete	DF, PT	DF: 37% ↓ PT: 36% ↓
	PS	12 men 28.1 ± 0.78	114 ± 8.6 days	Complete	DF. PT	DF: 13% ↓ in 16 months PT: 13% ↓ in 16 months

Reference	Study Design	Number of Participants Mean Age ± SD	Years Post Injury Mean ± SD	Complete/ Incomplete	Skeletal Sites Measured	Results (compare to control or other interpretation)
Garland et al, 2008 [57]	PS	27 men; 4 women 39.7 ± 10.6	14.6 ± 8.7 years	Complete	Spine, hip, DF, PT, LE	Spine: 0.3% ↑/year Hip: 0.4% ↓/year DF: 1.1% ↓/year PT: 1.5% ↓/year LE TBD: 1.2% ↓/year
Garland et al, 2001 [59]	PS	31 women; 3 groups ≤ 30 years 31-50 years > 50 years	 5.7 ± 2.3 years 16.1 ± 9.4 years 28.9 ± 11.4 years	Complete	Knee, Hip, Spine	Knee: 38-47% ↓ in BMD/year Hip: 18-25% ↓ in BMD/year Spine: -2 to 15% ↑ in BMD/year
Modlesky et al, 2005 [5]	CS	8 men 33.1 ± 9.2	2.3 – 20 years 7.4 ± 6.0 years	Complete	FS	aBMD: 25% ↓ THI_{cort}: 27-47% ↓ Cortical volume: 24% ↓ BMC: 21% ↓
Modlesky et al, 2004 [72]	CS	10 men 34.6 ± 9.2	2.3 – 20.1 years 8.5 ± 6.6 years	Complete	DF, PT	<u>DF</u> appBV/TV: 27% ↓ appTb.N: 21% ↓ appTb.Sp: 44% ↑ appTb.Th: 8% ↓ <u>PT</u> appBV/TV: 20% ↓ appTb.N: 20% ↓ appTb.Sp: 33% ↑ appTb.Th: no difference aBMD: 43% ↓ BMC: 49% ↓

Reference	Study Design	Number of Participants Mean Age ± SD	Years Post Injury Mean ± SD	Complete/ Incomplete	Skeletal Sites Measured	Results (compare to control or other interpretation)
Slade et al, 2005 [73]	CS	19 women, 3 groups 42.6 ± 4.66 54.5 ± 7.7 23.0 ± 2.55	≥ 2 years 12.2 ± 8.14 years 14.17 ± 11.9 years 5.6 ± 2.33 years	Complete	DF, PT	DF appBV/TV: 30.9% ↓ appTb.N: 26.5% ↓ appTb.Sp: 61.7% ↑ appTb.Th: 6.8% ↓ PT appBV/TV: 23% ↓ appTb.N: 18.5% ↓ appTb.Th: 5.8 ↓
Zehnder et al, 2004 [6]	CS	100 men 38 ± 0.97	1 month – 29.5years 10.4 ± 0.79 years	94 Complete 6 Incomplete	LS, FN, DT, TS	BMD ↓ with time at all LE sites Fractures occur after trabecular bone lost had levelled off

CS = cross-sectional study; PS = prospective study

DT = distal tibia; DF = distal femur; TS = tibial shaft; FS = femoral shaft; FN = femoral neck; FT = femoral trochanter; PT = proximal tibia; LE = lower extremity; DR= distal radius

2.3.1 SCI and Bone Geometry

Changes in bone micro-architecture and geometric structure have also been reported in conjunction with loss of bone mass after SCI (Table 2). In men with complete and long-term SCI, trabecular bone micro-architecture in the distal femur and proximal tibia was significantly deteriorated compared with control subjects. Men with SCI had fewer trabeculae that were further apart which resulted in a lower ratio of bone volume to total volume (BV/TV) [72]. Similar findings have been reported in women with complete SCI compared to ambulatory women [73]. The deterioration of trabecular micro-architecture in women with SCI was reported to be greater than in postmenopausal women with osteoporosis. Middle-aged ambulatory postmenopausal women who were not taking estrogen or bone medications did not show the deterioration of trabeculae that was seen in women with SCI [73]. Furthermore, an interaction between mechanical unloading and low estrogen levels was reported; postmenopausal women with SCI had 34% greater trabecular spacing in the tibia than premenopausal women with SCI [73]. Thus, immobilization following SCI significantly reduces bone architecture around the knee in both men and women. Changes in bone area and bone geometry after SCI have also been reported [74,75]. Cortical thickness has been shown to remarkably change in the tibia and femur after a SCI. In a cross-sectional study, men with complete SCI had thinner cortical walls by 19.78% compared to the control group [4]. The findings in this study were consistent with two previous cross-sectional studies which reported a reduction in cortical thickness by 33-35% [19] and 27-47% [5]. Consequently, the decrease in cortical thickness was attributed to an increase in endosteal resorption, occurring at approximately 0.3mm per year [4,19]. Another study found that individuals with SCI with a lower extremity fragility fracture had a lower area moment of inertia in the tibia compared to

individuals with SCI without a fracture and able-bodied control [74], indicating that the ability of the bone to resist bending load is much lower among individuals with SCI with a fracture. Ultimately, the distribution of bone mineral around the bone's bending axis has been reduced [74]. Changes in bone quality after SCI may contribute to a high incidence of lower extremity fractures. Therefore, analysis of bone structure, combined with measurements of aBMD may improve the ability to determine fracture risk among individuals with SCI.

2.3.2 Which Bone Strength Parameters are Important?

There are many bone strength parameters that can be measured, but selecting which ones may be of clinical importance is difficult. Many studies in men, women, and children have examined the association between bone strength parameters and fracture risk. In healthy adults, MacIntyre et al [76] demonstrated gender and age-dependent increases in average hole size (H_A). Furthermore, pQCT-based trabecular structure variables were related to bone strength in vitro [77]. Women with a history of forearm fractures had significant differences in trabecular bone structure than women with similar aBMD but no history of fracture [26], indicating that structure-based measurements, such as H_A may be useful for identifying those at higher risk for fractures such as individuals with SCI. Average hole size is the average area of each hole represented by the marrow space. As trabecular struts become thinner and begin to disappear, hole size increases. As a result, trabecular bone becomes weak and unstable leading to subsequent fractures.

Small changes in cortical bone have been shown to make a large difference in bone strength [78]. In 677 healthy young men with childhood fractures, prevalent fractures were associated with decreased cortical thickness. Childhood fractures were associated with a thinner cortex and smaller bone size (periosteal circumference), while fractures occurring later

than 15 years of age were associated with a thinner cortex and wider endosteal circumference, with no change in periosteal bone size [79]. This suggests that there are different mechanisms of fracturing during childhood versus in adult life. When a child fractures its bones, it may disturb the natural growth cycle causing a thinner cortex and suboptimal acquisition of peak bone mass resulting in an increased risk of fracture.

Cross-sectional moment of inertia is an indicator of bone's architectural design (how mass is distributed about the bones' central axis) which is able to predict the ability of bone to resist bending. For example, when bone mass is distributed progressively further from the axis (resulting in wider bones), the cross-sectional moment of inertia increases and bone's ability to resist bending forces also increases, resulting in lower chances of fracturing [80]. Polar moment of inertia is also a biomechanical term that describes the ability of bone to resist torsion. A bone with a large polar moment of inertia will resist twisting caused by torque. Both polar moment of inertia (OR=2.6, 95% CI=1.1-6.1, $p<0.05$) [81] and cross-sectional moment of inertia (HR=2.2, 95% CI= 1.4-3.3) [80] were found to be significantly related to fracture risk. In addition, polar moment of inertia at the ultra-distal tibia appears to be lower in postmenopausal women who have sustained a forearm fracture compared to age-matched controls [81].

Buckling ratio defined as the maximum distance from the center of mass to the medial or lateral edge of bone, divided by the average cortical thickness has also been found to correlate with fracture risk. In a retrospective study examining structural variables as assessed by DXA, fractures due to severe trauma were best correlated with femoral neck buckling ratio in postmenopausal women (OR=1.2, 95% CI=1.04-1.5) and intertrochanteric buckling ratio in men (OR=1.4, 95% CI=1.2-1.6) [81]. An attractive feature of assessing buckling ratio is that it

presents a possible mechanism to explain why greater bone loss and greater expansion of bone diameter reduces BMD.

To our knowledge, there are no studies investigating the relationship between fracture prevalence and average hole size, cortical thickness, cross-sectional moment of inertia, polar moment of inertia, and buckling ratio among individuals with SCI. Since these indices of bone strength have been found to be clinically important correlates of fracture risk in able-bodied men and women, it may be useful to investigate their association with fragility fractures sustained in individuals with SCI.

2.3.3 Mechanism of Bone Loss in SCI

The rapid loss of BMD and bone strength occurs invariably among conditions of immobilization such as SCI. According to Wolff's law, the direction, rate and magnitude of mechanical loading on bone has an influence on how bone remodelling will respond [82]. For this reason, the structural integrity of bone changes in response to gravity and mechanical stress. However, when bone is subjected to mechanical unloading, uncoupling occurs between bone formation and bone resorption. Individuals with SCI will experience an imbalance between high bone resorption and low (or normal) bone formation within the first week of injury which peaks around weeks 10 to 16 [6,67,68]. Therefore, individuals who experience minimal or no mechanical loading have excessive osteoclastic resorption and an inhibition of osteoblastic activity. Studies have also reported that in paralyzed extremities there is an increase in IL-6 (interleukin-6). IL-6 is a well-known cytokine which has been suggested to enhance osteoclastic formation and activity [83]. The enhanced osteoclast activity has been reported to begin one month after the injury [6,84]. IL-6 may be produced in large amounts to promote increases in OC-like (osteoclast-like) cells in areas below the lesion level. Due to the

increase in OC levels, there is an immediate increase in urinary hydroxyproline excretion which marks an increase in bone resorption [85]. The dramatic elevation of bone resorption exceeds osteoblastic activity, resulting in a higher bone turnover rate and poor bone quality. Mechanical unloading may not be the only factor contributing to bone loss; a study showed no increases in BMD following mechanical loading [86]. Other factors include neurological [4] and hormonal changes [6]. Each of these factors may independently influence bone metabolism affecting the overall quality of the bone.

2.3.4 Risk Factors Associated with Bone Loss in Individuals with SCI

Several factors appear to influence the severity of bone loss among individuals with SCI. Modifiable and non-modifiable risk factors for osteoporosis in SCI include low BMI (body mass index < 19kg/m^2), age, gender, lifestyle behaviours such as alcohol consumption, and impairment variables such as the level of injury (LOI), duration of injury (DOI), completeness of injury, [29,87]. BMI has been found to be a reliable correlate of osteoporosis among individuals with SCI. Garland et al reported that for each unit increase in BMI, the odds of being osteoporotic decreased by 11.29%; however they did not determined if BMI is linked to fractures [87]. Interpreting this finding is difficult because characterizing overweight and obesity using BMI in the SCI population is unreliable. BMI defined for the able-bodied population fail to identify individuals with SCI who are obese. Studies have reported that the mean BMI among individuals with SCI ranges from 23.1kg/m^2 to 25.7kg/m^2 [88-91]. However, the percent fat mass ranges from 27.5% to 36.3% [88-90] which is consistent with obesity fat mass values (>25%) in the able-bodied population [92], suggesting that BMI underestimates obesity in the SCI population, leading to a failure in the identification of

persons with SCI who are actually obese. Consequently, lower BMI (>22kg/m^2) cut-off points have been proposed in identifying individuals with SCI at high risk of obesity [91].

The current literature on alcohol consumption and the severity of bone loss among individuals with SCI is mixed. One study found that individuals drinking moderate amounts of alcohol were less likely to be considered osteoporotic. Unfortunately, the data for alcohol use only approached significance but was not established as a significant correlate of high amounts of bone loss [87]. There are only a few studies showing that modifiable factors such as BMI and alcohol consumption are risk factors for osteoporosis. As a result, further investigations examining the role of these risk factors with bone loss needs to be carried out.

The level of spinal cord injury has been reported to be a strong correlate of bone loss in the knee regions among individuals with SCI [29]. Many studies have demonstrated that tetraplegics lose more bone throughout the skeleton than paraplegics [2,61,62,67,70,93]; however the amount of bone loss in the sublesional area was similar between both groups [20,61,62,93]. Furthermore, a decrease in bone mass may be more severe among individuals with a motor complete SCI (AIS A and B) [2,29,62,87]. In a cross-sectional study of 46 males with SCI, Sabo et al [64] reported that males with a complete SCI had significantly lower BMD in the lumbar spine compared to those with an incomplete SCI.

Duration of injury is another factor that has been shown to influence bone loss [62,70]. A SCI twin study found that bone mineral content (BMC) and BMD in the leg declined at a continuous rate with duration of injury and appeared to be independent of age [94]. However, this is inconsistent with other studies which found no correlation between bone loss and duration of injury [95,96]. The inconsistent results may be due to the skeletal heterogeneity in the respective sample population, which were not evident in the twin study.

Age and gender have also been shown to contribute to bone loss in individuals with SCI. A cross-sectional study stratifying women with SCI into three groups according to age (≤ 30 years; 31-50 years; >50 years) found that BMD in the knee decreased by 38%, 41% and 47% and BMD at the knee decreased by 18%, 25%, and 25%, respectively compared to the corresponding control groups [59]. Kiratli et al [75] found similar results reporting a correlation between age and BMD in men (19-81years) and women (21-83 years) with SCI. With regards to gender, women with SCI have been reported to have lower BMD in the knee, hip and spine compared to males with SCI [57]. Contrary to the findings of Kiratli et al [75] and Garland et al [57,59], a cross sectional study found that age and gender were not related to bone loss in individuals with SCI [62]. The differences in outcomes found in these studies may be attributed to the age of the sample population. The studies that reported a relationship between age and gender of the participants and bone loss among individuals with SCI recruited older participants, while the study reporting no relationship recruited younger participants and premenopausal women. The study quality to date does not provide enough information to determine whether age and gender may influence bone loss among individuals with SCI.

There are many potential modifiable and non-modifiable risk factors that may contribute to bone loss (Table 3); however they have not been clearly established. Based on the current literature, age, gender, completeness of injury, and duration of injury may be the most important correlates of bone loss and need to be studied further to accurately understand the changes in bone that occur following a SCI.

Table 3: Modifiable and Non-modifiable Risk Factors for Osteoporosis among Individuals with SCI

Modifiable Risk Factors	Non-Modifiable Risk Factors
BMI < 19kg/m^2 Alcohol consumption	Level of injury Duration of injury Complete injury Age Gender (Female)

2.4 Risk Factors Associated with Fractures in Individuals with SCI

One clinical consequence of bone loss following SCI is an increased risk of fracture. In particularly, individuals with SCI are susceptible to low-energy fracture known as fragility fractures. A fragility fracture occurs as a result of minor trauma that would not normally cause a fracture such as transferring from chair to bed or colliding into unseen objects [8,9,12,30,97,98]. Thus, most of these fractures occur during activities of daily living. An individual with SCI has twice the risk of suffering from a lower extremity fracture than an able-bodied person in their lifetime [7]. Cross-sectional studies have reported a high prevalence of lower extremity fragility fractures among individuals with SCI ranging from 1% to 34% (Table 4). The prevalence may be underestimated as individuals with SCI may not seek medical attention for fracture because they are unaware of their fracture [11]. Fractures most commonly occur at the distal epiphysis of the femur and tibia, and the proximal epiphysis of the tibia [1,7,8,11-13,20]. Spiral fractures commonly occur at the diaphysis while bending fracture occur in the distal femur and proximal tibia [98]. Fracture rates have been reported to increase from 1% per year in the first year to 4.6% per year in individuals with SCI for more than 20 years [6]. Complications from fractures include pressure sores, infections, delayed union and illness, resulting in a diminished quality of life [8,10,12].

There are many factors that affect fracture risk in individuals with SCI. Fractures have been reported to occur more commonly in individuals with a complete SCI compared to an

incomplete SCI [9,11]. Individuals with a complete SCI lose more bone than individuals with an incomplete SCI [29,64], therefore individuals with complete SCI are more prone to fractures. In addition, paraplegics fracture more than tetraplegics [10]. A possible reason could be that paraplegics use manual chairs and transfer independently more often, which may result in more falls. BMD can also be used to quantify fracture risk in individuals with SCI by determining the number of SD below young adult mean BMD. For every 0.1g/cm^2 decrease in BMD at the femoral neck, fracture risk increased 2.2 times [14]. In studies comparing individuals with SCI who have a history of fractures to those who do not, duration of injury was also reported to be a strong correlate of fracture risk [6,14]. Other risk factors for fracture risk include female gender [7] and flaccid paralysis [8,11,99]. Individuals with lower motor neuron lesions (flaccid paralysis) were more prone to develop fractures than those with upper motor neuron lesions (spastic) [11,30] . Spasticity seems to preserve bone mass, resulting in a reduced fracture risk. However, other studies have not established an association between muscle spasticity and BMD [58,60].

Fragility fractures are a major problem in the SCI population; they lead to increased morbidity and prolonged immobilization, resulting in further deterioration of bone. Therefore, it is important to maintain or improve bone strength among individuals with SCI. Risk factors along with bone loss may distinguish individuals with SCI and prior fracture from those with no history of fracture. Larger prospective studies are needed to further examine risk factors related to bone loss and fracture so that future studies can better understand the pathophysiology of fractures in order to identify persons at risk of fragility fractures and implement appropriate treatment interventions prior to fracture onset. In addition, little is known about the effects of prior fragility fractures on individuals with SCI. A prior (or recent)

fracture confers one of the strongest risk factor for future fracture in postmenopausal women and men over the age of 50 years [17]. Whether or not fracture history improves our ability to predict future fracture in the SCI population needs to be examined.

Table 4: Fracture Prevalence among Individuals with SCI

Reference	Study Design	Prospective or Retrospective Data Collection	Number of Participants Mean Age ± SD	Years Post Injury Mean ± SD	Fracture Detection	Duration of Monitoring	Fracture Incidence
Commar et al, 2005 [9]	CS	Retrospective	1363 (total)		X-rays, Medical Charts		11% (6% lower extremity fracture)
Freehafer et al, 1983 [12]	CS	Retrospective	546 Men		Medical Charts	32 years	8%
Ingram et al, 1989 [13]	CS	Retrospective	526 (total) 13-70 years		Medical Charts	1971-1986	5%
Lazo et al, 2001 [14]	CS	Prospective	41 Men 56.0±13.3	0.7-54.9 years 17.8±14.1	Self-report, Radiological Studies		34%
Ragnarsson et al, 1981 [8]	CS	Retrospective	578 (total) 4-71 years (mean 31)	9 years	Medical Charts	Jan. 1970-Dec.1978	4%
Vestergaard et al, 1998 [7]	CS	Prospective	309 Men; 129 Women 17-80 years	12 years	Self-report		2%/yr
Zehnder et al, 2004 [6]	CS	Prospective	100 Men 38±0.97	10.4±0.79 < 1 year 1-9 years 10-19 years 20-29 years	Self-report, Medical Charts, X-rays		1%/year 1.3%/year 3.4%/year 4.6%/year Overall fracture incidence 2.2%/year

2.5 Diagnosing Osteoporosis and Fracture Risk in SCI

2.5.1 Assessment of aBMD using Dual Energy X-ray Absorptiometry

There is currently no specific guideline or screening protocol for assessing osteoporosis among individuals with SCI. DXA measurements of aBMD of the knee and screening for fracture risk factors (age at injury < 16 years, alcohol intake > 5servings/day, BMI < 19, DOI ≥10 years, female gender, motor complete, paraplegic, and prior fragility fractures) have been recommended for establishing fracture risk in individuals with SCI [32]. In able-bodied postmenopausal women and men over the age of 50, DXA at the hip along with clinical risk factors is the standard diagnostic method for assessing osteoporosis and fracture risk. DXA is a two dimensional non-invasive imaging technique that measures aBMD (g/cm^2) regionally at the lumbar spine, hip, or wrist, as well as the whole body. DXA can also be used to measure BMC, lean mass and fat mass. Radiation exposure is extremely low for DXA scans, approximately 10-30μSV, which is much lower than that experienced annually from natural background sources, 2400μSV [100]. Among individuals with SCI, the fracture-prone sites are the proximal femur and distal tibia. A validation study was recently conducted to determine the reliability of DXA scanning protocol at measuring knee BMD, specifically the proximal tibia and distal femur in individuals with SCI. The knee BMD measurements were reported to be very reliable with correlations of greater than 0.97 and 0.87 in the distal femur and proximal tibia, respectively [101]. When examining the precision of the DXA, ISCD recommends that aBMD testing be done on 15 patients three times or 30 patients two times with repositioning of the limbs for each scan to achieve statistical significance. For this study, each of the four technicians only conducted one scan for each participant which may not accurately assess precision error [102].

Although aBMD is considered to be a practical measure of bone strength, it does not provide any information on bone geometry that may contribute to fracture risk such as cortical and trabecular micro-architecture, and bone size and shape. The projectional nature of the x-rays produced by the DXA scan combines the influence of bone density and geometry on bone strength to give aBMD, rather than providing volumetric measurements of bone density [103]. Limitations in using DXA in individuals with SCI may include limited accessibility, longer scanning time, increased staffing during scans, and the need for ceiling-mounted hydraulic lifts need to be installed [104].

2.5.2 Assessment of Bone using Peripheral Quantitative Computed Tomography

Peripheral quantitative computed tomography (pQCT) is a non-invasive diagnostic technique that provides a three-dimensional (3D) image allowing for vBMD and cross-sectional bone dimensions to be measured. pQCT is able to differentiate between cortical and trabecular bone, estimate bone strength, and assess bone geometry [18]. pQCT may be a useful technique in assessing fracture risk because in addition to bone density, bone structure and geometry may also contribute to the integrity of the bone. Currently, there have been a few studies conducted on individuals with SCI examining bone geometry using pQCT [3,19,20,30,58,69,71,74]. Individuals with SCI experience a reduction in cortical thickness, reduced trabecular vBMD, and a decrease in polar moment of inertia [19]. Therefore, trabecular and cortical micro-architecture may be helpful in predicting fracture risk among the SCI population. Benefits of using pQCT among individuals with SCI include low doses of radiation and facilitation of transfer is not required; individuals with SCI can remain in their wheelchair during the scan, resulting in a decrease in burden upon the patient, a decrease in clinic time, and thus a reduction in healthcare costs. pQCT is a useful technique that provides

information on bone quality, which could potentially be related to bone fragility; however this technique is primarily being used in research settings and has not yet been adapted in the clinical setting.

2.5.3 Fracture Threshold and Fracture Break Point

Bone loss after SCI is said to reach a 'fracture threshold'. Fracture threshold is defined as BMD in a specific skeletal site below which osteoporosis-related fractures begin to occur, while fracture breaking point are values at which the majority of fractures occur [29,105]. Fracture threshold may be an alternative method for evaluating fracture risk. Fracture thresholds established for postmenopausal women at the spine, femoral neck and intertrochanteric regions of the femur are 0.97kg/m^2, 0.95 kg/m^2, and 0.92 kg/m^2, respectively [106]. However, the concept of fracture threshold in able-bodied osteoporotic postmenopausal women has been discarded because a meta-analysis demonstrated a linear relationship between aBMD and fracture risk. In the able-bodied population, fracture threshold can predict fracture risk, but is unable to identify those who will fracture [107]. However, the use of fracture threshold is gathering support among SCI physicians and researchers [32], based on data from studies identifying aBMD and vBMD threshold values below which there is an increase in lower extremity fragility fractures among individuals with SCI [29,30]. Low aBMD of distal femur and proximal tibia are able to distinguish individuals with SCI with and without a lower extremity fracture. Garland et al [29] reported DXA-based aBMD fracture threholds of 0.78g/cm^2 and a fracture breaking point to 0.49g/cm^2 at the knee among individuals with SCI which is significantly smaller than the fracture thresholds in postmenopausal women, suggesting other factors could explain the differences. Risk factors that should be considered include low BMD (<0.78g/cm^2), complete paraplegia, female

gender, prior fracture, duration of injury, and age [29]. Fracture thresholds have not yet been established for postmenopausal women at the knee, therefore a direct comparison of fracture threshold around the knee cannot be determined.

Recently, a cross-sectional study was conducted by Eser et al [30] suggesting that volumetric trabecular BMD (vBMD) of the lower extremity is the best parameter to identify those at risk of fracture and determine fracture threshold among individuals with SCI. Fractures occurred among individuals with SCI with trabecular vBMD of 114mg/cm^3 for the femoral distal epiphysis and 72mg/cm^3 for the tibial distal epiphysis. These vBMD values correspond to 46% and 29% of the femur and tibia mean aBMD values, respectively, of an able-bodied population [30].

The current literature to date on fracture threshold among individuals with SCI is limited to two studies. In addition, the aBMD fracture threshold reported by Garland et al [29] were obtained from men and included a small sample size (n=18), while the study by Eser et al [30] included individuals with just motor complete SCI. Therefore, until fracture threshold is validated, its utility remains uncertain whether it could help identify individuals with SCI at high risk of fracture.

2.6 Treatment and Prevention

2.6.1 Bisphosphonates

Bisphosphonates are the primary drug prescribed for osteoporosis and other bone-related diseases. Etidronate (Didrocal®), alendronate (Fosamax®), risedronate (Actonel®) and zoledronic acid (Aclasta®) are bisphosphonates that are currently approved by Canada for the prevention and treatment of postmenopausal osteoporosis. They are anti-resorptive agents that have been reported to inhibit bone resorption and reduce activation frequency of

osteoclasts in conditions characterized by increased bone resorption such as postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, Paget's disease, and male osteoporosis [108].

2.6.1.1 Mechanism of Action

Bisphosphonates can be classified into two groups: non-nitrogen based bisphosphonates; and nitrogen-based bisphosphonates. Non-nitrogen based bisphosphonates (Etidronate) are metabolically incorporated into non-hydrolysable analogues of adenosine triphosphate (ATP). The accumulation of toxic analogues to ATP within the OC inhibits OC function and may cause premature apoptosis of OC. Nitrogen based bisphosphonates (Alendronate, Risedronate, and Zoledronic Acid) target the mevalonate pathway which in turn inhibits OC resorptive activity and stimulates OC apoptosis (Figure 3) [108].

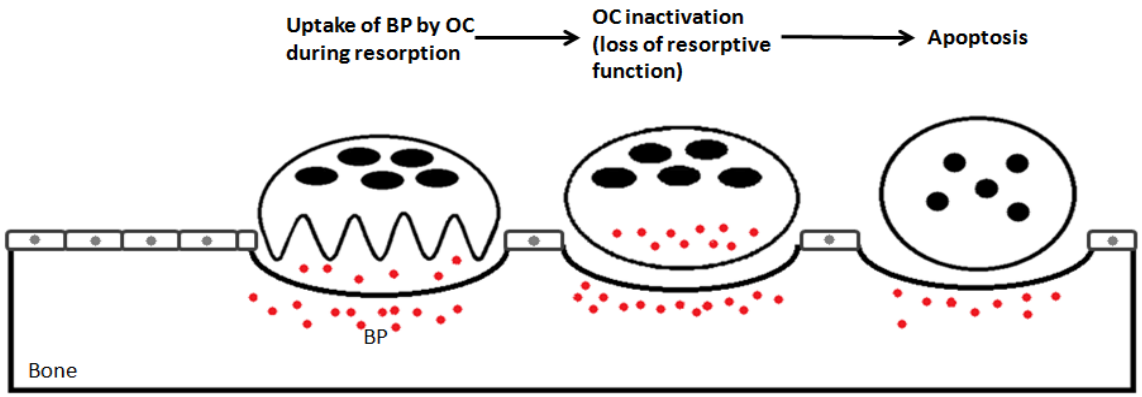


Figure 3: The pathway by which bisphosphonates affect osteoclasts

2.6.1.2 Bisphosphonate Therapy among Individuals with SCI

Oral bisphosphonates (alendronate) have been assessed among individuals with chronic SCI in two randomized control trials. In the first study conducted by Zehnder et al [109], subjects received alendronate (10mg daily) and elementary calcium (500mg daily) and compared them to control subjects receiving elementary calcium (500mg daily) over a 24

month period in 55 men with motor complete SCI (AIS A or B). BMD was maintained in the tibia epiphysis and total hip in the treatment group but was significantly decreased in the control- group. The lumbar spine BMD increased in both the treatment and control group, while there was no significant change in radial BMD. Biochemical markers of bone resorption were also reported to decrease among the treatment group which verified the results acquired by DXA.

The second randomized control trial conducted by Moran De Brito et al [110] examined the impact of alendronate (10mg daily) plus calcium (1000mg daily) versus calcium (1000mg daily) for 6 months in paraplegic and tetraplegic men (n=15) and women (n=4) with chronic SCI (AIS A, B or C). The results from this study demonstrated that alendronate and calcium have no significant impact on lower extremity BMD; however there was a mean increase in upper extremity BMD among the treatment group versus the control group.

While the results of these studies are predominately positive, there are limitations. The limitations to these studies include small sample sizes, short duration of follow up, choice of primary outcome (should have used knee region such as proximal tibia and distal femur rather than hip, lumbar spine or whole body), and inadequate details of the method of randomization. In addition, both randomized control trials examined the effects of alendronate on BMD in individuals with SCI. Whether etidronate, risedronate, or zoledronic acid has an effect on BMD among individuals with chronic SCI is unknown. Consequently, the effectiveness of bisphosphonates for the prevention and treatment of osteoporosis among individuals with SCI has not been clearly established and needs to be studied further.

2.6.1.3 Bisphosphonates and Atypical Fractures

Recently, there have been reports suggesting a relationship between atypical femoral fractures (subtrochanteric and femoral shaft fractures) and bisphosphonate use [111]. Lenart et al [112] performed a retrospective case-control study of postmenopausal women who experienced a low energy femoral fracture from 2000 to 2007 with prolonged bisphosphonate use. Bisphosphonate use was reported in 15 of the 41 subtronchanteric and shaft cases compared to nine of the 82 intertrochanteric and femoral neck controls. It is unclear whether the postmenopausal women in this study had low BMD prior to their fracture because there was no information about the degree of osteoporosis prior to their fractures, such as bone densitometry values. Therefore, if some of the postmenopausal women had low BMD prior to their fracture, their physician may have given them bisphosphonates to improve their bone health.

In another retrospective study [113], radiographs were examined by experts to identify features of fractures such as transverse or short oblique fractures, and thick femoral cortices. Out of 25 individuals being treated with alendronate, 19 (76%) had radiographic features of atypical fractures, while only one out of 45 (2%) had radiographic features of atypical fractures in individuals not being treated with alendronate. The risk of sustaining an atypical fracture pattern was found to be significantly associated with alendronate use (OR=139, 95% CI=19-939, $p<0.0001$).

However, the hypothesis that alendronate therapy is associated with atypical fractures was not found in a cross-sectional study. Approximately 12 000 Danish people over the age of 60 years conducted by Abrahamsen et al [114] found that 7% of individuals with atypical fractures were alendronate users. A matched cohort study was also performed in the same study to test the hypothesis that the increase in risk of atypical femur fractures in individuals

treated with alendronate exceeded the increase in 'typical' femur fractures caused by osteoporosis. The cohort reported a hazard ratio (adjusted for baseline comorbidites) for subtrochanteric and femoral shaft fractures with alendronate of 1.46 (0.91-2.35, p=0.12) compared with 1.45 (1.21-1.74, p<0.001) for hip fractures. In addition, subtrochanteric and femoral shaft fractures were equally common in the alendronate group (14%) and non-alendronate group (13%) suggesting that an increased risk of atypical fractures with alendronate use may be more likely due to osteoporosis than by alendronate therapy.

The studies to date regarding bisphophonates and atypical fractures include individual case reports or case series. No prospective randomized control trials have been conducted, therefore it cannot be stated that bisphosphonates cause atypical fractures. Further limitations include small sample sizes, narrow inclusion criteria (postmenopausal women; no studies have examined atypical fractures among individuals with SCI who are on bisphosphonate treatment), lack of radiological and clinical verification, and none of these studies looked at the number of individuals who sustained an atypical femoral fracture who have never received bisphosphonate therapy. The current research to date on the effect of bisphosphonate use on atypical femoral fractures is inconclusive. The studies to date highlight the scope of the problem, but they do not provide sufficient evidence that long-term bisphosphonate use is the only cause of atypical low-trauma subtrochanteric fractures [115]. More research is needed to confirm whether prolonged bisphosphonate use increases the risk of subtrochanteric and femoral shaft fractures.

2.7 Summary of Background

Bone mass significantly declines following a SCI, predisposing individuals with SCI to an increased risk of fracture. Analysis of the structure of bone combined with bone density

may improve the ability to assess fracture risk in individuals with SCI. pQCT is a method currently being introduced in the SCI population to help predict fracture risk. Examining the changes that occur in bone quality among individuals with chronic SCI may facilitate a clearer understanding of the risk factors and bone loss contributing to the increased risk of fracture. Therefore, the results of our study will inform efforts aimed at identifying individuals with SCI who are at greatest risk of fracturing and in need of drug and rehabilitation interventions. Furthermore, the findings of this study will increase our understanding of fragility fractures and bone structure in the SCI population.

3.0 CHAPTER 3: RESEARCH QUESTIONS AND HYPOTHESES

3.1 Research Questions

3.1.1 Primary Research Questions

1. Is there a relationship between the indices of bone strength (aBMD, trabecular vBMD [mg/cm^3]; average hole size, H_A [mm]; cortical thickness, CTh [mm]; buckling ratio, BR; cross-sectional moment of inertia, CSMI [cm^4]; polar moment of inertia, PMI [cm^4])) and gender, age, bisphosphonate use, time post-injury, completeness of injury, or fracture?

3.1.2 Secondary Research Questions

1. Can the indices of bone strength (aBMD [mg/cm^2], trabecular vBMD [mg/cm^3]; average hole size, H_A [mm]; cortical thickness, CTh [mm]; buckling ratio, BR; cross-sectional moment of inertia, CSMI [cm^4]; polar moment of inertia, PMI [cm^4]) in the tibia discriminate between individuals with SCI who have sustained a fragility fracture of the femur or tibia and those without a history of fractures? Are the indices of bone strength correlated with the number of fractures among our sample of individuals with chronic SCI?
2. What proportion of individuals with chronic SCI in each impairment strata (motor complete, AIS A and B; motor incomplete, AIS C and D) has a trabecular vBMD at the ultra-distal tibia that is below $72mg/cm^3$ [30]?

3.2 Research Hypothesis

3.2.1 Primary Research Hypothesis

1. It is hypothesized that an inverse relationship will exist between between aBMD, trabecular vBMD, cortical thickness, cross-sectional moment of inertia, polar moment of inertia and aging and time post-injury. However, it is predicted that a positive relationship will exist between average hole size, and buckling ratio and aging, and time post-injury. It is hypothesized that bisphosphonate use will positively affect bone structure. Bisphosphonate users will have a higher aBMD, trabecular vBMD, cortical thickness, cross-sectional moment of inertia, and polar moment of inertia, but a lower average hole size and buckling ratio compared to those who are not taking bisphosphonates. Furthermore, females, individuals with complete SCI, and individuals who have fragility fractures will have lower aBMD, trabecular vBMD, cortical thickness, cross-sectional moment of inertia, and polar moment of inertia, but a higher average hole size and buckling ratio compared to males, individuals with an incomplete SCI, and those with no history of fractures.

3.2.2 Secondary Research Hypotheses

1. SCI results in partial or complete unloading of the lower limbs. Therefore, it is predicted that individuals with chronic SCI who have sustained a fragility fracture will possess a lower aBMD, trabecular vBMD, cortical thickness, cross-sectional moment of inertia, polar moment of inertia and a larger average hole size compared to those with no history of fractures. It is also hypothesized that the buckling ratio will be greater among individuals with SCI who have sustained a fragility fracture compared to those without any history of fractures. Finally, it is hypothesized that individuals with chronic SCI who have sustained multiple fragility fracture will have lower aBMD, trabecular vBMD, cortical thickness, cross-sectional moment of inertia, polar

moment of inertia and a larger average hole size and buckling ratio compared to those with fewer fragility fractures.

2. It is hypothesized that our sample of individuals with chronic SCI in each impairment strata (motor complete, AIS A and B; motor incomplete, AIS C and D) will have a trabecular vBMD at the ultra-distal tibia that is below 72mg/cm^3. Specifically, there will be more individuals with a complete SCI (AIS A and B) who have fractured with a trabecular vBMD below 72mg/cm^3 than those with an incomplete SCI (AIS C and D) who have fractured. If the first fracture occurs at a trabecular vBMD that is greater than 72mg/ cm^3 then the fracture threshold needs to be moved up; however if the first fracture occurs at a trabecular vBMD value that is less than 72mg/cm^3 then the fracture threshold needs to be moved down.

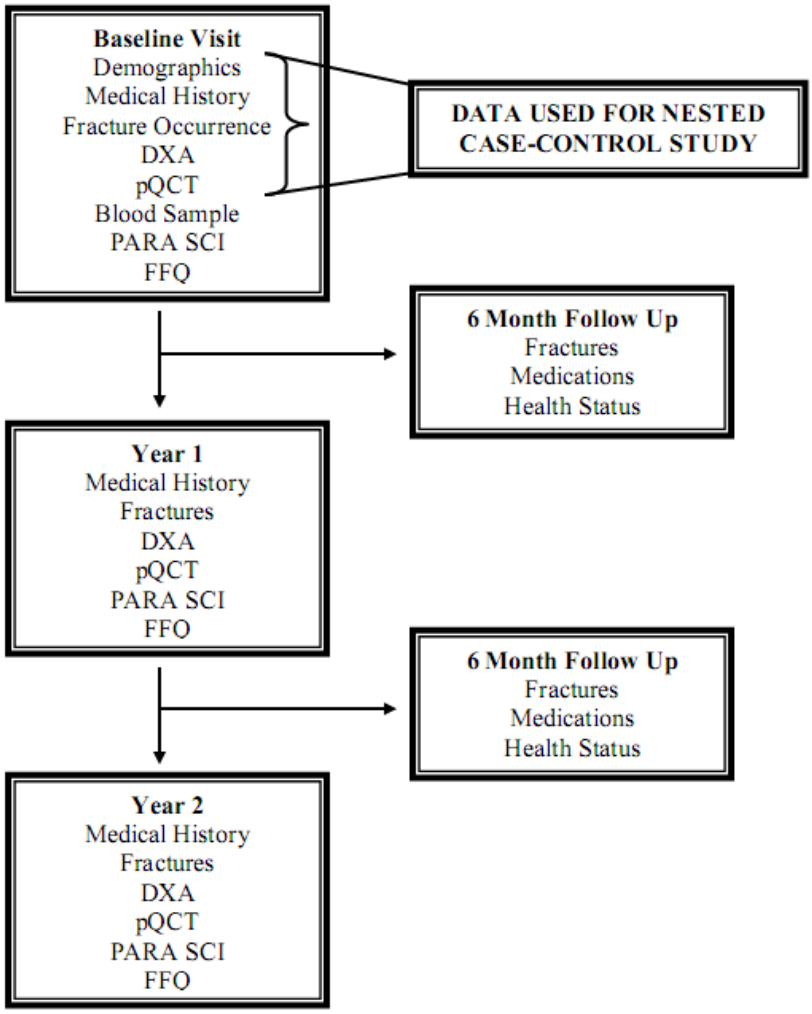
4.0 CHAPTER 4: METHODOLOGY

4.1 Overview of Study

The present study was a case-control study implemented from a larger 2-year prospective study, Bone Quality in Individuals with Spinal Cord Injury. The primary objective of the larger prospective study is to establish a cohort of individuals with SCI to create the potential for future prospective longitudinal studies evaluating predictors of fracture in the SCI population. As a result, guidelines can be developed to identify those at high risk of fracture. This study involves collaborations between the University of Waterloo, McMaster University, University of Toronto, and the Toronto Rehabilitation Institute, Lyndhurst Centre. Eighty individuals with SCI are being recruited to participate in this study, and data being collected for the larger prospective study include: a) medical history, including etiology and impairment descriptors; b) BMD and body composition assessed by DXA; c) vBMD, bone geometry, muscle area and trabecular structure assessed by pQCT; d) x-ray reports to verify fractures; and e) serum screening for markers of bone turnover. Figure 4 represents the study design and setting for the larger 2-year prospective study.

The primary focus of this nested case-control study was to examine the baseline data to determine whether indices of bone strength (aBMD, trabecular vBMD; average hole size, H_A; cortical thickness, CTh; buckling ratio; cross-sectional moment of inertia, CSMI; and polar moment of inertia, PMI) in the tibia can discriminate between individuals with SCI who have sustained a prior low-energy fracture in the tibia and femur compared to those with no history of fracture.

Figure 4: Study design and setting for the 2-year prospective study



4.2 Participants

4.2.1 Study population

A sample of 47 individuals with chronic SCI was recruited over a 21 month period in this study. Participants included both genders with a diverse level of impairment, motor complete injuries (AIS A and B) and motor incomplete injuries (AIS C and D), which established a more representative sample of individuals with SCI. To ensure that participants were neurologically and medically stable, and had experienced bone loss that normally occurs

one to two years following injury, only individuals who were two or more years post-injury were recruited.

4.2.2 Recruitment and Screening

Participants were recruited through various methods: 1) the Lyndhurst Long-term Follow-up Database; 2) Outpatient Services at Lyndhurst Centre; 3) Hamilton Clinic; and 4) MacWheelers program at McMaster University. The Lyndhurst Long-term Follow-up Database contains the socio-demographic, injury characteristics, health status and contact information of SCI individuals who have consented to be contacted regarding ongoing research projects at Lyndhurst Centre. Participants that were recruited through the Lyndhurst Long-term Follow-up Database or the Hamilton Clinic were sent a letter of invitation (Appendix A) to participate in this study. The letter stated that a research coordinator would contact them by telephone to determine their eligibility and interest in participating in the study. For individuals who preferred not be contacted, a phone number was provided in the letter where they could leave a message to opt out of the call.

Potential participants affiliated with the Outpatient Services at Lyndhurst Centre were identified by physicians and therapists. Potential participants' identified by physicians and therapists were informed of their possible eligibility for the study and were asked if they would be interested in learning more about the study. The physicians and therapists were required to complete referral forms (Appendix A) for eligible participants who expressed interest in the study and forward it to the research coordinator who contacted the potential participant via telephone. Recruitment through MacWheelers was performed by providing brochures to eligible participants. Other recruitment strategies included advertisements on the

Canadian Paraplegic Association (CPA) website and newsletter, and posters posted throughout the Lyndhurst Centre building.

Participants interested in partaking in this study were contacted via telephone by the research coordinator at Lyndhurst. Potential participants were provided with a detailed description of the study. Individuals interested in participating in the study were assessed to ensure that they met all the inclusion criteria (Table 5). Eligible participants were arranged a visit to Lyndhurst during which a written informed consent was obtained (Appendix A).

Table 5: Participant Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Able to understand instructions in English • A spinal cord impairment (C2-T12 AIS A-D) of sudden onset (< 24hrs) associated with a stable upper motor neuron, neurologic deficit of trauma-like etiology having occurred at least 24 months prior study inclusion • Ability to give informed consent • Age ≥ 18 years	• Current or prior known conditions other than paralysis that are known to influence bone metabolism including: oral glucocorticoid use for ≥ 3 months, malignancy, known liver or malabsorption condition • Weight > 270lbs (limit for bone density machine) • Contraindications to pQCT testing • Women who are pregnant or planning to become pregnant

4.2.3 Assessment Overview

During the participant's first visit to Lyndhurst, they were asked a series of question pertaining to their medical history and demographics (Appendix A). For example, questions regarding current and past medical health, lifestyle behaviours, and medications were of interest. The history was obtained by direct patient interview and medical chart review. Participants may have also been enquired to undergo an AIS exam if there was no record of a previous exam performed. Following the questionnaire and exam, participants underwent a bone density scan above and below the knee using the DXA. The scans took approximately 12 minutes.

A second visit to the McMaster University Medical Centre was arranged for the participant to participate in a pQCT scan. The scans were performed at the ankle (4% site of the tibia length) and the widest cross-section of the calf (66% site of the tibia length). The scans took approximately 45 minutes.

4.3 Outcome Measures

4.3.1 Primary Outcome Measures

4.3.1.1 Assessment of Fragility Fractures

Subjects were asked about the time, cause and location of any fragility fractures that had occurred after their SCI. Fragility fractures were those that occurred due to low trauma (i.e. occurring after falls from standing height or less) in the lower extremity (excluding toes). Fractures caused by high-energy trauma and fractures that occurred prior to or at the time of SCI were not included in the analysis. Details of prevalent fragility fractures of the lower extremity were verified through the participants' medical records and x-rays, in which a written consent was obtained for health record abstraction. Protocols for verifying fractures and obtaining records were modelled after those used in CaMOS, a population-based cohort study of 10,000 individuals across Canada [116].

4.3.1.2 Demographics and Medical History

Past and current medical health, medications, lifestyle and demographic data, and information related to the SCI were obtained via participant interview and chart abstraction, and recorded on case report forms and in an electronic database created by EMPOWER Data Management and Methods Centre. The Empower database was created to mirror the content and format of data collection forms to facilitate ease and accuracy of data entry. Database use is restricted to just the investigators of the two year prospective study with logon passwords to

the network. SCI history included date of onset, cause, level, and extent of SCI (complete or incomplete). A subset of questions from the CaMos medical history questionnaire was included to determine variables such as medication use, lifetime tobacco use, and co-morbidities. The CAGE questionnaire was used as an assessment of alcohol use [117]. Medical history, injury information and impairment descriptors was abstracted from the patient's medical record to confirm and supplement information provided by the participant. AIS classification for injury level, completeness of injury, and lower extremity motor scores in those individuals whose impairment has not been classified was determined by a physiatrist using the AIS Classification.

4.3.2 Secondary Outcome Measures

4.3.2.1 aBMD via DEXA

DXA scans (Hologic Inc. 4500, MA, USA) were used to obtain areal bone mineral density (aBMD, g/cm^2) measurements at the right distal femur, and right proximal tibia, using a standard protocol provided by the manufacturer. In cases of severe spasticity or other contraindications, the left leg was scanned instead. Participants reported to the Bone Density Lab at Lyndhurst Centre where trained technologists performed the scans. The site is equipped with a ceiling lift for transferring patients to the scanning table. The participant was positioned supine on the scanning table. Scanning each site took approximately 6 minutes. The body needed to be positioned in a specific manner in order to scan the distal femur and proximal tibia. Standardizing the position for each regional site reduced aBMD measurement errors. The scans were analyzed using commercial available software from Hologic. A lower extremity positioning device and protocol, whose reliability and accuracy have been previously determined [118] was used to acquire and analyze the scans for the distal femur

and proximal tibia. Intra-class correlation coefficients for repeated distal femur and proximal tibia BMD measure were 0.99 and 0.97, respectively.

4.3.2.2 Peripheral Quantitative Computed Tomography

A pQCT scanner (XCT-2000, Stratec Mezintechnik; Pforzheim, Germany) was used to scan the tibia. An image is created by reconstructing the 145 projection angles obtained by a narrow fan beam emitted from an x-ray tube. The pQCT is a relatively safe technique in that the total level of radiation exposure associated during the scans is approximately 1-2μSV, which is less than the amount of radiation received with an axial-CT (30-60μSV) or annually from background radiation (2500μSV). The right tibia was scanned except in cases of severe spasticity or other contraindications, such as the presence of metal or fracture in right leg. Bony landmarks at the knee joint and medial malleolus were palpated and a measuring tape was used to measure the distance between the two points. The subjects transferred from their wheelchair to a height-adjustable chair. The tibia distal endplate (anatomic reference line) was identified on a 30mm coronal view of the joint line from a scout scan. The scan site was automatically located proximally to this reference line at the following distances: 4% and 66% of the tibia length measuring proximally from the distal endplate. Single 2.5mm slices were obtained at the ultra-distal tibia (4% of tibia length), and proximal one-third of tibia (66% of tibia length). A voxel size of 0.2mm was used at the ultra-distal tibia to have sufficient resolution to quantify trabecular structure, while a voxel size of 0.5mm was used at the proximal one-third of the tibia.

Parameters measured at the 66% site of the tibia included cortical thickness (CTh), buckling ratio (BR), cross-sectional moment of inertia (CSMI), and polar moment of inertia

(PMI). At the 4% site of the tibia, trabecular vBMD and average hole size (H_A) were measured.

Analysis of the scans was performed using the manufacturer's software (Stratec XCT-2000 v.6.00) that applies an iterative contour detection algorithm. Contour mode 3 and peel mode 2 with an outer threshold of 130mg/mm^3 and inner threshold of 400mg/mm^3 was used to separate the bone from soft tissue and separate the cortical and subcortical/trabecular bone in the image [18]. Contour mode detects the outer bone edge and peel mode defines a method in which the subcortical and trabecular bones are separated. Peel mode uses inner thresholds to separate the total area into trabecular and subcortical bone, providing information on trabecular bone parameters.

Indices of trabecular bone structure such as average hole size was determined using custom developed software. Trabecular architecture was determined by detecting the edge of periosteal and endosteal borders by an active contour algorithm. A connectivity analysis was performed on the skeletonised trabecular bone segmentation. In addition, a threshold of two standard deviations above the soft tissue mean was used to segment the trabecular bone from the bone marrow. The long- and short-term precision for this technique has been reported elsewhere [119].

4.4 Indices of Bone Strength

4.4.1 Areal Bone Mineral Density

Areal BMD determined by DXA is the current gold standard in assessing osteoporosis. Areal BMD measurements of the distal femur and proximal tibia were acquired using DXA. For this study, the units for aBMD were converted from g/cm^2 to mg/cm^2 to

account for small changes in bone density and be able to interpret the results in a clinical manner.

$$aBMD = \frac{BMC}{Area}$$

4.4.2 Trabecular vBMD

A unique feature that is providing the pQCT with more attention is its ability to measure volumetric bone mineral densities (vBMD, mg/cm^3). Individuals with chronic SCI experience a substantial reduction in trabecular vBMD in the femur and tibia [19], which has been reported to be the best parameter in determining fracture threshold [30].

$$vBMD = \frac{mass}{volume} = \frac{BMC}{Weight}$$

4.4.3 Average Hole Size

Average hole size was defined as the average area of each hole (concealed around by bone) in the distal femur and proximal tibia.

4.4.4 Cortical Thickness

Cortical thickness of the tibia was assessed assuming the circular ring model derived by pQCT-based measurements. The circular ring model assumes that the shape of the measured object is a circular ring and estimates cortical thickness by calculating the difference between the outer and inner radius.

$$CTh = R - r = \frac{PERI\_C}{2 \times \pi} - \frac{ENDO\_C}{2 \times \pi}$$

4.4.5 Cross-sectional Moment of Inertia

Cross-sectional moment of inertia is an estimation of the resistance of bone to bending. It is a function of the cross-sectional area of a voxel (A) and the mean y-coordinate

for all voxels of the cortical area ($Y_{CRT_{Ay}}$). Bone distributed further from the axis of rotation, leads to larger resistance to bending. Cross-sectional moment of inertia units will be converted to cm^4 to account for large changes and be able to interpret the results in a clinical manner.

$$CSMI = \sum A \times (Y_{CRT_{Ay}})^2$$

4.4.6 Polar Moment of Inertia

Polar moment of inertia represents the ability of bone to resist bending. Polar moment of inertia takes into account the distance of the voxel (d) from the center of gravity (C) and the cross-sectional area of a voxel (A, in this study it is 0.5mm x 0.5mm = $0.25mm^4$) (Figure 5) [120,121]. The units for polar moment of inertia will be converted to cm^4 to account for large changes and be able to interpret it in a clinical manner.

$$PMI = \sum (d^2 \times A) = \sum A \left[\left(X_{CRT_{Ax}}\right)^2 + (Y_{CRT_{Ay}})^2 \right]$$

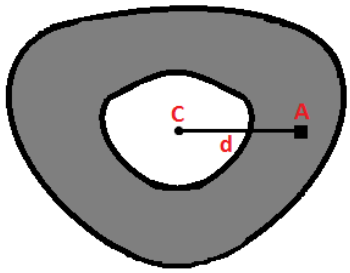


Figure 5: Calculation of Polar Moment of Inertia in the Tibia

4.4.7 Buckling Ratio

Bucking ratio expresses the likelihood of failure in bending due to excessive cortical thinning. Higher values would suggest a greater instability due to thin-walls that may contribute to fractures.

Buckling ratio was calculated using the following formula:

$$BR = \frac{Subperiosteal\ radius}{mean\ CTh} = \frac{(PERI \times PERI)}{2\pi\ \times CRT\_A}$$

4.5 Potential Correlates of Bone Strength Variables and Possible Confounders

4.5.1 Age

Peak bone mass is the maximum BMD achieved and has been shown to be a significant predictor of BMD later in life. BMD is accumulated throughout childhood into adolescence until peak bone mass is achieved between the ages of 20 and 25 years. Peak bone mass generally occurs much earlier in girls than in boys [122]. Peak bone mass is sustained until around 30 to 40 years of age, at which then they experience an average 1% per year decline in BMD with aging [123]. The decline in BMD can accelerate to 2% per year with the onset of menopause [124]. Therefore, the risk of osteoporotic fractures in later life may be the result of peak bone mass achieved during skeletal maturity and age-related bone loss.

Age was represented as mean±SD for descriptive analysis and was represented as a continuous variable for the regression model.

4.5.2 Gender

Gender has been reported to be a significant predictor of BMD. On average, men have larger bones and higher peak bone masses than women. Boys and girls acquire bone mass at similar rates before puberty; however after puberty, men generally acquire more bone mass than women [122].

After menopause, bone loss is accelerated in women because of a rapid decline in estrogen levels, resulting in an increase in bone turnover, which is dominated by an increase in bone resorption. During menopause, the levels of bone resorption markers are two times higher than in premenopausal women, whereas the bone formation markers are only

approximately a half higher than premenopausal levels [125]. Accordingly, a negative balance in bone remodelling occurs.

Among individuals with SCI, Garland et al [1] reported women lose more bone at all skeletal sites below the level of the lesion compared to men.

Gender was represented as a dichotomous variable in the regression models.

4.5.3 Time post Injury

A relationship between indices of bone strength and time post-injury/duration of injury is plausible among individuals with SCI as time post-injury has been suggested as a indicator of fracture risk in studies comparing individuals who have a history of fractures to those who do not [6,14]. Furthermore, time post injury may be an alternative method for measuring the changes that occur in cortical bone which occurs later than the changes that occur in trabecular bone. Cortical bone has a slower turnover rate compared to trabecular bone [126]. Therefore, time post injury may explain the rate of bone turnover for both cortical and trabecular bone.

Duration of injury was calculated as the date of injury minus the date of demographics and medical history assessment. Duration of injury was measured in years and represented as a continuous variable in the regression model.

4.5.4 Completeness of Injury

Completeness of injury has been shown to take precedence over most modifiable and non-modifiable factors for bone loss at the distal femur and proximal tibia leading to pathological fractures in a cross-sectional study of 152 individuals with chronic SCI. Individuals with a complete SCI were reported to be 6.17 times more likely to have an aBMD of the knee low enough to be a member of the osteoporotic category [87].

Motor completeness of injury was represented as a dichotomous variable (complete, AIS A and B versus incomplete, AIS C and D) for the regression models.

4.5.5 Bisphosphonate Use

Data from two randomized control trials suggest that the oral bisphosphonate, alendronate, may help in maintaining BMD in the lower extremities among individuals with SCI [109,110]. In another double-blinded, randomized, placebo-controlled trial, in 17 individuals with acute SCI, administration of 4 or 5mg of intravenous zoledronic acid was reported to increase section modulus at the intertrochanteric regions and decrease buckling ratio after 12 months in the proximal femur [127]. However, the effect of bisphosphonates on the structure of bone in individuals with chronic SCI has not been determined.

Current bisphosphonate users were represented as a dichotomous variable (users versus non-users) in the regression model.

4.5.6 Fragility Fractures

Previous fracture(s) is an important risk factor for future fractures in men and women [17,128]. In postmenopausal women, fractures were reported to most commonly occurred in women with a previous osteoporosis-related fracture (OR=3.3, 95% CI=1.75-5.66) [129]. Unfortunately, the effect of prior fragility fractures on individuals with SCI has not been examined.

The presence of fragility fractures were represented as a dichotomous variable (individuals with fractures, =1 versus those with no fractures, =0) in the regression model.

4.6 Statistical Analysis

Descriptive statistics were used to summarize anthropometric measurements of the study population and each index of bone strength (aBMD, trabecular vBMD; average hole

size, H_A; cortical thickness, CTh; buckling ratio, BR; cross-sectional moment of inertia, CSMI; polar moment of inertia, PMI). Descriptive statistics were also used to characterize the proportion of individuals that had a fracture, the skeletal sites of the fractures, and the cause of the fractures. Dichotomous variables were presented as counts (n) and percentage (%) and continuous variables were presented as means ± standard deviations (SD). Two-sided t-tests and Chi-Square test were used to make the comparison between individuals with SCI with and without fractures.

Linear regression analysis was performed to determine whether the indices of bone strength (aBMD, trabecular vBMD; average hole size, H_A; cortical thickness, CTh; buckling ratio, BR; cross-sectional moment of inertia, CSMI; polar moment of inertia, PMI) were associated with gender, age, bisphosphonates, time post injury, completeness of injury, and fracture among our sample of individuals with SCI. Correlates found to be statistically significant at alpha=0.20 in linear regression were entered into multivariable linear regression models to identify correlates of each of the indices of bone strength. To assess model assumptions, the residuals were examined.

The relative risk of a fragility fracture was estimated by odds ratio (OR) and 95% confidence intervals (CI) obtained from logistic regression where the presence of a fragility fracture was the dependent variable and the indices of bone strength (aBMD, trabecular vBMD; average hole size, H_A; cortical thickness, CTh; buckling ratio, BR; cross-sectional moment of inertia, CSMI; polar moment of inertia, PMI) were the potential correlates. Models were adjusted for any risk factors that were significant correlates of indices of bone strength in a secondary analysis. Further analysis with Poisson regression occurred to model the number of fractures per participant as a function of the indices of bone strength (aBMD,

trabecular vBMD; average hole size, H_A; cortical thickness, CTh; buckling ratio, BR; cross-sectional moment of inertia, CSMI; polar moment of inertia, PMI).

Proportions were calculated to report the number of individuals with chronic SCI in each impairment strata (motor complete, AIS A and B; motor incomplete, AIS C and D) that had a trabecular vBMD at the ultra-distal tibia that was below 72mg/cm^3.

All statistical analysis was performed on SAS 9.2 software (Cary, North Carolina), in which all statistical tests were two-sided. The criterion for statistical significance was set at alpha = 0.05. The proportion of variance from a linear regression was determined by interpreting the regression coefficients (R^2). Correlation coefficient (r) from regression models were interpreted as follows: ≤0.29=very weak, 0.30-0.49=weak, 0.50-0.69=moderate, 0.70-0.89=strong, and ≥0.90=very strong [130].

4.7 Ethical Considerations

4.7.1 Potential Risks to the Participants

Participants were exposed to small amounts of radiation during the DXA and pQCT scans. The total level of radiation exposure associated with the scans is approximately 30µSv, which is less than the amount of radiation received during an axial CT scan (30-60µSv) or annually from background radiation (2500µSv).

4.7.2 Anonymity

Each participant was assigned a unique identification (ID) number that was used on all forms and in the electronic database. The key file linking participant information to the ID was stored in a separate password protected database. All hardcopy data was stored at the Research Department at Toronto Rehabilitation Institute, Lyndhurst Centre in lockable and

secured filing cabinets. A compilation of all the research data was inputted and securely stored on an online electronic database, Empower, on the servers at Lyndhurst Centre.

4.7.3 Ethics

Ethical approval for this study was obtained from the Ethics Review Boards of University of Waterloo, Toronto Rehabilitation Institute, and McMaster University.

5.0 CHAPTER 5: RESULTS

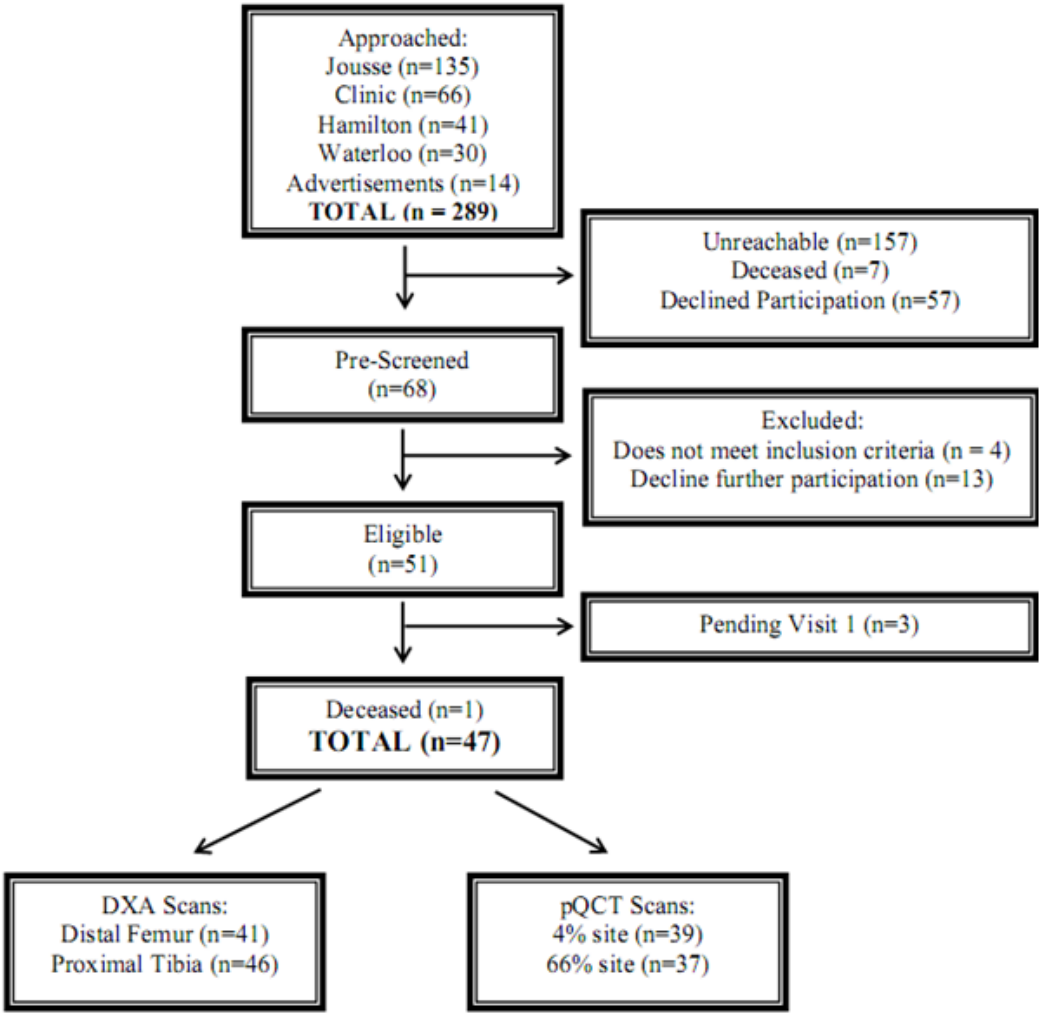
5.1 Recruitment and Sample Size

Two hundred and eight nine individuals with SCI were approached for the larger two year prospective study, Bone Quality in Individuals with chronic SCI. Of the 289 individuals, 157 individuals were unreachable by phone, seven were deceased, and 57 had declined to participate, resulting in 68 individuals to be pre-screened for eligibility. Four individuals did not meet the inclusion criteria and 13 individuals declined further participation in the study. Of the 51 individuals who met the eligibility criteria, three were pending baseline assessment completion and one was deceased, leaving 47 individuals with chronic spinal cord injury to be included in this study (Figure 6).

DXA scans could not be performed at the distal femur in five participants, three because of hardware located in both femurs, and the other two because of bilateral fractures of the knee. In addition, DXA scans for both the proximal tibia and distal femur could not be performed in one participant due to hardware located in the both knee regions. As a result, measurements of aBMD at the distal femur and proximal tibia obtained by DXA were performed on 41 and 46 individuals with SCI, respectively. pQCT scans could not be performed at both the ultra-distal tibia (4% site) and the proximal one-third of the tibia (66% site) in three participants; one individual experienced spasms, which could lead to movement artefacts and prevent safe scanning; one participant had died and one declined to participate in the pQCT scan. Furthermore, two additional pQCT scans could not be performed at the 66% site because the participants' calves were too large to fit in the gantry. Four individuals' pQCT scans were still pending at the time of analysis and one individual was not able to

travel to Hamilton within the three month window period for baseline completion. Therefore, 39 individuals were scanned at the 4% site and 37 individuals were scanned at the 66% site.

Figure 6: Flow chart of cohort refinement



5.2 Participant Characteristics

5.2.1 Sociodemographics and Impairment

The sample population consisted of 47 individuals with SCI; 33 males (70.2%) and 14 females (29.8%) (Table 6). The participants' age ranged from 32 to 77 years, with a mean age of 51.1±11.4 years. The mean time post injury was 15.9±10.2 years which ranged from 2 to 41 years. Twenty nine individuals with SCI were reported to have a motor complete SCI (AIS

A and B), in which 12 were tetraplegics and 17 were paraplegics. Eighteen individuals were classified as motor incomplete (AIS C and D); 11 tetraplegics and seven paraplegics. All of the SCI were of traumatic etiology. The majority of SCI occurred as a result of MVA (n=24), followed by falls (n=10), sports-related (n=8), work-related (n=3), others (n=2), and violence (n=1) (Table 7). One individual sustained two spinal cord injuries; one sports related and one work-related.

Table 6: Sociodemographic and Impairment Characteristics

	All SCI Subjects	**Subjects with Fragility Fractures**	**Subjects without Fragility Fractures**	**P-value**
No Subjects, n (%)	47	14 (29.8%)	33 (70.2%)	
Sex, n (%)				0.905
Male	33 (70.2%)	10 (71.4%)	23 (69.7%)	
Female	14 (29.8%)	4 (28.6%)	10 (30.3%)	
Age (years)	51.1±11.4	51.8±9.93	50.8±12.1	0.794
Duration of injury (years)	15.9±10.2	22.6±10.9	13±8.5	0.002*
Height (cm)	174.3±9.7	174.8±11.7	174.1±8.9	0.897
Weight (kg)	80.9±19.8	81.2±21.4	80.8±19.4	0.954
Waist Circumference (cm)†	97.9±14.9	101.0±17.4	96.7±13.9	0.387
Injury Characteristic, n (%)				0.033*
Motor Complete Paraplegia	17 (36.2%)	8 (57.1%)	9 (27.3%)	
Motor Incomplete Paraplegia	7 (14.9%)	1 (7.1%)	6 (18.2%)	
Motor Complete Tetraplegia	12 (25.5%)	5 (35.7%)	7 (21.2%)	
Motor Incomplete Tetraplegia	11 (23.4%)	0 (0.0%)	11 (33.3%)	
AIS, n (%)				0.017*
A	28 (59.6%)	12 (85.7%)	16 (48.5%)	
B	1 (2.1%)	1 (7.1%)	0 (0.0%)	
C	7 (14.9%)	1 (7.1%)	6 (18.1%)	
D	11 (23.4%)	0 (0.0%)	11 (33.3%)	
LEMS‡	12.2±16.7	2.1±5.1	16.3±18.0	0.008*
Sensory Score‡	101.3±54.9	93.8±55.7	104.4±55.1	0.562

†Indicates n=46

‡Indicates n=45 due to incomplete data

*Significant difference between fracture and non-fractured group (Student's t-test p value reported for continuous variables, Chi square p-values reported for categorical variables)

Table 7: Cause of the Spinal Cord Injuries

Cause of SCI	Number of Subjects (n=47)
MVA	24 (51.0%)
Falls	10 (21.3%)
Violence	1 (2.1%)
Sports	8 (17.0%)
Work-related	3 (6.4%)
Other	2 (4.3%)

Note: one participant had two spinal cord injuries (one sports and one work-related)

5.2.2 Supplement Intake

The use of supplements was generally high, with 86.9% (n=40) of the cohort reporting the use of a calcium supplement, 89.7% (n=42) reporting the use of vitamin D, and 58.1% (n=25) reporting the use of a multivitamin.

At the time of assessment, twenty-seven participants (58.7%) were on bisphosphonate therapy for prevention and treatment of osteoporosis: etidronate (n=1, 2.1%), risedronate (n=6, 12.8%), alendronate (n=14, 29.8%), and alendronate with vitamin D (fosavance, n=6, 12.8%) (Table 8).

Table 8: Supplement Intake

	All SCI Subjects	Subjects with Fragility Fractures	Subjects without Fragility Fractures
Bisphosponate User, n (%)			
Etidronate	1 (2.1%)	1 (7.1%)	0 (0.0%)
Risedronate	6 (12.8)	1 (7.1%)	5 (15.1%)
Alendronate	14 (29.8%)	5 (35.7%)	9 (27.3%)
Fosavance	6 (12.8%)	3 (21.4%)	3 (9.1%)
Calcium Supplement, n (%)	40 (86.9%)	14 (100%)	26 (81.3%)
Vitamin D Supplement, n (%)	42 (89.7%)	14 (100%)	28 (84.8%)
Multivitamin Supplement, n (%)	25 (58.1%)	8 (57.1%)	17 (58.6%)

5.2.3 Lifestyle Behaviours

There were eleven smokers (23.4%) in the cohort. Sixty eight percent of the participants were prior smokers (n=32), with a mean of 13 cigarettes per day, while 15 participants had never smoked. The cohort also reported alcohol intakes ranging from 0 to 14 drinks per week; twenty four individuals were current drinkers (one or more drinks per week), while 31 individuals reported having a history of alcohol intake (Table 9).

Table 9: Lifestyle Behaviours

	All SCI Subjects	Subjects with Fragility Fractures	Subjects without Fragility Fractures
No Subjects, n (%)	47	14 (29.8%)	33 (70.2%)
Smoking, n (%)			
Never	15 (31.9%)	4 (28.6%)	11 (33.3%)
Current Smoker	13 (23.4%)	3 (21.4%)	10 (30.3%)
Previous Smoker	32 (68.1%)	10 (71.4%)	22 (66.6%)
Alcohol consumption, n (%)			
Current Alcohol	24 (51.1%)	8 (57.1%)	16 (48.5%)
History of Alcohol	31 (66.0%)	13 (92.9%)	18 (54.5%)

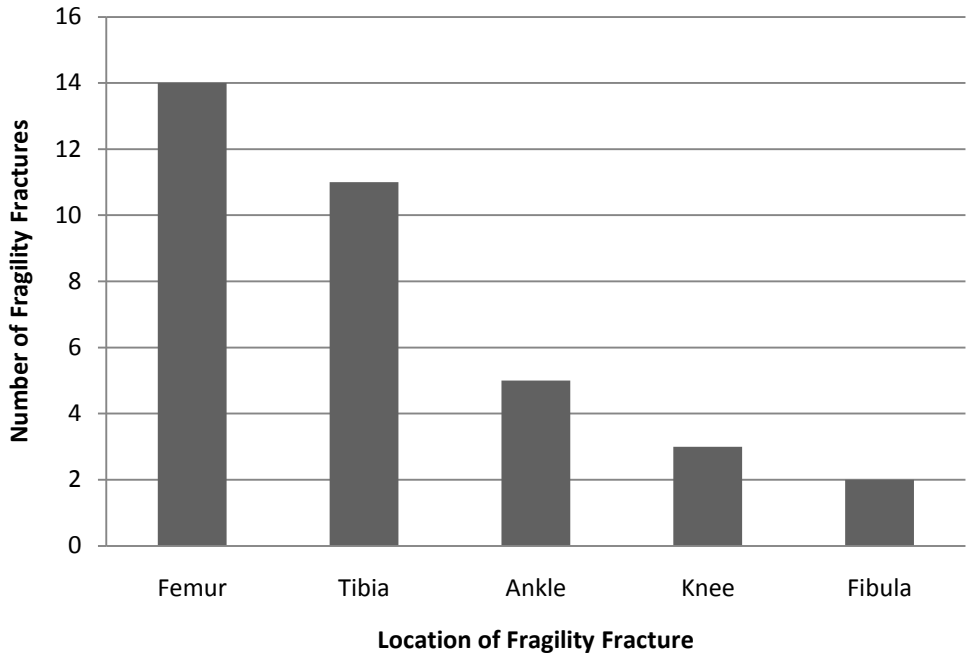
5.3 Fragility Fractures

Thirty percent of participants (n=14) had a sustained a fragility fracture following their SCI in which eight participants had sustained multiple fragility fractures (range 2-7 fractures) after their SCI. Ten were males (71.4%) and four were females (28.6%). Fragility fractures occurred as a result of torsion (n=5), low velocity falls (n=17), transfers (n=11), and other methods (n=3) such as during intercourse, by spasms, and being hit in the leg (Table 10). Lower extremity fragility fractures occurred more frequently at the femur (n=14) followed by the tibia (n=11), ankle (n=5), knee (n=3), and fibula (n=2) (Figure 7). One individual reported three fractures in the knee because he/she was unsure where exactly around the knee (proximal femur, distal tibia, or patella) the fracture had occurred.

Table 10: Causes of Fragility Fractures

Cause of Fragility Fracture	No of Subjects (n=14)	Males (n=10)	Females (n=4)
Torsion	5	4	1
Low Velocity Fall	17	15	2
ROM	0	0	0
Hyperflexion	0	0	0
Transfer	11	3	8
Other	3	1	2
TOTAL	*36*	*23*	*13*

Figure 7: Location of lower extremity fragility fractures



5.4 Indices of Bone Strength

Table 11 summarizes the indices of bone strength for all subjects, those who have a history of fragility fractures and those who did not. Trabecular vBMD (p=0.0006), cortical thickness (p=0.0137), cross-sectional moment of inertia (p=0.0027), polar moment of inertia (p=0.0149), and aBMD at the distal femur (p=0.0004) and proximal tibia (p=0.0006) were found to be significantly lower in those who had sustained a fragility fracture compared to

those who had not. In addition, those who had fractured had a significantly higher average hole size (p=0.0007) compared to non-fractured subjects.

Table 11: Comparison of Indices of Bone Strength between those with a History of Fragility Fractures and those without

Measuring Site	Measuring Parameter	All Subjects (Mean±SD)	Subjects with Fractures (Mean±SD)	Subjects without Fractures (Mean±SD)	P-Value
4%	Trabecular vBMD (mg/cm^3)	137.4±56.1	87.7±25.2	154.5±53.7	0.0006*
	H_A (mm^2)	12.6±20.0	30.2±30.6	6.6±9.6	0.0007*
66%	CTh (mm)	3.3±0.9	2.7±0.7	3.5±0.9	0.0137*
	BR	5.2±1.8	6.1±2.0	4.9±1.7	0.0886
	CSMI (cm^4)	2.5±1.0	1.7±0.5	2.8±1.0	0.0027*
	PMI (cm^4)	4.3±1.7	3.2±0.9	4.7±1.8	0.0149*
Distal Femur	aBMD (mg/cm^2)	619.5±209.6	427.7±82,6	681.3±201.0	0.0004*
Proximal Tibia	aBMD (mg/cm^2)	488.7±163.6	360.9±102.9	544.6±153.6	0.0006*

*Significant difference between fractures and non-fractured subjects (p<0.05)

5.5 Identifying Risk Factors Related to Indices of Bone Strength

Completeness of injury, bisphosphonate use, and fractures were correlates of aBMD in the distal femur (R^2=0.5692, Table 12). Completeness of injury, duration of injury, and bisphophosphonate use were correlates of proximal tibia aBMD (R^2=0.6075). Duration of injury and completeness of injury were found to be correlates of trabecular vBMD (R^2=0.4518), while duration of injury and fractures were correlates of average hole size at the ultradistal tibia (R^2=0.4290). Duration of injury was found to be the sole correlate of cortical thickness (R^2=0.2133) and buckling ratio (R^2=0.1634). Finally, gender, completeness, bisphosphonate use, and fractures were correlates of cross-sectional moment of inertia

(R^2=0.5751), while these risk factors with the exception of fractures were found to be correlates of polar moment of inertia (R^2=0.5149).

Table 12: Risk Factors Associated with Indices of Bone Strength

	Dependent Variables							
Independent Variables	**aBMD-DF (mg/cm^2)**	**aBMD-PT (mg/cm^2)**	**vBMD (mg/cm^3)**	**H_A (mm^2)**	**CTh (mm)**	**BR**	**CSMI (cm^4)**	**PMI (cm^4)**
Subjects, n	41	46	39	39	37	37	37	37
Gender	–	–	–	–	NS	–	Significant	Significant
Age	NS	–	–	–	–	–	–	–
Duration of Injury	NS	Significant	Significant	Significant	Significant	Significant	NS	NS
Completeness of Injury	Significant	Significant	Significant	NS	NS	NS	Significant	Significant
Bisphosphonate Use	Significant	Significant	NS	NS	NS	-	Significant	Significant
Fractures	Significant	NS	NS	Significant	NS	NS	Significant	NS
P-Value for Model	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0040**	**0.0131**	**<0.0001**	**<0.0001**
R-Square for Model	**0.5692**	**0.6075**	**0.4518**	**0.4290**	**0.2133**	**0.1634**	**0.5751**	**0.5149**

– =not significant in linear regression models ($p>0.2$); NS=not significant in multiple linear regression models ($p>0.05$)

5.6 Fractures and Indices of Bone Strength

Logistic regression was performed to identify the indices of bone strength associated with having at least one fragility fracture. Unadjusted and adjusted odds ratio (OR), 95% confidence intervals (CI), and p-values are reported in Table 13. When a univariate analysis was performed, all of the indices of bone strength except for buckling ratio were associated with fragility fractures. However, after adjusting for the correlates associated with the indices of bone strength, we only found aBMD at the distal femur, average hole size, and cross-sectional moment of inertia were significantly associated with fractures. Individuals with chronic SCI who have a higher average hole size in the ultra-distal tibia (OR=1.081, 95% CI=1.001-1.166, p=0.0470) and lower cross-sectional moment of inertia (OR=0.098, 95%CI=0.012-0.838, p=0.0338) are at increased odds of experiencing a fragility fracture. In addition, individuals with SCI with higher aBMD at the distal femur were at decreased odds of fracturing (OR=0.988, 95% CI=0.978-0.998, p=0.0226). Each one SD ($0.1 mg/cm^2$) increase in aBMD at the distal femur was associated with 1.2% decrease in fragility fractures after adjusting for completeness of injury and bisphosphonate use. We attempted to put aBMD at the distal femur and average hole size, and aBMD at the distal femur and cross-sectional moment of inertia into a multivariable logistic regression model to determine if average hole size or cross-sectional moment of inertia improves the ability of aBMD at the distal femur to differentiate between individuals with SCI with fractures and those without. We found that average hole size and cross-sectional moment of inertia did not explain any additional variance. We found that pQCT measures of average hole size (aBMD: OR=0.989, 95% CI=0.977-1.000, p=0.0584; H_A: OR= 1.020, 95% CI=0.966-1.078, p=0.4692) and cross-sectional moment of inertia (aBMD: OR=0.989, 95% CI=0.976-1.002, p=0.1022; CSMI:

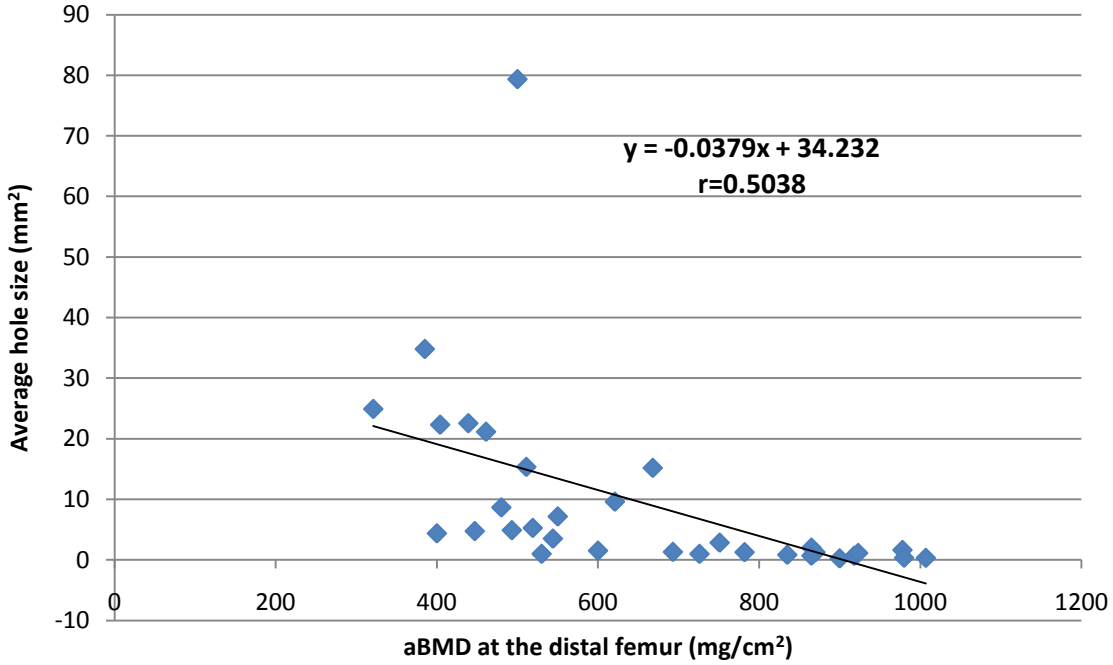
OR=0.131, 95%CI=0.011-1.519, p=0.1041) did not improve fracture correlations over aBMD at the distal femur alone. However, aBMD at the distal femur was found to be moderately negatively correlated with average hole size (r=-0.5038, p=0.0011, Figure 8) and moderately positively correlated with cross-sectional moment of inertia (r=0.6918, p<0.0001, Figure 9).

Based on the poisson regression model, the bone strength variables were significantly correlated with the number of fragility fractures sustained (Table 14). Adjusting for risk factors related to the bone strength variables did not alter the regression models predicting the number of fractures and therefore were not included in the final analysis. The expected change in log count for a one unit increase in cross-sectional moment of inertia and buckling ratio were -1.1456 and 0.2030, respectively. In other words, individuals with SCI with a higher cross-sectional moment of inertia will have 68.2% [1-exp (-1.1456)] fewer fragility fractures than individuals with SCI with lower cross-sectional moment of inertia. In addition, individuals with SCI with a higher buckling ratio will have 23% [exp (0.2030)] more fragility fractures than individuals with SCI with a lower buckling ratio.

The results examining the relationship between bone strength variables and fragility fractures were based on pQCT scans with and without movement artefacts. Therefore, a sensitivity analysis was performed to determine whether excluding the scans with movement artefacts would affect the results obtained from the odds ratio and poisson regression (Appendix B). We found that aBMD at the distal femur and cross-sectional moment of inertia remained significant while average hole size became insignificant (OR=1.082, 95% CI= 0.999-1.172, p=0.0521). In addition, aBMD at the proximal tibia (OR=0.985 95% CI=0.971-0.998, p=0.0278) and polar moment of inertia (OR=0.346 95% CI=0.122-0.983, p=0.0463) became significant. With regards to the poisson analysis, all of the indices of bone strength,

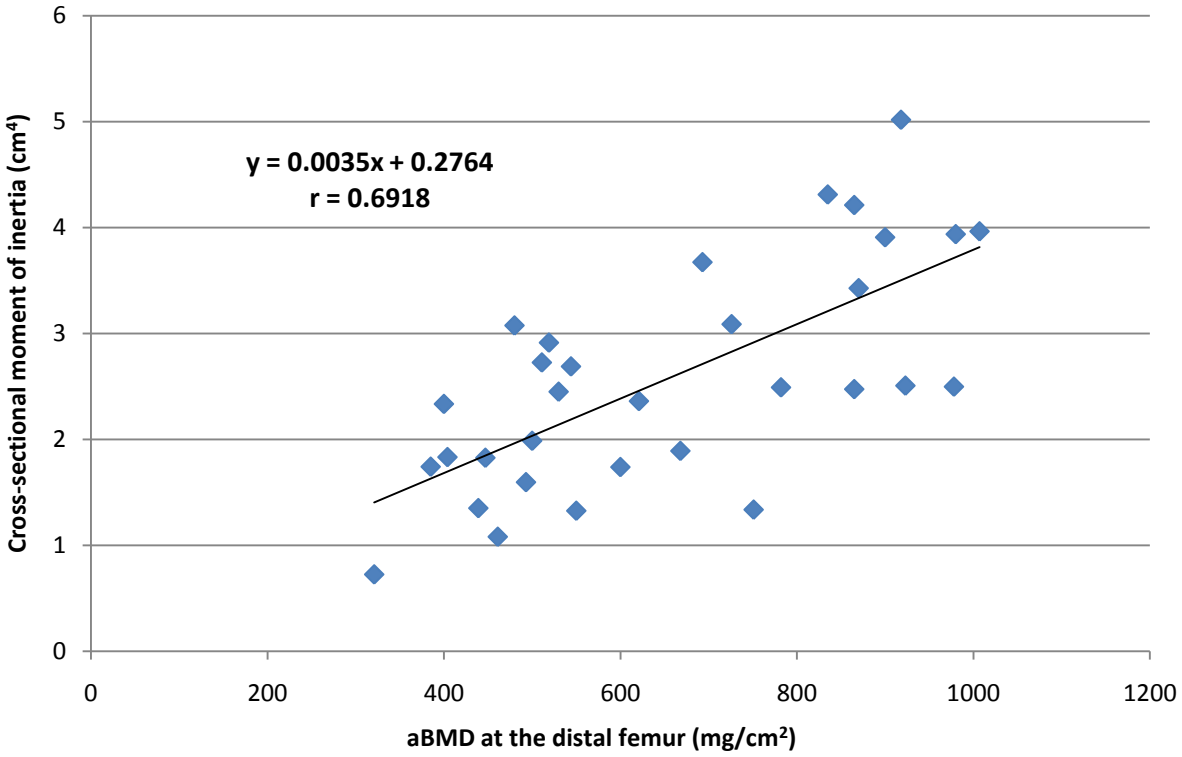
except for buckling ratio (p=0.0957) remained significantly correlated with the number of fragility fractures.

Figure 8: Relationship between average hole size at the ultra-distal tibia and aBMD at the distal femur



Note: When the outlier (500, 79.333) was removed r=0.688

Figure 9: Relationship between cross-sectional moment of inertia and aBMD at the distal femur



Note: When outlier (918, 5.017) was removed r=0.674

Table 13: Adjusted Odds Ratio and 95% Confidence Intervals for Indices of Bone Strength Associated with Fragility Fracture

	Fractures (Unadjusted)		Fractures (Adjusted)	
	OR (95% CI)	**p-value**	**OR (95% CI)†**	**p-value**
aBMD-DF (mg/cm^2)	0.989 (0.981-0.997)	0.0090*	0.988 (0.978-0.998)	0.0226*
aBMD-PT (mg/cm^2)	0.987 (0.979-0.996)	0.0035*	0.989 (0.978-1.000)	0.0535
vBMD (mg/cm^3)	0.963 (0.937-0.990)	0.0084*	0.971 (0.937-1.005)	0.0931
H_A (mm^2)	1.089 (1.013-1.170)	0.0216*	1.081 (1.001-1.166)	0.0470*
CTh (mm)	0.327 (0.124-0.859)	0.0234*	0.453 (0.162-1.263)	0.1300
BR	1.387 (0.933-2.060)	0.1056	1.175 (0.766-1.803)	0.4609
CSMI (cm^4)	0.146 (0.032-0.669)	0.0132*	0.098 (0.012-0.838)	0.0338*
PMI (cm^4)	0.422 (0.196-0.908)	0.0274*	0.419 (0.170-1.031)	0.0584

Notes: CI = confidence interval; OR = odds ratio; DF = distal femur; PT = proximal tibia
†adjusted for correlates of bone strength variables: aBMD at the distal femur and proximal tibia were adjusted for completeness of injury and bisphosphonate use; trabecular vBMD was adjusted for duration of injury and completeness of injury; H_A, CTh, and BR were adjusted for duration of injury; CSMI and PMI were adjusted for gender, completeness of injury, and bisphosphonate use.
**Statistically significant at alpha=0.05*

Table 14: Indices of Bone Strength Associated with the Number of Fragility Fractures Sustained

	Change in log count	Upper 95% CI	Lower 95% CI	p-value
aBMD-DF (mg/cm^2)	-0.0065	-0.0093	-0.0038	<0.0001*
aBMD-PT (mg/cm^2)	-0.0063	-0.0088	-0.0037	<0.0001*
vBMD (mg/cm^3)	-0.0224	-0.0329	-0.0118	<0.0001*
H_A (mm^2)	0.0237	0.0150	0.0324	<0.0001*
CTh (mm)	-0.6835	-1.1252	-0.2418	0.0024*
BR	0.2030	0.0031	0.4029	0.0465*
CSMI (cm^4)	-1.1456	-1.6123	-0.6789	<0.0001*
PMI (cm^4)	-0.5848	-0.9421	-0.2275	0.0013*

Notes: CI = confidence interval; DF = distal femur; PT = proximal tibia;
**Statistically significant at alpha=0.05*

5.7 Fracture Threshold and Fracture Breaking Point

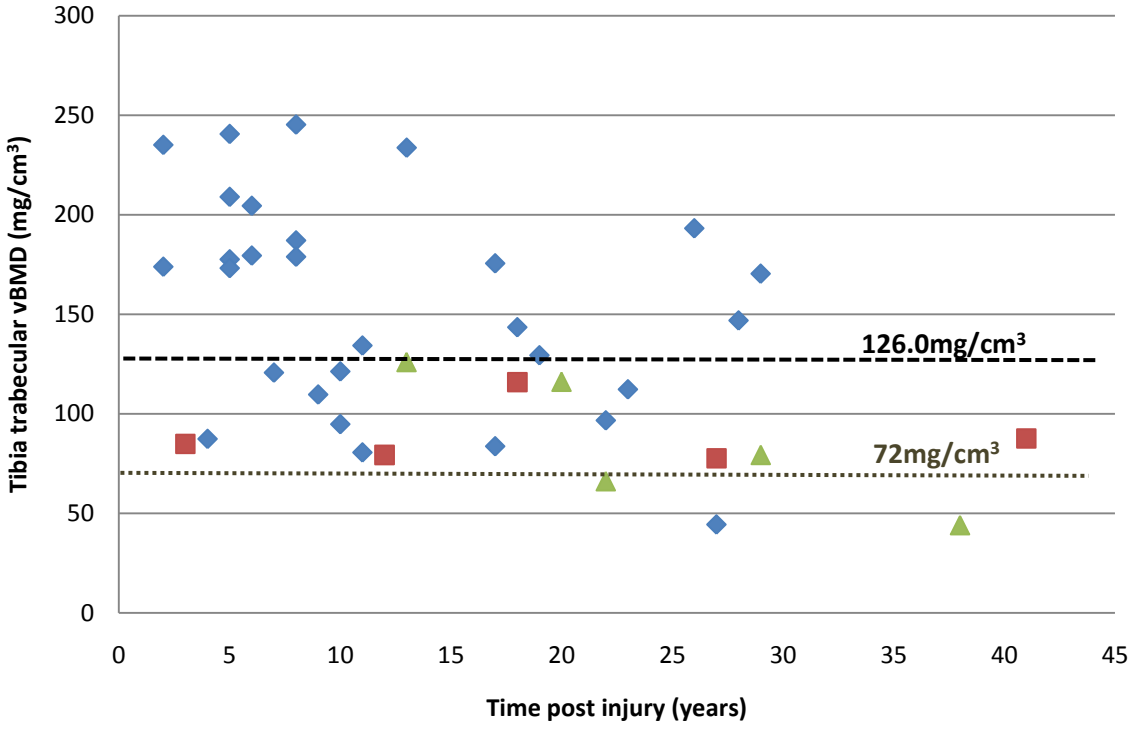
Based on SCI-specific fracture thresholds ($\leq 0.78 g/cm^2$) and fracture breaking point ($\leq 0.49 g/cm^2$) at the distal femur obtained by Garland et al [29], approximately 78% and 39% of individuals with SCI were at risk of fracture, respectively. A larger proportion of individuals with motor complete SCI compared to individuals with motor incomplete SCI had a fracture threshold of less than or equal to $0.78 g/cm^2$ (72% versus 28%) and a fracture breaking point of less than or equal to $0.49 g/cm^2$ (88% versus 13%). Based on Eser et al's [30] trabecular vBMD fracture threshold in the tibia ($<72 mg/cm^3$), 7.7% (three out of 39) of individuals with chronic SCI were at risk of fracture in which 100% of individuals had motor complete injuries (Table 15).

All of the subjects who had sustained a fragility fracture had trabecular vBMD in the tibia of less than or equal to $126 mg/cm^3$ (Figure 10). One individual with seven fragility fractures had a trabecular vBMD of $66.1 mg/cm^3$. Individuals with chronic SCI who had never had a fragility fracture had trabecular vBMD in the tibia ranging from $44.3 mg/cm^3$ to $245.2 mg/cm^3$.

Table 15: Proportion of Individuals with Chronic SCI who are Below Previously Defined Fracture Thresholds

	Fracture Thresholds		Fracture Breaking Point
	≤0.78g/cm^2 (aBMD)	**<72mg/cm^3 (Tibia vBMD)**	**≤0.49g/cm^2 (aBMD)**
All Subjects, n (%)	41	39	41
AIS A-B	23 (56.1%)	3 (7.7%)	14 (34.2%)
AIS C-D	9 (22.0%)	0 (0.0%)	2 (4.9%)
Subjects with one Fragility Fracture, n (%)	5	5	5
AIS A-B	4 (80.0%)	0 (0.0%)	3 (60.0%)
AIS C-D	1 (20.0%)	0 (0.0%)	1 (20.0%)
Subjects with Multiple Fractures, n (%)	5	5	5
AIS A-B	4 (80.0%)	2 (40.0%)	4 (80.0%)
AIS C-D	0 (0.0%)	0 (0.0%)	0 (0.0%)

Figure 10: Trabecular vBMD of the Distal Epiphysis of the Tibia versus Time after Injury



Legend: ♦, subjects who had never had a fracture; ■, subjects who had 1 fracture; ▲, subjects who had multiple fractures; upper dashed line represents the highest trabecular vBMD where a fracture was found; lower line represents highest trabecular vBMD previously established [30].

6.0 CHAPTER 6: DISCUSSION

6.1 Summary

To our knowledge, this is the first study to examine the relationships between indices of bone strength obtained by pQCT and fragility fractures in the lower extremity in men and women with chronic SCI. Most studies on bone loss in individuals with SCI focus on changes in bone density employed by DXA. In this study, we found that the presence of specific risk factors, namely duration of injury, completeness of injury, bisphosphonate use, fractures, and gender are potential correlates of DXA and pQCT-based bone strength measures. In addition, individuals with SCI with fractures had significantly lower indices of bone strength than those without fractures. Our preliminary data found that individuals who had lower aBMD at the distal femur, larger average hole sizes, or lower cross-sectional moment of inertia may be at increased risk of sustaining at least one fragility fracture in the lower extremity. Furthermore, we found that each of the bone strength variables were significantly correlated with the number of fragility fractures sustained. Finally, we found a trabecular vBMD fracture breaking point of approximately 126mg/cm^3 at the distal tibia.

6.2 Risk Factors Associated with Indices of Bone Strength

In the able bodied population, female gender, age, fracture history, glucocorticoid use and T-score for the femoral neck are the major risk factors that contribute to osteoporotic fractures. However, other clinical factors that contribute to fractures as a result of low BMD include current smoker, high alcohol intake, low body weight, disorders associated with osteoporosis, rheumatoid arthritis, parental history of fractures, prolonged glucocorticoid use, and prior fragility fractures [17,131,132]. Applying these risk factors to assess fracture risk in individuals with SCI may not be appropriate as bone loss is distinct from that seen in the able-

bodied population with respect to rate of onset, severity of decline in aBMD and bone architecture [66,133], etiology [66], and location of fracture risk [134].

In the present study, the risk factors associated with the indices of bone strength in individuals with SCI are completeness of injury, bisphosphonate use, fractures, duration of injury, and gender. Completeness of injury, bisphosphonate use, and fractures were the overriding risk factors for low aBMD in the distal femur, while duration of injury, completeness of injury, and bisphosphonate use were correlates of aBMD at the proximal tibia among individuals with SCI. In fact, these risk factors contribute to more than half of the possible reasons as to why individuals with SCI may be experiencing low aBMD in the knee. Completeness of injury has been previously determined to have a very strong influence on low BMD, suggesting that individuals with complete injuries are more than 6 times more likely to have BMD of the knee low enough to place them into the osteoporotic category [87]. Individuals with incomplete injuries have the ability to contract their muscles, and possibly weight bear which may account for the higher BMD compared to individuals with motor complete injuries.

Our findings also suggest that bisphosphonate use may be an important correlate of aBMD; however, there is minimal evidence currently available in the literature that suggests bisphosponate use can be used for the prevention and treatment of BMD loss following a SCI [135]. Administration of 10mg daily oral alendronate plus elemental calcium to a group of individuals with chronic and acute SCI for a period of 24 months showed statistically significant ($p=0.017$) treatment effect ($-2.0\pm2.9\%$) compared with the control group who were only being administered elemental calcium ($-10.8\pm2.7\%$). BMD remained stable in the distal tibia epiphysis and total hip in the alendronate group compared to the control group [109].

Another study found no variation in BMD values in the lower extremity in the treatment group (0.01±0.02%) relative to the control group (-0.01±0.05%) following a six month intervention [110]. A major limitation to the above randomized controlled studies is that they did not examine the role of alendronate on fracture-prone SCI sites such as the distal femur and proximal tibia. In addition, these studies only looked at the bisphosphonate alendronate. Our study found that bisphosphonate use, whether it be on alendronate, etidonate, fosavance, or risedronate, was associated with aBMD at the distal femur and proximal tibia. With respect to the able-bodied population, there is good evidence that alendronate, etidronate, and risedronate prevent vertebral fractures, nonvertebral fractures and hip fractures more than the placebo group [136]. A study in which women were assigned to either placebo or 5mg daily of alendronate for two years followed by 10mg daily of alendronate for another two years found that individuals assigned to the alendronate group had statistically higher BMD ($p<0.001$) in the total hip, lumbar spine, and femoral neck compared with the placebo group. Alendronate also significantly reduced the risk of clinical fractures by 36% in women whose initial femoral neck T-score was -2.5 or less (RH=0.64, 95% CI=0.50-0.82), but four years of alendronate did not affect the risk of clinical fractures in those with an initial T-score greater than -2.5 (RH=1.08, 95% CI=0.87-1.35) [137]. Based on our results and previous work, bisphosphonate treatment is important to maintain and/or improve bone density among individuals with SCI.

Duration of injury was also found to be a strong correlate of bone strength variables. It was significantly associated with all of the bone strength variables, expect for aBMD at the distal femur, cross-sectional moment of inertia and polar moment of inertia. Using a multiple linear regression model with age, BMI, and duration of injury, Garland et al found a similar

relationship in which duration of injury was not associated with aBMD at the knee, but the association did approach significance (p=0.07) [138]. The reason for why duration of injury was a correlate of aBMD at the proximal tibia and not aBMD at the distal tibia could be due to skeletal heterogeneity of the sample population. In a monozygotic twin study, Bauman et al [94] found a negative association between bone density and duration of injury such that twins with SCI lost BMD in the leg over approximately three decades in amounts proportional to duration of injury. However, this study performed a single linear regression analysis examining the direct relationship between aBMD at the knee and duration of injury. Our study is unique in that we performed a multiple linear regression analysis examining the effects of many different potential correlates of losses in bone density at the knee. Initially, we performed a linear regression model that did not adjust for completeness of injury, bisphosphonate use, or fractures, and found that duration of injury was associated with aBMD at the distal femur (p=0.0040). This is line with previous studies which found a direct relationship between duration of injury and aBMD at the knee [6,20]. Therefore, our study supports the idea that duration of injury is an important correlate of bone strength variables.

Our study also found that gender is an important correlate of cross-sectional moment of inertia and polar moment of inertia. Cross-sectional moment of inertia and polar moment of inertia are a function of bone's distribution from the axis of rotation; the wider the bone, the more resistance it has to torsion or bending. During growth, boys generally obtain wider bones with a thicker cortex, while women obtained more thinner narrow bones [45]. As a result, females are a higher risk of fracturing compared to males. There was no evidence that gender or age of the participant were significant confounders for any of the other indices of bone strength assessed. Previous studies have reported that gender [87] and age [14,96,138]

are not significantly associated with BMD of the knee in individuals with SCI, while one previous study did find an association between age and BMD z-score at the knee [87]. In the able-bodied population, female gender and age are the most important predictors for osteoporosis [132,139]. Post-menopausal women and men over the age of 50 are at higher risk of osteoporosis and subsequent fractures [17]. Gender and age were not found to be a risk factor associated with aBMD perhaps because the number of men (n=33) included in this study was much larger than women (n=14), and there were no individuals with SCI below the age of 32 or above age 77. Therefore, any confounding effects of gender or age would have been difficult to detect because of the small sample size and unequal number of males and females. Furthermore, it may be that other risk factors may be stronger correlates of aBMD, so a relationship between gender and aBMD was not seen. No previous study has examined the role of gender and age on average hole size, cortical thickness, buckling ratio, cross-sectional moment of inertia, and polar moment of inertia in individuals with SCI. However, Slade et al [73] and Modlesky et al [72] have examined trabecular bone microarchitecture in men and women with SCI at the knee and found similar deteriorations in trabecular bone and found fewer trabeculae that are thinner trabeculae and further apart compared to controls. A study examining the role of anthropometric and lifestyle factors on trabecular vBMD in able-bodied men found that age was negatively correlated with cortical and trabecular vBMD [140]. Thus, age and gender seem to be important correlates of bone strength variables in healthy men and women; whether these factors are important in predicting bone strength in individuals with SCI still remains uncertain. Our results must be confirmed with larger and more diverse sample populations.

Our results suggest that the initial assessment of the extent of bone loss in individuals with SCI should include completeness of injury, duration of injury, bisphosphonate use, and fracture history. Gender should also be included in the screening protocol as this risk factor was found to be a potential correlate of cross-sectional moment of inertia and polar moment of inertia; however further research examining the role of gender and age on other indices of bone strength is required as the literature to date is inconclusive and these risk factors are strong predictors of fractures in the able-bodied population. Since aBMD is currently the only diagnostic tool available for the diagnosis of osteoporosis and fracture risk in the clinical setting, duration of injury, completeness of injury, bisphosphonate use, and prior fragility fractures should be the primary risk factors examined by clinicians to determine those at high risk of fracturing. Future initiatives should also consider the effects of modifiable risk factors (alcohol intake [141], physical activity [69], smoking [99], other bone affecting medications, such as vitamin D and calcium [142], and BMI [87]) previously found to be correlates of bone strength variables in individuals with SCI as our results only account for less than or equal to half of the possible outcomes contributing to poor bone strength. The modifiable risk factors should be addressed by clinicians during the patient's initial assessment of bone loss to inform the patient of ways to minimize the amount and rate of bone loss. Longitudinal studies are needed to have a clearer understanding of the main risk factors associated with bone loss and fractures in the SCI population.

6.3 Indices of Bone Strength Related to Fragility Fractures

Structure-based measurements may be useful for identifying individuals with SCI at high risk of fracture. Our preliminary study found that men and women with chronic SCI and fractures had significantly lower bone strength variables than those without fractures. The

primary distinctions between the fracture group and non-fracture group was average hole size, aBMD in the distal femur, and cross-sectional moment of inertia; individuals with SCI who had sustained a fragility fracture have a larger average hole size (intertrabecular spacing) at the ultra-distal tibia, and a lower aBMD in the distal femur and cross-sectional moment of inertia at the tibia shaft than individuals with no history of fragility fractures. No other estimates of tibial bone strength measured by pQCT or DXA discriminated between the groups after important clinical correlates were controlled for. It is important to note that aBMD at the proximal tibia, trabecular vBMD, and polar moment of inertia were close to becoming significant based on the odds ratio and the odds ratio and 95% confidence interval suggest they may have become significant with an increase in sample size. Therefore, we should not reject the hypothesis that aBMD at the proximal tibia, trabecular vBMD, and polar moment of inertia are important correlates of fragility fractures. If we were to conclude these non-significant bone variables as having no effect we may be introducing type II error, accepting the null hypothesis when the null hypothesis is false. A larger population-based study is required to help us identify the true relationship between these indices of bone strength and fractures among individuals with SCI.

Our findings are consistent with the findings of MacIntyre et al [26] who reported that postmenopausal women with a history of forearm fractures had significant differences in average hole sizes than women with similar aBMD but with no history of fractures. The larger average area of the hole size found in individuals with SCI who have fracture may be caused by thinning trabeculae and loss of trabecular struts. In nine human cadaver radii, Gordon et al [143] demonstrated that changes in trabecular structure are important in determining the amount of load that can be withstood prior to fracturing; larger hole sizes in the distal radius

are susceptible to collapse under low loading forces. This concept is consistent with previous findings that age-related increases in trabecular spacing and thinning of horizontal struts in the vertebrae effect the strength of the bone [49,53]. In individuals with SCI, two cross-sectional studies reported fewer trabeculae that are thinner and further apart compared to able-bodied controls [72,73]. Frost hypothesized that the mineralization and structure of bone is dictated by the amount of load imposed on the bone [82,144]. Since some individuals with SCI are subjected to no weight bearing, trabecular structure becomes demineralised and deteriorated.

aBMD in the distal femur was also found to be a significant correlate of fractures. A one SD (1mg/cm^2) increase in aBMD at the distal femur was associated with a decrease in fracture by 1.2%. Areal BMD at the proximal tibia was not a significant factor in discriminating individuals with SCI who have fractured to those who have not; however the odds did approach significance (p=0.0535) and could possibly become significant with a few more concurrent values in both the fracture and non-fracture group. The odds ratio could have also been compromised because fewer fragility fractures were seen in the proximal tibia (n=11) versus the distal femur (n=14) in our sample population. Furthermore, 20% of the fractures occurred in the ankle (n=5) and fibula (n=2); areas where aBMD was not assessed. A similar age-adjusted relationship between aBMD and fractures was reported previously in a cross-sectional study evaluating BMD and fracture history in individuals with SCI. This study reported that for every 10mg/cm^2 and every unit standard deviation (t-score) decrease in aBMD at the femoral neck, the risk of fracturing increased by 2.2 and 2.8 times, respectively [14]. The strength of our study is that we adjusted aBMD for completeness of injury and bisphosphonate use, correlates found to be associated with aBMD. Our study reported a negative relationship between aBMD and the number of fragility fractures sustained. Only

one other study assessed this relationship and found a similar negative relationship [14]. Ultimately, these results coincide with previous studies that found aBMD is a correlate of fracture risk in individuals with SCI.

Cross-sectional moment of inertia may also be an important predictor of fracture risk as it was found to be a significant correlate of fractures. De Bruin et al [74] reported that individuals with SCI with a fracture had significantly smaller moments of inertia at the proximal, distal and middle sections of the tibia compared to able-bodied controls, but there was no significant difference between individuals with SCI without fractures. In addition, when comparing the bone strength between individuals with SCI who had fractured to those who have not, the fractured group had a lower bending stiffness than the non-fractured group, suggesting those with fractures are at higher risk of future fractures [74]. Our data is also consistent with a prospective study conducted by Sheu et al [80] that found that able-bodied men with non-vertebral fractures had lower cross-sectional moment of inertias at the radii than those without non-vertebral fractures. Additionally, they found that for every SD decrease in cross-sectional moment of inertia, there was approximately 2 fold increase in fracture risk [80]. Compared to their results, we found that for every SD decrease in cross-sectional moment of inertia, the risk of fracturing increased by 90%. The width of bone and the thickness of the cortex are key determinants of cross-sectional moment of inertia. Cross-sectional moment of inertia is best achieved when bone's cross-sectional area is as far from the neutral axis as possible. Individuals with a larger cross-sectional moment of inertia have stronger and stiffer bones, while individuals with a smaller cross-sectional moment of inertia are weak and usually more prone to bending [145]. During growth, the skeleton responds to load by increasing the diameter of long bone via periosteal apposition. However, when there

is an absence or reduction in mechanical loading, the shape and size of bone changes [146,147]. In individuals with SCI, the presence of smaller and weaker bones may lead to the increased number of fragility fractures. Our study found that a lower cross-sectional moment of inertia is associated with fractures, therefore this bone strength variable may have clinical relevance as a risk factor in individuals with SCI. Based on the logistic regression analysis modeling the relationship between cross-sectional moment of inertia and a fracture, it is important to note that the 95% confidence interval was quite wide, therefore we may need to perform a similar analysis with a larger sample size to see the true relationship. pQCT is a technique that is practical and not costly; therefore, future research should consider examining the changes in bone width obtained by pQCT as it may be a strong predictor of fragility fractures.

In our study, cortical thickness was found to be one of the better correlates of fragility fractures in individuals with SCI. However, it was no longer statistically significant after adjustment for duration of injury. Previous case-control studies have demonstrated similar correlations between cortical thickness and fractures. For example, after adjusting for age, sex, and weight, Jamal et al [24] reported that a decrease in cortical density, cortical area, and cortical thickness were associated with increased odds of fracturing among individuals on dialysis. In another study comparing 101 postmenopausal women with and 101 postmenopausal without prevalent fractures using high resolution pQCT (HR-pQCT) at the tibia and wrist, cortical thickness was found to be significantly associated with fragility fractures [27]. Our study also found that cortical thickness has an influence on the number of fragility fractures, where a thinner cortex leads to more fractures. Individuals with SCI experience a decrease in cortical cross-sectional area due to increases in endosteal and

periosteal resorption [19,148]. We need to also consider age-related periosteal apposition because periosteal expansion at the tibia may have been reduced following the spinal cord injury as these individuals are subjected to little or no weight bearing. When thinned walled cylinders are subjected to bending, they tend to fail by buckling; collapsing from the inner curvature, rather than cracking from the outer curvature like thick walled cylinders [25]. Section modulus characterizes the ability of a thick walled cylinder to resist bending and failure. However, section modulus cannot be used to predict failure in thin cortices because it would overestimate the amount of load required to cause bone failure [149]. Therefore, the thickness of the cortex wall is expressed as buckling ratio. The buckling ratio is bone instability depicted by the critical balance between cortical thickness and bone width. Our findings suggest that the thinning of cortices plays a key role in the susceptibility to fracture by producing an increase in buckling ratio. Although buckling ratio was not a correlate of fractures, a relationship was seen between buckling ratio and the number of fragility fractures sustained in our cohort. Our data is consistent with a prospective study which reported that cortical thickness and area predict incident fractures, whereas buckling ratio does not in men, signifying that a narrow bone with a thin cortex can have a low cross-sectional area (CSA) and low bending strength, regardless of a normal buckling ratio [145]. In contrary, a previous nested case-control study performed in 232 elderly community-dwelling women reported that increases in buckling ratio were associated with a higher risk of hip fracture [149]. The associations we observed between cortical thickness and fracture may be mediated by secondary hyperparathyroidism, a common problem seen in individuals with SCI [150]. Hyperparathyroidism occurs as a result of low serum calcium concentrations. Parathyroid hormone (PTH) is released in order to stimulate osteoclast resorption to increase levels of

calcium in the blood. Studies have found that hyperparathyroidism most likely affects cortical bone causing decreases in cortical thickness by endosteal resorption and increases in cortical porosity [151,152]. Vitamin D has been identified as being an essential hormone in maintaining serum calcium homeostasis and has been shown to have an inverse relationship with PTH [152]. In addition, vitamin D has been strongly linked to the maintenance of skeletal health in the able-bodied population [153]. Among individuals with SCI, vitamin D levels have been reported to be significantly lower than controls [150], and therefore may be a contributing factor to decreases in bone health. However, a relationship may exist between vitamin D and bone health in the SCI population which may provide therapeutic effects for the prevention of fractures in individuals with SCI. In a randomized control trial, BMD was evaluated in individuals in given 4µg/day of vitamin D_2 anolog, 800IU/day of vitamin D and 1.3g/day of calcium (treatment group), and in individuals given a placebo, 800IU/day of vitamin D and 1.3g/day of calcium (control group). Leg BMD did not statistically change in 24 months in the control group; however, in the treatment group, percent leg BMD increased significantly in a subgroup of individuals who had never smoked [142]. The vitamin D mediated increase in BMD may be attributable to the prevention of cortical thinning, but there are no studies that confirm a clear relationship between cortical thickness or density and vitamin D in individuals with SCI. Since cortical thinning has been linked to hyperparathyroidism, an exploratory analysis should be conducted to examine the relationship between vitamin D or PTH and cortical thickness in the SCI population. If a relationship is reported, vitamin D intake would be an important risk factor to include when creating guidelines and screening protocols for the prevention and treatment of osteoporosis and fracture risk in the SCI population.

The use of pQCT in clinical and epidemiologic research among individuals with SCI has been limited. However, there is a growing interest in understanding the changes in bone strength after SCI in addition to bone density, as it provides additional information about skeletal health. Our data is in line with a number of studies that have demonstrated the utility of quantitative computed tomography to detect micro-architectural deterioration in different groups with fractures and to detect changes in bone loss over time. Cross-sectional moment of inertia, polar moment of inertia, and stress-strain index at the radius have been shown to be strong predictors of fracture risk in men with non-vertebral fractures and these pQCT-based bone strength variables improved fracture prediction over femoral neck aBMD alone. The addition of pQCT-based estimates to aBMD models increased fracture prediction ability by approximately 10% [80]. Unfortunately, the addition of pQCT measures of average hole size and cross-sectional moment of inertia to models with aBMD at the distal femur in our study appeared to decrease fracture correlations. It is likely that our sample size was not large enough to answer this question. Studies have also reported that women with fractures have lower trabecular vBMD, cortical thickness, trabecular number and thickness, and higher trabecular separation at the radius, and lower cortical thickness, trabecular vBMD, and trabecular thickness at the tibia compared with age and aBMD-matched controls without fractures [154,155]. Individuals with chronic kidney disease with fractures have significantly lower vBMD, cortical thickness and number at the radius and tibia compared with healthy matched controls [156,157]. Based on previous studies, it seems that many bone strength variables seem to be important determinants of fracture risk in other groups of individuals; future research should examine the most useful and appropriate bone strength variables to describe fracture risk among individuals with SCI with and without fractures.

The mechanostat theory is a possible explanation for the reduction in bone strength experienced in individuals with SCI. This theory suggests that bone strength is adapted by strains caused by physiological loads. The largest physiological load exerted on bone is from muscle contractions, producing the muscle-bone unit [158,159]. In the able-bodied population, many studies have reported strong associations between muscle strength and BMC or aBMD [160-163]. There has only been a few studies that have examined the relationship between muscle and bone in individuals with SCI. A cross-sectional comparative study found a strong linear relationship between BMC and lean tissue mass in the legs among individuals with incomplete SCI [88], while a strong relationship between lean tissue and BMC in the arms was reported in the monozygotic twin with SCI, regardless of the level or completeness of injury [164]. A positive relationship between leg lean tissue and BMC in the non-SCI twin was found but there was no relationship found in those with SCI [164]. Since a muscle-bone relationship has been reported in individuals with SCI, muscle atrophy is a probable explanation for the ensuing decreases in bone strength.

Our findings reinforce the importance of bone density obtained by DXA as a clinical tool for identifying those who are at high risk of fractures. In addition, we found that architectural changes of trabecular and cortical bone obtained by pQCT may refine the ability of clinicians to predict fractures. Our results are preliminary; therefore, prospective studies need to be performed to confirm the associations we found between indices of bone strength and fractures. Furthermore, it is important to determine the most appropriate indices of bone strength to identify individuals with SCI at greatest risk for fracturing. Understanding the risk factors and changes in bone structure in individuals with SCI will help clinicians pin point those individuals who are at greatest risk of fracturing. In turn, clinicians can determine the

most appropriate next step to reduce fracture risk whether it is through drug interventions such as bisphosphonates [109], vitamin D and calcium [142], or via exercise interventions such as functional electrical stimulation (FES) [165].

6.4 Fracture Threshold and Fracture Breaking Point

Contrary to our hypothesis, only 7.7% of the sample population had a trabecular vBMD fracture threshold of less than or equal to 72mg/cm^3. In addition, among those who had sustained a fragility fracture, only 20% were a risk of fracturing again. Fracture threshold, a point at which fractures begin to occur, is being used in the wrong context by Eser et al [30]. Since the study conducted by Eser et al [30] has a cross-sectional design, they did not measure trabecular vBMD at the time of the fracture; it is incorrect to state that fractures began at a trabecular vBMD of 72mg/cm^3 if the study was not conducted in a prospective manner. Therefore, the term 'fracture breaking point' would probably be a more appropriate term to use in this context. As a result, our data implies that there is a trabecular vBMD fracture breaking point at approximately 126mg/cm^3 in the distal femur, above which no fractures have occurred and below which low trauma fractures are common. The present study clearly shows that the trabecular vBMD fracture breaking point of the distal tibia previously suggested [30] may not accurately predict fracture risk among individuals with chronic SCI. Possible reasons for this discrepancy may be the difference in SCI populations studied. The study conducted by Eser et al [30], included men with motor complete SCI, whereas the present study included men and women with motor complete and incomplete SCI. The completeness of injury influences the extent of bone loss that occurs in the lower extremity following their injury. Individuals with motor complete injuries experience a greater degree of bone loss compared to those with incomplete injuries [2,29,62,87]. This is consistent with our

findings in which we found that completeness of injury was related aBMD at the distal femur and proximal tibia, trabecular vBMD, cross-sectional moment of inertia, and polar moment of inertia. Acknowledging that individuals with complete SCI experience more bone loss than individuals with incomplete SCI suggests that perhaps separate fracture breaking points be established to distinctly determine fracture risk in both groups. Alterations in muscle mass and changes in voluntary muscle contractions exhibited between individuals with complete and incomplete SCI may partly elucidate why individual fracture breaking points should be created. Individuals with incomplete SCI experience partial muscle contraction thus exerting forces indirectly on bone, while individuals with complete SCI experience complete inactivation of muscle fibres, exerting no forces on bone; as a result, there is greater muscle atrophy in the lower extremity among those with complete SCI than incomplete SCI. The muscle-bone relationship [160] directly explains why individuals with incomplete SCI may have a higher fracture breaking point than individuals with complete SCI; a higher force is required to cause a fracture among individuals with complete SCI. Our fracture breaking point is approximately 75% higher than the recommended 72mg/cm^3 threshold. However, if individuals with motor incomplete SCI were removed from the analyses, the fracture breaking point would be 115mg/cm^3; 43mg/cm^3 higher than the previously recommended trabecular vBMD fracture breaking point. According to our findings, individuals with SCI seem to be fracturing despite having higher BMD. Many of our subjects were on interventions such as bisphophonates, calcium, vitamin D supplements, and multivitamins which may account for the higher BMD. Strong inhibitors of bone resorption, such as bisphosphonates can reduce the activation frequency and mineralizing surface by 87% and 92%, respectively causing increases in bone mineral density [166]. In our study, we were able to demonstrate that

bisphosphonate use is related to bone density at the knee. Therefore, the true fracture breaking point may be masked due to the high proportion of individuals on treatments to improve bone health. Another possible reason for the discrepancy may be because our sample population had greater skeletal heterogeneity, producing more differences in bone structure deterioration from one individual to another. Finally, values of trabecular vBMD may be different because Eser et al [30] used the XCT 3000 pQCT while we used the XCT 2000 pQCT. The XCT 3000 provides a larger gantry than the XCT 2000 in order to better accommodate larger limbs such as the lower leg. A study comparing measurements in the distal radius obtained by XCT 3000 and XCT 2000 found a strong correlation (r=0.99) between the two devices when measuring trabecular vBMD and a mean difference (XCT 3000-XCT 2000) expressed as a percent of the measurement's mean of only 1.9% [167]. Therefore, the difference in devices used should only account for a small difference and not the large difference we observed in trabecular vBMD fracture breaking point. Eser et al [30] also reported using a higher contour threshold of 180mg/cm^3 compared to our 130mg/cm^3. The contour mode detects the outer bone edge (periosteal boundary) and provides information on total bone parameters, while the addition of a threshold provides a boundary line which informs the software of a starting position in which to begin analysis. When a higher threshold is used, the software will cut away some of the bone, causing the segmented bone structure to become small. We decided to use a lower threshold in order to include areas of lower trabecular density in addition to the denser trabecular area. Although, in a validation study previously conducted, we have found that changing the threshold from 130mg/cm^3 to 280mg/cm^3 does not dramatically change trabecular vBMD (unpublished data, Appendix B).

Of 47 subjects, approximately 30% had sustained at least one fracture in the lower extremity. Our results are in between previous reports which found 25% [30] and 34% [14] of their study sample had experienced at least one fracture. We found that fractures generally occurred more frequently in the femur than in the tibia, which is in agreement with previous studies [7,8,11,13]. In addition, our study confirms the notion that fractures of the lower extremities are more common in subjects with paraplegia than tetraplegia [8], probably due to their higher activity levels and mobility. We found only 11 fractures occurred in participants with tetraplegia and 23 fractures occurred in participants with paraplegia.

The indices of bone strength were significantly lower in those individuals with a fragility fracture compared to those without. Therefore, it is important that clinicians obtain fracture history following a SCI in order to determine the prevalence of fractures in those individuals with trabecular vBMD below the fracture threshold. Due to the discrepancy seen in trabecular vBMD fracture threshold of the tibia, further investigations and evaluations are required with a larger and more diverse sample population. Ultimately, the fracture threshold concept could be used as a diagnostic technique for fracture risk assessment in individuals with SCI.

6.5 Limitations

Although this study provides important information in our understanding of subsequent fragility fractures among individuals with chronic SCI, there are several limitations. First, we did not match cases (fragility fractures) and control (no fragility fractures). Our sample included many more controls than cases for the logistic regression. The number of individuals with fragility fractures was 14, which represents only 29% of the sample size, while then number of individuals with no history of fractures was 33,

representing 71% of the sample size. The sample size among individuals with fractures further decreased due to missing bone strength variables, reducing the sample size to ten for the following indices of bone strength: aBMD of the distal femur, vBMD, average hole size, cortical thickness, and buckling ratio. The sample size seemed to be small when performing odds ratio and 95% confidence interval obtained by multivariable logistic regression models to identify indices of bone strength associated with having at least one fracture. If we were to redesign this study, creating a priori matching criteria would help us eliminate other confounding variables. Based on the sociodemographic and impairment characteristic chart (Table 6), adjusting for injury characteristic (p=0.033), AIS (p=0.018), and LEMS (p=0.008) would help eliminate the matching limitation. In addition, BMI should also be considered as a risk factor since it has been found to be a correlate of bone density. We chose to not include BMI as a confounding variable because it fails to identify persons with SCI who are truly obese [91]. Finally, the sample population with fractures needs to be larger in order to improve the effect size and increase the statistical power of the results.

Another weakness in the present study is that bone status was not measured at the time of the fragility fracture. In several cases, the fractures occurred years (approximately 6 years) before the bone measurements were made in the study, thus, a causal relationship between fractures and indices of bone strength could not be established. A prospective study needs to be performed to identify an actual causal relationship. Furthermore, a large number of our sample population was recruited by physician referral from the bone clinic at the Lyndhurst Centre. As a result, many of participants for this study were on interventions to improve bone health such as calcium (n=40), vitamin D (n=42), bisphosphonates (n=26), and exercise. Therefore, the results of this study may not be generalizable to all individuals with chronic

SCI, as bone health may have improved since the occurrence of the fractures, resulting in higher bone quality measurements.

We did not consider the role of bisphosphonates as an effect modifier. The term 'effect modification' is applied to indicate that the effect of a particular variable (aBMD) on another (fractures) varies according to a third factor (bisphosphonates). There has been considerable concern that long-term bisphosphonate use might be adversely affecting bone quality in postmenopausal women. There have been reports of an unusual (atypical) type of bone fracture that are low energy femur fractures, typically transverse or slightly oblique at the diaphysis or subtrochanteric. Furthermore, these individuals with atypical fractures have a higher ratio of cortical thickness to femoral diameter than individuals with normal fracture patterns [112]. A recent population-based nested case control study found that women taking bisphosphonates for five or more years were at increased risk of subtrochanteric or femoral shaft fractures (OR=2.74 95%CI=1.25-6.02) compared with transient bisphosphonate users. The study found that 71 (0.13%) and 117 (0.22%) out of 52 595 women with at least five years of bisphosphonate therapy sustained a femoral fracture within the subsequent year and within two years, respectively [168]. Based on our data collection assessment forms, we were unable to determine whether fractures were due to bisphosphonates. We know the number of individuals who were currently on bisphosphonates at the time of the assessment, but we do not know whether they were taking the drugs when they sustained their fragility fracture. Before the larger prospective study, Bone Quality in Individuals with SCI moves forward, it is critically important to fix the fracture ascertainment form (Appendix A). Table 16 outlines possible questions that should be considered to help us determine if their fragility fractures were caused by bisphosphonates.

Table 16: Possible Questions to be Included in the Fracture Ascertainment Form

Questions
1. Were you on bisphosphonates when you fractured? 2. How long were you on bisphosphonates? (Provide approximate dates) 3. Which bisphosphonates were you on? What was the dose? 4. On average, how well were you at taking the bisphosphonates? a. 0-25% b. 26-50% c. 51-75% d. 76-100%

Fourthly, four pQCT scans at the ultra-distal tibia (4% site) and two pQCT scans at the proximal one-third of the tibia (66% site) had very minor movement artefacts and were not removed from the analysis. However, the scans were still of good quality and did not affect the integrity of cortical circumference. There were also three pQCT scans at the proximal one-third of the tibia (66% site) that had clearly visible movement artefacts with disruption in cortical edge causing them to be of insufficient quality, but were also kept in the analysis. Partial volume effect (PVE) could also cause inaccurate estimates of bone strength variables obtained by pQCT. PVE occurs when a single voxel contains tissues of different densities, such as the boundary between bone tissue and soft tissue, and therefore the attenuation coefficient assigned is some middle ground between the two. Movement artefacts and PVE could have caused overestimations or underestimations in bone strength variables, decreasing the accuracy of pQCT-based measurements. However, we found that removing the scans with movement artefacts only resulted in very small changes in the associations between fractures and bone strength variables.

Finally, there are some potential measurement biases that must also be considered when making conclusions about this study. Using recall to ascertain an outcome has its problems. Fractures may be underreported due to lack of saliency of the exposure and subsequent poor recollection of fractures that occurred in the past, leading to reporting bias.

Reporting bias would predominately affect the observed association by underestimating overall events, making the association between fragility fractures and indices of bone strength appear weaker than it may be. The current work confirms that fragility fractures are common among individuals with chronic SCI; however the number of individuals with fragility fractures may be higher than estimated.

6.6 Conclusion

In summary, we found that gender, completeness of injury, duration of injury, fractures, bisphosphonate use were associated with indices of bone strength in individuals with SCI. Our findings also suggest that, in individuals with SCI, aBMD at the distal femur, average hole size at the ultra-distal tibia, and cross-sectional moment of inertia were the best correlates of fragility fractures. However, we found that each of the indices of bone strength were able to model the number of fragility fractures sustained. Our data supports a trabecular vBMD fracture breaking point at the ultra-distal tibia of approximately 126mg/cm^3 and 115mg/cm^3 for individuals with complete SCI and those with incomplete SCI, respectively. The findings presented in this study provide the framework for future enquiry of the relationship between indices of bones strength assessed non-invasively by pQCT and fragility fractures and the risk factors associated with lower extremity osteoporosis. Further studies are needed to determine the most appropriate risk factors that contribute to bone loss and understand the role and importance of these and other indices of bone strength on skeletal fragility in individuals with SCI. Prospective studies should also be undertaken to determine whether indices of bone strength by pQCT can predict the risk of multiple frailty fractures. In due course, a fracture prediction model integrating various risk factors and indices of bone

strength can be developed to evaluate fracture risk of individuals with SCI, which in turn can help in the diagnosis and prevention of fractures.

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APPENDICES

Appendix A

1.Letter of Invitation
2.Physician Referral Form
3.Telephone Screening Form
4.Information and Consent
5.Past Medical History
6.Concurrent Medications
7.Health Demographics
8.Current Health Status
9.Disease/Conditions Affecting BMD
10. Current Health Status
11. Fracture Ascertainment Questionnaire
12. DXA
13. pQCT

Primary Investigators:
Dr. Lora Giangregorio
Dr. Catharine B. Craven

Co-investigators:
Dr. A. Papaioannou
Dr. M. Popovic
Dr. L. Thabane
Dr. N. McCartney
Dr. J.D. Adachi

Bone quality in individuals with chronic spinal cord injury

Lyndhurst Centre 520 Sutherland Drive Toronto, Ontario M4G3V9

<Date>

<Address>

RE: Research Study

Dear <Name>:

You are being asked to take part in a research study called “Bone quality in individuals with chronic SCI”. Myself and other researchers at McMaster University, the University of Waterloo, University of Toronto and the Toronto Rehabilitation Institute are conducting the study. The Canadian Institutes of Health Research are funding this study (www.cihr-irsc.gc.ca). The purpose of the study is to examine the bone health of men and women with chronic spinal cord injury.

If you agree to take part in the study, you will be asked to have your bone density measured once a year for 2 years. You will also be asked to report your past and current medical history and medications, followed by a brief examination of your sensation and muscle activity. You will participate in two types of bone density scans in the study; one at Lyndhurst and one at McMaster University. Transportation to McMaster University will be provided. The overall time commitment for the study is 10-15 hours over the 2 year period. This includes three visits to Lyndhurst (2-3 hours each) as well as three visits to McMaster (30 minutes each) and five telephone follow-up calls (30 minutes each). All participants will receive a $40 honorarium at the 0 (start), 1 year and 2 year time points.

At some point in the next two weeks you will receive a telephone call from a research assistant. The assistant will ask you if you are interested in participating in this study. If you are not interested, you can tell the assistant at this time. If you would prefer not to have the assistant call you at all, please call (416) 597-3422, extension 6301. Leave a message with our research coordinator, Lindsie Robertson, saying that you would prefer not to be contacted. Alternatively, you can also e-mail robertson.lindsie@torontorehab.on.ca.

It is important for us to know if people who participate in the study are very different from people who choose not to participate. If you choose not to participate, the research assistant will ask you if you mind answering a few brief questions, such as your age or

whether you have ever broken a bone before. Your name will not be stored with this information. You can choose not to answer these questions if you wish.

If you decide to participate in the study, all information you provide will be confidential. Your name will not appear on any forms. You can stop participating at any time without having to give a reason. A decision not to volunteer or to withdraw from the study after you have enrolled will not have any impact on the care you receive at Lyndhurst. If you have any questions about the study you can contact Lindsie Robertson at the number listed above or Dr. Cathy Craven at (416) 597-3422 extension 6122.

Your contribution to this research will help us better understand who is at risk for bone loss and broken bones. We eventually want to understand better ways to diagnose and prevent broken bones among people with spinal cord injury. Thank you for your consideration.

Sincerely,

insert physician name here

This study has been reviewed and received ethics clearance through the Office of Research Ethics at the University of Waterloo, the Research Ethics Board at the Toronto Rehabilitation Institute and the Research Ethics Board of Hamilton Health Sciences/McMaster University Faculty of Health Sciences.. If you have any questions regarding your rights as a research participant, you may contact: Dr. Gaetan Tardif, Research Ethics Board at (416) 597-3422 x 3730 or Dr. Susan Sykes University of Waterloo Research Ethics Board at 519-888-4567, x 36005, ssykes@uwaterloo.ca or Office of the Chair of Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board at (905) 521- 2100 x42013.

Toronto Rehab
Everything Humanly Possible

Lyndhurst Centre
520 Sutherland Drive
Toronto, Ontario M4G 3V9

Tel: 416-597-3422
www.torontorehab.com

Insert patient label here

RESEARCH: **Bone Quality in Individuals with Chronic Spinal Cord Injury**

Background: A cohort of 80 adult men and women, with traumatic SCI, two years post-injury, will be established. Data collected will include: medical history; bone density (BMD) and body composition; tibia volumetric BMD, bone geometry, muscle area and trabecular structure; and x-ray reports to verify fractures (if any). Data will be collected at 6 month intervals over a 24 month period. This research will form the basis for studies of bone quality and fractures in the SCI population.

Patient has verbally consented to the above personal health information being forwarded to a research team member and being approached with more information about the study

☐ **YES**

☐ **NO**

If no, is patient agreeable to completing a refusal questionnaire by phone?

☐ **YES**

☐ **NO**

Please forward to Lindsie Blencowe (x6301, room 206-D)

Thanks!

_____

Date Signature of Physician

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Telephone Screening Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐

Y Y Y Y M M D D

Gender: ☐ M ☐ F

	Inclusion Criteria	Yes	No	Comments
1.	Participant is ≥18 years of age	☐	☐	
2.	Participant is able to understand instructions in English.	☐	☐	
3.	"What is the level of your spinal cord injury?" Potential participant has a level of injury at or between C2 and T12	☐	☐	*Insert Level of Injury* ☐☐☐
4.	"What was the cause of your spinal cord injury?" Potential participant has a neurological impairment secondary to a spinal cord injury of sudden onset (<24 hours onset).	☐	☐	*Insert Cause of Injury*
5.	"When did you have your spinal cord injury?" Potential participant's spinal cord injury occurred at least 24 months prior to screening.	☐	☐	Date of Injury: ☐☐☐☐/☐☐/☐☐ Y Y Y Y M M D D
6.	"Do you know if you have or have had any conditions that might affect your bones, such as cancer or liver disease?" Potential participant has no secondary causes of osteoporosis.	☐	☐	
7.0	"Are you willing to attend three visits to Lyndhurst and three visits to McMaster University over the course of two years?" Potential participant is willing to attend 3 visits to Lyndhurst & McMaster.	☐	☐	

If potential participant is eligible for the study, arrange for a visit to Lyndhurst to complete information and consent form and first testing visit (if consent is provided).

Primary Investigators:
Dr. Lora Giangregorio
Dr. Catharine B. Craven

Co-investigators:
Dr. A. Papaioannou
Dr. M. Popovic
Dr. L. Thabane
Dr. N. McCartney
Dr. J.D. Adachi

Bone quality in individuals with chronic spinal cord injury

Lyndhurst Centre 520 Sutherland Drive Toronto, Ontario M4G3V9

Participant Information Sheet and Consent Form

Title of Study: Bone Quality in Individuals with Chronic Spinal Cord Injury
Primary Investigators: Dr. Lora Giangregorio and Dr. Catharine B. Craven
Co-investigators: Dr. Papaioannou, Dr. Popovic, Dr. Thabane, Dr. McCartney, and Dr. Adachi
Student Investigators: Kayla Hummel, Deena Lala, and Julia Totosy de Zepetnek, Dept. of Kinesiology, University of Waterloo
Sponsor: Canadian Institutes of Health Research, Ontario Neurotrauma Foundation, and SCI Solutions Network

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You are being invited to participate in a research study. To decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign the form at the end of this information letter if you wish to participate. If you are not able to sign the form but are able to provide verbal consent, it will be documented by the person obtaining consent. Please take your time to make your decision. Feel free to discuss it with your friends and family, or your family physician.

WHY IS THIS RESEARCH BEING DONE?

Individuals with spinal cord injury (SCI) often experience bone loss. Bone loss can cause a person to be more likely to break a bone in the future. We are conducting this study to examine in more detail the bone loss that occurs after SCI.

WHAT WILL I BE ASKED TO DO IF I DECIDE TO TAKE PART IN THE STUDY?

This study will require 10-15 hours of your time over a 2 year period.
This study is being conducted at multiple sites. You may participate at Lyndhurst Hosptial (Toronto) OR Chedoke Hospital (Hamilton) – whichever is most convenient for you.

If you decide to participate in the study, we will ask you to do the following things:
Visit to Lyndhurst or Chedoke

- Complete a medical history that asks questions about your injury characteristics as well as your past and current medical health, medications and lifestyle. You may be asked to have an ASIA exam, which tests your sense of touch and your sense of movement, if we do not have record of an exam for you. This will take approximately 45 minutes.
- On your first visit to Lyndhurst, you will be asked to provide a blood sample. Fasting conditions will be required. Participants will be asked to fast for at least 12 hours. For those participants unable to fast, a breakfast of toast and apple juice or orange juice will be allowed and blood will be drawn 4 hours after. The blood sample will be used to measure protein markers of bone metabolism, vitamin D, parathyroid hormone (PTH), and ionized calcium levels in your blood. The blood sample will be draw by a trained phlebotomist. We will take about two tablespoons of blood by inserting a needle in a vein in your arm.
- Participate in 1 set of 6 bone density scans. Bone density scans are x-rays that measure how much bone mineral you have in certain bones. Individuals with low amounts of bone mineral may be at increased risk of fracture. The scans will be taken of your hips, above and below your knee, your spine and your whole body. During the scans you will be transferred to a scanning table. If you are not able to transfer yourself, we will use a special lift device. You will not feel anything when the scanner is on. The scanning will take approximately 60 minutes.
- Complete some questionnaires by phone three days after your visit. The questionnaires will gather information regarding your activity and diet. This telephone call will last approximately 30 minutes.

Visit to McMaster

- Participate in a second visit at McMaster University Medical Centre for a second type of bone density scan. The scanner is called a peripheral

quantitative computed tomography scanner and also uses x-rays to measure bone density. During this visit, you will be asked to participate in 1 set of 3 scans that measure the shape and structure of your bones. A researcher will take 3 scans, one at your ankle, the second at mid-calf and the third at the widest cross-section of your calf. During the scans the limb being measured will be placed in a positioning device. Please refer to the pictures we have provided. We will conduct the scans while you are seated in a chair or wheelchair. You will not feel anything when the scanner is on. This visit will take 45 minutes.

Yearly Follow-up for 2 years

- You will be asked to return annually for the next two years to repeat the medical history, bone density scans, and scans at McMaster. You will be called at 6 and 18 months during the two year study to monitor any changes in your health, medication and record if you have had any fractures. You will also be asked to report any broken bones to the study coordinator over the two-year period when they occur. These phone calls will take approximately 30 minutes or less.

If you have severe spasticity: During the scans at McMaster, it may be difficult for the technologist to position you if you have lower body muscle spasms. **Only if you have severe lower body muscle spasms**, you will be asked to take a small dose of Lorazepam (otherwise known as Ativan, dose is 0.5-1.0 mg below the tongue) to prevent spasms while the scan is taking place. **If you do not have severe spasticity, you will not need to take Lorazepam.** Lorazepam is a short acting muscle relaxant that reduces muscle spasms. Many people with SCI have taken Lorazepam early after their injury to help with sleeping while in hospital. Adverse reactions to Lorazepam, when they occur, are usually observed at the beginning of the dose and generally decrease in severity or disappear after 2-3 hours. If you become very drowsy with Lorazepam, you may not remember having the pQCT scan. If needed, the Lorazepam will be prescribed for you by Dr. Craven on the day of your scan. These precautions are taken mainly to reduce the chance of injury in the event that a spasm occurs when your leg is placed in the scanning device. **You do not have to agree to take Lorazepam if you do not wish to do so.** However, we may decide not to try to scan you if the spasticity limits our ability to position you safely. If you have metal implants in both lower legs, have broken your shinbones in the past, or have severe leg spasms and are allergic to Lorazepam, you will not be able to participate in the study. Also, women who may be pregnant or who plan on becoming pregnant

cannot participate. If you are a woman, a urine pregnancy test may be performed to ensure that it is safe for you to participate.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

The risks to participants are small. Bone Density scans involve exposure to small amounts of radiation. The level of exposure associated with the scans proposed in this study is ~30 μSv, which is less than doses received during a computed tomography (CT) scan of the chest (30-60μSv) or annually from background radiation (2500 μSv). The radiation dose is roughly equal to the dose of radiation received over 3 days by every Canadian from natural sources of radiation in the environment. Repeated exposure to radiation has a cumulative risk over time but the radiation risk from participating in this study considered minimal.

If you are asked to take Lorazepam to reduce your leg spasms during scans in Hamilton, there is a risk of side effects. Amongst a study of 3500 people, the most common side effects were sedation (15.9%), dizziness (6.9%), weakness (4.2%) and unsteadiness walking (3.4%). Less frequent side effects include disorientation, depression, nausea, change in appetite, headache and agitation. Most side effects, if they occur, occur with the first dose of the drug. Lorazepam will only be given to you if necessary. If you need Lorazepam, it will provided to you at no cost. After taking Lorazepam, the study staff will monitor you for an hour or so, to make sure you have not had any side effects. A physician will be available for supervision. You should not drive or perform other tasks that require alertness immediately after taking Lorazepam. Also, you cannot take Lorazepam if you are currently taking the fungal medications ketoconazole (Nizoral or Xolegel) or itraconazole (Sporanox).

Women who may be pregnant or who plan on becoming pregnant cannot participate in the study as there are risks to exposing a fetus or unborn baby to ionizing radiation.

Fasting blood draws can also have side effects and discomforts. Fasting may cause hunger, headache, dizziness and/or weakness. As a result of the blood draw, there is a possibility that you may experience pain, bruising, bleeding or infection at the site of the needle puncture. Blood draws may also temporarily cause headache, nausea and lightheadedness.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

80 individuals with SCI will be recruited to participate.

WHAT ARE THE POSSIBLE BENEFITS OF THE STUDY FOR ME AND/OR SOCIETY?

We cannot promise any personal benefits to you from your participation in the study. If you are interested in learning what your bone density is, we can send your bone density scan results to your physician. The study will help us understand bone loss in individuals with SCI, and determine risk factors related to bone loss in SCI.

CONFIDENTIALITY AND SECURITY OF DATA

Your data will not be shared with anyone except with your consent or as required by law. All personal information will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The data will be securely stored in a locked office. For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Office of Research Ethics at the University of Waterloo, Hamilton Health Sciences Research Ethics Board or Toronto Rehab Research Ethics Board may consult your research data and medical records. However, no records that identify you by name or initials will be allowed to leave the hospital. By signing this consent form, you authorize such access. If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your specific consent to the disclosure. However, it is important to note that a copy of your signed consent form and the data that follows may be included in your health record. The data will be retained indefinitely.

CAN PARTICIPATION IN THE STUDY END EARLY?

If you volunteer to be in this study, you may withdraw at any time and this will in no way affect the quality of care you receive at this institution. You have the option of removing your data from the study. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which make it unsafe for you to continue participating and it is in your best interest to withdraw. You will also be informed in a timely manner of any new

information that arises during the course of the study that may influence your decision to participate.

WILL I BE PAID TO PARTICIPATE IN THIS STUDY?

You will receive a $40 honorarium to participate in the study. We will provide transportation for the study visits and you are welcome to have someone accompany you on the trip. For those wishing to use their own transportation for travel, we will reimburse the costs of parking and mileage ($0.50 per kilometer) associated with participating in the study.

WILL THERE BE ANY COSTS?

Your participation in this research project will not involve any additional costs to you or your health care insurer.

WHAT HAPPENS IF I HAVE A RESEARCH-RELATED INJURY?

If you are injured as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. However, if you sign this consent form it does not mean that you waive any legal rights you may have under the law, nor does it mean that you are releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?

If you have any questions about the research now or later, if you wish to withdraw from the study at any time or if you think you have a research-related injury, please contact the research coordinator for the study, Lindsie Robertson at (416) 597-3422 x6301, pager (416) 644-6936 or one of the study investigators below:
Dr. Craven (416)597-3422 x6122
Dr. Lora Giangregorio (519) 888-4567 x36357
Kayla Hummel via e-mail, khummel@uwaterloo.ca

This study has been reviewed and received ethics clearance through the Office of Research Ethics (ORE) at the University of Waterloo, the Research Ethics Board at the Toronto Rehabilitation Institute and the Research Ethics Board of

Hamilton Health Sciences/McMaster University Faculty of Health Sciences. If you have any questions regarding your rights as a research participant, you may contact any/all of the offices listed below:

Office of Research Ethics (ORE) at the University of Waterloo (519) 888-4567 x6005

Dr. Gaetan Tardif - Chair, Toronto Rehab Research Ethics Board (416) 597-3422 x 3730

Office of the Chair of Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board (905) 521- 2100 x42013

IF I DO NOT WANT TO TAKE PART IN THE STUDY

It is important for you to know that you can choose not to participate in the study. Your doctor can do tests to look at your bone density even if you do not participate in this study. Choosing not to participate will in no way affect the regular therapy or health care that you receive.

If do not want to participate, it is important for us to know if there are significant differences between people who choose to participate in our study and people who don't. We ask if you would mind answering 7 brief questions that will be used to determine if the group of people who did not participate are different than those who did. You can also choose not to answer these questions, it is entirely your decision. If you do not want the be in the study but might want to answer the questions, we will review them with you and let you decide. Neither your name or any identifying information will be used with this information.

CONSENT STATEMENT

SIGNATURE OF PARTICICIPANT/LEGALLY-AUTHORIZED REPRESENTATIVE

I have read the preceding information thoroughly. I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction. I agree to participate in this study. I understand that I will receive a signed copy of this form.

_____

Name of Participant

_____ _____

Signature of Participant Date

If verbal consent is obtained in lieu of a signature, the person obtaining consent will initial here: _____

Consent form administered and explained in person by:

I confirm that I have explained the nature and purpose of the study to the participant name above. I have answered all questions. I believe the participant has the legal capacity to give informed consent to participate in this research study.

_____

Name and title

_____ _____

Signature Date

SIGNATURE OF PRINCIPAL INVESTIGATOR:

I have delegated the informed consent discussion to _____

_____ _____

Signature of Principal Investigator Date

Access to Medical Charts

Title of Study: Bone Quality in Individuals with Chronic Spinal Cord Injury
Primary Investigators: Dr. Lora Giangregorio and Dr. Catharine B. Craven
Co-investigators: Dr. Papaioannou, Dr. Popovic, Dr. Thabane, Dr. McCartney and Dr. Adachi
Student Investigators: Kayla Hummel, Deena Lala, and Julia Totosy de Zepetnek, Dept. of Kinesiology, University of Waterloo
Sponsor: Canadian Institutes of Health Research, Ontario Neurotrauma Foundation, and SCI Solutions Network

We would like to access your medical chart to verify your medical history. We would like to confirm your ASIA classification to see if it has changed, check your surgical and medical history and see any bone density scans you have had. By signing below, you are giving your consent to allow the coordinator of the study and lead investigators to look at your chart. You have the right to choose not to have anyone look at your chart if that is your wish. The information collected from your chart will be used for research purposes only.

Consent to give access to chart at Toronto Rehab:

_____	_____	_____
Name	Signature	Date

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Past Medical History

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**

Y Y Y Y M M D D

Gender: ☐ Male ☐ Female	Date of Birth: ☐☐☐☐/☐☐/☐☐ Y Y Y Y M M D D
Date of injury/onset: ☐☐☐☐/☐☐/☐☐ Y Y Y Y M M D D	Time Post Injury: ☐☐☐ years
Level of Injury (e.g. T12, C06): ☐☐ ☐ ☐ N/A	Cause of injury : _____
ASIA Impairment (A-D): ☐	ASIA Total Motor Score: ☐☐☐ ASIA LEMS: ☐☐☐ ASIA Sensory Score: ☐☐☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

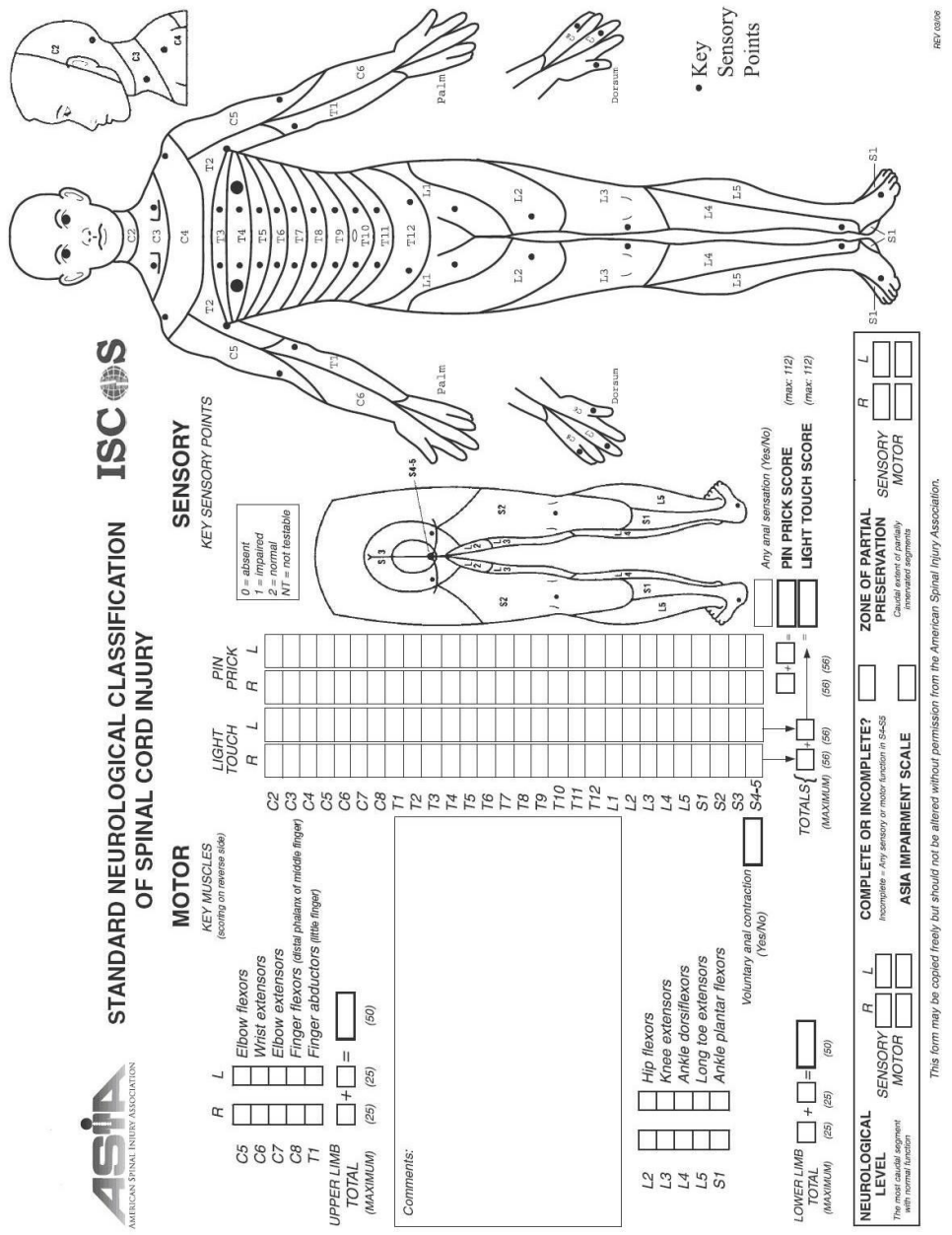
Participant ID | | | | | | |

Past Medical History

Date of Assessment | | | | | / | | | / | | |

Y Y Y Y M M D D

Visit **01**



Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID | | | | | | |

Past Medical History

Date of Assessment | | | | | / | | | / | | |
Y Y Y Y M M D D

Visit **01**

STEPS IN CLASSIFICATION

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete (sacral sparing).
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores* = **0** *AND any anal sensation* = **No**, *then injury is COMPLETE. Otherwise injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete?
NO → If **YES**, AIS=A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)

Is injury motor incomplete?
YES → If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)

Are at least half of the key muscles below the (single) neurological level graded 3 or better?
NO → AIS=C
YES → AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

ASIA IMPAIRMENT SCALE

☐ **A = Complete**: No motor or sensory function is preserved in the sacral segments S4-S5.

☐ **B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ **C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ **D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ **E = Normal:** Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

☐ Central Cord
☐ Brown-Sequard
☐ Anterior Cord
☐ Conus Medullaris
☐ Cauda Equina

MUSCLE GRADING

0 total paralysis
1 palpable or visible contraction
2 active movement, full range of motion, gravity eliminated
3 active movement, full range of motion, against gravity
4 active movement, full range of motion, against gravity and provides some resistance
5 active movement, full range of motion, against gravity and provides normal resistance
5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present
NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

Assessors Initials:____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**
Y Y Y Y M M D D

FRACTURES

HAVE YOU EVER BROKEN A BONE BEFORE? ☐ YES ☐ NO

IF **YES**, PLEASE COMPLETE THE FOLLOWING FOR EACH FRACTURE EVENT:

1. BONE FRACTURED:_____

WHEN IT OCCURRED: ☐☐☐☐/☐☐/☐☐ ☐ BEFORE SCI ☐ AFTER SCI
Y Y Y Y M M D D

HOW DID FRACTURE OCCUR?:
☐ TORSION ☐ LOW VELOCITY FALL ☐ ROM
☐ HYPERFLEXION ☐ TRANSFER ☐ OTHER *specify:*_____

FRACTURE VERIFIED BY MEDICAL RECORDS: ☐ YES ☐ NO

NOTES: _____
_____

_____
_____

2. BONE FRACTURED:_____

WHEN IT OCCURRED: ☐☐☐☐/☐☐/☐☐ ☐ BEFORE SCI ☐ AFTER SCI
Y Y Y Y M M D D

HOW DID FRACTURE OCCUR?:
☐ TORSION ☐ LOW VELOCITY FALL ☐ ROM
☐ HYPERFLEXION ☐ TRANSFER ☐ OTHER *specify:*_____

FRACTURE VERIFIED BY MEDICAL RECORDS: ☐ YES ☐ NO

NOTES: _____
_____
_____

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**
Y Y Y Y M M D D

3. BONE FRACTURED:_____

WHEN IT OCCURRED: ☐☐☐☐/☐☐/☐☐ ☐ BEFORE SCI ☐AFTER SCI
Y Y Y Y M M D D

HOW DID FRACTURE OCCUR?:
☐ TORSION ☐ LOW VELOCITY FALL ☐ ROM
☐HYPERFLEXION ☐TRANSFER ☐ OTHER *specify:*_____

FRACTURE VERIFIED BY MEDICAL RECORDS: ☐ YES ☐ NO

NOTES: _____
_____

_____
_____

4. BONE FRACTURED:_____

WHEN IT OCCURRED: ☐☐☐☐/☐☐/☐☐ ☐ BEFORE SCI ☐AFTER SCI
Y Y Y Y M M D D

HOW DID FRACTURE OCCUR?:
☐ TORSION ☐ LOW VELOCITY FALL ☐ ROM
☐HYPERFLEXION ☐TRANSFER ☐ OTHER *specify:*_____

FRACTURE VERIFIED BY MEDICAL RECORDS: ☐ YES ☐ NO

NOTES: _____
_____
_____

Additional sheets as needed

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**
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SUPPLEMENTS

HAVE YOU TAKEN CALCIUM OR VITAMIN D SUPPLEMENTS IN THE PAST?

Calcium Supplement ☐ Yes ☐ No ☐ Unknown If Yes, Mg per day: ☐☐☐☐

Type of Calcium Supplement : ☐ Calcium Carbonate ☐ Calcium Citrate ☐ Unknown

☐ Other (*Specify*): _____

Duration (months): ☐☐☐

Vitamin D ☐ Yes ☐ No ☐ Unknown

If Yes, (iu) per day: ☐☐☐☐ Duration (months): ☐☐☐

Multivitamin ☐ Yes ☐ No ☐ Unknown

Duration (months): ☐☐☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**
Y Y Y Y M M D D

BISPHOSPHONATES

HAVE YOU EVER BEEN PRESCRIBED A BISPHOSPHONATE?

Didrocal (Etidronate)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Fosamax (Alendronate)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Actonel (Risedronate)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Aredia (Zolendronate)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Bonefos/Clasteon/Ostac (Clodronate)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Skelid (Tiludronate)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Other: (*Specify*) _____	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Other: (*Specify*) _____	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**

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PAST MEDICATION ADVERSELY AFFECTING BONE DENSITY

HAVE YOU EVER BEEN PRESCRIBED ANY OF THE FOLLOWING?

Prednisone	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Tegretol or Dilantin	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Thyroid Medication	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Coumadin (Warfarin)	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Diuretic (Water Pill) (*Specify*): _____	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Oral Contraceptive (*Specify*): _____	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**

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Hormone Replacement	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Testosterone tablets or gel	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Miacalcin	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Other: (*Specify*): _____	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%
Other: (*Specify*): _____	☐ Yes ☐ No ☐ Unknown	If Yes, # months : ☐☐☐ Adherence : ☐ 0%-25% ☐ 26%-50% ☐ 51%-75% ☐ 76%-100%

-Assessors Initials:____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Past Medical History**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit **01**
Y Y Y Y M M D D

X-RAY - Post SCI of the hip or knee region:

Date: ☐☐☐☐/☐☐/☐☐ Anatomic Location :_____
Y Y Y Y M M D D

Any Fracture ☐ Yes ☐ No ☐ Unknown

If yes, Complete description of fracture location and type in the table below:

Fracture Location	Side	Fracture Type	Union	Time to Union
☐ Hip ☐ Mid shaft femur ☐ Distal Femur ☐ Proximal tibia ☐ Midshaft tibia ☐ Distal tibia ☐ Other _____	☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left	☐ Spiral ☐ Bending ☐ Stress/ Undisplaced Fracture ☐ Compound ☐ Other _____	☐ Yes ☐ No ☐ Unknown	☐☐ months
☐ Hip ☐ Mid shaft femur ☐ Distal Femur ☐ Proximal tibia ☐ Midshaft tibia ☐ Distal tibia ☐ Other _____	☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left	☐ Spiral ☐ Bending ☐ Stress/Undisplaced Fracture ☐ Compound ☐ Other _____	☐ Yes ☐ No ☐ Unknown	☐☐ months

Answer only if x-ray was done of the hip/ knee region:

Subluxation:	☐ Yes	☐ No	☐ Unknown
Dislocation:	☐ Yes	☐ No	☐ Unknown
Avascular Necrosis:	☐ Yes	☐ No	☐ Unknown
Heterotopic Ossification:	☐ Yes	☐ No	☐ Unknown
Prior Surgery:	☐ Yes	☐ No	☐ Unknown

Comments:_____
_____
_____

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Concurrent Medication

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit **01**

Drug			**Dates of Use (MM/YYYY is mandatory)**
Generic Name ____________________ Dose:_______________	Route ☐Oral ☐IV ☐IM ☐SC ☐Rectal ☐Topical ☐Other: ______ Indication:	Frequency ☐QD ☐BID ☐TID ☐QID ☐HS ☐PRN ☐Other:______	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y Stop Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
Generic Name ____________________ Dose:_______________	Route ☐Oral ☐IV ☐IM ☐SC ☐Rectal ☐Topical ☐Other: ______ Indication:	Frequency ☐QD ☐BID ☐TID ☐QID ☐HS ☐PRN ☐Other:______	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y Stop Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
Generic Name ____________________ Dose:_______________	Route ☐Oral ☐IV ☐IM ☐SC ☐Rectal ☐Topical ☐Other:______ Indication:	Frequency ☐QD ☐BID ☐TID ☐QID ☐HS ☐PRN ☐Other: ______	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y Stop Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y

Additional pages as required

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Health Demographics

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐
Y Y Y Y M M D D

HEIGHT: ☐☐☐.☐ cm ☐ Not Available	WEIGHT: ☐☐☐.☐ kg ☐ Not Available

WAIST CIRCUMFERENCE: ☐☐☐.☐ cm ☐ Not Available
(taken at lowest rib)

FEMALES ONLY:

ARE YOU PRE-MENOPAUSAL, PERI-MENOPAUSAL OR POST-MENOPAUSAL?
If they are unsure, skip to next question.
☐ PRE ☐ PERI ☐ POST

If they are pre- or peri-menopausal, or unsure ask: **HOW LONG AGO WAS YOUR LAST PERIOD?** (do not count periods that occurred while taking hormones)

☐ LESS THAN ONE YEAR ☐ 1-3 YRS
☐ 3-10 YRS ☐ MORE THAN 10 YEARS

If they are post-menopausal, ask: **WAS YOUR LAST PERIOD GREATER THAN 10 YEARS AGO?**
☐ NO ☐ YES

If NO, ask: **WAS YOUR LAST PERIOD LESS THAN 5 YEARS AGO?**
☐ NO ☐ YES

HAVE YOU EVER HAD A HYSTERECTOMY OR HAD BOTH YOUR OVARIES REMOVED OR RADIATED?
☐ NO ☐ YES: SPECIFY PROCEDURE, AND AGE WHEN PERFORMED

_____

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Health Demographics**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐
Y Y Y Y M M D D

DO YOU CURRENTLY SMOKE? ☐ YES ☐ NO #/DAY ☐☐☐

HAVE YOU EVER BEEN A SMOKER? ☐ YES ☐ NO

IF **YES TO ABOVE**, PLEASE WRITE DOWN WHEN THEY STARTED AND STOPPED SMOKING (YEAR). ALSO PLEASE INDICATE HOW MANY CIGARETTES PER DAY, ON AVERAGE. IF AMOUNT SMOKED VARIED OVER TIME, PLEASE DESCRIBE.

START ☐☐☐☐ STOP ☐☐☐☐ #/DAY ☐☐☐
Y Y Y Y **Y Y Y Y**

DO YOU CURRENTLY DRINK ALCOHOL? ☐ YES ☐ NO #/DAY ☐☐☐ ☐ n/a
BEER (bottles per week) ☐☐☐
WINE (glasses per week) ☐☐☐
LIQUOR (oz. per week) ☐☐☐

DO YOU HAVE A HISTORY OF ALCOHOL CONSUMPTION?
☐ YES ☐ NO #YEARS ☐☐☐ ☐ n/a
BEER (bottles per week) ☐☐☐
WINE (glasses per week) ☐☐☐
LIQUOR (oz. per week) ☐☐☐

CAGE

HAVE YOU EVER FELT YOU SHOULD CUT DOWN ON YOUR DRINKING?
☐ YES ☐ NO
HAVE PEOPLE ANNOYED YOU BY CRITICISING YOUR DRINKING?
☐ YES ☐ NO
HAVE YOUR EVERY FELT BAD OR GUILTY ABOUT YOUR DRINKING?
☐ YES ☐ NO
HAVE YOUR EVER HAD A DRINK FIRST THING IN THE MORNING TO STEADY YOUR NERVES OR GET RID OF A HANGOVER (EYE-OPENER)?
☐ YES ☐ NO

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Health Demographics**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐

Y Y Y Y M M D D

COMPLICATIONS

PLEASE INQUIRE IF THE PARTICIPANT HAS EXPERIENCED ANY OF THESE COMPLICATIONS IN THE PAST 3 MONTHS (CHECK ALL THAT APPLY):

☐ AUTONOMIC DYSREFLXIA ☐ BLADDER INFECTION
☐ PAIN ☐ DEEP VEIN THROMBOSIS
☐ PRESSURE SORE ☐ CONSTIPATION
☐ SPASTICITY ☐ HETEROTOPIC OSSIFICATION
☐ HEMORRHOIDS ☐ BLADDER/KIDNEY STONES
☐ INGROWN TOE NAIL ☐ DRUG ADDICTION
☐ GI BLEED ☐ NEUROLOGIC DETERIORATION
☐ LOW BLOOD PRESSURE ☐ GYNECOLOGICAL PROBLEMS
☐ SURGERY
☐ OTHER (SPECIFY)_____

DETAILS:

_____

_____

_____

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Current Health Status

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Neurological (Related to SCI)	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Other Neurological (not related to SCI	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Skin	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Current Health Status

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Head (Eyes, Ears, Nose, Throat)	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Respiratory	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Cardiovascular	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Gastrointestinal	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Current Health Status

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Endocrine/Metabolic	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Genitourinary/ Reproductive	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Blood/Lymphatic	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Musculoskeletal	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes, record details:			Ongoing at End of Study ☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐		**Current Health Status**
Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Y Y Y Y M M D D		Visit ☐☐ Phone Call ☐☐

Other, specify: ________________ –	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes,record details:			Ongoing at End of Study ☐

Other, specify: ________________ –	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes,record details:			Ongoing at End of Study ☐

Other, specify: ________________ –	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes,record details:			Ongoing at End of Study ☐

Other, specify: ________________ –	Medical History? ☐ Yes ☐ No	Start Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y	Resolution Date : ☐☐/☐☐/☐☐☐☐ D D M M Y Y Y Y
If yes,record details:			Ongoing at End of Study ☐

Additional pages as required

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Diseases/Conditions Affecting Bone Density**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐

Y Y Y Y M M D D

DISEASES/CONDITIONS AFFFECTING BONE DENSITY ACCRURAL

DISEASE/SYSTEM	HISTORY OF DISEASE	CURRENT DISEASE	DETAILS
CHEMOTHERAPY	☐ YES ☐ NO	☐ YES ☐ NO	
RADIOTHERAPY	☐ YES ☐ NO	☐ YES ☐ NO	
HYPOGONADISM	☐ YES ☐ NO	☐ YES ☐ NO	
THYROID DISEASE	☐ YES ☐ NO	☐ YES ☐ NO	
HYPERTHYROIDISM	☐ YES ☐ NO	☐ YES ☐ NO	
HYPOTHYROIDISM	☐ YES ☐ NO	☐ YES ☐ NO	
INFLAMMATORY BOWEL DISEASE	☐ YES ☐ NO	☐ YES ☐ NO	
HYPERPARATHYROIDISM	☐ YES ☐ NO	☐ YES ☐ NO	
MYELOMA	☐ YES ☐ NO	☐ YES ☐ NO	
VITAMIN D DEFICIENCY	☐ YES ☐ NO	☐ YES ☐ NO	
LIVER DISEASE	☐ YES ☐ NO	☐ YES ☐ NO	
RENAL FAILURE	☐ YES ☐ NO	☐ YES ☐ NO	
CANCER	☐ YES ☐ NO	☐ YES ☐ NO	
MUSCULOSKELETAL PROBLEMS (I.E. JOINT PROBLEMS, ARTHRITIS, CONTRACTURES)	☐ YES ☐ NO	☐ YES ☐ NO	
CARDIOVASCULAR DISEASE (OR FAMILY HISTORY)	☐ YES ☐ NO	☐ YES ☐ NO	
HIGH BLOOD PRESSURE	☐ YES ☐ NO	☐ YES ☐ NO	
HIGH CHOLESTEROL	☐ YES ☐ NO	☐ YES ☐ NO	
CHEST PAIN / ANGINA	☐ YES ☐ NO	☐ YES ☐ NO	
BRONCHITIS/PNEUMONIA	☐ YES ☐ NO	☐ YES ☐ NO	

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Diseases/Conditions Affecting Bone Density**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐

Y Y Y Y M M D D

OTHER DISEASES/CONDITIONS AFFECTING BONE DENSITY

DISEASE/SYSTEM	HISTORY OF DISEASE	CURRENT DISEASE
OTHER: _____	☐ YES ☐ NO	☐ YES ☐ NO
OTHER: _____	☐ YES ☐ NO	☐ YES ☐ NO
OTHER: _____	☐ YES ☐ NO	☐ YES ☐ NO

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Ascertainment Questionnaire

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

1. (a) Have you had any hospital admissions in the past six months which required an overnight stay? *(not in emergency)* ☐ (1) Yes ☐ (2) No (if no go to question 2)

(b) For what reason were you admitted to hospital? *(check all that apply)*

☐ (1) Heart Disease
☐ (2) Pressure Sores
☐ (3) Blood Clot
☐ (4) Cancer Treatment *specify:*_____
☐ (5) Bladder/Kidney Infection
☐ (6) Fracture *specify:*_____
☐ (7) Surgery *specify:*_____
☐ (8) Medical or Diagnostic Test *specify:*_____

2. (a) Have you broken one or more bones in the past six months?
☐ (1) Yes *-go to (b)* ☐ (2) No (If no, thank participant, questionnaire complete)

How many times have you fractured a bone in the last six months? ☐☐☐

Complete the following pages (one fracture incident form for each fracture)

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

Complete the following pages (one fracture incident form for each fracture)

What was the date of the fracture?

☐☐☐☐/☐☐/☐☐
Y Y Y Y M M D D

☐ Don't know

Which bone was broken?

☐ 1 Back (specify if available)_____		
☐ 2 Hip	☐ 1 Left	☐ 2 Right
☐ 3 Ribs/Sternum	☐ 1 Left	☐ 2 Right
☐ 4 Forearm/ Wrist	☐ 1 Left	☐ 2 Right
☐ 5 Pelvis		
☐ 6 Shoulder (upper arm)	☐ 1 Left	☐ 2 Right
☐ 7 Elbow	☐ 1 Left	☐ 2 Right
☐ 8 Hand	☐ 1 Left	☐ 2 Right
☐ 9 Finger(s)	☐ 1 Left	☐ 2 Right
☐ 10 Knee	☐ 1 Left	☐ 2 Right
☐ 11 Ankle	☐ 1 Left	☐ 2 Right
☐ 12 Foot	☐ 1 Left	☐ 2 Right
☐ 13 Upper Leg	☐ 1 Left	☐ 2 Right
☐ 14 Lower Leg	☐ 1 Left	☐ 2 Right
☐ 15 Toe(s)	☐ 1 Left	☐ 2 Right
☐ 16 Other (specify) _____	☐ 1 Left	☐ 2 Right ☐ 3 N/A

Based on the Interviewers discretion and participant history, was this an incident or fragility fracture?

☐ 1 Incident
☐ 2 Fragility

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

How did the fracture happen?

☐ 1 Fell out of bed or off a chair (from sitting position)
☐ 2 Fell climbing a chair or ladder
☐ 3 Fell on stairs
☐ 4 Motor vehicle accident
☐ 5 Sporting injury
☐ 6 Slipped or tripped inside the home
☐ 7 Slipped or tripped outside the home
☐ 8 Heavy object fell or struck body causing the fracture
☐ 9 Catching foot or ankle in doorway
☐ 10 Bone(s) broke with no fall or injury
☐ 11 Car Transfer
☐ 12 Other Transfer *specify:*_____
☐ 13 Unknown
☐ 14 Other (specify) _____

What time of day did the fracture occur?

☐ 1 Day (8am to 4pm) ☐ 2 Evening (4pm to midnight) 3 ☐Night (midnight to 8am)

Were X-rays of the fracture taken? ☐ 1 Yes ☐ 2 No ☐ 3 Don't know

If Yes or Don't know, obtain consent from participant to acquire the X-ray from health record

MAIL CONSENT FORM TO PARTICIPANT

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

Was the fracture treated by a physician? ☐ 1 Yes ☐ 2 No (go to question 9)

Where was the fracture first noticed? (Check all the apply)

☐ Hospital ☐ Physician's office
(go to question 10) (go to question 11)

☐ Home ☐ Other
(go to question 12) (go to question 12)

Where was the decision made on how to manage your fracture? (Check all the apply)

☐ Hospital ☐ Physician's office
(go to question 10) (go to question 11)

☐ Home ☐ Other
(go to question 12) (go to question 12)

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

10. IN HOSPITAL -

Date of Admission :
☐☐☐☐/☐☐/☐☐
Y Y Y Y M M D D

☐ Don't know

☐ 1 Emergency Clinic ☐ 2 Fracture Clinic ☐ 3 In-Patient → Length of stay ☐☐☐ days

Hospital Name _____ ☐ Don't know

Treating Doctor _____ ☐ Don't know

Treatment received ☐ 1 Surgery ☐ 2 Cast ☐ 3 Other (specify) _____

↓

☐ 1 Internal and or external fixation (pins, nails, screws)

☐ 2 Joint replacement

Where did you go when you left the hospital?

☐ 1 Home

☐ 2 Rehabilitation centre → What was the name? _____ Length of stay: ☐☐☐ days

☐ 3 Convalescent home ↗

☐ 4 Other (specify) _____

11. IN PHYSICIAN'S OFFICE Physician's name _____

Date of first visit: Total number of visits: ☐☐

☐☐☐☐/☐☐/☐☐
Y Y Y Y M M D D

Treatment received: ☐ 1 Cast ☐ 2 Other (specify) _____

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

12. As a consequence of your fracture, were you treated with Physiotherapy? ☐ 1 Yes ☐ 2 No

	# of visits	# of weeks
☐ in hospital	☐☐☐	☐☐☐
☐ in public rehabilitation centre	☐☐☐	☐☐☐
☐ in private convalescent centre	☐☐☐	☐☐☐
☐ community health centre	☐☐☐	☐☐☐
☐ private clinic	☐☐☐	☐☐☐
☐ at home from a private clinic	☐☐☐	☐☐☐
☐ in senior's home	☐☐☐	☐☐☐

As a consequence of your fracture were you visited by an occupational therapist?
☐ 1 Yes ☐ 2 No

If yes, hours per week ☐☐☐ # of weeks ☐☐☐

If subject has not yet returned home from inpatient stay, go to question 17

As a consequence of your fracture, were you visited at home by a nurse?
☐ 1 Yes ☐ 2 No

If yes, hours per week ☐☐☐ # of weeks ☐☐☐

As a consequence of your fracture, did you receive help from a homemaker? (meals on wheels, housekeeping, personal hygiene)
☐ 1 Yes ☐ 2 No

If yes, hours per week ☐☐☐ # of weeks ☐☐☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

As a consequence of your fracture, did you receive help from an attendant?
☐ 1 Yes ☐ 2 No
If yes, hours per week ☐☐☐ # of weeks ☐☐☐
As a consequence of your fracture, did you receive help from a family member or friend?
☐ 1 Yes ☐ 2 No↓
How many days did you receive help? ☐☐☐ days
Did this person have a paying job? ☐ 1 Yes ☐ 2 No
↓
How many days off work did this person take as a result of your fracture? _____ days

Since the fracture, have you temporarily given up any of your usual activities?
☐ 1 Yes ☐ 2 No If yes, specify:_____

Since the fracture, have you permanently given up any of your usual activities?
☐ 1 Yes ☐ 2 No If yes, specify:_____

Since the fracture do you go out: ☐ 1 Less often ☐ 2 The same ☐ 3 More often

Have you been told that your fracture is osteoporosis related?
☐ 1 Yes ☐ 2 No ☐ 3 Don't know

For each fracture incidence, complete the following X-ray Form

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Fracture Incident Form

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐
Y Y Y Y M M D D

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

Was the consent for medical records abstraction received?

☐ 1 **Yes** ☐ 2 **No**

X-ray Source: ☐ 1 Hospital ☐ 2 Physician's Office ☐ 3 Clinic

Any Fracture? ☐ 1 Yes ☐ 2 No ☐ 3 Unknown

If yes, complete description of fracture location and type in table below:

Fracture site identified by X-ray

Fracture Location	Side	Fracture Type
☐ Hip	☐ Right ☐ Left	☐ Spiral
☐ Mid shaft femur	☐ Right ☐ Left	☐ Bending
☐ Distal Femur	☐ Right ☐ Left	☐ Stress/Undisplaced Fracture
☐ Proximal tibia	☐ Right ☐ Left	☐ Compound
☐ Midshaft tibia	☐ Right ☐ Left	☐ Other
☐ Distal tibia	☐ Right ☐ Left	
☐ Other	☐ Right ☐ Left	
_____		_____

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **DXA**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐
Y Y Y Y M M D D

Site *(check if N/A)*		**BMC** *(g)*	**BMD** *(g/cm^2)*	**Z score**	**T score**
Whole Body	☐	☐☐☐☐.☐☐	☐.☐☐☐	☐ + ☐ - ☐.☐☐	☐ + ☐ - ☐.☐☐
Spine	☐	☐☐☐☐.☐☐	☐.☐☐☐	☐ + ☐ - ☐.☐☐	☐ + ☐ - ☐.☐☐
Hip ☐Right ☐Left	☐	☐☐☐☐.☐☐	☐.☐☐☐	☐ + ☐ - ☐.☐☐	☐ + ☐ - ☐.☐☐
Distal Femur ☐Right ☐Left	☐	☐☐☐☐.☐☐	☐.☐☐☐	☐ + ☐ - ☐.☐☐	☐ + ☐ - ☐.☐☐
Proximal Tibia ☐Right ☐Left	☐	☐☐☐☐.☐☐	☐.☐☐☐	☐ + ☐ - ☐.☐☐	☐ + ☐ - ☐.☐☐

Body Composition Data from Whole Body Scan

Fat-free soft tissue mass	Whole Body ☐☐☐☐.☐☐ kg	Legs ☐☐☐☐.☐☐ kg
Fat mass	Whole Body ☐☐☐☐.☐☐ kg	Legs ☐☐☐☐.☐☐ kg
Bone+FFST+Fat	Whole Body ☐☐☐☐.☐☐ kg	Legs ☐☐☐☐.☐☐ kg

Scans completed by (initials) ☐☐☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **pQCT**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐
Y Y Y Y M M D D

pQCT Participant #: ☐☐☐☐☐	Side: Right ☐ Left ☐	
Leg Length: ☐☐☐ mm	Voxel Size: ☐☐☐	Name of ROI:_____
Comments:_____		

4% CT ID: ☐☐☐	CONTMODE: ☐☐☐	PEELMODE: ☐☐☐	
Threshold 1 : ☐☐☐	Threshold 2 : ☐☐☐	Threshold 3 : ☐☐☐	
Total	BMC / 1mm slice: ☐☐☐.☐ mg/mm	BMD: ☐☐☐.☐ mg/cm^3	Area: ☐☐☐.☐ mm^2
Trabecular	BMC / 1mm slice: ☐☐☐.☐ mg/mm	BMD: ☐☐☐.☐ mg/cm^3	Area: ☐☐☐.☐ mm^2
Cortical Thickness: ☐☐☐.☐ mm	Mean Hole Size: ☐☐☐.☐ mm	Max. Hole Size: ☐☐☐.☐ mm	
Connectivity Index: ☐☐☐	# Nodes: ☐☐☐		

Scans completed by (initials) ☐☐☐

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **pQCT**

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Visit ☐☐
Y Y Y Y M M D D

38% CT ID: ☐☐☐	CONTMODE: ☐☐☐		PEELMODE: ☐☐☐
Threshold 1 : ☐☐☐	Threshold 2 : ☐☐☐		Threshold 3 : ☐☐☐
Total	BMC / 1mm slice: ☐☐☐.☐ mg/mm	BMD: ☐☐☐.☐ mg/cm^3	Area: ☐☐☐.☐ mm^2
Cortical & Sub-cortical	BMC / 1mm slice: ☐☐☐.☐ mg/mm	BMD: ☐☐☐.☐ mg/cm^3	Area: ☐☐☐.☐ mm^2
Cortical Thickness: ☐☐☐.☐ mm		Polar x-sectional MOI: ☐☐☐.☐ mm^4	
Connectivity Index: ☐☐☐	# Nodes: ☐☐☐		

66% CT ID: ☐☐☐	CONTMODE: ☐☐☐		PEELMODE: ☐☐☐
Threshold 1 : ☐☐☐	Threshold 2 : ☐☐☐		Threshold 3 : ☐☐☐
Total	BMC / 1mm slice: ☐☐☐.☐ mg/mm	BMD: ☐☐☐.☐ mg/cm^3	Area: ☐☐☐.☐ mm^2
Cortical & Sub-cortical	BMC / 1mm slice: ☐☐☐.☐ mg/mm	BMD: ☐☐☐.☐ mg/cm^3	Area: ☐☐☐.☐ mm^2
Cortical Thickness: ☐☐☐.☐ mm		Polar x-sectional MOI: ☐☐☐.☐ mm^4	
Connectivity Index: ☐☐☐	# Nodes: ☐☐☐		

Scans completed by (initials) ☐☐☐

Appendix B

1.Odds ratio and 95% CI analysis with pQCT scans with movement artefacts removed
2.Poisson regression analysis with pQCT scans with movement artefacts removed
3.Trabecular vBMD Values with Contour Thresholds 130mg/cm^3 and 280mg/cm^3

Odds ratio and 95% CI analysis with pQCT scans with movement artefacts removed

	Fractures (Unadjusted)		Fractures (Adjusted)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
aBMD-DF (mg/cm^2)	0.989 (0.981-0.997)	0.0099*	0.987 (0.976-0.998)	0.0224*
aBMD-PT (mg/cm^2)	0.986 (0.976-0.996)	0.0045*	0.985 (0.971-0.998)	0.0278*
vBMD (mg/cm^3)	0.963 (0.936-0.991)	0.0097*	0.968 (0.935-1.003)	0.0731
H_A	1.090 (1.010-1.176)	0.0268*	1.082 (0.999-1.172)	0.0521
CTh	0.308 (0.100-0.942)	0.0389*	0.381 (0.118-1.234)	0.1075
BR	1.452 (0.871-2.418)	0.1525	1.284 (0.755-2.183)	0.3562
CSMI (cm^4)	0.138 (0.027-0.709)	0.0177*	0.030 (0.001-0.678)	0.0276*
PMI (cm^4)	0.434 (0.197-0.958)	0.0388*	0.346 (0.122-0.983)	0.0463*

Notes: CI = confidence interval; OR = odds ratio; DF = distal femur; PT = proximal tibia
†adjusted for correlates of bone strength variables: aBMD at the distal femur and proximal tibia were adjusted for completeness of injury and bisphosphonate use; trabecular vBMD was adjusted for duration of injury and completeness of injury; H_A, CTh, and BR were adjusted for duration of injury; CSMI and PMI were adjusted for gender, completeness of injury, and bisphosphonate use.
**Statistically significant at alpha=0.05*

Poisson regression with pQCT scans with movement artefacts removed

	Change in log count	Upper 95% CI	Lower 95% CI	p-value
aBMD-DF (mg/cm^2)	-0.0066	-0.0096	-0.0036	<0.0001*
aBMD-PT (mg/cm^2)	-0.0064	-0.0092	-0.0036	<0.0001*
vBMD (mg/cm^3)	-0.0218	-0.0321	-0.0115	<0.0001*
H_A (mm^2)	0.0222	0.0136	0.0309	<0.0001*
CTh (mm)	-0.6920	-1.1730	-0.2110	0.0048*
BR	0.2056	-0.0362	0.4474	0.0957
CSMI (cm^4)	-1.1279	-1.6048	-0.6509	<0.0001*
PMI (cm^4)	-0.5537	-0.9048	-0.2027	0.0020*

Notes: CI = confidence interval; DF = distal femur; PT = proximal tibia
**Statistically significant at alpha=0.05*

Trabecular vBMD Values with Contour Thresholds 130mg/cm^3 and 280mg/cm^3

	Contour threshold 280mg/cm^3 (mg/cm^3)	Contour threshold of 130mg/cm^3 (mg/cm^3)	Difference (130mg/cm^3-280mg/cm^3) (mg/cm^3)
1	218.7	218.9	0.2
2	230.9	232.1	1.2
3	223.6	225.0	1.4
4	256.9	257.9	1.0
5	258.1	258.5	0.4
6	179.9	180.0	0.1
7	229.2	230.4	1.2
8	208.8	211.0	2.2
9	229.5	228.2	1.3
10	221.5	223.0	1.5
11	223.7	225.0	1.3
12	253.1	254.2	1.1
13	258.5	259.4	0.9
14	260.2	260.0	-0.2
15	191.5	193.6	2.1