Vitamin D, Parathyroid Hormone and Bone Quality in Persons with Chronic Spinal Cord Injury

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: Following spinal cord injury (SCI) dramatic declines in sub-lesional bone mineral density (BMD) and deterioration of bone microarchitecture occur, and are associated with a high prevalence of fractures. Conventional risk factors for osteoporosis diagnosis in the non-SCI population put all individuals with SCI at a high risk of fracturing, however not all experience fractures. Vitamin D and parathyroid hormone (PTH) levels have been linked to skeletal health in the non-SCI population, and therefore may be a modifiable risk factor worth targeting to prevent bone loss post-SCI.

Objectives: To evaluate: 1) the prevalence of suboptimal vitamin D (Serum 25(OH)D <75nmol/L) status and identify the relationships between 25(OH)D and bone quality; and 2) the prevalence of secondary hyperparathyroidism (Serum intact PTH ≥ 7.0 pmol/L) and identify the relationships between serum PTH and bone quality, in males and females with chronic SCI.

Methods: Individuals were assessed via cross-sectional study design. Serum 25(OH)D was measured using a chemiluminescent immunoassay and serum intact PTH was measured using an electrochemiluminescent immunoassay. Bone quality parameters evaluated include: 1) DXA assessed distal femur and proximal tibia aBMD; and 2) pQCT assessed vBMD at the 4% tibia trabecular and 66% tibia cortical sites, and 66% tibia cortical thickness. Correlates of suboptimal vitamin D status were identified through univariate logistic regression analaysis. Pearson correlations were run to assess the relationships between the serum measures and the bone quality outcomes. Significance was $p<0.05$.

Results: Thirty-eight percent of the included 45 adult males and females with chronic SCI had suboptimal serum 25(OH)D levels. Additionally, those with vitamin D assessed in the winter months (OR=6.3, p=0.022), not taking calcium supplements (OR=7.1, p=0.038), not taking

vitamin D supplements (OR=10.5, p=0.049), and of younger age (OR=0.92, p=0.038) were associated with suboptimal vitamin D levels. A weak, non-significant association was observed between PTH and serum 25(OH)D (r=-0.327, p=0.068) and there was a trend towards an inverse association between PTH and 66% tibia cortical thickness (r=-0.353, p=0.071).

Conclusions: Many individuals with chronic SCI have suboptimal serum 25(OH)D levels, particularly in the winter months. Disruption of the vitamin D-PTH axis may contribute to the bone loss seen in the chronic SCI population, particularly in cortical bone. Optimal serum 25(OH)D levels in the chronic SCI population may be higher than in the non-SCI population. This exploratory corrrelational study provides a framework for evaluation of relationships between 25(OH)D and bone quality in a larger cohort, adjusting for factors known to influence these outcomes in the SCI population.

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TABLE OF CONTENTS

1.0.0. BACKGROUND

1.0.1 SUMMARY

In the years following SCI, individuals develop many secondary health complications. To ensure quality of life for those living with SCI, it is important to manage complications such that maximum independence resumes. Following SCI extensive bone loss occurs, leaving individuals highly susceptible to fracturing. Fractures, for the SCI population, may require hospitalization resulting in further immobility and increased attendant care needs. Severe bone loss in those with SCI is particularly evident at sub-lesional levels and has been thought to be primarily a result of unloading; however other mechanisms have also been postulated. Current WHO guidelines for diagnosing osteoporosis in the non-SCI population are unsuitable for diagnosis in the SCI population; it does not allow for risk stratification, or for the ability to target treatments specifically. Potential fracture risk factors in persons with SCI include: injury completeness, alcohol consumption, increasing age and longer time post injury, low knee region aBMD and trabecular vBMD, low cortical vBMD, and low serum vitamin D and secondary hyperparathyroidism. Vitamin D, which primarily maintains serum calcium and phosphorus homeostasis, has been strongly linked to skeletal health in the non-SCI population, and therefore may be a modifiable risk factor worth targeting in those with chronic SCI. Based on the limited evidence to date, the prevalence of suboptimal vitamin D status and secondary hyperparathyroidism in the SCI population cannot be determined. Furthermore, the relationship between vitamin D status and bone quality in individuals with SCI is not clear. Ultimately, identification of the relationship between vitamin D status and bone quality in individuals with SCI could aid in the development of a fracture risk assessment tool specific to persons with SCI, thereby providing more optimal treatment strategies for bone loss in this population.

1.1.0. INTRODUCTION

The number of Canadian's living with a spinal cord injury (SCI) has been estimated to be greater than 36 000, with approximately 1100 new SCI's occurring every year (1). The most commonly reported causes of SCI are trauma related, and include: motor vehicle accidents, sports injuries, and falls (1). Greater than 80% of injuries occur in people under the age of 35 years, and on average 80% of newly injured individuals are male (1). With the available expertise and advances in medical care, many who experience a traumatic SCI will live a normal lifespan, and, depending on the severity, will cost the Canadian Health Care system between 1.25 and 25 million dollars each, over the course of their lifetime (1). It is necessary for continual progression in research on the management of the secondary complications which will burden those with an SCI for their entire lives. Body composition changes following SCI are suggested to increase risk of developing diseases including: coronary heart disease (2), diabetes mellitus (3), and osteoporosis (4; 5; 6); all of which affect quality of life. Changes in body composition that occur following SCI include: increased fat mass; muscle atrophy; and severe bone loss, particularly below the level of the lesion (7). Preventing complications associated with body composition changes secondary to SCI will help provide a better quality of life for those living with an SCI.

The international standard for classification of a SCI includes the neurological level and severity of the injury as well as the American Spinal Cord Injury Association Impairment Scale (AIS) motor and sensory scores. Injuries are described based on the pattern and severity of motor and sensory fibre involvement. An AIS score of A indicates no preservation of motor or sensory fibres below the level of injury; where as a score of B indicates sensory preservation but no motor fibre preservation below the level of the injury. In other words both AIS scores of A and B are indicative of a motor complete injury. An AIS score of C or D means the injury is incomplete; that is, there is some motor preservation below the level of injury. Depending on the

amount of motor control preserved according to the motor scores for key muscle groups, individuals are classified differently; those with less motor control are given a score of C and those with more motor control are given a score of D. A score of E indicates normal motor and sensory function below the level of the injury. The neurological level of injury, whether they are paraplegic or tetraplegic and the AIS classification contribute to the type and severity of the secondary health complications after SCI.

1.2.0. SPINAL CORD INJURY AND BONE HEALTH

1.2.1. THE BURDEN OF FRACTURES POST-SCI

Osteoporosis is a skeletal system disease characterized by low bone mass and compromised structural integrity of bone, resulting in an increased risk of fracture (8). The World Health Organization (WHO) defines osteoporosis as an areal bone mineral density (aBMD) 2.5 standard deviations or more below that of the young adult mean (9). Of 41 males with SCI assessed, Lazo and colleagues (10) showed that 61% met the WHO criteria for osteoporosis, and 19.5% were said to be osteopenic. More recently, in a cohort of 132 males with SCI, about 82% were diagnosed osteoporotic as defined by the WHO (11). Current guidelines for assessing osteoporosis and a ten-year fracture risk incorporate factors such as: femoral neck aBMD, glucocorticoid use, body mass index, alcohol consumption, smoking, secondary osteoporosis, as well as others (12). Many of the factors associated with declining bone health in the non-SCI population may not associate the same way in those with an SCI. For example, aBMD at the femoral neck in the SCI population is not measured because of technical artefacts such as contractures. Further, having an SCI is a cause of secondary osteoporosis, immediately increasing the ten-year fracture risk in those individuals. Therefore, the osteoporosis assessment

strategies used in the non-SCI population are not appropriate to predict fracture risk in the SCI population.

Bone loss following SCI is of particular concern because of the high incidence of fragility, low trauma related, fractures in the lower limbs experienced in this population (13; 14). Fracture occurrence in individuals with SCI was identified as double that of the non-SCI population, with 19% of fractures classified as fragility in the SCI population, versus 1.4% classified as fragility in the non-SCI population (15). Furthermore, 25-34% of individuals with SCI have been reported to have sustained at least one fracture in the lower extremity during the time since their SCI (10; 13). Fractures in individuals with SCI often require hospitalization, resulting in further immobility, and greatly affect their quality of life. In the SCI population, the most frequent sites of fracture are the distal femur and proximal tibia (13; 16; 17), which are also the most commonly reported fracture sites requiring hospitalization (14). It is also noted that generally fractures above the knee joint line often requires open-reduction internal fixation versus fractures below the knee joint line which can often be treated with conventional casting (18). Common causes of fractures in the SCI population include falling from a wheelchair, transferring, and catching a foot or bumping into objects while manoeuvring a wheelchair (14; 13); all low trauma related, and occur during activities of daily living. With so many individuals with SCI diagnosed with osteoporosis, it is necessary to identify SCI-specific risk factors that distinguish those who will experience fractures from those who will not, in order to provide the most effective treatment and thereby reducing fracture occurrence.

1.2.2. WHY FRACTURES OCCUR POST-SCI

Sub-lesional declines in bone mass are well established complications following SCI. Acute aBMD losses in the lower limbs range from 20-32% (4; 6; 19). Similarly, a decrease in aBMD in the lower limbs from 10-25% is reported to occur within the first year of injury (5; 20). It has been previously suggested that aBMD reaches a steady state 1-2 years post injury (4), however few prospective studies have been done to verify this theory. One 3-year prospective study showed a 50% decrease in bone mineral content to occur in the lower limbs post SCI, suggesting that perhaps a steady state is not established at 2 years post injury, and bone loss continues to occur (21). Furthermore, the annual percent aBMD lost at the proximal tibia and distal femur in individuals with chronic SCI has been reported to be 1.5% and 1.1%, respectively (22).

It is suggested that epiphysis trabecular bone mass loss occurs earlier, and to a greater extent, than diaphysis cortical bone mass loss, however cortical thinning has also been shown to be significant in the SCI population (23). Trabecular volumetric bone mineral density (vBMD) in the tibia has been shown to decrease 5% at 6 months post-injury and 15% at 12 months post-injury, whereas cortical vBMD only decreased 7% at one year post-injury (24). More recently, Eser and colleagues (23) reported that in individuals with chronic SCI, trabecular vBMD decreased by 73% and 54% in the tibia and femur, respectively; and cortical thickness decreased by 33% and 35% in the tibia and femur, respectively. Additionally, Eser and colleagues (13) established a distal tibia trabecular vBMD fracture threshold of 72 mg/cm^3, reporting about 33% of individuals with SCI to have lower limb vBMD values below this fracture threshold, and suggested lower limb trabecular vBMD to be the most sensitive measure to identify individuals with SCI at high risk of fracturing.

1.2.3. FACTORS CONTRIBUTING TO SUB-LESIONAL BONE LOSS POST-SCI

Osteoporosis following SCI is considered to be caused by disuse and resultant unbalanced osteoblast and osteoclast activity. Normally, mechanical loading on bone tissue increases the amount of osteoblast activity, strengthening bones in regions of high stress, and reducing bone turnover and bone loss. Unloading, as occurs in SCI, is suggested to suppress osteoblast cells and induce osteoclast cell activation, leading to bone loss (25). Loss of muscle force post SCI has also been suggested to contribute to bone demineralization at rates as high as 4% per month (20). However, studies have reported no changes in BMD following the implementation of weight-bearing activities in groups with disuse osteoporosis (26; 27); suggesting that unloading may not be the only factor influencing the pathogenesis of osteoporosis in the SCI population. In the non-SCI older population, vitamin D was demonstrated to positively associate with cortical vBMD, and parathyroid hormone (PTH) was inversely associated with cortical vBMD (28); implicating vitamin D as a modifiable risk factor associated with bone loss. Bauman and colleagues (29) demonstrated mild secondary hyperparathyroidism to be present in a group of individuals with chronic SCI and low serum 25(OH)D levels. Acknowledging the role vitamin D plays in maintaining serum calcium and phosphorus homeostasis, along with the relationship existing between vitamin D and osteoporosis in non-SCI populations (30), both vitamin D and secondary hyperparathyroidism have been identified as potential contributors to the development of osteoporosis post-SCI (31). Although disuse is justified as a major contributor to bone loss following SCI, identification of fracture risk factors involved in the pathogenesis of osteoporosis after injury should be considered to appropriately identify those at highest risk of fracturing.

1.2.4. OSTEOPOROSIS MANAGEMENT POST-SCI

Several strategies have been evaluated for the management of osteoporosis in individuals with SCI, including: anti-resorptive drugs, lower limb loading, and lower limb electrical stimulation. Anti-resorptive drugs, also known as bisphosphonates, act to slow down osteoclastic reabsorption of bones, through induction of apoposis. When treated weekly for 12 months with 70mg of alendronate, an oral bisphosphonate, declining aBMD acutely following SCI was attenuated (32). Pearson and colleagues (33) demonstrated lower limb aBMD preservation when individuals were treated with 800mg of the bisphosphonate etidronate, daily for 30 weeks; these results were however, only in a group of participants with an incomplete impairment who returned to walking within 3 months of their injury. The intervention of lower limb loading has also been tested for its affect on the declining BMD following SCI. Giangregorio and colleagues (27) showed no significant changes from baseline in peripheral BMD following 12 months of 3x/week body-weight-supported treadmill training. In contrast, individuals with SCI who performed daily standing for greater than 1 hour and at least 5x/week, demonstrated higher BMD in the lower extremities after 2 years (34). In addition, Chen and colleagues (35) evaluated the effect of functional electrical stimulation cycle ergometry on bone health after SCI and showed that after 6 months of 5x/week training, BMD at the distal femur and proximal tibia region increased significantly. Morse and colleagues (36) identified, in clinicians treating individuals with SCI, that only 40% of clinicians prescribe bisphosphonates, and about 50% prescribe vitamin D to their patients; and that lack of osteoporosis treatment following SCI is because there are no standardized protocols for diagnosing and evaluating the extent of bone loss. Although strategies have been evaluated with regards to preventing bone loss following SCI, there are no clinical guidelines for implementing them.

1.2.5. DIAGNOSING INCREASED RISK OF FRACTURES POST-SCI

The WHO has criteria for diagnosing osteoporosis in the non-SCI population, using aBMD measured from dual energy x-ray absorptiometry (DXA) (9). Until recently, the clinical diagnosis of osteoporosis based only on aBMD from DXA scans has been the gold standard. In the non-SCI population, DXA scans are generally taken of the hip, the wrist and the spine, sites where there are available reference data for comparison. Diagnosing the degree of bone loss is based upon the number of standard deviations away from young normal aBMD values in the reference database. More recently there has been a shift toward using aBMD along with other important risk factors to clinically diagnose osteoporosis and determine a 10-year fracture risk. Risk factors pertaining to the non-SCI population include: glucocorticoid treatment and previous fragility fractures (37). The methods of diagnosing osteoporosis and fracture risk in the general population cannot be applied to individuals with SCI because all would be considered at an increased risk of fracturing; it does not allow for risk stratification or the ability to target those at highest risk (10). Although fracture risk factors for individuals with SCI have been identified, they have not been validated in prospective studies, and there is no standard protocol for including them in osteoporosis assessment; as such, these risk factors are not used by clinicians (36). Craven and colleagues (38) have suggested a paradigm for clinical assessment of osteoporosis following SCI, which includes risk factors specific to the SCI population. Fracture risk factors suggested for the SCI population include: injury completeness (14; 39), >5 alcoholic beverages consumed per day (14), increasing age and longer time post-injury (16; 39), knee region aBMD <0.78 g/cm^2 (16), trabecular vBMD in tibia <72 g/cm^3 and in the femur <114 g/cm^3 (13), and low cortical vBMD (40). Other potential risk factors suggested to target in an osteoporosis diagnosing regimen in individuals with SCI are assessment of serum vitamin D and

parathyroid hormone (PTH) levels, however these have not yet been well evaluated (41). Although bone loss following SCI is well established, risk factors may be able to distinguish between individuals with SCI who fracture from those who do not fracture. Furthermore, if modifiable risk factors could be identified, more informed treatment strategies could be implemented. Vitamin D deficiency and secondary hyperparathyroidism have been reported to be prevalent in SCI and should be considered as a potential modifiable risk factor worth targeting in the SCI population.

1.3.0. VITAMIN D AND BONE HEALTH

1.3.1. VITAMIN D METABOLISM

Vitamin D is a vital hormone for the musculoskeletal system to maintain calcium homeostasis and has been implicated as a factor affecting bone health (42). Refer to Figure 1 (Appendix B) for an illustration of the following description of vitamin D metabolism, which was also explained by Holick (43). Vitamin D can be acquired by the human body via two mechanisms: through cutaneous synthesis with UVB exposure, and through ingestion as part of one's diet or by supplementation. Synthesis in the skin is the primary method through which the body acquires necessary vitamin D; it is also attained through diet mainly from fatty fish sources such as salmon, as well as fortified milks and cereals. Whether vitamin D is synthesized in the skin or ingested, it is in an inactive state. Cutaneous synthesis of vitamin D involves UVB radiation interaction with 7-dehydrocholesterol in the skin to form pre-vitamin D_3, which then through a heat-dependent process quickly forms vitamin D. Vitamin D from both ingestion and cutaneous synthesis travel in the blood via vitamin D binding proteins; first to the liver where it is then converted to 25-hydroxyvitamin D (25(OH)D), also referred to as calcidiol, by the enzyme 25-

hydroxylase. Calcidiol is the major circulating form of vitamin D and is what clinician's measure when assessing vitamin D status; it is also a biologically inactive form. The kidney cells, along with many other cells in the body, express 1α-hydroxylase and are responsible for converting 25(OH)D into the active state 1, 25 dihydroxyvitamin D ($1,25(OH)_2D$), also known as calcitriol. The amount of circulating $1,25(OH)_2D$ is regulated in two ways; self regulation via negative feedback, and by serum levels of PTH, calcium, phosphorus and fibroblast growth factor-23 levels. If serum levels of $1,25(OH)_2D$ are sufficient, the kidneys turn excess into calcitroic acid which is then excreted into bile. The primary stimulus for hydroxylation of calcidiol in the kidneys to the active form of vitamin D is increased serum PTH levels, in response to low serum calcium and phosphorus concentrations. Accordingly, the most well recognized action of calcitriol is to increase serum calcium and phosphorus levels through regulation in the small intestine, bones, and the kidneys.

1.3.2. ROLE OF VITAMIN D IN THE BODY

Due to the primary responsibility vitamin D has in serum calcium and phosphorus homeostasis, it has been strongly linked to the maintenance of skeletal health. Vitamin D, once in its' active form, acts similarly to that of other steroid hormones; the actions of $1,25(OH)_2D$ are mediated by vitamin D receptors which initiate suppression or activation of gene transcription in target tissues (44). Refer to Figure 1 (Appendix B) for an illustration of the roles vitamin D has with respect to the bones, intestine, and kidney. The main actions of $1,25(OH)_2D$ are regulation of calcium and phosphorus flux in the bones, intestine and kidneys. However, vitamin D receptors are also found in many other tissues, whereby having implications other than those related to calcium and phosphorus homeostasis (44; 44). With respect to bone tissue, active vitamin D can increase

calcium reabsorption as well as increase calcium deposition: 1) In states of low serum calcium concentrations, and decreased calcium availability from other sources, $1,25(OH)_2D$ along with the resultant increased PTH is suggested to stimulate osteoclast maturation by up-regulating receptor activator for nuclear factor κ B ligand (RANKL), and thus initiate calcium reabsorption; or 2) In states of high serum calcium concentrations vitamin D has been identified as a down-regulator of osteoprotegrin, an osteoclastogenesis inhibitory factor, as well as stimulating production of osteoblasts and thus is implicated in bone formation (44). Another action of $1,25(OH)_2D$ in the body, the most "classical" action and ultimately also influencing skeletal health, is to increase intestinal absorption of calcium and phosphorus, in an effort to maintain adequate serum levels. The process of increasing intestinal absorption of calcium and phosphorus occurs when $1,25(OH)_2D$ interacts with specific membrane receptors, increasing gene expression encoding for calcium transport proteins, such as calbindin (45). The third main role of $1,25(OH)_2D$ in the body takes place in the kidneys, where it is implicated indirectly in serum calcium homeostasis via PTH stimulation of renal resorption of calcium, increasing serum concentrations of calcium (45). Recall that in states of low serum calcium, PTH release is increased. To summarize, the primary role of vitamin D is to maintain adequate serum calcium and phosphorus levels. If serum calcium levels decline, PTH release is enhanced and mobilization of calcium from the bones, kidneys, and intestine increase. If vitamin D is low and there is not enough calcium being absorbed from the intestines and kidneys, reabsorption from the bone stores increases, which can severely compromise skeletal health. Thus, it is clear why vitamin D deficiency has been implicated in the development of osteoporosis.

Vitamin D receptors are found in many tissues throughout the body and thus vitamin D levels have been implicated in the development of diseases other than just osteoporosis,

including: multiple sclerosis (MS), cancer, and heart disease. Hypovitaminosis D has been identified as a risk factor for MS (46). Burton and colleagues (47) demonstrated a 41% reduction in the number of disease relapses following 1 year of vitamin D supplementation with 14000 IU per day. Additionally, in a cohort of 39 MS patients, treatment with 1000 IU per day of vitamin D for 6 months resulted in significantly increased anti-inflammatory cytokines (48). Vitamin D levels have also been implicated in cancer risk due to its effect in tissues such as the breast, colon and prostate through inhibiting angiogenesis and promoting apoptosis as well as controlling proliferation (49). Garland and colleagues (50) have suggested the incidence of breast cancer could be reduced by 30% if serum 25(OH)D levels are maintained above 100 nmol/L. The $1,25(OH)_2D$ that is produced in the kidneys is also suggested to down-regulate rennin and thus is involved in blood pressure maintenance (49). A randomized placebo controlled trial demonstrated that vitamin D therapy significantly decreases systolic and diastolic blood pressure following 6 months of therapy (51). Although the classical action of vitamin D in the health maintenance is through its effects on bone health, vitamin D has implications in many other tissues in the body, and as such vitamin D sufficiency may differ depending on the body system of interest.

1.3.3. DEFINING OPTIMAL/SUBOPTIMAL VITAMIN D

Currently, there is no universal definition of an optimal serum 25(OH)D level for bone health, therefore recommendations regarding sufficiency are controversial. As serum 25(OH)D levels decline, there is less mobilization of calcium from the intestine, bones, and kidneys into the blood, thus stimulating the parathyroid gland to increase PTH release. Subsequently, increased serum PTH stimulates greater conversion of 25(OH)D to the active form $1,25(OH)_2D$, which in

turn increases mobilization of calcium from the intestine, kidneys, and bones into the blood. In situations of low calcium availability from the intestine and kidneys calcium is predominately reabsorbed from bone tissue. Martinez and colleagues (30) demonstrated that lower bone mass was seen in individuals with elevated PTH levels in states of low serum 25(OH)D, suggesting that serum 25(OH)D levels should be maintained such that PTH release is maximally suppressed and consequently reabsorption of calcium from bones is minimized. The inverse relationship between serum 25(OH)D and PTH has been examined to determine the vitamin D level at which PTH begins to significantly rise; significant increases in PTH have been reported at 25(OH)D levels of 40 nmol/L (52), 78 nmol/L (53), and 110 nmol/L (54). A potential reason for such discrepancies in the level at which 25(OH)D affects serum PTH is the populations studied and their associated vitamin D status. Furthermore, it has been suggested that vitamin D sufficiency levels should consider the 25(OH)D levels at which maximum calcium absorption in the intestine is promoted, thereby maintaining serum calcium levels such that PTH release is suppressed (55). Heaney and colleagues (55) demonstrated that intestinal calcium absorption at an average 25(OH)D level of 86 nmol/L was 45-65% greater than that in individuals with an average 25(OH)D level of 50 nmol/L. Therefore, based on the relationship between PTH and 25(OH)D as well as maximum intestinal calcium absorption, guidelines for the general population regarding sufficient vitamin D levels for maintaining skeletal health are generally considered to be serum 25(OH)D levels between 70 and 80 nmol/L (56). Accordingly, guidelines regarding the vitamin D intake needed to achieve serum levels in the 70 – 80 nmol/L range have been suggested to be 1000 IU per day (56; 57).

Many factors, including: measurement technique, seasonal variation, skin pigmentation, dietary sources, and age, contribute to difficulties in defining “normal” or “optimal” vitamin D

levels. Differences in the assays used to measure serum 25(OH)D may limit the ability for a collaborative interpretation and a consensus of what adequate 25(OH)D levels are for health (58; 59; 60). The lack of standardization and calibration procedures underline the problems that arise with the validity of serum 25(OH)D measurement techniques (59). Holick (61) proposed that radioimmunoassay and vitamin D binding protein assays, which are typically used for 25(OH)D evaluation, can overestimate levels by approximately 10-20%. Another limitation to reports of vitamin D status is that some groups measured vitamin D based on food frequency questionnaires, which do not include estimates of vitamin D obtained from UVB exposure; the primary source of vitamin D in many individuals. Also, when evaluating food sources of vitamin D, it is important to know the bioavailability for each source in order to accurately estimate the amount of vitamin acquired. Through analysis of vitamin D content in a variety of fish, said to be the greatest dietary source of vitamin D besides fortified milk products, Chen and colleagues (62) identified that farmed salmon (the most widely consumed type of salmon in the US) contains only one quarter of the vitamin D provided from wild caught salmon. It is therefore important to be specific when recording vitamin D intake from dietary sources. Aside from differences in measurement techniques, there are seasonal differences in vitamin D synthesis, particularly in northern latitudes, which must be considered when attempting to establish the vitamin D status of a population. At 43˚N latitude, 25(OH)D levels were reported to be lowest between the months of November to April (52) due to the resultant zenith angle of the sun's UVB rays (49). Another factor identified to significantly affect the amount of vitamin D that can be synthesized in the skin is pigmentation (62), which should be considered when assessing why certain populations may be more or less deficient. Conversion of 7-dehydrocholesterol to pre-vitamin D_3 in fair skin is shown to be 5-10 fold more efficient than in highly pigmented skin

(62), which contains more melanin and consequently absorbs more of the UVB rays (49). Finally, age has been identified as a factor limiting the amount of vitamin D that can be synthesized in the skin (49), and will affect what is considered "normal" depending on the population being studied. Due to the limitations in procedures for evaluating vitamin D and other non-modifiable factors such as skin pigment, latitude, and age, it is understandable why there is much controversy when attempting to establish what "normal" vitamin D values are in the general population. However, based on the general consensus that sufficient vitamin D status is at serum 25(OH)D levels between 70 and 80 nmol/L (56), it has been suggested that: 14% (53), greater than 28% (52) and greater than 61% (60), of healthy adults have insufficient vitamin D status.

1.3.4. SUBOPTIMAL VITAMIN D AND OSTEOPOROSIS

Vitamin D status has been identified as a factor of interest in the pathophysiology of osteoporosis due to its inverse relationship with PTH and the consequent effects on calcium reabsorption in bones. Serum 25(OH)D levels have been positively correlated with BMD at several skeletal sites, indicating that at lower levels of vitamin D, BMD tends to be lower (30; 63). Martinez and colleagues (30) demonstrated BMD at the femoral neck, trochanter, and Ward's triangle to be significantly ($p<0.05$) correlated ($r=0.29$, $r=0.27$, $r=0.30$; respectively) with serum 25(OH)D levels in postmenopausal women over 60 years of age. In addition, Hannen and colleagues (63) found a significant positive correlation between BMD and 25(OH)D levels at five sites in a group of white men of varying ages. Lips and colleagues (64) evaluated vitamin D status in a large group of women with osteoporosis from 18 countries in varying degrees of latitude, and found that overall approximately 64% of women have serum 25(OH)D levels less than 75

nmol/L. Similarly, Kocjan and colleagues (65) found about 66% of patients attending an osteoporosis clinic to have serum 25(OH)D levels below 50nmol/L; and identified them as insufficient or deficient. It is important to note that calcium levels should also be reported when evaluating the relationship between vitamin D and bone health parameters to better identify whether changes in bone are associated with the vitamin D status or the calcium levels. Overall, low levels of vitamin D have been identified as a contributing factor to low BMD, and a greater proportion of individuals with osteoporosis appear to be vitamin D deficient compared to the non-osteoporotic population. Therefore, aside from the barriers involved in evaluating vitamin D status, the link between low serum 25(OH)D levels and poor bone health is recognized and should be considered when evaluating factors affecting osteoporosis development, treatment and fracture prevention.

1.3.5. VITAMIN D SUPPLEMENTATION AND FRACTURE RISK

Vitamin D supplementation has been evaluated with respect to fracture prevention in persons at risk of fracture in the non-SCI osteoporotic population. A significant reduction in risk of sustaining a hip or other non-vertebral fracture of 26% and 23%, respectively, was concluded from trials supplementing participants with vitamin D doses of 700 or 800 IU daily; whereas supplementation with 400 IU daily did not reduce fracture risk (66). It is not clear what dose of calcium should be administered along with vitamin D to optimize the reduction in fracture risk, or if doses higher than 800 IU daily of vitamin D are more beneficial in reducing the risk of fractures. Further, it is unclear if fracture risk reduction with vitamin D supplementation transfers to populations who experience bone loss and an increased risk of fracture, other than the elderly.

1.4.0. SPINAL CORD INJURY AND SUBOPTIMAL VITAMIN D

1.4.1. PREVALENCE OF SUBOPTIMAL VITAMIN D AND HYPERPARATHYROIDISM IN SCI

As is suggested in the non-SCI population, vitamin D and calcium insufficiency/deficiency may be prevalent in the SCI population, and therefore a contributing factor to the declining bone health reported following injury. Serum 25(OH)D levels in individuals with SCI are reported to be significantly lower than controls (67), and no different from controls (29; 68). However, one-third of individuals with chronic SCI were reported to have serum 25(OH)D levels less than the normal range suggested for the non-SCI population (29). More recently, the prevalence of vitamin D deficiency in the SCI population has been estimated as high as 93% (69). Further, a negative correlation has been identified between serum 25(OH)D and PTH, implying that vitamin D insufficiency and secondary hyperparathyroidism may be prevalent among individuals with SCI and result in accelerated bone reabsorption (29). Based on the limited evidence to date, the prevalence of vitamin D deficiency and/or secondary hyperparathyroidism in the SCI population cannot be established. It is not known whether the prevalence of vitamin D deficiency among men and women with varying injury levels differs. Furthermore, it is not known if the suggested sufficiency level for vitamin D to adequately suppress PTH is the same in the SCI population as it is in the non-SCI population.

1.4.2. ACQUIRING VITAMIN D IN SCI

Due to decreased mobility following SCI, many individuals in this population are exposed less to the sun than non-SCI individuals, suggesting vitamin D synthesis may be low (29). Also, individuals with SCI are often instructed to limit ingestion of calcium-containing foods acutely post injury to avoid hypercalciuria. As a result, vitamin D intake from food sources also declines

since many foods containing vitamin D contain calcium as well. Walters and colleagues (70) evaluated the nutrition of men and women with chronic SCI and identified, from a 24-hour recall, that median usual intakes of both vitamin D and calcium were significantly lower than the adequate intake levels for the general population of 200-600 IU/d and 1000-1200 mg/d, respectively. Opperman and colleagues (71) recently reported that of a cohort of 77 adults with SCI, 50% were consistent supplement users and that multivitamins, calcium, and vitamin D were the most frequently consumed; 25%, 20%, and 16% respectively. Accordingly, preliminary studies have been done evaluating the effect of vitamin D supplementation on vitamin D status among persons with SCI. Bauman and colleagues (72) demonstrated that with 800 IU of daily vitamin D supplementation for 12 months, average 25(OH)D levels were significantly increased to 56.16 nmol/L from 26.7 nmol/L at baseline. However, after 12 months of supplementation 9 of the 40 participants were 25(OH)D deficient (<40 nmol/L), and only 8 participants reached levels greater than 75 nmol/L, as well it was suggested that vitamin D doses greater than 800 IU per day are needed for greater than 12 months in order to replace vitamin D deficient individuals with SCI (72). Although preliminary work has been done to evaluate what doses of vitamin D are necessary to increase serum 25(OH)D to sufficient levels, sufficiency and deficiency levels in the SCI population have not been established. Identification of optimal levels of vitamin D required in the SCI population is required before recommended intake levels can be identified.

1.4.3. SUBOPTIMAL VITAMIN D AND BONE HEALTH IN SCI

A relationship may exist between vitamin D and bone health in the SCI population which could provide a potential therapeutic target for prevention of fracture in those with an SCI. Bauman and colleagues (73) evaluated the effect of 800 IU of vitamin D, plus 1.3g of calcium, plus 4µg of a vitamin D_2 analog, versus vitamin D and calcium supplementation plus a placebo, on BMD

in individuals with SCI. They found that in the placebo group, leg BMD was not significantly different at 24 months versus baseline: 1.030 g/cm^3 versus 1.045 g/cm^3, respectively (73). In the treatment group, percent leg BMD increased significantly in a subgroup of individuals who had never smoked, therefore it was suggested that the interaction of smoking and vitamin D status may be important links to bone loss following SCI (73).

Research regarding the relationships between vitamin D status and BMD in persons with SCI is limited. Future research is necessary to define optimal vitamin D status, the implications of vitamin D levels on specific bone parameters, and potential interactions of vitamin D with other bone-modifying risk factors among persons with SCI. Based on work done to date, it is likely that vitamin D, PTH levels, and resultant alterations in calcium homeostasis contribute to bone loss following SCI. The ultimate goal would be to elucidate the relationship between vitamin D status and fracture risk in individuals with SCI enabling treatment implementation for sub-lesional osteoporosis after SCI.

2.0.0. RESEARCH QUESTIONS/HYPOTHESES

2.1.0. RESEARCH QUESTIONS

Based on the literature to date, the following research questions were proposed:

2.1.1. PRIMARY RESEARCH QUESTIONS

1. In a sample of males and females with complete or incomplete, chronic SCI, what proportion of participants have suboptimal vitamin D status and what proportion of participants have optimal vitamin D status defined as:
    - Suboptimal: Serum 25(OH)D concentration of <75 nmol/L;
    - Optimal: Serum 25(OH)D concentration of ≥75 nmol/L?
2. What are correlates of suboptimal vitamin D status in those with chronic SCI?
3. In a sample of males and females with complete or incomplete, chronic SCI, what is the relationship between serum 25(OH)D level and indices of bone quality at the tibia and femur; including distal femur and proximal tibia aBMD, 4% tibia trabecular vBMD, and 66% tibia cortical vBMD and cortical thickness?

2.1.2. SECONDARY RESEARCH QUESTIONS

4. Among a sample of males and females with complete or incomplete, chronic SCI, what proportion of participants have secondary hyperparathyroidism, and what proportion of participants have PTH levels within the normal range defined as:
    - Secondary hyperparathyroidism: Serum PTH concentration of ≥ 7.0 pmol/L;
    - Normal PTH: Serum PTH concentration of 1.6 – 6.9 pmol/L?
5. Among a sample of males and females with complete or incomplete, chronic SCI, what is the relationship between serum PTH and serum 25(OH)D, as well as between serum PTH and serum ionized calcium?

6. In a sample of males and females with complete or incomplete, chronic SCI, what is the relationship between serum PTH level and indices of bone quality at the tibia or femur; including distal femur and proximal tibia aBMD and 4% tibia trabecular vBMD, and 66% tibia cortical vBMD and cortical thickness?

2.2.0. HYPOTHESES

It is predicted that the 4% tibia trabecular vBMD, from pQCT, will be positively associated with serum levels of 25(OH)D. It is also expected that knee aBMD, measured from the DXA scans, will be positively associated with serum 25(OH)D levels. Cortical thickness at the 66% tibia site, from pQCT analysis, is predicted to associate positively with serum 25(OH)D levels and negatively with serum PTH.

Additionally, it is predicted that an inverse relationship will be seen between serum 25(OH)D level and PTH level, and that a large proportion of the population will have suboptimal 25(OH)D and also demonstrate secondary hyperparathyroidism by increased PTH levels.

3.0.0. METHODS

3.1.0. RESEARCH DESIGN, SETTING AND POPULATION

3.1.1. STUDY DESIGN

The primary and secondary research questions were addressed via a cross-sectional study design, evaluating the baseline data from a larger 2-year prospective study. The data collected to address the objectives of the entire 2-year study include: a) medical history, including injury etiology and impairment descriptors; b) DXA scans of the whole body, spine, hips, and knee region to determine aBMD; c) pQCT scans to obtain tibia vBMD, bone geometry, and trabecular structure data; and d) blood to measure serum levels of 25(OH)D, intact PTH, BSAP, CTX-I, and ionized calcium.

3.1.2. STUDY SETTING

Collaborations were established between the University of Waterloo, McMaster University, and the Toronto Rehabilitation Institute to run the current study. Participant's medical history, DXA scans and blood draws were completed at Toronto Rehab Lyndhurst Centre, and the pQCT scans were performed at the Hamilton Health Sciences' McMaster University Site. Data was transferred to the University of Waterloo for analysis.

3.1.3. STUDY POPULATION

A convenience sample of 45 adults with chronic SCI was assembled over an 18 month time period. To ensure that recruited participants were neurologically stable, and had established bone loss that typically occurs in the first two years following injury, only individuals who were two years post-injury were eligible to participate. In an attempt to establish a representative sample of

the SCI population, males and females as well as those with motor complete (AIS classification A and B) and motor incomplete (AIS classification C and D) injuries were recruited.

3.2.0. PROTOCOL

3.2.1. RECRUITMENT

Participants were recruited primarily from: a) the Lyndhurst Long-term Follow-up Database of over 800 individuals with SCI who had previously consented to be contacted for research purposes; and b) Outpatient services at Lyndhurst Centre. Physicians and therapists from Outpatient Services in the Spinal Cord Rehab Program at Lyndhurst Centre identified and referred potential participants to the study. Potential participants identified by physicians were informed of their eligibility and were then asked if they were interested in learning more about the study. If the individual consented to be contacted, a referral form (Appendix A) was completed by the physician/therapist and sent to the research coordinator, who then contacted interested individuals by telephone. Other recruitment strategies employed include: advertisements on the Canadian Paraplegic Association website and newsletter, and a brief presentation at the Lyndhurst Fitness Centre.

Potential participants, identified from the database or physician referral, were sent a letter of invitation (Appendix A) stating that a research assistant would contact them to determine their interest and eligibility for enrolment. For individuals who did not want to be contacted, a phone number was provided in the letter where they could leave a message opting out of the call. During the phone call to interested potential participants, the details of the study were explained (Appendix A). For interested individuals, eligibility for participation was evaluated on the phone via a telephone screening form (Appendix A). Eligible individuals were then scheduled for their

baseline testing visit, when written informed consent (Appendix A) was obtained, and further screening was completed (Appendix A).

The following were the study 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 (<24 hours) associated with a stable upper motor neuron, neurologic deficit of trauma or trauma-like etiology having occurred at least 24 months prior to study inclusion • Ability to give informed consent • Age ≥ 18 years	• Current or prior known conditions other than paralysis known to influence bone metabolism including: oral glucocorticoid use for ≥3 months, malignancy, known liver or malabsorption condition • Weight > 270 lbs (limit for bone density machine) • Contraindications to pQCT testing (e.g. bilateral metal implants, severe spasticity and allergy to Ativan) • Women who are pregnant or planning to become pregnant

3.2.2. MEDICAL HISTORY AND DEMOGRAPHICS

At the baseline visit, several questionnaires/forms were completed in interview format. Data regarding past and current medical health, medication use, lifestyle and demographic data, fracture history, and information related to the SCI were collected (Appendix A). Medical history, injury information, and impairment descriptors were abstracted from the patient's medical record to confirm and supplement information provided by the participant. A physiatrist (C. Craven) determined the participants' AIS classification by verifying the injury level and completeness for individuals whose impairment descriptors were not available in their medical record. Height, weight, waist circumference, calcium intake, and supplement use were also collected. Dietary calcium intake was assessed via a food frequency questionnaire (74), and severity of spasticity was evaluated using the Penn Spasm Frequency and Severity Scale (75) to determine the safety of performing the pQCT scans (Appendix A).

3.2.3. BLOOD COLLECTION FOR SERUM ANALYSIS

At the baseline visit, blood collection was performed by a trained phlebotomist. For proper analysis of the serum measures, participants were required to fast for at least 12 hours prior to blood collection. For those participants unable to fast, a standard breakfast of toast and apple or orange juice was allowed, in which case blood was drawn 4 hours following food consumption. Blood samples were drawn using a closed, sterile Vacutainer® system. The skin superficial to the vein was cleaned with an alcohol wipe and a tourniquet applied 5-10 cm above the intended site of venous puncture. The needle was inserted through the skin and into the vein at an angle of 15-30 degrees. Upon completion of the blood collection, two 10mL Vacutainers® per participant, the tourniquet was removed, the needle withdrawn from the vein quickly, and sterile cotton was pressed on the site of venous puncture. Pressure was applied for up to ten minutes to stop the bleeding and reduce the risk of bruising. Once the bleeding had subsided or stopped (2-3 min), a sterile bandage was applied over the site. Immediately following blood collection, the blood from one 10 mL Vacutainer® serum separater tube was left to clot for 10-30 minutes, and then was centrifuged at 4°C, 2800 rpm, for 15 minutes. The serum layer was carefully removed and distributed into 2 labelled 1.5mL microcentrifuge tubes that were stored in a -70^{o}C freezer for back up analysis. The second 10 mL tube was placed on ice and sent to the Research Laboratory at Mt. Sinai Hospital for analysis. All analyses were completed on the day of the blood draw. All samples were stored in tubes labelled with an ID number; no identifying information was written on any storage tubes.

Analysis for serum levels of 25(OH)D; PTH; BSAP, a marker of bone formation; C-telopeptide of type I collagen (CTX-I), a marker of bone resorption; and ionized calcium were

completed for each participant. To address the primary and secondary research questions serum 25(OH)D, PTH and ionized calcium were evaluated.

Serum 25(OH)D was determined with a chemiluminescent immunoassay (CLIA) using the DiaSorin LIAISON® instrument as the platform (DiaSorin, Stillwater, MN); which detects both $25(OH)D_2$ and $25(OH)D_3$ to estimate the total 25(OH)D circulating in the body. The DiaSorin LIAISON® CLIA uses an antibody against 25(OH)D to isolate serum 25(OH)D from other materials and metabolites. Once the 25(OH)D is isolated, reagents are added to the sample to initiate a flash chemiluminescent signal which can then be measured and related to the 25(OH)D concentration (76). Serum 25(OH)D is particularly difficult to measure due to its lipophilic nature, and because the assay must be able to detect both $25(OH)D_2$ and $25(OH)D_3$ equally (77). A common 25(OH)D measurement method used in other research evaluating the relationship between 25(OH)D and bone health is the DiaSorin 25(OH)D radioimmunoassay (RIA) kit (78). The DiaSorin LIAISON® CLIA has however demonstrated acceptable within assay precision (2.8 – 13%) and interassay precision (7.3 – 17.5%) when evaluated against the DiaSorin RIA as a reference method (79; 80). Additionally, the LIAISON® CLIA exhibits 100% cross-reactivity for both $25(OH)D_2$ and $25(OH)D_3$ (80).

PTH was determined with an electrochemiluminescent immunoassay (ECLIA) using the Roche Elecsys 1010/2010 and modular analytics E170 immonoassay analyzers (Roche Diagnostics, Mannheim, Germany). The Roche Elecsys 1010/2010 ECLIA uses a similar process to a CLIA to measure the serum intact PTH concentration. The ELCIA method differs from CLIA analysis in that a voltage is applied to initiate the chemiluminescent reaction (81). The Elecsys platform for measurement of intact PTH is demonstrated to be a reliable tool for

measuring intact PTH with within-run precision of 3.1 – 6.6% and between-day precision of 3.4 – 15.6% found from a multicentre trial with 11 participating labs (82).

Serum ionized calcium concentration was determined using potentiometers (ABL 735 Analyzer). The ABL 735 Analyzer uses electrodes to relate the electrical potential of the ionized calcium in the serum sample to its concentration using the Nernst equation.

Serum C-telopeptide of type I collagen was evaluated in post-hoc analyses. Serum CTX-I was measured with an ECLIA on the Roche Elecsys 1010/2010 and modular analytics E170 immonoassay analyzers (Roche Diagnostics, Mannheim, Germany).

3.2.4. PQCT SCANS

PQCT scans were obtained at two sites on the tibia; one at the distal end for trabecular bone analysis and one at the tibia shaft for cortical bone analysis. The trabecular site was chosen for analysis based on previous work identifying trabecular vBMD as a good parameter for fracture prediction in the SCI population (13). Also, the cortical site was chosen based on previous work identifying an association between fractures and cortical bone parameters in a population with secondary hyperparathyroidism (83). In all participants, except those with severe spasticity or other contraindications, the right tibia was scanned. PQCT images were obtained with a Stratec XCT-2000 scanner (Stratec Medizintechnik, Germany), a translate-rotate small bore CT scanner that acquires a transaxial image from 145 projection scans. To obtain a measurement of leg length, the knee joint line and medial malleolus at the ankle joint were palpated and a measuring tape was used to measure the distance between them. The anatomic reference point, the tibia distal endplate, was identified on a 30mm coronal view of the ankle joint line on a scout scan. The scanning sites (at 4% and 66% of tibia length) were located measuring proximally from the

reference line identified in the scout scan. Single 2.5 mm slices were obtained at the ultradistal tibia (4% site) and the proximal one-third of the tibia (66% site). To obtain a resolution great enough to evaluate trabecular structure at the 4% site, a voxel size of 0.2 mm was used; whereas scans at the 66% site were done with a voxel size of 0.5 mm.

To address the primary and secondary research questions, trabecular vBMD at the 4% site, and cortical vBMD and cortical thickness at the 66% site were assessed using the Stratec XCT commercial software package for the pQCT device.

Trabecular vBMD at the 4% site was obtained using the CALCBD analysis mode in the commerical software package. The CALCBD analysis mode allows for the analysis of total bone and trabecular bone parameters separately. Within the CALCBD mode, contour mode 3 and peel mode 2 were applied, along with outer and inner thresholding of 130 and 400 mg/cm^3, respectively, based on previous research demonstrating their accuracy (84). Contour mode 3 uses an iterative contour detection algorithm to find the outer bone edge. As stated, a threshold of 130 mg/cm^3 was applied to the outer edge detection method. Within the region of interest, one voxel is found with bone density equal to or above 130 mg/cm^3 on the outer edge of the bone. The software then searches the adjacent voxels for a density equal to or greater than the previous. This process is continued until the whole outer edge of the bone is detected, which separates the bone from all muscle, fat and skin around it. Next, peel mode analysis was applied to separate the trabecular bone from the total bone. The trabecular bone is determined as all the voxels remaining which are below the applied threshold in the peel mode. Using the 400 mg/cm^3 threshold, the trabecular bone was distinguished from the subcortical bone. From the remaining area, trabecular vBMD was determined and extracted from the analysis.

The 66% site was analyzed using the CORTBD analysis mode, which provides cortical bone parameters. CORTBD mode 1 was used with a threshold of 711 mg/cm^3, based on manufacturer's suggestion. CORTBD mode 1 removes any voxels on the inner or outer edge with a density below the defined threshold. The remaining area is the cortical bone separated from the subcortical and trabecular bone, as well as any muscle, fat, and skin. From the CORTBD analysis, cortical vBMD and cortical thickness parameters were extracted for evaluation.

3.2.5. DXA SCANS

Areal BMD (g/cm^2), or aBMD, of the right distal femur and right proximal tibia were gathered from densitometric scans using the Hologic 4500 dual-energy x-ray absorptiometry device (Hologic Inc., MA, USA). The knee region is a common site of fracture in the SCI population and was therefore chosen as the primary region of interest. Further, the DXA tool is the current standard for clinical assessment of BMD. Distal femur and proximal tibia scans were obtained and analyzed using a lower extremity positioning device and protocol, which has been previously determined as reliable and accurate (85). The method of distal femur and proximal tibia analysis uses a modified version of the manufacturer developed lumbar spine analysis protocol. The lower extremity positioning device was used to minimize movement during the scan and to ensure reliable overlap of the patella and proximal fibula with respect to the tibia. All DXA scans were performed and analyzed by trained technologists in the Bone Density Lab at Lyndhurst Centre. The DXA device at Lyndhurst is equipped with a lifting assist for safe transferring of participants to and from the scanning table.

To address the primary and secondary research questions, aBMD of the distal femur and proximal tibia were retrieved.

3.2.6. OVERVIEW OF ASSESSMENT PROCESS

After obtaining written informed consent at the baseline visit, each individual: 1) completed the questionnaires pertaining to demographic and medical history information at Lyndhurst Centre (~30 minutes); 2) participated in blood collection at Lyndhurst Centre (~10 Minutes); 3) participated in DXA scans at Lyndhurst Centre (~1 hour); 4) attended McMaster University Medical Centre to participate in pQCT scans of the tibia (~45 minutes); and 5) participated in a telephone interview when the physical activity and food frequency questionnaires were completed (~30-45 minutes).

3.2.7. STATISTICAL ANALYSES

To address the primary research questions and identify the proportion of the population with suboptimal vitamin D status, serum 25(OH)D levels were summarized using descriptive statistics: mean (standard deviation), as well as number (percent) for each suboptimal (<75 nmol/L) and optimal categories (≥75 nmol/L). Additionally, univariate logistic regression analysis was performed to identify characteristics associated with suboptimal vitamin D status. The following characteristics were chosen to be assessed based on previous work in the non-SCI population: time of year, (52), age (49), gender (86), hyperparathyroidism (87), and obesity (88). Obesity was defined based on age and gender specific percent body fat ranges proposed by Gallagher and colleagues (89). Further, injury level (67), injury completeness (70), duration of injury (90), and supplement use (70) were chosen for assessment based on previous work

evaluating vitamin D in the SCI population. Additional characteristics assessed include: bisphosphonate use (91), and smoking status (12), due to their implications with bone health in the SCI and non-SCI populations. Odds ratios, 95% confidence intervals (CI), and p values were reported.

To characterize and describe the bone health of the population, Z scores at the hip region, commonly used to assess fracture risk in the pre-menopausal non-SCI population, were calculated. The Z score compares the bone mass to an age and gender matched distribution. A BMD with a corresponding Z score ranging from -1 to -2.5 was considered to have low bone mass and increased risk of fracturing, whereas a Z score of -2.5 or below was considered osteoporotic and at the highest risk of fracturing (9). Additionally, bone quality was assessed based on SCI-specific aBMD fracture thresholds in the knee region and vBMD fracture thresholds for the 4% trabecular site in the tibia (13; 16). Previous work reports that the fracture threshold, the value at which fractures begin to occur, and the fracture breakpoint, the value at which fractures are likely to occur, at the knee region using DXA assessed aBMD in individuals with SCI is 0.78 g/cm^2 and 0.49 g/cm^2, respectively (16). Additionally, fractures have been demonstrated to occur at the distal tibia in individuals with SCI whose vBMD values were below 72 mg/cm^3 measured through pQCT (13). Although trabecular vBMD is suggested to be a more sensitive parameter for bone quality assessment compared to cortical thickness and cortical vBMD parameters (13), lower extremity cortical vBMD has been shown to change in the first 5 years following an SCI (92), and thus was included in the current analyses assessing relationships between bone parameters and serum 25(OH)D, post-SCI. To evaluate the relationship between serum 25(OH)D levels and all bone parameters, Pearson correlation and simple regression analyses were completed.

To address the secondary research questions and identify the proportion of the population with secondary hyperparathyroidism, serum PTH levels were summarized using descriptive statistics: mean (standard deviation), as well as number (percent) within each category; those within the normal serum PTH range (1.6 – 6.9 pmol/L) and those above the upper limit of the normal range (≥7 pmol/L). Additionally, Pearson correlation and simple linear regression analyses were completed to evaluate the relationship between serum PTH and serum 25(OH)D, and between serum PTH and ionized calcium. To evaluate the relationship between serum PTH levels and all bone parameters, Pearson correlation and simple regression analyses were completed. Post-hoc analyses included Pearson correlations between serum PTH and CTX-I and between serum 25(OH)D and CTX-I. Serum C-Telopeptide is a biomarker of bone resorption.

Correlation coefficients (r) and p values were reported for all correlation analyses. A p value of 0.05 was considered significant. For correlation coefficients from 0.00 – 0.09, variables were considered not associated, 0.10 – 0.29 weakly associated, 0.30 – 0.49 moderately associated, and >0.50 strongly associated. Additionally, linear regression equations and the proportion of variance explained by the independent variables analyzed (R^2) were reported for all simple regression analyses. All analyses were done with SAS version 9.1 (Cary, North Carolina).

3.3.0. ETHICAL CONSIDERATIONS

3.3.1. POTENTIAL RISKS TO PARTICIPANTS

During both the DXA and pQCT scans, participants were exposed to small amounts of radiation. The total amount of radiation exposure from both scans is approximately 30-35μSv; less than that received during an axial CT scan (30-60μSv) or annually from background radiation (2500μSv). Participants with severe spasticity were assessed by a physician (C. Craven), and

prescribed 0.5-l mg sublingual Ativan (anti-spasticity medication) prior to pQCT scanning if indicated. Administration of Ativan was a precaution taken to reduce the potential for injury if a spasm were to occur when the leg was positioned in the scanning device. Side effects associated with Ativan include: dizziness, weakness, drowsiness, dry mouth, and potentiating other anti-spasticity medications. Participants were provided the opportunity to decline using Ativan.

3.3.2. ANONYMITY

The current research project was conducted following the Tri-Council Policy Statement regarding research with human participants (93). The current project holds Research Ethics Board approval at each site: The University of Waterloo, Toronto Rehabilitation Institute, and McMaster University. Each participant was assigned a unique identification (ID) number which was used on all forms and files in an electronic database. The key file linking participant information to the ID numbers was stored on a password protected computer. A CD backup copy and hard copy of the key file and data files were stored in separate, locked filing cabinets.

Empower, at the University of Western Ontario, created a database for electronic compilation of all research data obtained. Indirect identifiers collected and entered in the database were date of birth and date of spinal cord injury. At the end of the 2-year prospective study all information from this database will be downloaded by Dr. Craven and Dr. Giangregorio and kept on file at Lyndhurst Centre indefinitely.

3.3.3. FEEDBACK TO PARTICIPANTS

After the completion of the larger 2-year study, a letter (Appendix A) will be sent to participants thanking them for their participation and briefly explaining the general outcomes of the study.

4.0.0. RESULTS

4.1.0. RECRUITMENT AND SAMPLE SIZE

Two-hundred and fifty-two individuals were approached to participate in a larger two-year prospective study looking at bone quality over time in individuals with chronic SCI. Of those approached, 139 were unreachable by phone, 52 declined participation, and the remaining 61 were pre-screened for eligibility. Four potential participants did not meet inclusion criteria, nine declined further participation, and 48 were determined eligible and agreed to participation. At the time of data analysis, 39 were included, and nine were pending assessment completion. Six additional subjects were included in the analysis from another ongoing study which provided some of the same outcome assessments, therefore increasing the total sample size to 45 individuals with chronic spinal cord injury.

Five participants were unable to have either their distal femur or proximal tibia scanned by DXA due to having hardware in the knee region; hardware interferes with the x-ray attenuation and would facilitate an invalid BMD measurement if scanned. Additionally, one individual was not scanned because their weight exceeded the tolerance of the scanning bed, and one individual only provided a proximal tibia scan due to a broken distal femur. Therefore, 38 distal femur and 43 proximal tibia BMD measurements via DXA were included in the final analyses. Three serum samples were not obtained due to difficulty drawing blood by the phlebotomist, and one individual declined the blood draw. In three additional cases, measurement tests were missed by the analysis lab (2 PTH, 1 25(OH)D), and the six participants data added from the other study did not provide PTH or ionized calcium measurements. Therefore, 39 25(OH)D, 33 PTH and 34 ionized calcium measurements were included in the

final analyses. Some individuals were unable to travel to Hamilton to complete the pQCT scan, or were not scanned within the three month window of time for the baseline assessment to be completed. One participant experienced spasms, preventing safe scanning at the 66% site, and two additional 66% scans were not obtained due to positioning difficulties. Therefore, 38 scans at the 4% site and 37 scans at the 66% site of the tibia were included in the final analyses. Figure 2 (Appendix B) summarizes participant recruitment and the sample sizes attained for the various outcomes.

4.2.0. PARTICIPANT CHARACTERISTICS

All 45 participants acquired their SCI from a traumatic event, and were at least two years post injury. The cohort consisted of thirty-four male and eleven female participants, with a mean age of 51±11.9 years and a mean percent body fat of 31.0 ± 7.5 (Table 1). The time post injury of participants ranged from 2 – 41 years with a mean of 14.7±10.3 years. Twenty-six participants were paraplegic; of which twenty-one had motor complete injuries, and five had motor incomplete injuries. Twenty-two participants were tetraplegic; of which nine had motor complete injuries and thirteen had motor incomplete injuries.

Table 1. Participant Characteristics

	Male	Female	Total
Total n	34	11	45
Age (years)	51 (±11.5)	53 (±13.4)	51 (±11.9)
Height (cm)	177.7 (±7.7)	166.7 (±5.1)	175.0 (±8.6)
Weight (kg)	87.9 (±24.3)	73.9 (±19.1)	84.4 (±23.7)
Body Fat (%)	29.4 (±6.7)	37.0 (±8.1)	31.0 (±7.5)
Injury Characteristics			
Motor Complete Paraplegia (n)	16	5	21
Motor Incomplete Paraplegia (n)	3	2	5
Motor Complete Tetraplegia (n)	8	1	9
Motor Incomplete Tetraplegia (n)	10	3	13
Time post injury (years)	14.2 (±10.5)	16.2 (±10.2)	14.7 (±10.3)

*Note. Values are mean (SD)

At the time of assessment, 89% of participants were taking vitamin D supplements, and 82% of participants were taking calcium supplements. The range of vitamin D supplement doses consumed was from 200 IU to 5000 IU per day, with one individual self reporting a vitamin D intake of 50 000 IU per day for the last 18 months. Of those taking vitamin D supplements, 57% reported consuming greater than 1000 IU per day. Less than 50% of participants were currently taking a multivitamin. Average daily dietary calcium intake, as reported from the participants' recall of their usual dietary habits in a month, was 991.4±1850 mg/day. At the time of assessment, twenty-six participants were currently on bisphosphonate therapy for improving their bone health, zero reported consuming an average of greater than five alcoholic beverages per day, eleven were current smokers, and twenty-five reported a history of smoking. Of the thirty-nine serum 25(OH)D measurements collected, twenty-seven were assessed in the summer months (May through October), and twelve were assessed in the winter months (November through April). The participants' assessments were completed between April 2009 and August 2010. Table 2 summarizes additional population descriptors for the cohort.

Table 2. Population descriptors and potential confounders for cohort (n=45)

	n (%)
On Vitamin D	40 (89%)
On Calcium	37 (82%)
On Multivitamin	22 (49%)
Average Dietary Calcium Intake/Day (mg/day)(Mean ± SD)*	991.4 (±1850.4)
Using Bisphosphonates	26 (58%)
Current Smoker	11 (24%)
History of Smoking*	25 (64%)
Consume >5 alcoholic drinks/day*	0 (0%)
Summer Assessment (May-Oct)*	27 (69%)
Winter Assessment (Nov-April)*	12 (31%)

***Indicates n=39 due to incomplete data sets

4.3.0. BONE QUALITY

The distal femur and proximal tibia DXA scans and the tibia pQCT outcomes reveal the bone loss in the current cohort of individuals living with an SCI. Mean (SD) of the distal femur aBMD and proximal tibia aBMD were 0.634 (± 0.218) g/cm^2 and 0.497 (± 0.168) g/cm^2, respectively (Table 3). Based on Z-scores at the total hip, 37% have low bone mass (Z = -1- -2.5), putting them at an increased risk of fracturing. Further, 29% have osteoporosis (Z ≤ -2.5), putting them at the highest risk of fracturing. Mean (SD) of the 4% tibia trabecular vBMD, 66% tibia cortical thickness, and 66% cortical vBMD were 140.12 (±54.9) mg/cm^3, 3.26 (±1.01) mm, and 1081.1 (±58.3) mg/cm^3, respectively.

Table 3. Summary of bone quality outcomes for cohort

Outcome	Mean (SD)	Minimum	Maximum	95% CI
DXA				
Distal Femur aBMD (g/cm^2) (n=38)	0.634 (±0.218)	0.311	1.007	0.562 – 0.706
Proximal Tibia aBMD(g/cm^2) (n=43)	0.497 (±0.168)	0.157	0.880	0.445 – 0.549
pQCT				
4% Tibia Trabecular vBMD (mg/cm^3) (n=38)	140.12 (±54.9)	44.3	245.2	122.1 – 158.2
66% Tibia Cortical vBMD (mg/cm^3) (n=37)	1081.1 (±58.3)	889.1	1180.8	1061.6 – 1100.6
66% Tibia Cortical Thickness (mm) (n=37)	3.26 (±1.01)	0.78	5.66	2.92 – 3.60

Based on SCI population specific fracture thresholds developed mainly from males with motor complete injuries, our cohort of participants are representative of those at high risk of fracturing. In the current study 67% and 30% of participants had distal femur aBMD values below the fracture threshold and fracture breakpoint, respectively. Of the 30% below the fracture breakpoint, 30% had suboptimal vitamin D status. Also, 92% and 54% of participants had proximal tibia aBMD values below the fracture threshold and fracture breakpoint, respectively. Of the 54% of participants with proximal tibia aBMD values below the breakpoint, 25% demonstrated values below optimal vitamin D status. The current study demonstrated 6% of the sample to have pQCT measured distal tibia vBMD values below the fracture threshold suggested by Eser and colleagues (13). Of those below the threshold, only 1 individual had suboptimal vitamin D status. Based on the fracture threshold and breakpoint from DXA assessed knee aBMD in the literature, a large proportion of our sample are at an increased risk of fracture in that location. Based on the fracture threshold from pQCT assessed distal tibia vBMD in the literature, a small proportion of our sample are at risk of fracturing in that location. The studied cohort of individuals with chronic SCI has quite poor bone health and is at high risk of fracturing. Evaluating the relationships between bone health and 25(OHD in the current group of individuals at a high risk of fracturing provides information specific for the population that may benefit most from optimal vitamin D levels.

4.4.0. VITAMIN D STATUS

Thirty-eight percent (95% CI, 22.7 – 53.3) and 62% (95% CI, 46.7 – 77.3) of the population had serum 25(OH)D levels in the suboptimal (<75 nmol/L) and optimal (≥75 nmol/L) ranges, respectively. The mean (SD) serum 25(OH)D levels in nmol/L, and the 95% confidence intervals

within the suboptimal category was 55.9 (± 11.8) nmol/L (95% CI, 49.4 – 62.4) and ranged from 33.0 – 74.0 nmol/L, whereas that in the optimal category was 109.3 (± 33.7) nmol/L (95% CI, 95.1 – 123.5) and ranged from 76.0 – 226.0 nmol/L. The median serum 25(OH)D level in the suboptimal and optimal groups were 57 nmol/L and 102 nmol/L, respectively. Figure 3 illustrates the scatter of serum 25(OH)D levels for all participants.

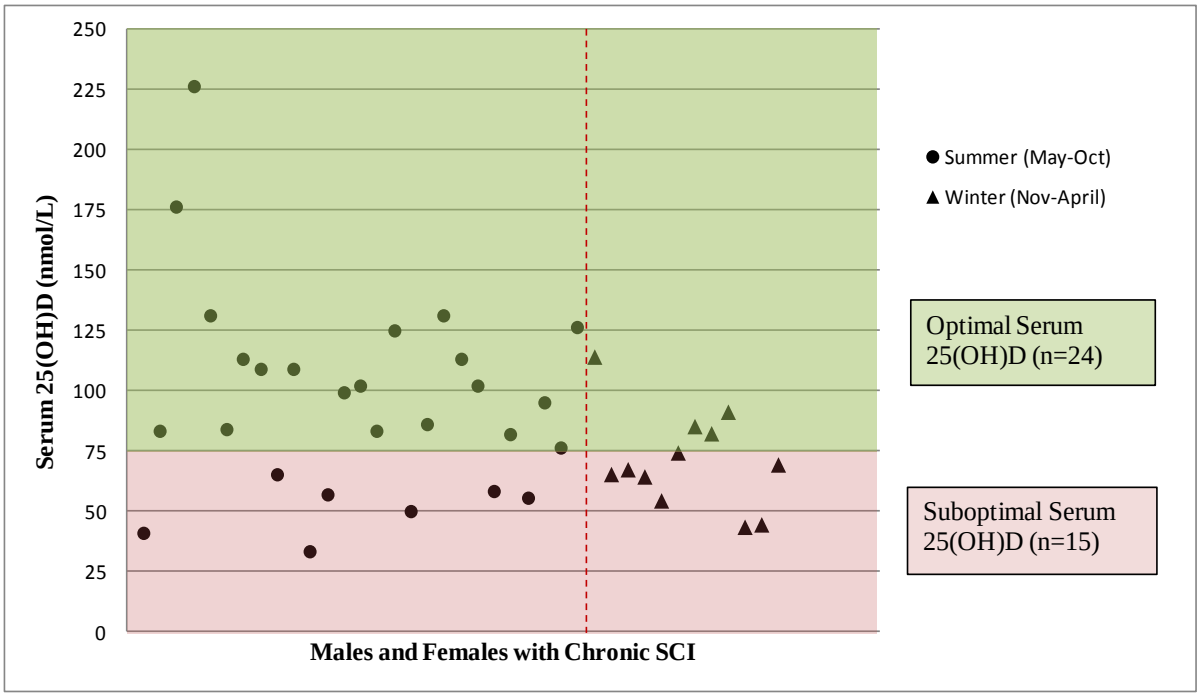

Figure 3. Serum 25(OH)D level (nmol/L) for all participants (n=40) illustrating those in the suboptimal and optimal ranges.

Univariate logistic regression analysis was performed to identify which population characteristics were associated with vitamin D deficiency. Table 4 identifies the variables included in the analysis, the associated odds ratio (OR), and the 95% CI and p value. Those with vitamin D assessments performed in the winter months (OR=6.3, C.I.=1.3-30.5, p=0.022), and those not taking vitamin D (OR=10.5, C.I.=1.0-108.7, p=0.049) or calcium (OR=7.1, C.I.=1.1-45.5, p=0.038) supplements were at an increased odds of being vitamin D deficient. Additionally, age was a significant correlate of vitamin D deficiency; each year younger an

individual was increased the odds of being vitamin D deficient (OR=0.92, C.I.=0.8-0.9, p=0.038).

Table 4. Characteristics associated with vitamin D deficiency from univariate logistic regression analysis (n=34)

Characteristic	OR	95% CI	P value
Vitamin D Assessed in Winter Months	6.3	1.30 – 30.53	0.022*****
Female Gender	1.1	0.22 – 5.86	0.881
Age	0.92	0.847 – 0.995	0.038*****
Duration of Injury	0.98	0.914 – 1.048	0.532
Motor Complete Injury	1.1	0.26 – 5.23	0.860
Paraplegic	3.0	0.636 – 14.15	0.165
Not on a Vitamin D Supplement	10.5	1.014 – 108.68	0.049*****
Not on a Calcium Supplement	7.1	1.121 – 45.52	0.038*****
Not on a Multivitamin	0.97	0.232 – 4.042	0.966
Not on a Bisphosphonate	2.7	0.613 – 11.60	0.191
Currently Smoking	2.4	0.531 – 11.12	0.253
Hyperparathyroidism	0.53	0.09 – 3.178	0.490
Obesity	1.2	0.282 – 4.84	0.832

*****Significant ($p<0.05$)

4.5.0. RELATIONSHIP BETWEEN 25(OH)D AND BONE QUALITY OUTCOMES

Serum 25(OH)D level was not significantly correlated with any bone quality outcomes. There was a weak negative, non-significant correlation between distal femur aBMD and serum 25(OH)D level (r=-0.160, p=0.374) (Figure 4; Appendix B). Similarly, there was a weak negative correlation between proximal tibia aBMD and serum 25(OH)D level (r=-0.197, p=0.242), which was not significant (Figure 5; Appendix B). At the 4% tibia trabecular site, no correlation was found between serum 25(OH)D level and trabecular vBMD (r=-0.003, p=0.990) (Figure 6; Appendix B). Additionally, at the 66% tibia cortical site no correlations were evident between serum 25(OH)D and cortical vBMD (r=-0.018, p=0.923) (Figure 7; Appendix B) or cortical thickness (r=-0.066, p=0.716) (Figure 8; Appendix B). Knowing serum 25(OH)D level did not add significant value for predicting any of the assessed bone quality outcomes.

4.6.0. SECONDARY HYPERPARATHYROIDISM

Fifteen percent (95% CI, 4.8 – 25.2) of the population demonstrated serum intact PTH levels above the upper limit of the normal range (≥ 7.0 pmol/L), with the remaining 85% (95% CI, 72.8 – 97.2) exhibiting serum intact PTH in the normal range (1.6 – 6.9 pmol/L). The mean (SD) serum intact PTH level within the normal hormonal range was 3.99 (±1.44) pmol/L (95% CI, 3.4 – 4.6) with levels ranging between 1.9 and 6.9 pmol/L, whereas the mean (SD) serum intact PTH level in the group with hyperparathyroidism was 9.64 (±2.63) pmol/L (95% CI, 6.4 – 12.9) with levels ranging from 7.7 to 13.6 pmol/L. Figure 9 illustrates the scatter of the serum intact PTH levels for all participants.

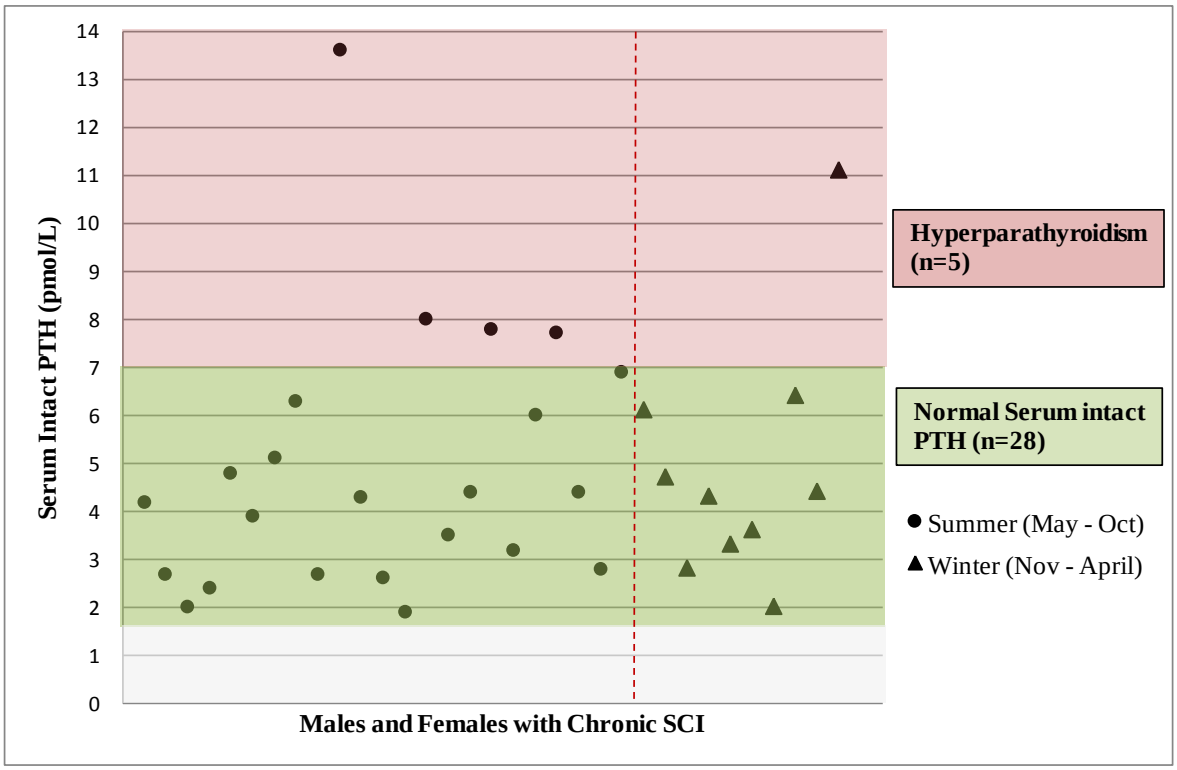

Figure 9. Serum intact PTH (pmol/L) for all participants (n=33) illustrating those in the normal range and those with hyperparathyroidism.

The mean (SD) of serum ionized calcium for the whole cohort was 1.23 (±0.041) mmol/L. Serum ionized calcium levels ranged from 1.08 – 1.30 mmol/L. One participant had

serum ionized calcium below the normal and two had serum ionized calcium levels near the lower end of the normal range, which is from 1.17 – 1.33 mmol/L, with only one of these participants demonstrating secondary hyperparathyroidism.

4.7.0. RELATIONSHIP BETWEEN PTH AND 25(OH)D AND CALCIUM

Prediction of serum intact PTH levels with known serum 25(OH)D levels could be done with some certainty in the current study group of individuals with chronic SCI. There was a moderate inverse correlation between serum intact PTH and serum 25(OH)D levels, approaching significance (r=-0.327, p=0.068) (Figure 10). Additionally, there was a weak negative, non-significant correlation between serum ionized calcium and serum intact PTH (r=-0.227, p=0.204) (Figure 11; Appendix B).

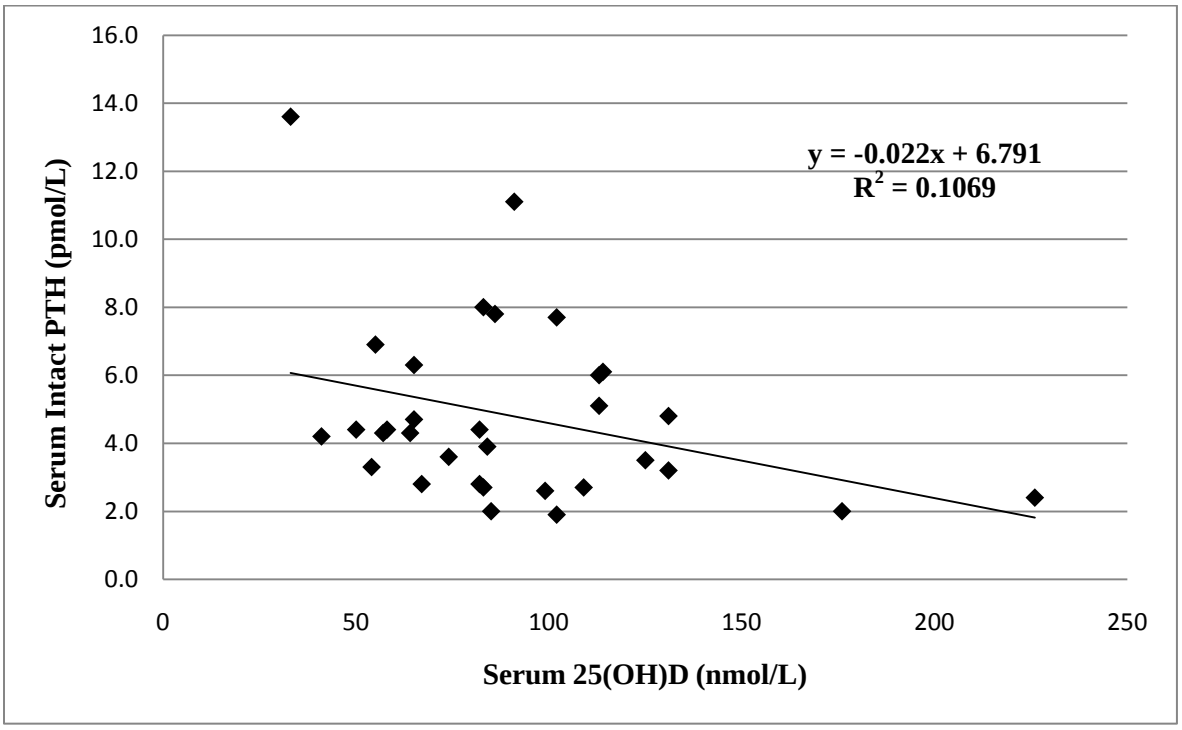

Figure 10. Linear regression of serum intact PTH (pmol/L) and 25(OH)D (nmol/L).

4.8.0. RELATIONSHIP BETWEEN PTH AND BONE QUALITY OUTCOMES

There were no significant correlations between the assessed bone quality outcomes and PTH. A moderate negative correlation between 66% tibia cortical thickness and serum intact PTH was evident, and approached significance (r=-0.353, p=0.071) (Figure 12). There were weak negative, non-significant correlations between 4% tibia trabecular vBMD and serum intact PTH (r=-0.293, p=0.123) (Figure 13; Appendix B) and between 66% tibia cortical vBMD and serum intact PTH (r=-0.243, p=0.222) (Figure 14; Appendix B). There were no evident associations between distal femur aBMD and serum intact PTH (r=0.005, p=0.980) (Figure 15; Appendix B), or between proximal tibia aBMD and serum intact PTH (r=-0.054, p=0.774) (Figure 16; Appendix B).

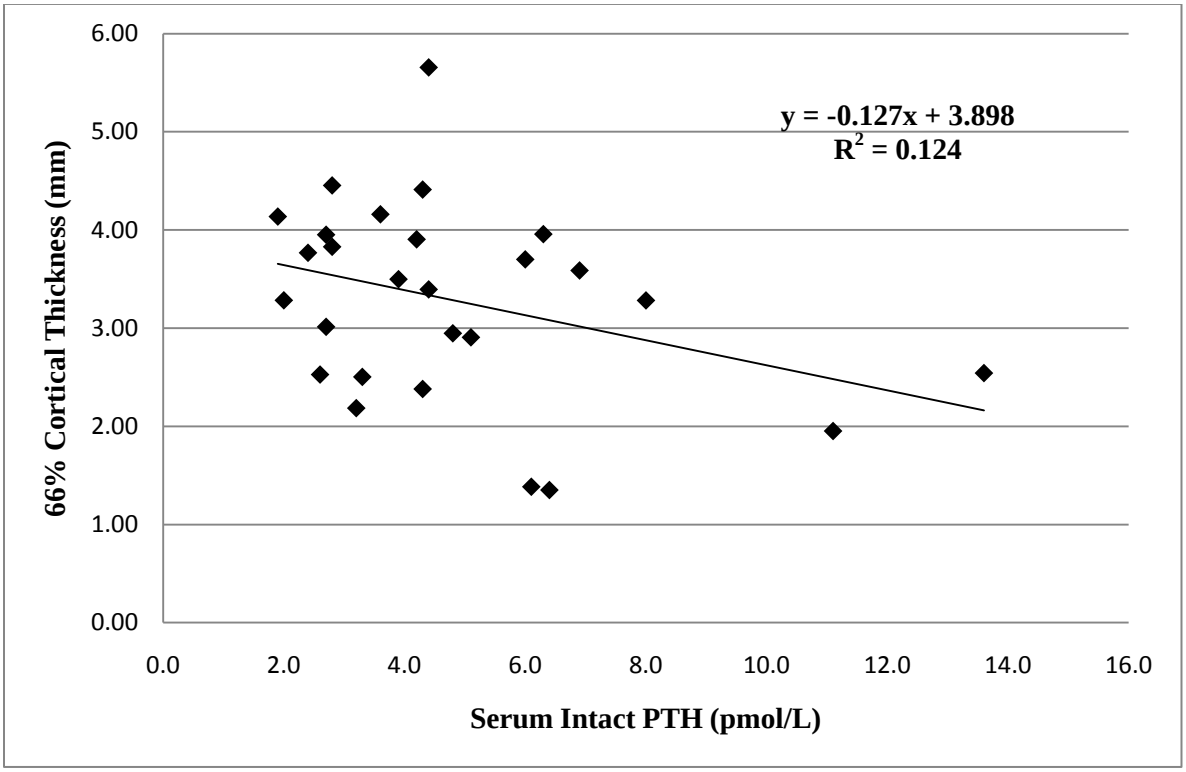

Figure 12. Linear regression of 66% tibia cortical thickness (mm) and serum intact PTH (pmol).

4.9.0. POST HOC ANALYSES WITH SERUM C-TELOPEPTIDE

There was a significant positive correlation between serum C-Telopeptide, a biomarker of bone resorption, and serum intact PTH (r=0.509, p=0.016) (Figure 17). There was no relationship found between serum C-Telopeptide and serum 25(OH)D (r=-0.011, p=0.962) (Figure 18; Appendix B).

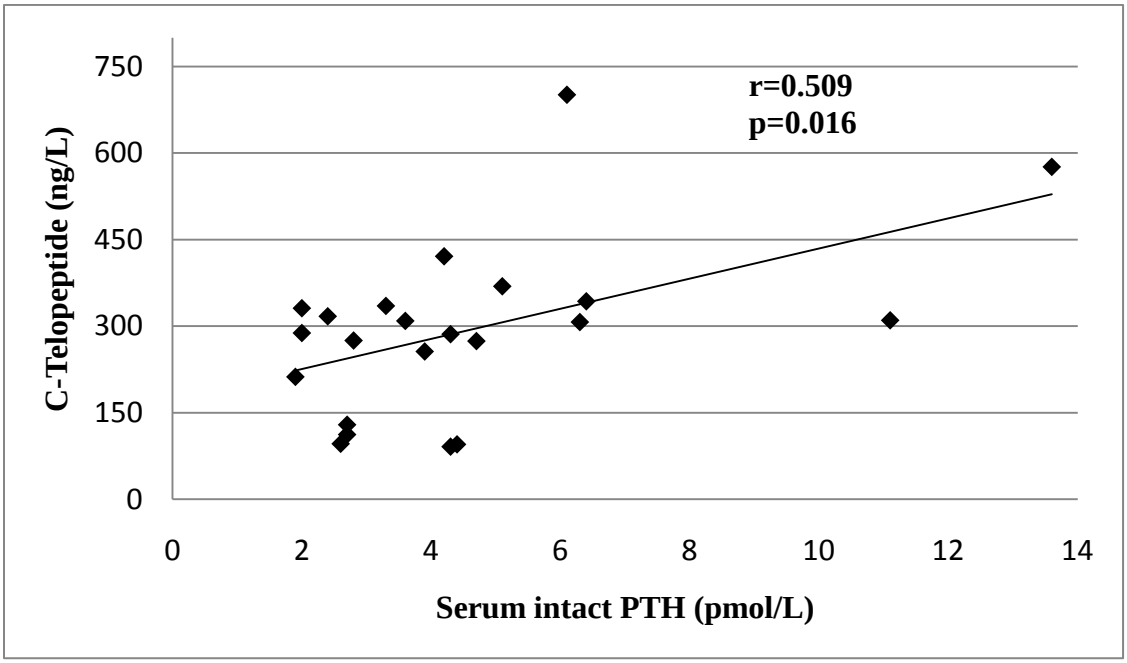

Figure 17. Relationship between serum C-Telopeptide (ng/L) and serum intact PTH (pmol/L)

5.0.0. DISCUSSION

5.1.0. SUMMARY

A cohort of 45 adult individuals with chronic SCI were evaluated regarding their serum 25(OH)D level, serum intact PTH level, and the relationships of these hormones with indicators of lower extremity bone quality; including aBMD, vBMD and cortical thickness measurements. Sixty-two percent of the study population with chronic SCI, a greater proportion than expected, presented with serum 25(OH)D levels in the optimal range (≥75 nmol/L). Additionally, having 25(OH)D assessed in the winter months, not being on a calcium supplement, not being on vitamin D supplement and being younger may be important risk factors for identifying individuals at highest risk for suboptimal levels of 25(OH)D. Although no relationships between 25(OH)D or PTH and any of the indicators of lower extremity bone health were demonstrated, there was a trend towards an inverse relationship between 25(OH)D and PTH, suggesting that vitamin D status could still be an important part of bone health in the chronic years of SCI through PTH levels.

5.2.0. INTERPRETATION

5.2.1. VITAMIN D STATUS

The current evaluation of vitamin D status in individuals with chronic SCI is representative of a group of males and females with complete or incomplete injuries and with varying levels and years post-injury. Thirty-eight percent of the chronic SCI population studied demonstrated suboptimal 25(OH)D levels (<75nmol/L). Further, the median of the serum 25(OH)D level in the suboptimal and optimal groups were 57 nmol/L and 102 nmol/L, respectively, identifying that many of those in the suboptimal range are much lower than the optimal cut-off of 75nmol/L.

Although one previous report of vitamin D status in the SCI population similarly identified greater than 32% of participants to have suboptimal serum 25(OH)D levels (29), more recent work has suggested that as much as 96% of individuals with SCI have suboptimal vitamin D levels (69; 90). Bauman (29) and colleagues were first to report vitamin D status in SCI however may have underestimated the true prevalence of vitamin D deficiency. They determined about 32% of their population with SCI to have levels in the deficient range; however deficiency was defined as 40nmol/L. It is now generally understood that for optimal bone health benefits serum 25(OH)D levels should be above 75nmol/L; which is necessary for adequate suppression of PTH release and stimulation of intestinal calcium absorption. More recently, Oleson (90) and colleagues identified 96% of participants with chronic SCI and less than 55 years of age to be deficient, defined as <80nmol/L. However, their evaluation of vitamin D status excluded individuals consuming greater than 400IU of vitamin D per day; indicating that the true proportion of the chronic SCI population may be less than 96% if those taking supplements exceeding 400IU of vitamin D were included in the analysis. Another more recent study of vitamin D status in individuals with SCI, using the updated definition of deficiency (<75nmol/L), found 93% to have inadequate 25(OH)D levels (69). This study was limited to an inpatient rehabilitation setting of acutely injured patients. The 25(OH)D levels were assessed at the time of admission to rehab and therefore cannot be applied to out-patients in the chronic years after injury. Although a high prevalence of vitamin D deficiency in individuals with SCI has been suggested, gaps in the literature remain for community dwelling males and females at varying times post injury. The current study demonstrates vitamin D status in a group of males and females with chronic SCI, including a diverse range of impairments. Given many of the current study population were being monitored annually regarding their bone health and being treated

for low BMD at the time of data collection, the true prevalence of vitamin D deficiency in the SCI population may be higher than estimated, and may be closer to that in the non-SCI population. In the non-SCI post-menopausal osteoporotic population, 64% of people have been shown to have suboptimal serum 25(OH)D levels (94). Of the 38% found to have suboptimal serum 25(OH)D in the current study, 73% reported being on a vitamin D supplement, demonstrating that even in those being treated with supplements, serum 25(OH)D concentrations are not reaching optimal levels and indicate that greater supplementation and additional monitoring is necessary. Additionally, a major source of acquiring vitamin D is through sun exposure, therefore quantifying the amount of sun exposure in participants may increase our understanding of vitamin D status in this population. The current work confirms that vitamin D deficiency is prevalent and a concern in the chronic SCI population, however the proportion of those with suboptimal vitamin D levels may be higher than estimated. Supplementation alone may not ensure optimal levels suggesting serum 25(OH)D should be monitored over time in each person with an SCI, with supplements prescribed on an individual basis.

Correlates of suboptimal vitamin D status exist in the chronic SCI population and should be considered when evaluating vitamin D status and identifying those at higher risk of deficiency. Factors that influence the risk of having suboptimal vitamin D status in the non-SCI population include: obesity (88), living at latitudes where the wintertime zenith angle of the sun is not sufficient to initiate synthesis of 25(OH)D in the skin (52; 95), older age (49; 96), high skin pigmentation (62; 97), having a diagnosis of osteoporosis (98), and the techniques used to measure vitamin D (61). Results of the current study identified correlates of suboptimal vitamin D status to be: vitamin D status assessed in the winter months, not taking a vitamin D supplement, not taking a calcium supplement and younger age. More specifically, with respect

to the associated increased risk of deficiency with measurements assessed in the wintertime, of the 12 25(OH)D measurements obtained in the winter months, 8 were in the suboptimal range, whereas 6 out of the 27 measurements obtained in the summer months were in the suboptimal range. With cautious regard to the small sample of measurements obtained in the winter months, it is suggested that in the SCI population supplement use and increased dietary intake of vitamin D may be necessary to decrease the odds of having suboptimal vitamin D levels. Additionally, it may seem obvious that if not taking a vitamin D supplement, one would be at an increased risk of being vitamin D deficient; however this finding emphasizes that individuals with SCI are not acquiring enough vitamin D through sun exposure or in their diet to put them in the optimal vitamin D range for health benefits. Opperman (71) reported vitamin D and calcium supplement use to be in the top three supplements used in the SCI population, and given that vitamin D is often prescribed in conjunction with calcium supplementation to maximize the calcium absorption, it is not surprising that those not taking calcium supplements are at an increased risk of vitamin D deficiency. In a larger sample, assessing the odds of suboptimal vitamin D levels in those not taking calcium supplements, when the variance associated with not taking a vitamin D supplement is removed, would help discern whether or not taking a calcium supplement is truly associated with an increased risk of vitamin D deficiency. Interestingly, in the evaluated group of individuals with SCI, being younger was associated with an increased odds of suboptimal serum 25(OH)D levels. In the non-SCI population, declining bone health is generally problematic for older individuals, and therefore younger people may not be as aware of the importance of vitamin D to their bone health. Perhaps younger individuals with SCI are unaware that their bone health declines post-injury regardless of their age, and therefore may not be concerned with vitamin D supplementation. Alternatively, vitamin D metabolism in younger individuals with

SCI may be different to that of older individuals with SCI. Decreased renal function, common post-SCI, and history of medication use may affect older and younger individuals differently. Repeat results in a much larger sample is necessary to warrant further investigation into the mechanism in which younger age increases the odds of vitamin D deficiency in the SCI population. Future studies evaluating the vitamin D status in individuals with chronic SCI should also assess correlates of vitamin D deficiency to identify those at highest risk for having suboptimal vitamin D status. The current results suggest that assessing vitamin D status in the winter months, not taking a vitamin D supplement, not taking a calcium supplement and younger age should be factors targeted when evaluating risk of vitamin D deficiency in individuals with chronic SCI, and should be used in future models predicting deficiency.

5.2.2. RELATIONSHIP BETWEEN 25(OH)D AND BONE QUALITY OUTCOMES

No relationships were observed between serum 25(OH)D and bone health outcomes in our cohort of individuals with chronic SCI. In the non-SCI population, hip BMD, a common site of fracture, is shown to be significantly correlated with serum 25(OH)D in women over 60 (30). Similarly, in men over the age of 55 years, 25(OH)D level is identified as a significant determinant of hip BMD (99). Further, an intervention trial with 400 IU of vitamin D and 1000 mg of calcium supplementation per day, in post-menopausal women, demonstrated increased hip BMD compared with a placebo group (100). Due to the proposed relationships between vitamin D and bone loss in the non-SCI population, vitamin D has been suggested to be a modifiable factor potentially affecting BMD in the chronic stages of SCI (31). To date, few studies identify if vitamin D deficiency is actually prevalent in individuals with SCI (69; 90), and no studies have identified what the relationship between 25(OH)D and bone quality is in the SCI population.

Previous work regarding vitamin D and bone health in individuals with SCI has evaluated the effect of vitamin D supplementation on serum vitamin D status (72), as well as the effect of vitamin D analog supplementation on lower extremity aBMD (73). The current study demonstrated 38% to have suboptimal vitamin D levels. Interestingly, even though a significant proportion of the population studied demonstrated suboptimal vitamin D levels, and a large proportion of the study sample had aBMD values measuring below the fracture threshold, there were no significant relationships between 25(OH)D levels and bone quality outcomes. It is possible that the reason no relationship was observed between bone quality outcomes and 25(OH)D is because all the other factors known to influence the variation of bone loss in the SCI population were not adjusted for in the current analysis, due to the small sample size. Factors known to increase the risk of lower extremity fractures or low BMD following an SCI include: BMI less than 19 (6), having a duration of injury greater than 10 years (16), being female (16), having a motor complete injury (101), being paraplegic (17), having secondary hyperparathyroidism (31), not being treated with a bisphosphonate (102) and excessive cigarette smoking (103; 23). Therefore, the true relationship between 25(OH)D and bone quality may be masked by the variation in bone density due to, for example, having a motor complete injury. Additionally, the relationships between 25(OH)D and bone quality outcomes may be better elucidated if vitamin D status is known over a period of time; conceivably it is not vitamin D status today that is associated with BMD today. The serum measurement of vitamin D at one time may not be representative of lifetime vitamin D status, and may be exceptionally high or low depending on factors such as history of vitamin D supplement use, sun exposure and skin pigmentation, as well as season of measurement. In 577 men and 1335 women studied all across Canada, suboptimal (<75 nmol/L) vitamin D levels were evident in about 60% of both men and

women in the spring and up to 78% in the winter (104). Further, in 351 young men and women studied prospectively in the Toronto area, mean serum 25(OH)D levels were lower in the winter at 38.4 nmol/L compared to 54.4 nmol/L in the fall; serum 25(OH)D levels in both the fall in winter were suboptimal, however levels were much lower in the winter (105). Similar to previous work, the current evaluation of factors associated with vitamin D deficiency found supplement use and season of assessment to be significantly associated with suboptimal vitamin D levels. Prospective study of the relationship between serum 25(OH)D and bone health outcomes over more time points would be useful in evaluating the true relationships between these variables. Future investigations should adjust for correlates of bone health and factors associated with vitamin D deficiency in the SCI population to demonstrate the true association between vitamin D and bone quality.

5.2.3. SECONDARY HYPERPARATHYROIDISM AND 25(OH)D AND CALCIUM

Secondary hyperparathyroidism, induced from low serum calcium levels, may be associated with low vitamin D levels in chronic SCI. Vitamin D aids in the suppression of excessive PTH secretion by increasing serum ionized calcium levels through enhanced intestinal calcium absorption. Based on the known function of vitamin D in maintaining serum calcium levels, it is expected that in a population without known primary hyperparathyroidism, lower serum 25(OH)D levels would be associated with higher PTH levels, and that higher PTH levels would also be associated with lower serum ionized calcium levels. Identifying such a relationship provides evidence that serum vitamin D level could be an important mediator in PTH stimulated resorption of calcium stores in bones. An inverse relationship between serum 25(OH)D and intact PTH has been demonstrated in older persons with no SCI (106; 107). In addition, serum

PTH has been shown to fluctuate seasonally with serum 25(OH)D, but in the opposite direction (108), further demonstrating the importance of vitamin D in maintaining normal levels of PTH and minimizing the release of calcium stores from bones. In a group of individuals with long-standing SCI, a significant negative correlation was demonstrated between serum 25(OH)D and PTH illustrating that low vitamin D could be implicated in the bone loss seen in the years following a SCI (29). The current study demonstrated about 15% of the population to have serum PTH above the upper limit of normal. Given that 38% of the population had serum 25(OH)D levels in the suboptimal range, it is somewhat surprising that the number with secondary hyperparathyroidism is not higher. However, the cross sectional design of this study, and the unknown duration that these individuals have been in the suboptimal 25(OH)D range, could influence the number of people demonstrating hyperparathyroidism. Additionally, the threshold of vitamin D needed to maximally suppress PTH release varies in the literature from 30nmol/L to 99 nmol/L (53; 109; 110; 111; 112; 113), and may be different in the SCI population than the non-SCI population. Furthermore, the degree of neurologic impairment in those with SCI has been associated with PTH suppression (114), hence grouping all impairments may be why closer to equal proportions of suboptimal vitamin D and hyperparathyroidism were not demonstrated. The current study demonstrates the expected trend between serum 25(OH)D levels and serum intact PTH. Additionally, the trend towards an inverse relationship between serum intact PTH and ionized calcium was also demonstrated. Furthermore, a significant positive relationship was seen between serum C-Telopeptide and serum intact PTH; identifying that higher PTH levels are associated with more bone resorption. In this group of individuals with SCI, lower levels of 25(OH)D likely contribute to decreased calcium absorption and increased PTH secretion. Further, adequate calcium and vitamin D are important in those with chronic SCI for bone health

maintenance through minimizing PTH stimulated bone resorption. To better understand the relationship between serum intact PTH and serum 25(OH)D, particularly in individuals with known renal dysfunction, measurement of $1,25(OH)_2D$ would help identify if low 25(OH)D is truly leading to the high PTH levels. Based on the relationships demonstrated in the current study it is suggested that in those with chronic SCI the serum 25(OH)D threshold for maximum suppression of PTH is around 125 nmol/L. With a larger sample of individuals with chronic SCI, it would be interesting to evaluate at which level of 25(OH)D the PTH plateaus, aiding in identifying whether the optimal 25(OH)D level in the SCI population matches the currently used standard of 75nmol/L or is closer to the 125 nmol/L identified in the current cohort of males and females with chronic SCI.

5.2.4. RELATIONSHIP BETWEEN PTH AND BONE QUALITY OUTCOMES

Identifying a relationship between PTH and bone quality outcomes would provide evidence that the vitamin D-PTH axis is a modulator of bone health in SCI. No correlation was found between PTH and aBMD parameters. One explanation for this could be that DXA is not sensitive enough to distinguish differences in bone health due to differences in PTH. Cortical and trabecular compartments of bone cannot be separated when analyzing DXA scans. Hyperparathyroidism, a common complication of chronic kidney disease, has been shown to influence cortical measures of bone in the non-SCI population (115). Further, in a group of men and women with chronic kidney disease, cortical vBMD, thickness, and area were associated with fractures (83). In chronic kidney disease, the renal hydroxylation of 25(OH)D decreases regardless of the amount of circulating 25(OH)D (116), which decreases vitamin D assisted intestinal calcium absorption and thereby increases the stimulation of PTH secretion. Although fractures in the SCI population

have mostly been attributed to trabecular bone loss (13), to fully understand the impact of suboptimal vitamin D status for bone quality in SCI, it is important to identify any association between PTH and cortical bone parameters given prior implications on cortical bone in populations with hyperparathyroidism. In the current study there were weak negative, non-significant correlations found between PTH and vBMD at both the 4% and 66% sites; however, PTH was shown to moderately correlate in the negative direction with cortical thickness, and approached significance. Results from the current study suggest that higher levels of PTH may be associated with smaller cortical thicknesses. With a larger sample, allowing for control of other factors that contribute to the bone loss post-SCI, certain subgroups of the SCI population with PTH associated low cortical bone parameters could be distinguished. The results, although not what was completely expected based on previous literature, indicate that the vitamin D-PTH axis is important to bone health in the SCI population. Perhaps the primary implication of low vitamin D and high PTH in the SCI population is linked to cortical thickness, and while not regarded as the best indicator of fracture prediction in this population, it does contribute to overall bone health.

5.3.0. LIMITATIONS

The current study has limitations that must be considered carefully when making conclusions. The cross-sectional design of the current study did not allow for any conclusions regarding the chronology of any observations made, nor causality of the relationships. The results cannot distinguish between newly occurring or longstanding suboptimal vitamin D levels, low aBMD, low vBMD, or cortical thickness measurements. Cross-sectional study design is particularly problematic when assessing bone health outcomes due to the length of time of the bone turnover

cycle. The physiological process of bone resorption could be initiated months before lower bone density is detected on a bone density scan, therefore, the serum 25(OH)D level at the time of BMD measurement may not reflect the true relationship between it and the bone quality parameters assessed. The current study design and exploratory correlational analyses were employed to identify the potential importance of serum 25(OH)D level for evaluating bone health in the SCI population. To establish an actual causal relationship between vitamin D deficiency and bone health outcomes, it would have to be demonstrated that variation in the bone health outcomes could only be due to the variation in serum 25(OH)D level, and that no other variables are causing them to co-vary. Additionally, assessments of vitamin D status over time could reveal the importance of vitamin D to bone health in the SCI population.

All potential correlates of poor bone quality or low vitamin D levels could not be accounted for, as well the sample size achieved did not allow for correlates of poor bone health outcomes, or factors known to influence vitamin D status to be controlled for. Some types of drugs taken by participants in the current study, such as anticonvulsants, can effect vitamin D metabolism in the body, and thus affect the apparent relationships observed. Serum 25(OH)D levels were shown to decline below normal after six months of taking anticonvulsant drugs (117). Additionally, calcium and vitamin D supplements consumed in this population may vary from what was reported by participants, depending on adherence to supplement use and their dietary intake. Better assessment of calcium and D supplements use could change the risk factors associated with suboptimal vitamin D levels. Other factors that may influence vitamin D status or bone health outcomes, that were not assessed include: sun exposure and sex hormone levels. Quantifying the amount of sun exposure is difficult and depends on other factors such as: time of day, whether sunscreen was used, skin exposure and pigment, as well as others. Although sun

exposure could not be included in the analysis, we attempted to account for some aspect of this factor by looking at season as a risk factor. Low sex steroid hormones have been significantly associated with faster rates of BMD loss in older men with no SCI (118). Additionally, it has been suggested that 60% of men with SCI have low testosterone levels (119). Future studies evaluating the relationship between bone parameters and vitamin D should evaluate the interaction of sex steroid hormone levels. To infer that the relationships between 25(OH)D and the bone health outcomes assessed in the current study are not masked, attenuated, or amplified, the variance associated with all the variables known to affect bone health outcomes and serum 25(OH)D would have to be controlled for in a much larger sample of individuals with chronic SCI.

The results of the current study may not be generalizable to all individuals with SCI. Many of the participants were recruited from physician referral at the bone clinic in outpatient services at the Toronto Rehabilitation Institute, thereby introducing some degree of recruitment bias. As a result, many of the participants were currently on treatment for low bone mineral density. Participants had been prescribed treatments including: bisphosphonte drugs, calcium and vitamin D supplements, and exercise. In a group of men with motor complete SCI's treated with bisphosphonates, BMD decline was demonstrated to slow over a 2 year period (91). However, prevalence of suboptimal 25(OH)D in a non-SCI population was shown to be independent of whether or not persons were on prescription osteoporosis treatment (58). Therefore, although the serum 25(OH)D status of our population may not be affected by bisphosphonate use, the true relationship between 25(OH)D and bone health measures may be masked in those participants taking bisphosphonate drugs. Additionally, our participants had an average time post injury of about 15 years. We know that bone loss in this population is considerably different in the first

few years post injury when compared to many years post injury (23) therefore no conclusions can be made about the relationship between vitamin D status and BMD in the early years post-injury. Some participants included in our study were unable to have their aBMD measured in the knee region as a result of having hardware from a previous fracture, likely due to low aBMD. Therefore, we may not have captured well the relationship between 25(OH)D and bone quality measures in those with severe enough bone loss to cause fracture. Furthermore, three-quarters of the population studied were male and two-thirds of the population had motor complete injuries. Although the study population may correctly represent the demographics of the SCI population, it did not allow for subgroup analysis to distinguish who specifically in the SCI population may have an association between bone quality and vitamin D levels. The current study mainly consisted of older individuals, the average age at data collection was 51 years, however many individuals have their SCI when they are quite young; consequently, there is an underrepresentation of young people with SCI. Although there are some factors affecting the external validity based on the demographics of the population studied, there is no other literature evaluating vitamin D status and the relationships between serum 25(OH)D and bone quality in a well-represented cohort of individuals with SCI.

One final potential source of bias comes from measurement uncertainty. It is suggested that serum 25(OH)D assays can measure vitamin D levels 10% lower or higher than the true serum level (120). Therefore, someone measuring near the optimal vitamin D cut-off level may be misplaced in either the optimal or suboptimal group, either overestimating or underestimating the number of participants presenting with optimal vitamin D levels. In the current study all samples were measured at the same lab, with the same technique, in attempt to limit bias introduced from the serum 25(OH)D assessment technique.

5.4.0. CONCLUSIONS

The prevalence of vitamin D deficiency and the relationship between serum 25(OH)D or PTH and bone quality has not been well evaluated in individuals with chronic SCI. About 40% of the population studied demonstrated suboptimal vitamin D levels, despite a large proportion taking vitamin D and calcium supplements. Identified risk factors for suboptimal vitamin D levels in the SCI population include: assessing vitamin D in the winter months, not taking vitamin D or calcium supplements, and being younger; suggesting that many individuals with SCI are not obtaining sufficient quantities of vitamin D in their diet or through supplementation, particularly in the winter months. The observed trend towards negative correlations between PTH and 25(OH)D and between PTH and ionized calcium identify that disruption in the vitamin D-PTH axis could be important to the bone loss seen in the chronic SCI population. Further, a trend towards a negative association between PTH levels and cortical thickness measures was observed. Serum 25(OH)D level, therefore may be important for bone health in the SCI population through maintaining adequate serum calcium and normal PTH levels. The current study adds unique value to vitamin D and bone quality research in SCI. The current study provides the framework for future investigations of the relationships between 25(OH)D and bone quality in SCI, with high external validity. Ultimately, identifying a relationship between a disrupted Vitamin D – PTH axis and bone quality could contribute to the development of an SCI specific fracture risk assessment tool.

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APPENDIX A

RECRUITMENT AND DATA COLLECTION

1. Physician referral form
2. Letter of invitation
3. Recruitment script
4. Telephone screening form
5. Information and consent
6. Additional screening forms
7. Past medical history
8. Disease/conditions affecting BMD
9. Current health status
10. Concurrent medications
11. Health demographics
12. Fracture ascertainment questionnaire
13. Food frequency questionnaire
14. Penn Spasm Frequency Scale
15. Participant feedback letter

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Insert patient label here

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

Background: A cohort of 80 adult men and women, two years post SCI, 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 Robertson (x6301, room 206-D)

Thanks!

_____

Date Signature of Physician

Bone quality in individuals with chronic spinal cord Injury

Primary Investigators:
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<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 of Toronto Rehabilitation Institute 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 Deborah Mazzetti of Office of the Chair of Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board at (905) 521- 2100 x42013.

Telephone Script for Recruitment

"Hello, my name is _____ and I am calling from Lyndhurst Centre about a research study that is being conducted by Dr. Craven at Toronto Rehab, Dr. Lora Giangregorio at the University of Waterloo and several other researchers. Did you receive a letter in the mail about it? (Did Dr. _____ speak to you about this study?)"

If YES, continue with script. **If NO, tell them you can mail the letter and let them read it and then call back, or you can explain it now.**

"It is a research study that will explore bone health among individuals with spinal cord injury, and determine how bone health changes over time. Individuals who participate in the study will be asked to report their medical history and participate in a medical exam and bone density tests once a year for two years. An honorarium for travel expenses will be provided. I can explain the study in more detail if you would like to hear more. Does this sound like something you might be interested in?"

If YES, continue with script. **If NO, move to refusal questionnaire script.**

"Before I go into more detail explaining the study, I would like to know if you fit the criteria for being in the study. I have a few questions I would like to go through with you to determine if you are eligible. Do you have a few minutes to do this now?"

If YES, continue with pre-screening. **If NO, ask if there is a better time for you to call. Record this time.**

"Before I begin, let me remind you that you can decide not to answer any questions or decide not to be in the study at any time."

Begin filling out pre-screening form.

If this person is **NOT** eligible for the study, thank them for taking the time to answer your questions. Explain that they do not fit all of the criteria for entering the study.

If they **ARE** eligible for the study, thank them for taking the time to answer your questions. Indicate they may be eligible, and you would like to tell them more about the study.

"As I mentioned before, the study will explore bone health among individuals with spinal cord injury. We are interested in finding out if people who have a chronic spinal cord injury continue to lose bone, and use new technologies to assess their bone health. The study involves coming to Lyndhurst centre for one visit per year for three years, as well as one visit to McMaster University each year. Each annual visit to Lyndhurst will take approximately 2 hours during which; you will complete a medical history and undergo a short examination, and have your bone density measured. Each annual visit to McMaster University will take 30 minutes; you will have two bone density scans done on your lower leg (shin). We can arrange for transportation to McMaster for you. We also provide a $40 honorarium each year when you complete your visit to

cover any additional costs you may have. Do you have any questions so far?"

If YES, answer any questions. **If NO, continue with pre-screening.**

"If you think you might be interested in participating in the study, the next step is to have you come to Lyndhurst to learn about the study in more detail. If you change your mind and do not want to participate, you can decline participation at any time. Declining will have no impact on the health care you receive at Lyndhurst. If you are still interested in participating we will have you read the information package and complete a consent form before your first assessment. The information and consent process will take one hour, and the assessments will take approximately 2 hours. We will then arrange for you to go to Hamilton for your visit there. Do you think you might be interested in participating in the study?"

If YES, schedule a date/time. **If NO, continue with refusal questionnaire.**

We want to inform you that this project has been reviewed and received ethics clearance through the University of Waterloo's Office of Research Ethics and the Toronto Rehab Research Ethics Board.
If you have any further questions you may contact me at: 416 597 3422 x 6301.

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 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).	☐	☐	
4.	"When did you have your spinal cord injury?" Potential participant's spinal cord injury occurred at least 24 months prior to screening.	☐	☐	
5.	"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.	☐	☐	
6.	"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 Investigator: Kayla Hummel, Dept. of Kinesiology, University of Waterloo
Sponsor: Canadian Institutes of Health Research

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 be aware of 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 involve 10-15 hours of your time over a 2 year period. If you decide to participate in the study, we will ask you to do the following things:

Visit to Lyndhurst (Toronto) or Chedoke (Hamilton)

- 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 (American Spinal Cord Injury Association) impairment 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. The blood sample will be used to measure protein markers of bone metabolism and vitamin D levels in your blood. The blood sample will be draw by a trained phlebotomist by inserting a needle in a vein in your arm. We will take about two tablespoons of blood.
- 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. The scanning will take approximately 60 minutes.
- Complete some questionnaires by phone three days after your visit. The questionnaires will ask you questions regarding your physical 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. 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.

Blood draws can also have side effects and discomforts. 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. 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 be reimbursed $40 per visit each year ($120 in total over the course of the study) to assist with transportation costs to Lyndhurst or Chedoke. For participants traveling to Hamilton from the Toronto area (>50km), transportation is provided and you are welcome to have someone accompany you on the trip. For those wishing to use their own transportation for travel between Hamilton and Toronto, the stipend will be increased to $140 per visit.

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:

Dr. Susan Sykes, 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

Deborah Mazzetti, 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 <u>not</u> 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 is different than those who did. You can also choose not to answer these questions; it is entirely your decision. If you do not want tO be in the study but might want to answer the questions, we will review them with you and let you decide. Neither your name nor 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 INVESTIGATOR:

I have delegated the informed consent discussion to _____

_____ _____

Signature of 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 Investigator: Kayla Hummel, Dept. of Kinesiology, University of Waterloo
Sponsor: Canadian Institutes of Health Research

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:

_____	_____	_____
Name	Signature	Date

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐ **Screening**

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

Y Y Y Y M M D D

HAS THE CONSENT FORM BEEN SIGNED? Yes ☐ No ☐

If yes, proceeed

Inclusion Criteria	**Yes**	**No**
Age ≥18 years of age	☐	☐
Able to understand instructions in English	☐	☐
Spinal Cord Impairment of sudden onset for duration of atleast 24 months (sudden onset <24 hours, C2-T10 ASIA A-D with a stable upper motor neuron, neurological deficit of trauma or trauma-like etiology)	☐	☐
Ability to give informed consent	☐	☐

If NO to any of these criteria, the participant should be excluded

Exclusion Criteria	**Yes**	**No**
Current or prior known condition(s) other than paralysis that are known to influence bone metabolism, including;		
Oral glucocorticoid use for >3 months	☐	☐
Known malignancy	☐	☐
Known liver condition	☐	☐
Known malabsorption condition	☐	☐
Other: _____	☐	☐
Weight ≥ 270 lbs	☐	☐
Contraindications to pQCT testing		
Bilateral metal implants	☐	☐
Severe spasticity and known allergy to Ativan	☐	☐
Other: _____	☐	☐

Participant is Male ☐

Participant is Female ☐ *Please provide the following details and complete following page*

If Female:

Participant is Pregnant or planning to become pregnant (Please see following page "Pregnancy Risk and Urine Pregnancy Test")	Yes ☐	No ☐

If YES to any of these criteria, the participant should be excluded

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID | | | | | | |

Screening

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

Y Y Y Y M M D D

Visit **01**

Pregnancy Risk and Urine Pregnancy Test

Please also refer to Exclusion Criteria

Pregnancy Risk		**Comments**
Is the participant of child bearing potential? (unless postmenopausal for 12 months, does not have a uterus and/or ovaries, OR has been surgically sterilized for 6 months prior to study)	☐ Yes ☐ No	

If Yes,

Is the participant a sexually active female?	☐ Yes ☐ No ☐ Not Applicable	
Is the participant using a reliable method of contraception? (hormonal methods or intrauterine device 30 days prior to study, barrier methods plus spermicidae in use atleast 14 days prior to study OR sexual abstinence as a lifestyle)	☐ Yes ☐ No ☐ Not Applicable	
Risks of ionized radiation exposure during pregnancy reiterated?	☐ Yes ☐ No ☐ Not Applicable	

B-Hcg Test		**Comments**
Was the test indicated?	☐ Yes ☐ No	
Was the test performed?	☐ Yes ☐ No	
If yes, what was the result?	☐ Positive ☐ Negative	

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**

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:_____

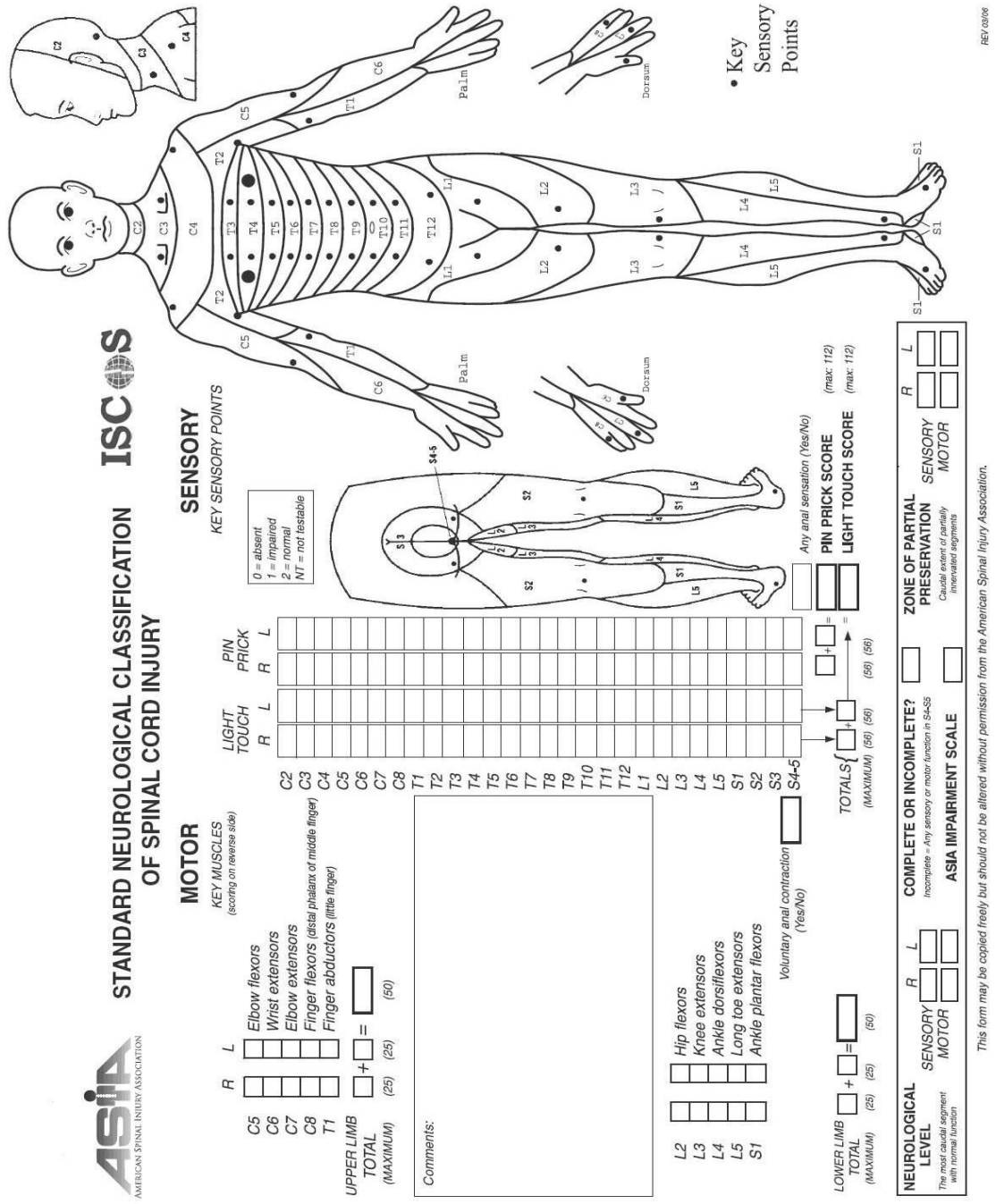
Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID | | | | | | |

Past Medical History

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

Visit **01**



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 → **Is injury motor incomplete?**
  - If **YES**, AIS=A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)
  - If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)
- YES → **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 ☐☐☐☐ / ☐☐ / ☐☐ (Y Y Y Y / M M / D D)

Visit **01**

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: ☐☐☐☐/☐☐/☐☐ (**Y Y Y Y M M D D**) ☐ BEFORE SCI ☐ AFTER SCI

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: ☐☐☐☐/☐☐/☐☐ (**Y Y Y Y M M D D**) ☐ BEFORE SCI ☐ AFTER SCI

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 ☐☐☐☐ / ☐☐ / ☐☐ (Y Y Y Y / M M / D D)

Visit **01**

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 ☐☐☐☐ / ☐☐ / ☐☐ (Y Y Y Y / M M / D D)

Visit **01**

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 ☐☐☐☐ / ☐☐ / ☐☐ (Y Y Y Y / M M / D D)

Visit **01**

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 ☐☐☐☐ / ☐☐ / ☐☐ (Y Y Y Y / M M / D D)

Visit **01**

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 ☐☐☐☐ / ☐☐ / ☐☐ (Y Y Y Y / M M / D D)

Visit **01**

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

Date: ☐☐☐☐/☐☐/☐☐ (Y Y Y Y M M D D)

Anatomic Location :_____

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 | | | | | | |

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 ☐☐☐☐☐☐

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 ☐☐☐☐☐☐

Concurrent Medication

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

Drug			Dates of Use (MM/YYYY is mandatory)
Generic Name ______________ Dose:__________	Route ☐Oral ☐IV ☐IM ☐SC ☐Rectal ☐Topical ☐Other:______	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
	Indication:		
Generic Name ______________ Dose:__________	Route ☐Oral ☐IV ☐IM ☐SC ☐Rectal ☐Topical ☐Other:______	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
	Indication:		
Generic Name ______________ Dose:__________	Route ☐Oral ☐IV ☐IM ☐SC ☐Rectal ☐Topical ☐Other:______	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
	Indication:		

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

1. HAVE YOU EVER FELT YOU SHOULD CUT DOWN ON YOUR DRINKING?
   ☐ YES ☐ NO
2. HAVE PEOPLE ANNOYED YOU BY CRITICISING YOUR DRINKING?
   ☐ YES ☐ NO
3. HAVE YOUR EVERY FELT BAD OR GUILTY ABOUT YOUR DRINKING?
   ☐ YES ☐ NO
4. 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
- ☐ PAIN
- ☐ PRESSURE SORE
- ☐ SPASTICITY
- ☐ HEMORRHOIDS
- ☐ INGROWN TOE NAIL
- ☐ GI BLEED
- ☐ LOW BLOOD PRESSURE
- ☐ SURGERY
- ☐ OTHER (SPECIFY)_____
- ☐ BLADDER INFECTION
- ☐ DEEP VEIN THROMBOSIS
- ☐ CONSTIPATION
- ☐ HETEROTOPIC OSSIFICATION
- ☐ BLADDER/KIDNEY STONES
- ☐ DRUG ADDICTION
- ☐ NEUROLOGIC DETERIORATION
- ☐ GYNECOLOGICAL PROBLEMS

DETAILS:

_____

_____

_____

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)

(b) 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 Ascertainment Questionnaire

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

Visit ☐☐

Phone Call ☐☐

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

1. What was the date of the fracture?

☐☐☐☐/☐☐/☐☐
Y Y Y Y M M D D

☐ Don't know

2. 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

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 ☐☐

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

☐ 1 Incident

☐ 2 Fragility

4. 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) _____

5. What time of day did the fracture occur?

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

6. 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 Ascertainment Questionnaire

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

Visit ☐☐

Phone Call ☐☐

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

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

☐ Hospital (go to question 10)
☐ Physician's office (go to question 11)
☐ Home (go to question 12)
☐ Other (go to question 12)

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

☐ Hospital (go to question 10)
☐ Physician's office (go to question 11)
☐ Home (go to question 12)
☐ Other (go to question 12)

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 ☐☐

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 Ascertainment Questionnaire

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

Visit ☐☐

Phone Call ☐☐

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	☐☐☐	☐☐☐

13. 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

14. 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 ☐☐☐

15. 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 Ascertainment Questionnaire

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

Visit ☐☐

Phone Call ☐☐

16. As a consequence of your fracture, did you receive help from an attendant?

☐ 1 Yes ☐ 2 No

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

17. 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

18. Since the fracture, have you temporarily given up any of your usual activities?

☐ 1 Yes ☐ 2 No If yes, specify:_____

19. Since the fracture, have you permanently given up any of your usual activities?

☐ 1 Yes ☐ 2 No If yes, specify:_____

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

21. 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 ☐☐☐☐☐☐

X-RAY Form

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

Visit ☐☐

Phone Call ☐☐

Fracture Incident # ☐☐

For each fracture, complete an X-ray Form

1. 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 ☐☐☐☐☐☐

Food Frequency Questionnaire

Date of Assessment ☐☐☐☐ / ☐☐ / ☐☐ Call ☐☐

Y Y Y Y M M D D

Food Type	Standard Serving Size	Usual Serving Size	Frequency					Frequency serving size	Mg Calcium per portion	Mg Calcium per month
			A Each Day	B Each week	C Each Month	D < Once a Month	E Never			
1. Milk (any type)	250 mL								308	
2. Ice cream or other	250 mL								211	
3. Hard Cheese	3 cm^3 or 1g slice								210	
4. Yogurt	250 mL								305	
									TOTAL	

Average Dietary Calcium (mg/day) = Total of mg Calcium Per Month / 30 = ☐☐☐☐.☐ mg/day

Please update participant's contact information and obtain an alternate contact, in the event that the participant becomes unreachable in future.

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Spasm Frequency & Severity Scale

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

Visit ☐☐

SPASM FREQUENCY		
0 = No Spasm 1 = Spasm induced only by stimulation 2 = Infrequent spontaneous spasms occurring less than once per hour 3 = Spontaneous spasms occurring more than once per hour 4 = Spontaneous spasms occurring more than ten times per hour		
Right		Left
☐0 ☐1 ☐2 ☐3 ☐4	Arm	☐0 ☐1 ☐2 ☐3 ☐4
☐0 ☐1 ☐2 ☐3 ☐4	Leg	☐0 ☐1 ☐2 ☐3 ☐4
☐0 ☐1 ☐2 ☐3 ☐4	Trunk	☐0 ☐1 ☐2 ☐3 ☐4
SPASM SEVERITY		
1= Weak 2 = Moderate 3 = Strong		
Right		Left
☐1 ☐2 ☐3	Arm	☐1 ☐2 ☐3
☐1 ☐2 ☐3	Leg	☐1 ☐2 ☐3
☐1 ☐2 ☐3	Trunk	☐1 ☐2 ☐3

If severe and frequent lower extremity spasticity, complete following page prior to administration of Ativan and pQCT scan

Assessors Initials:_____

Bone Quality in Individuals with Chronic Spinal Cord Injury

Participant ID ☐☐☐☐☐☐

Ativan Safety Form

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

Visit ☐☐

If severe and frequent lower extremity spasticity, complete this form.

	Yes	No
Is Ativan indicated?	☐	☐

Any contraindication to Ativan administration?	☐	☐
Is the participant currently taking ketoconazole or itraconazole?	☐	☐
Does the participant have a history of respiratory insufficiency?	☐	☐
Does the participant us BT-PAP or C-PAP at night?	☐	☐
Does the participant have a history of allergy or adverse reaction to Ativan?	☐	☐
Are there any concomitant medications that may interact with Ativan (Viagra, Narcotics, SSRIs)	☐	☐
If contraindications, subject should <u>NOT</u> be given Ativan prior to pQCT		

Was Ativan administered?	☐	☐

Primary Investigators:
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Dr. Catharine B. Craven

Co-investigators:
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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

Feedback for Research Participants

Title of Study: Bone quality in individuals with chronic spinal cord injury

Primary Investigators: Dr. Lora Giangregorio and Dr. Cathy Craven

Contact Information for Primary Investigators:

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Student Investigator: Kayla Hummel **khummel@uwaterloo.ca**

Funding Source: Canadian Institutes of Health Research

Recently you took part in a research study where your bone health was evaluated. We would like to thank you for taking the time to participate in the study. The purpose of the study was to better understand how bone changes occur after spinal cord injury.

The main findings of the study are as follows:

(include findings here in point form)

Please remember that any data pertaining to yourself as an individual participant will be kept confidential. Once all the data are collected and analyzed for this project, I plan on sharing this information with the research community through seminars, conferences, presentations, and journal articles

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, Toronto Rehabilitation Institute of Research Ethics Board at (416) 597-3422 x 3730 or Dr. Susan Sykes of University of Waterloo Research Ethics Board at 519-888-4567, x 36005, ssykes@uwaterloo.ca or Deborah Mazzetti of Office of the Chair of Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board at (905) 521- 2100 x42013.

APPENDIX B

FIGURES

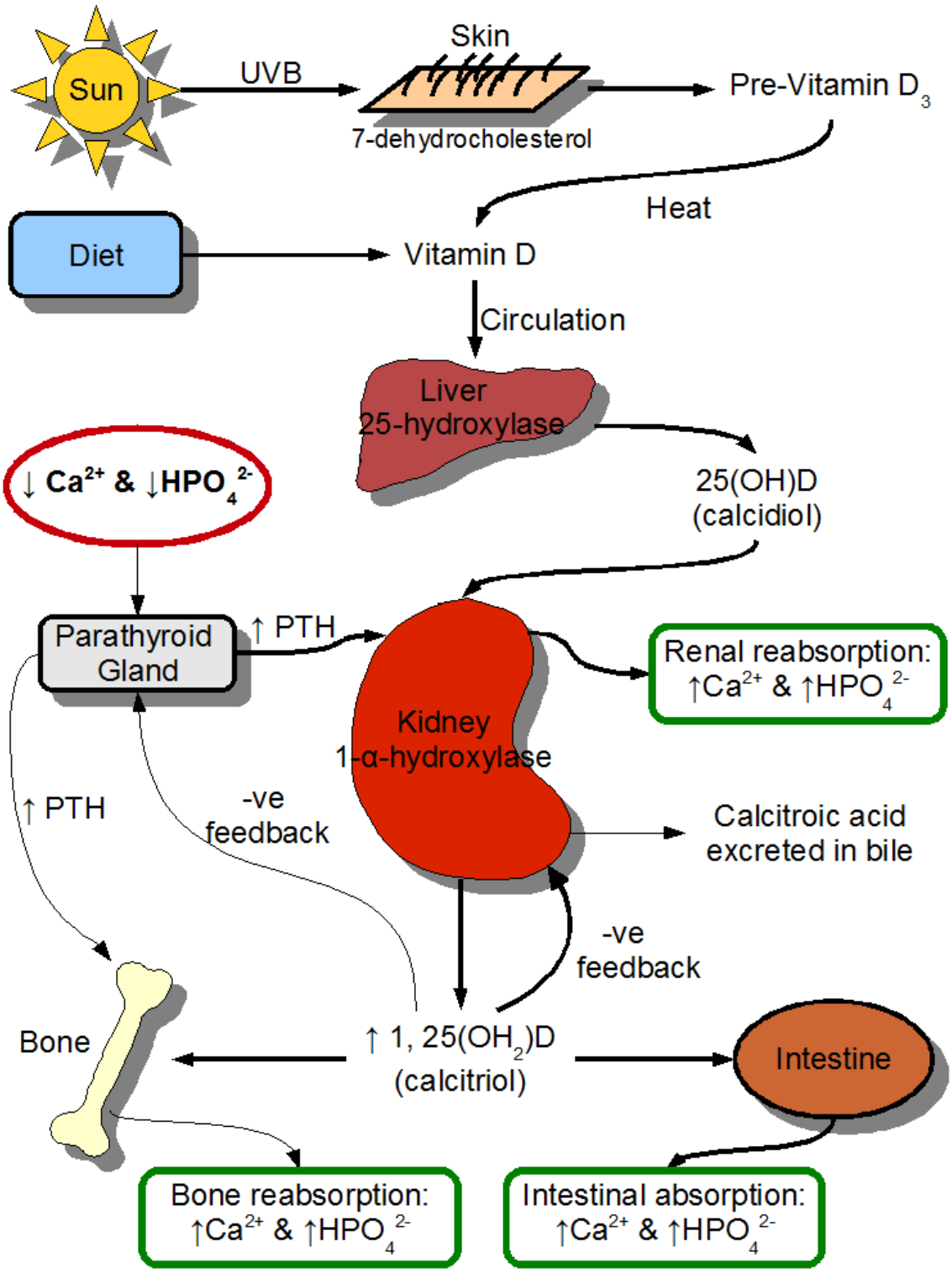

Figure 1. Vitamin D metabolism and its role in bone tissue, kidneys and intestine

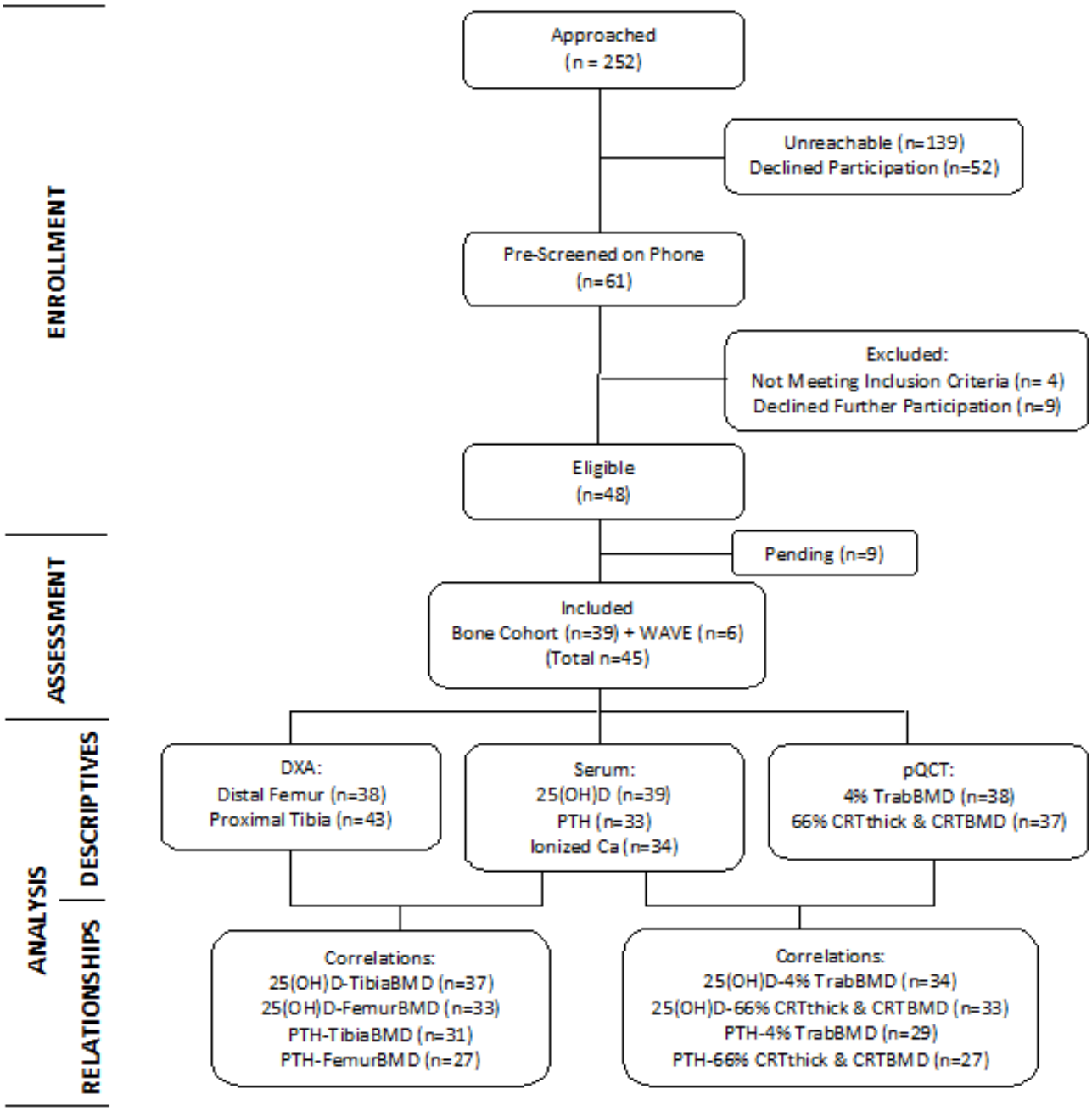

Figure 2. Participant recruitment flow diagram

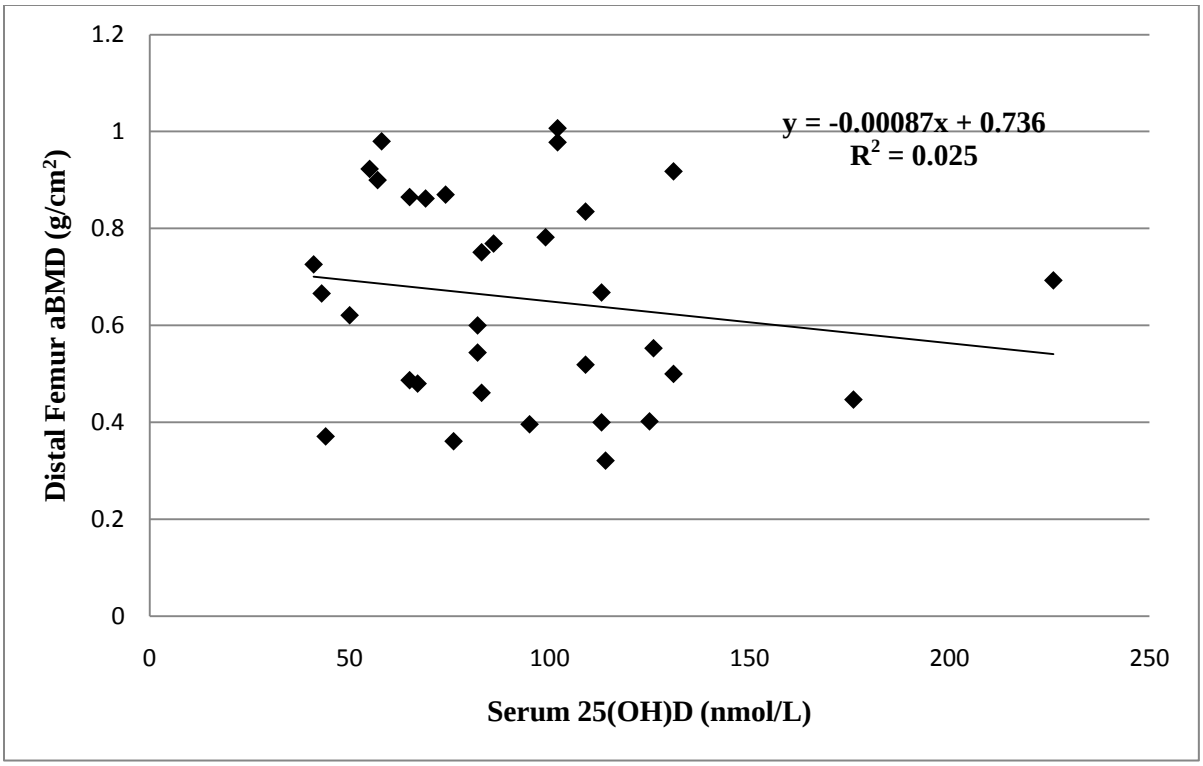

Figure 4. Linear regression of distal femur aBMD (g/cm^2) and serum 25(OH)D (nmol/L).

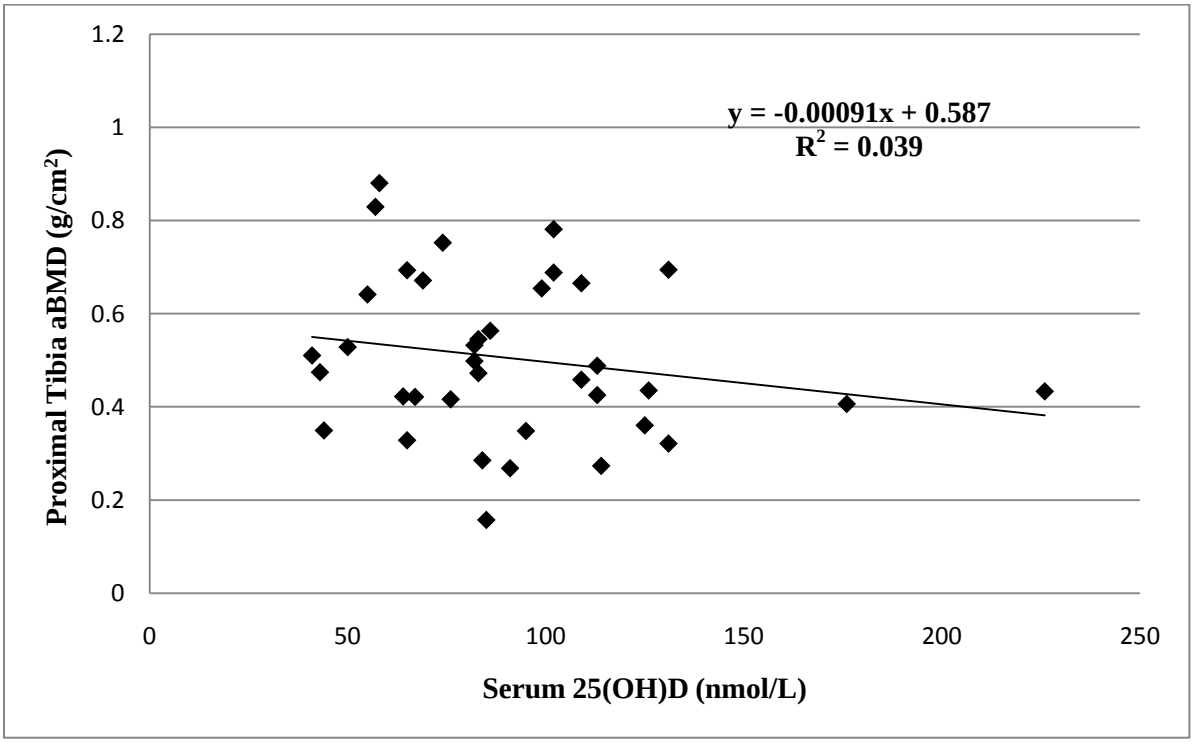

Figure 5. Linear regression of proximal tibia aBMD (g/cm^2) and serum 25(OH)D (nmol/L).

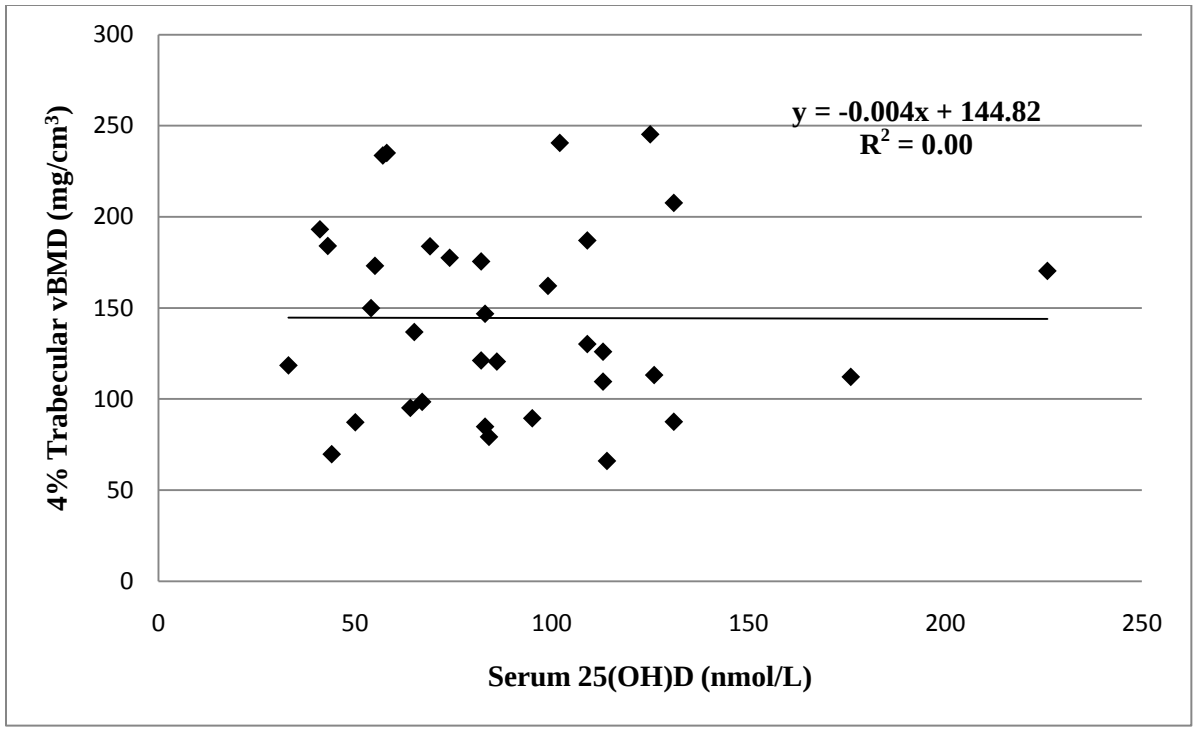

Figure 6. Linear regression of 4% tibia trabecular vBMD (mg/cm^3) and serum 25(OH)D (nmol/L).

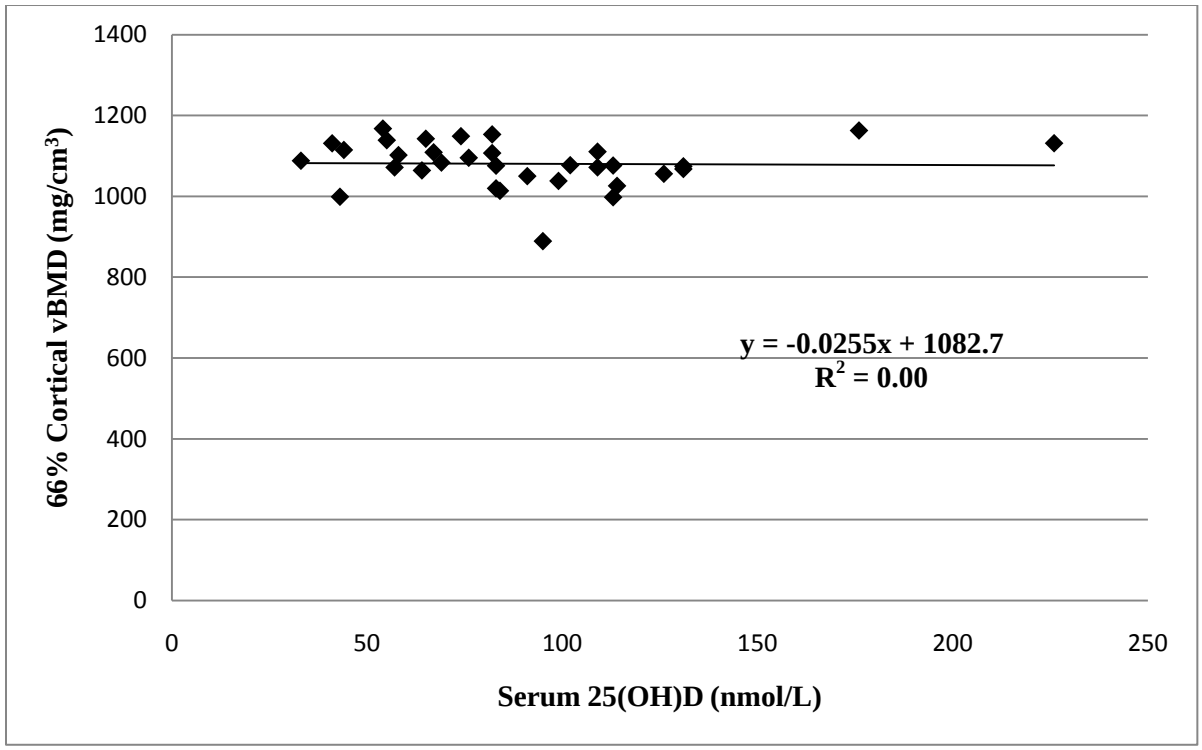

Figure 7. Linear regression of 66% tibia cortical vBMD (mg/cm^3) and serum 25(OH)D (nmol/L).

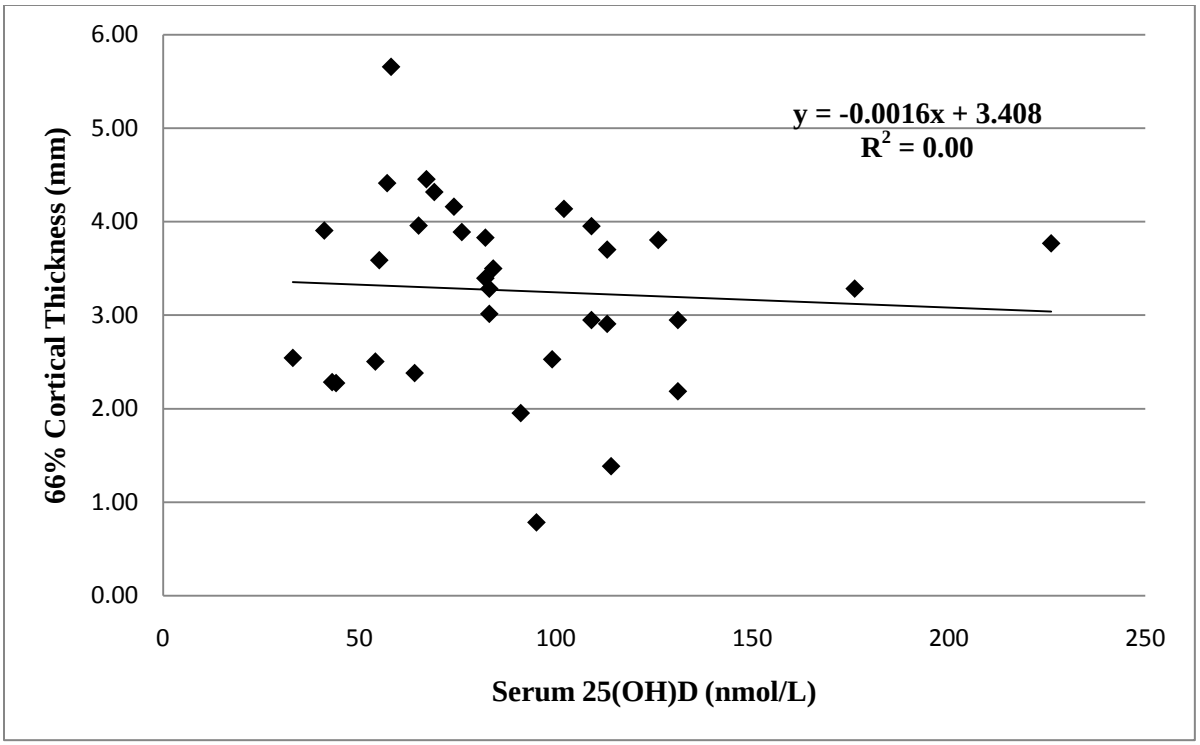

Figure 8. Linear regression of 66% tibia cortical thickness (mm) and serum 25(OH)D (nmol/L).

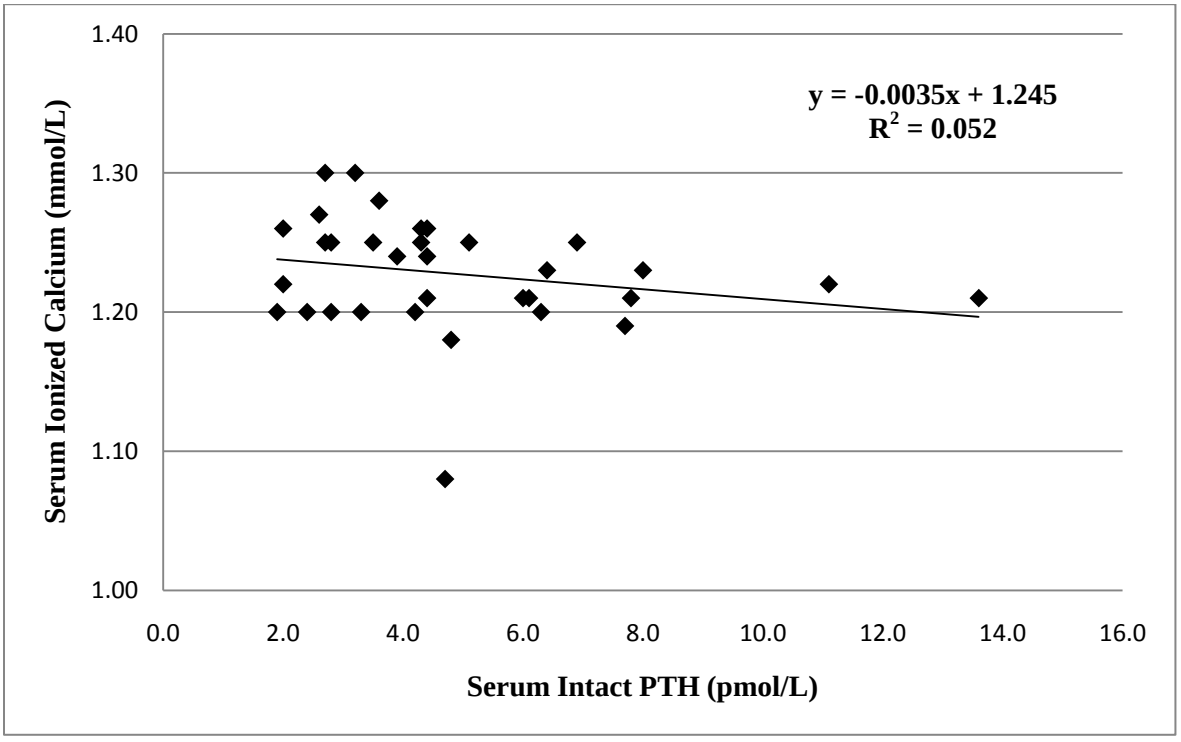

Figure 11. Linear regression of serum ionized calcium (mmol/L) and intact PTH (pmol/L).

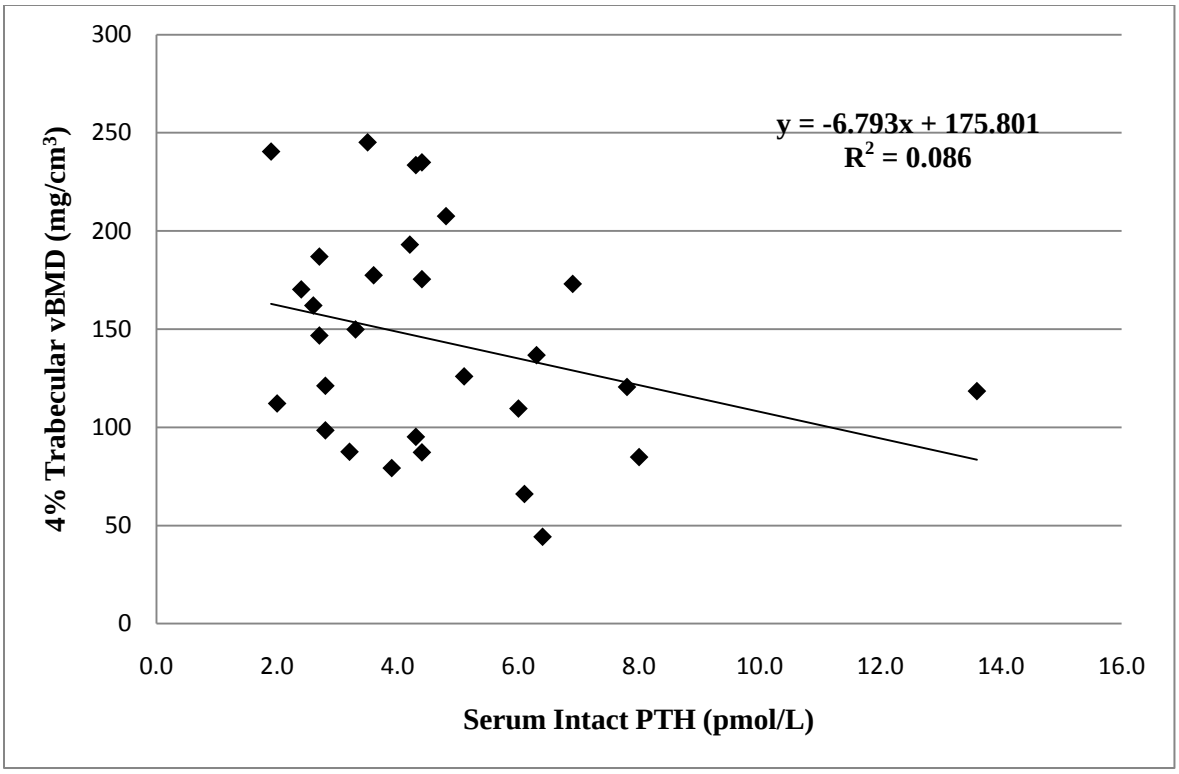

Figure 13. Linear regression of 4% tibia trabecular vBMD (mg/cm^3) and serum intact PTH (pmol/L).

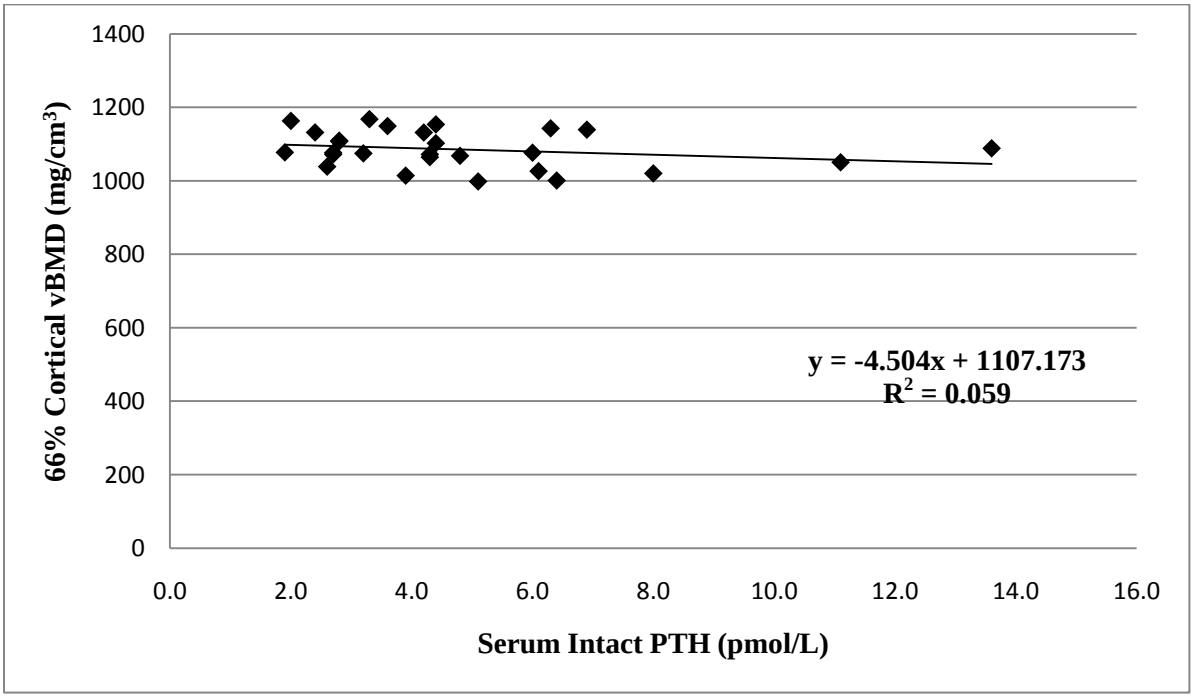

Figure 14. Linear regression of 66% tibia cortical vBMD (mg/cm^3) and intact serum PTH (pmol/L).

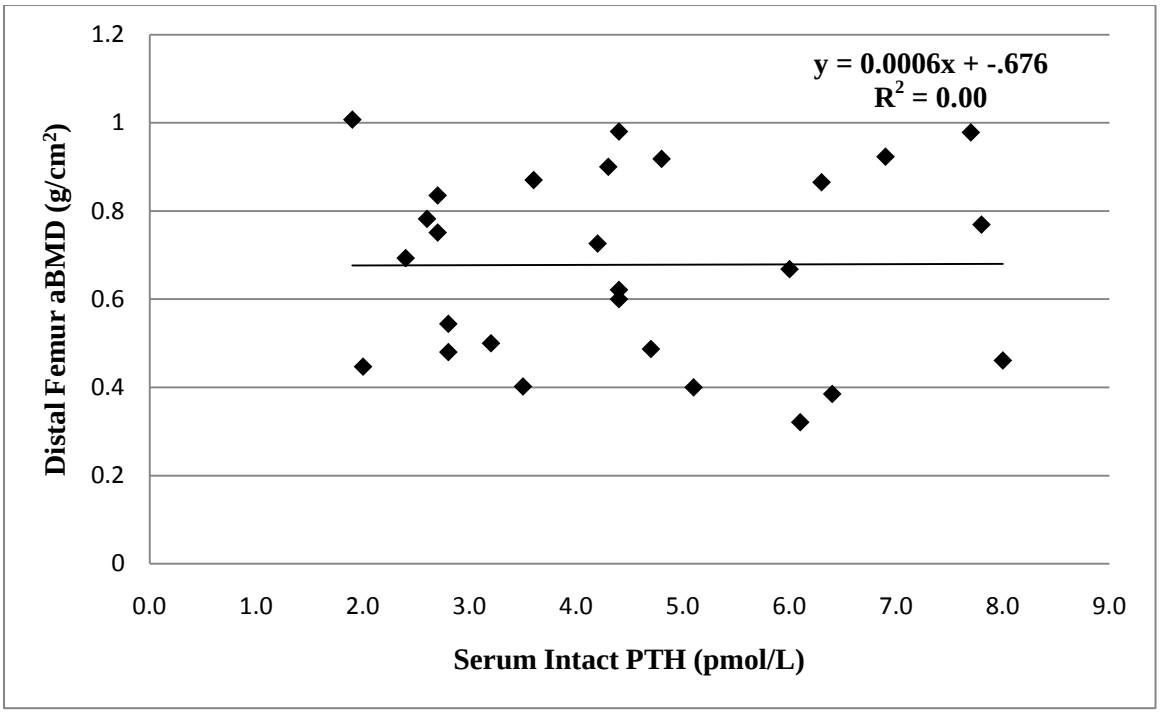

Figure 15. Linear regression of distal femur aBMD (g/cm^2) with serum intact PTH (pmol/L).

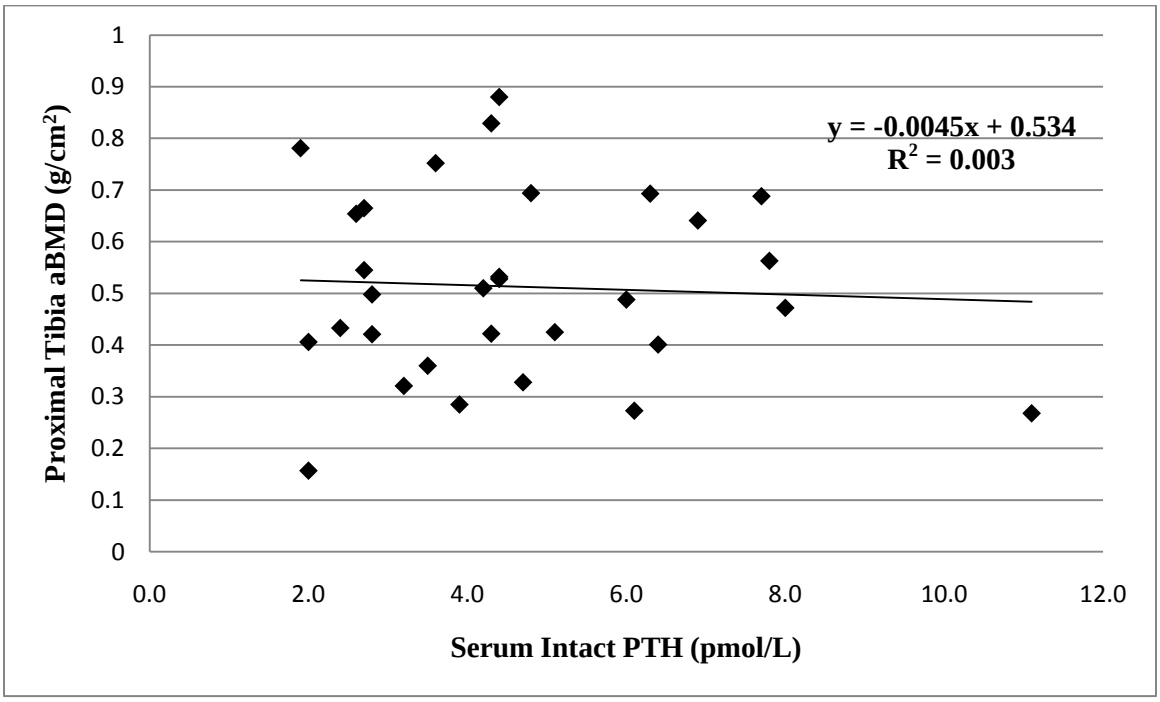

Figure 16. Linear regression of proximal tibia aBMD (g/cm^2) with serum intact PTH (pmol/L).

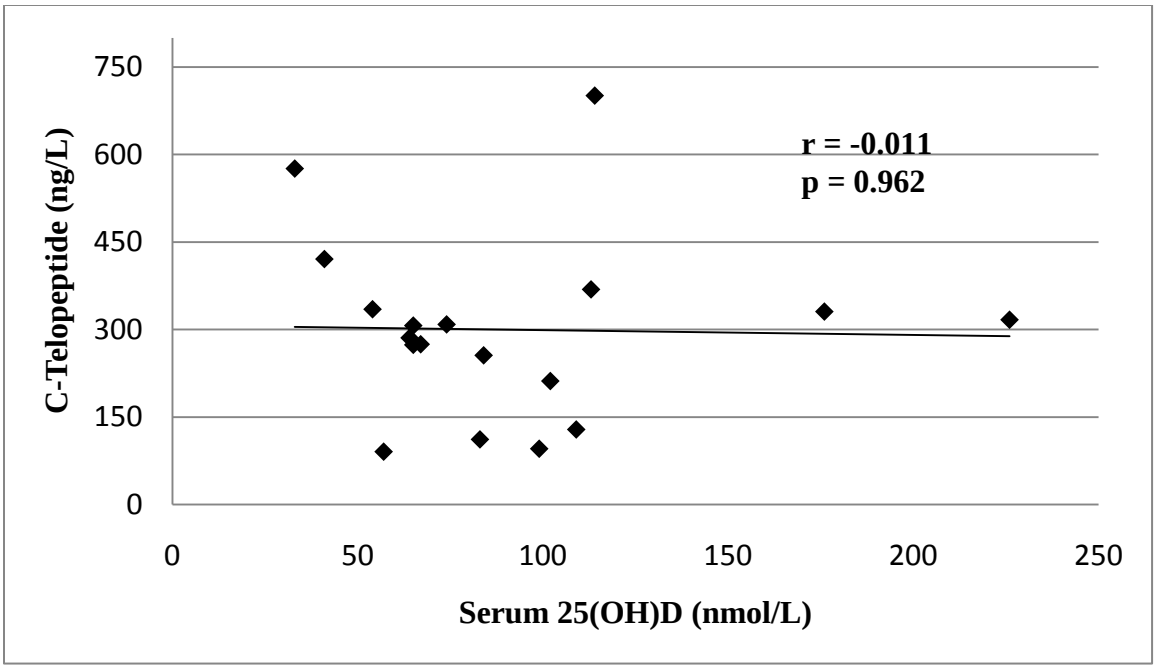

Figure 18. Relationship between serum C-Telopeptide (ng/L) and serum 25(OH)D (nmol/L)