

# Bone loss at the distal femur and proximal tibia in persons with spinal cord injury: imaging approaches, risk of fracture, and potential treatment options

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**Abstract** Persons with spinal cord injury (SCI) undergo immediate unloading of the skeleton and, as a result, have severe bone loss below the level of lesion associated with increased risk of long-bone fractures. The pattern of bone loss in individuals with SCI differs from other forms of secondary osteoporosis because the skeleton above the level of lesion remains unaffected, while marked bone loss occurs in the regions of neurological impairment. Striking demineralization of the trabecular epiphyses of the distal femur (supracondylar) and proximal tibia occurs, with the knee region being highly vulnerable to fracture because many accidents occur while sitting in a wheelchair, making the knee region the first point

of contact to any applied force. To quantify bone mineral density (BMD) at the knee, dual energy x-ray absorptiometry (DXA) and/or computed tomography (CT) bone densitometry are routinely employed in the clinical and research settings. A detailed review of imaging methods to acquire and quantify BMD at the distal femur and proximal tibia has not been performed to date but, if available, would serve as a reference for clinicians and researchers. This article will discuss the risk of fracture at the knee in persons with SCI, imaging methods to acquire and quantify BMD at the distal femur and proximal tibia, and treatment options available for prophylaxis against or reversal of osteoporosis in individuals with SCI.

**Keywords** Distal femur · Dual energy x-ray absorptiometry · Peripheral quantitative computed tomography · Proximal tibia · Quantitative computed tomography · Spinal cord injury

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## Abbreviations

SCI	Spinal cord injury
DXA	Dual energy x-ray absorptiometry
CT	Computed tomography
MRI	Magnetic resonance imaging
QCT	Quantitative computed tomography
MDCT	Multidetector computed tomography
pQCT	Peripheral quantitative computerized tomography
HR-pQCT	High-resolution peripheral quantitative computed tomography
mSv	Millisievert
DF	Distal femur
PT	Proximal tibia
LE	Lower extremity
ROI	Region of interest

RMS-CV%	Root mean square coefficient of variation percent
LSC	Least significant change
BMC	Bone mineral content
aBMD	Areal bone mineral density
vBMD	Volumetric bone mineral density
vBMD <sub>Tb</sub>	Trabecular volumetric bone mineral density
vBMD <sub>Ct</sub>	Cortical volumetric bone mineral density
App	Apparent
BV/TV	Bone volume/tissue volume
Tb.N	Trabecular number
Tb.Sp	Trabecular spacing
Tb.Th	Trabecular thickness
SSI <sub>pol</sub>	Polar stress strain index
PI	Polar moment of inertia
ES	Electrical stimulation
FES	Functional electrical stimulation
ZA	Zoledronic acid
IOF	International Osteoporosis Foundation
AIS	American Spinal Injury Association Impairment Scale

### General considerations regarding bone loss in individuals with SCI and imaging methodologies

Histomorphometric studies of the sublesional skeleton early after spinal cord injury (SCI) reveal an increase in osteoblast and osteoclast activity that shifts fairly quickly to an increase in osteoclastic activity and a suppression of osteoblastic activity [1–3]. This uncoupling of osteoblast/osteoclast function is supported by the clinical findings of hypercalciuria and dramatic elevation of biochemical markers of bone resorption [4], leading to a rapid loss in bone mineral density (BMD) and deterioration of the trabecular lattice structure that is ultimately replaced by fatty marrow [5]. Contrary to that of normal skeleton remodeling, in which the quantity of bone resorbed is almost completely replaced by new bone formation, after SCI, the immediate unloading of the skeleton results in a pathological scenario of the uncoupling of bone formation and resorption that rapidly results in severe bone loss of the sublesional skeleton. The most precipitous loss of bone occurs during the initial 12 to 24 months after acute SCI [6–8]. The loss of structure and strength in the lower extremity places a person with SCI at an increased risk of fracture. While it is appreciated that extreme demineralization occurs throughout the entire lower extremity, the distal femur (DF) epiphysis and proximal tibia (PT) epiphysis are the regions most vulnerable to fracture in persons with SCI; because a large fraction of accidents occur while sitting in a wheelchair, this makes the DF and PT region the first point of contact to any externally applied force. As a result of these anatomical considerations, the DF and PT are the most common sites for low-energy

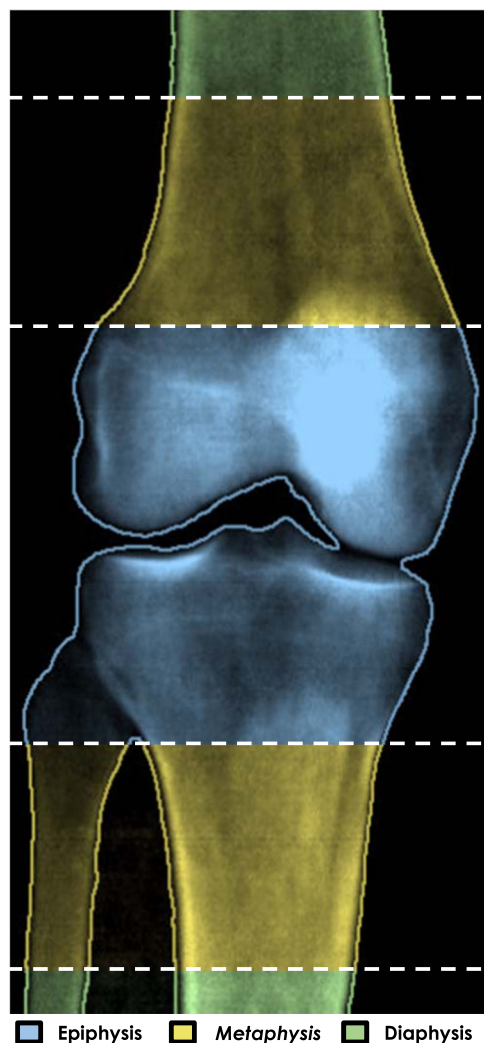
fracture in persons with SCI while performing activities of living [9]. In approximately 50 % of all cases, fractures result in contractures at the hip and knee, osteomyelitis, and concurrent pressure ulcers that may further serve to diminish mobility [10–12]. These outcomes adversely affect activities of daily living, interfere with the ability to maintain employment, and add significant medical costs to rehabilitative care [12, 13]. Several small cross-sectional and prospective cohort reports have quantified the loss of bone in persons with acute (<3 months from date of injury) [14] and chronic SCI (>1 year from date of injury) [15]. After acute SCI, an areal BMD (aBMD) loss of 27 % at 4 months and 32 % loss 14 months after initial assessment has been documented at the distal femur [16]. The reduction in BMD has been reported to approach a steady state for bone turnover approximately 3–8 years post-injury [17, 18]. Other investigations have observed a slower rate of bone loss that appears to continue into the chronic phase of injury [19, 20]. Compared to other well-recognized conditions of rapid bone loss, this incredibly high rate of bone loss after acute SCI is considerably higher than that observed in postmenopausal osteoporosis (3–5 % annually) [21], long-term bed rest (0.1 % per week) [22], and space flight (0.25 % per week) [23]. Dual energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT), peripheral quantitative computed tomography (pQCT), and Magnetic resonance imaging (MRI) are commonly used imaging technologies to quantify BMD of the DF and PT, with the latter being used more frequently in the research setting [24, 25]. The rate of absolute BMD loss has been reported to be highly variable in persons with SCI when applying DXA or pQCT imaging methodologies [8, 26]. This observed variability is most likely the result of acquiring skeletal images with DXA and/or QCT/pQCT machines by different manufacturers and software applications or by acquiring similar, but inconsistent, parameters for the reported regions of interest (ROI) of the lower extremity that vary in the proportion of trabecular to cortical bone. A recent review article by Troy et al. [27] has recommended pQCT be considered as a first-line approach providing the primary outcomes that address skeletal changes in clinical trials in persons with SCI [27], a point that will be expanded upon in this review. An in-depth review of the two different imaging methodologies for acquiring BMD at the DF and PT in persons with SCI has yet to be reported. The objectives of this article are to review the considerations, experience, and use of DXA, QCT/pQCT, and MRI imaging methods to acquire BMD at regions representative of the DF and PT. To achieve this objective, a literature review was conducted in PubMed (MEDLINE), Cochrane, and CINAHL databases with the following bone loss-related keywords and Boolean operators: “Bone Mineral Density”[Mesh] OR “Bone Mineral Content” AND “DXA” OR “Dual Energy X-ray Absorptiometry” AND “Tomography Scanners, X-Ray Computed” [Mesh] OR

“QCT” OR “Quantitative Computerized Tomography” OR “Peripheral Quantitative Computerized Tomography” OR “pQCT” AND “Spinal Cord Injury” AND “Distal Femur” AND “Proximal Tibia” AND “Femur” AND “Tibia.” A secondary search of references from articles found in primary search and an electronic search of the *Journal of Clinical Densitometry* (all issues since the journal’s inception) on the International Society for Clinical Densitometry website ([www.iscd.org](http://www.iscd.org)). For the purposes of this review, the distal femur and proximal tibia are the regions constituting approximately 30 % of the distal region of the femur and 30 % of the proximal region of the tibia, with this 30 % area further stratified into the epiphyseal (0–10 %), metaphyseal (10–20 %), and diaphyseal (20–30 %) subregions (adapted from the study by Edwards et al. [28]; Fig. 1). Using these criteria, the authors incorporated only this information when summarizing the severity of bone loss that occurs at the DF and PT in persons with SCI (Tables 1 and 2), with all reports that addressed femoral and tibia shaft and distal tibia regions. To further limit this review, additional criteria used to exclude articles were as follows: DXA studies that measured the knee region using a custom ROI from a total body scan, studies performed in the pediatric SCI population, descriptive case reports and the baseline evaluations from pharmacological and mechanical interventions in persons with SCI. From this compilation of articles describing bone loss at the DF and PT, in cross-sectional and prospective investigations, a synthesis of the lower extremity bone loss that occurs in acute and chronic SCI as determined by DXA and QCT/pQCT is presented, along with a summary of fracture risk, as was determined by imaging methodologies. Finally, a brief review of conventional and emerging pharmacological and mechanical interventions to preserve bone mass at the DF and PT in persons with SCI has also been presented.

## Lower extremity BMD with emphasis at the knee in individuals with SCI

### DXA: areal BMD assessment

In cross-sectional investigations, DXA has been used as the primary imaging modality to acquire lower extremity BMD in persons with SCI, which is understandable because a predominance of studies was performed prior to the advent of QCT and pQCT technology. In one of the early cross-sectional studies of participants with SCI, Biering-Sorensen et al. [29] compared bone mineral content (BMC) of the PT in 26 SCI subjects 2 to 25 years after acute injury and observed that the PT was greater than 50 % lower than the values obtained in an able-bodied cohort. In agreement with these findings, Garland et al. [30] compared the combined BMD of the DF and PT in 28 individuals with chronic SCI (DOI 3–43 years) to 10



**Fig. 1** Illustration of the diaphysis (highlighted green), metaphysis (highlighted yellow), and epiphysis (highlighted blue) that comprises the distal area of the femur and proximal area of the tibia (adapted from previous work by Edwards et al. [28])

able-bodied controls; the mean BMD of the knee region was 50 % lower when compared to an age-matched able-bodied control group, with similar findings documented in a cross-sectional study of women with chronic SCI [31]. These cross-sectional findings support those of other investigators who compared lower extremity BMD values in those with SCI to that of healthy able-bodied controls [32] and a subgroup of persons with SCI with a history of fragility fracture [33].

Prospective studies using DXA have documented a loss in BMD over time in acute and chronic SCI populations (studies obtaining a baseline and at least one additional DXA scan). To evaluate loss of BMD shortly after SCI, Warden et al. [16] performed a prospective study in 15 SCI patients who had sublesional bone loss observed within 6 months of SCI and observed a rapid decrease in BMD of 5.3 % in the PT 6 weeks

**Table 1** Summary of descriptive studies using dual energy X-ray absorptiometry to assess areal bone mineral density at the DF and PT in a cohort with spinal cord injury

Author, year	SCI population (gender), age, DOI (range)	Study design	Comparative group or variable	Site, software application, ROI method (reference)	Primary findings
Battaglino et al., 2012 [123]	155 SCI (all M) Age, 25–88 DOI, 2–61 years	CS	18 short-term ( $\leq 5$ years) vs. 137 long-term ( $> 5$ years) SCI	DF and PT, GE orthopedic knee software, Morse et al. [46]	Short-term SCI significantly greater aBMD at the DF and PT
Biering-Sorensen et al., 1990 [6]	8 SCI (6 M, 2 F) Age, 18–49 years DOI, 9–167 days	PS	5–13 scans, 31–53 months post-SCI	PT, forearm software, Schaadt and Bohr [39]	BMC of the PT $\downarrow$ 60–70 % at follow-up
Biering-Sorensen et al., 1988 [29]	26 SCI (24 M, 2 F) Age, 20–65 years DOI, 2–25 years	CS	98 AB (47 M, 51 F), age 20–85 years	PT, forearm software, Schaadt and Bohr [39]	SCI < AB; PT aBMD $\downarrow$ >50 %
Doherty et al., 2014 [124]	149 SCI (all M) Age, 27–88 years DOI, 5–61 years	CS	95 wheelchair dependent vs. 54 ambulatory SCI	DF and PT, GE orthopedic knee software software, Morse et al. [46]	aBMD of the DF and PT $\downarrow$ in wheelchair dependent SCI
Garland et al., 2001 [31]	31 SCI (all F) Age, (Y $\leq$ 30, M 31–50, O $>$ 50) DOI, 2–44 years	CS	17 AB (all F)	DF and PT, forearm software, NR	SCI < AB: aBMD of the DF and PT $\downarrow$ Y (38 %), M (41 %), O (47 %)
Garland et al., 2005 [30]	18 SCI (all M) Age, 26–52 years DOI, 3–43 years	CS	10 AB (all M)	DF and PT, forearm software, NR	SCI < AB: aBMD of the knee $\downarrow$ 50 %.
Garland et al., 2004 [34]	6 SCI (5 M, 1 F) Age, 21–28 years DOI, 24–53 days	PS	523 days post-SCI	DF and PT, forearm software, NR	aBMD $\downarrow$ 27 % in DF and $\downarrow$ 32 % in the PT
LaLa et al., 2014 [33]	70 SCI (50 M, 20 F) Age, 37–60 years DOI, 6–26 years	CS	19 with Fx Hx vs. 51 without Fx Hx	DF and PT, lumbar spine software, Moreno et al. [125]	aBMD $\downarrow$ in Fx Hx group
Modlesky et al., 2004 [20]	10 SCI (all M) Age, 35 $\pm$ 9 DOI, 2–20 years	CS	8 AB (all M), age: 33 $\pm$ 10 years	PT, forearm software, 30mm ROI from scan 94mm in length	SCI < AB: aBMD $\downarrow$ 43 % and BMC $\downarrow$ 49 % at the PT
Morse et al., 2012 [126]	39 SCI (all M) Age, 30–78 years DOI, 4–43 years	CS	10 AB (all M), age, 8–80 years	DF and PT, GE orthopedic knee software, Morse et al. et al. [46]	SCI < AB: aBMD $\downarrow$ at the DF and PT
Morse et al., 2013 [127]	39 SCI (all M) Age, 30–78 years DOI, 4–43 years	CS	10 AB (all M), age 61.7 $\pm$ 8.2 years	DF and PT, GE orthopedic knee software, Morse et al. [46]	SCI < AB: aBMD and aBMC $\downarrow$ at the DF and PT
Shields et al., 2005 [32]	11 SCI (10 M, 1 F) Age, 28–67 years DOI, 2–35 years	CS	11 AB (10 M, 1 F), age 22–62 years	DF and PT, lumbar spine software, Shields et al. [32]	SCI < AB: aBMD $\downarrow$ at the DF and PT (~30 % lower than AB group)
Warden et al., 2002 [16]	15 SCI (all M) Age, 17–40 years DOI, 46–153 days	PS	6-week post-BL scan	PT, lumbar spine software, NR	aBMD of the PT $\downarrow$ at the follow-up visit
Zehnder et al., 2004 [83]	100 SCI (all M) Age, 18–60 years DOI, 3 months–30 years	CS	Time since injury	TDIA, lumbar spine software, NR	Z-score of the proximal TDIA $\downarrow$ 10 years after injury date

GE general electric, DXA dual energy X-ray absorptiometry, DOI duration of injury, aBMD areal bone mineral density, BMC bone mineral content, TDIA tibial diaphysis, DF distal femur, PT proximal tibia, SCI spinal cord injury, AB able-bodied, M men, F women, Fx fracture, Hx history, CS cross-sectional, PS prospective study, NR not reported, NA not applicable, Y youngest, M middle, O oldest, < less than

after the baseline measurement. In another study documenting the rapid loss of bone that occurs within the first 2 years after initial motor-complete SCI, Biering-Sorensen et al. [6] performed follow-up DXA scans on six men and two women with initial scans performed 9–167 days (median 43 days) after acute paralysis. Two years after the initial DXA evaluation, BMC at the PT was 40–50 % lower than it was at the baseline assessment. In a study documenting bone loss within

the first 2 years after injury, Garland et al. [34] determined BMD of the DF and PT soon after injury (33.5  $\pm$  10.8 days) with follow-up measurements at 523  $\pm$  96.2 days post-injury in five patients with acute motor-complete SCI; results from the follow-up assessment revealed BMD at the DF and PT were reduced by 27 and 32 %, respectively. However, there has been only one longitudinal study using DXA imaging that has documented bone loss into the chronic phase of injury in

**Table 2** Summary of descriptive studies using advanced imaging to assess volumetric bone mineral density, bone geometry, and microarchitecture at the DF and PT in a cohort with spinal cord injury

Author, year	Population (gender), age, DOI (range)	Study design	Comparative group	Site/regions imaged	Primary findings
Studies using CT and pQCT to evaluate vBMD and bone geometry at the DF and PT					
Coupaud et al., 2015 [55]	26 acute SCI (21 M, 5 F) Age, 17–76 years DOI, 8–13 months	PS	4, 8, and 12 months post-SCI	DF 4 % and PT 96 % Tb region	vBMD <sub>Tb</sub> and vBMD <sub>Cl</sub> ↓ at the same rate (↓ 20 % DF and PT)
Coupaud et al., 2009 [66]	47 SCI (38 M, 9 F) Age, 37.3 ± 13 DOI, 6 years	PS	Time since injury	DF 4 %, Epi region	vBMD <sub>Tb</sub> decreased exponentially with time since injury
Edwards et al., 2014 [28]	13 SCI (9 M, and 4 F) Age, 19–64 years DOI, 1–4 years	PS	3.5 months post-BL scan	DF and PT, 0–10 % Epi, 10–20 % Met, and 20–30 % Dia	Similar loss at the DF/PT at follow-up: vBMD <sub>Tb</sub> -2.7 to -4.7%/month and vBMD <sub>Cl</sub> -0.3 to -0.6 %/month; DF: CSI -1.8 to -5.4 %/month and TSI -1.2 to -3.8 %/month; PT: CSI -0.8 to -6.3 %/month and TSI -0.7 to -4.2 %/month
Eser et al., 2004 [18]	89 SCI (all M) Age, 19–83 years DOI, 2 months–48.5 years	CS	21 AB (all M), age 42 ± 16 years	DF Epi 4%	SCI< AB: vBMD <sub>Tb</sub> of the DF ↓ 54 %
Frotzler et al., 2008 [17]	39 SCI (all M) Age 21–64 years	PS	15 and 30 months post-BL scan	DF Epi	Small nonsignificant ↓ from -1.7 % to 0.51 %vBMD <sub>Tb</sub> at the DF
McCarthy et al., 2012 [128]	17 SCI (all M) Age: 20–52 years DOI: 1–151 months	CS	14 AB Age: 37±9 years	PT 98 % Epi	SCI< AB: vBMD <sub>Tb</sub> ↓ 40 % at the PT and ↓ IP of the PT Dia
Rittweger et al., 2010 [54]	9 SCI (all M) Age, 18–30 years DOI, 9–32 years	CS	9 AB (all M) Age: 40 +/- 8 years	PT Epi	SCI< AB: vBMD <sub>Tb</sub> of the PT ↓ 47 %
Tan et al., 2014 [129]	27 SCI (all M) Age, 21–64 years DOI, 0.12–38 years	CS	Fx Hx versus no-Fx Hx group	DF and PT Epi	vBMD <sub>Tb</sub> ↓ in the post-SCI Fx group
Dudley-Javoroski et al., 2012 [65]	29 SCI (26 M, 3 F) Age, 16–72 years DOI <6 months	PS	21 AB Age: 22-62 years	PT 86 % and DF 12 %	SCI< AB: vBMD <sub>Tb</sub> ↓ DF, and PT at >1-2 years post-SCI and vBMD <sub>Tb</sub> of the DF ↓ 56 % >4 years post-SCI group
Dudley-Javoroski et al., 2010 [130]	15 SCI (14 M, 1 F) Age DOI: 0.19–7 years	PS	10 AB (9 M, 1 F) Age: 22-37 years	DF Met 12 %	SCI< AB: vBMD <sub>Tb</sub> of the DF ↓ 15-35 % over 1-year post SCI
Studies using MRI to evaluate the DF and PT					
Slade et al., 2005 [74]	19 SCI (all F) Age: NR total group DOI: NR total group	CS	17 AB (all F) Age: NR total group" after	DF and PT: 60 adjoining 1 mm slices started at the distal femoral condyles and subchondral proximal tibia	DF: SCI< AB: app.BV/TV (-33 %), app.Tb.N (-26 %), app.Tb.Th (-6.8 %), with an increase in app. Tb.Sp (62 %) in SCI PT: SCI<AB: app.BV/TV (-22 %), app.Tb.N (-19 %), app. Tb.Th (-6 %), with an increase in app.Tb.Sp (40 %) in SCI
Modlesky et al., 2004 [20]	10 SCI (all M), age 34 ± 10 years, DOI, 2.3–20.1 years	CS	8 AB (all M), age 33 ± 10 years	DF and PT	DF: SCI< AB: app.BV/TV (-27%), app.Tb.N (-21%), with an increase in app.Tb.Sp (44%) in SCI PT: SCI< AB: app.BV/TV (-20%), app.Tb.N (-20%), with an increase in app.Tb.Sp (33%) in SCI

CT computed tomography, DOI duration of injury, pQCT peripheral quantitative computed tomography, MRI magnetic resonance imaging, vBMD volumetric bone mineral density, Tb Trabecular, Ct cortical, Epi epiphysis, Met metaphysis, Dia diaphysis, DF distal femur, PT proximal tibia, SCI spinal cord injury, AB able-bodied, M men, F women. CS cross sectional, PS prospective study, RS retrospective study, LS longitudinal study, IP polar moment of inertia, CSI compressive strength index, TSI torsional strength index, app.BV/TV apparent bone volume/total volume ratio, app.Tb.N apparent trabecular number, app.Tb.Sp apparent trabecular spacing, app.Tb.Th apparent trabecular thickness, NR not reported, < less than

men with SCI ( $n = 31$ ) and a small cohort of women ( $n = 4$ ) [35]. In this study of 31 men with chronic motor-complete SCI (DOI  $14.6 \pm 8.7$  years; 13 with paraplegia and 14 with tetraplegia) and 4 women (DOI  $19.8 \pm 12.1$  years; all with paraplegia), Garland and colleagues [35] demonstrated that not all persons with SCI had a continuous loss of bone into the chronic phase of SCI. Participants were stratified into participants who had increases and decreases in areal bone mineral density (aBMD) at the 5-year DXA follow-up measurement. In men, the mean aBMD at the DF decreased in slightly more than half of the participants and at the PT in two thirds of the participants, with an annual percent change in aBMD of  $-1.1\%$  at the DF and  $-1.5\%$  at the PT over a 5-year period. These findings demonstrate the overall loss of bone several years after acute immobilization. In women, the annual percent change in aBMD was  $-1.8\%$  at the DF with an increase at the PT of  $1.0\%$ . These findings should be interpreted with a degree of caution considering the lack of studies reported in larger cohorts of men and women with SCI that incorporate advanced imaging techniques which would optimally be performed during the acute and then in the chronic phase of SCI. Thus, it is important for clinicians and investigators to understand that the bone loss which continues into the chronic phase of injury has not been thoroughly defined and that the time course to establish a relatively steady state for the sublesional skeleton in persons with SCI also needs to be further addressed. Because the majority of reports that documented bone loss in persons after SCI are of relatively small sample sizes, and participants had varying degree of motor function below the level of lesion, the rate and absolute loss in aBMD has varied considerably among studies to date. Furthermore, the possibility of obtaining less than optimum precision due to difficulty in proper positioning of the leg when scanning the knee due to increased spasticity, tone, and contractures makes it necessary to interpret the results with caution from relatively small changes that occur from clinical interventions. The use of DXA can be further confounded by the existence of heterotopic ossification at the knee region, spuriously elevating BMD results. In addition to the necessity of DXA precision assessment outlined by the ISCD guidelines [36], the International Osteoporosis Foundation (IOF) has published guidelines for treatment failure from changes in BMD at the individual level [37]. To account for the inter-participant variability in lower extremity bone loss and the differential effects of any treatment intervention, clinicians and researchers can compare the percent change in the aBMD of the DF and PT from a given intervention to the least significant change (LSC) (for the CI at 95 and 99 %) to determine true intervention-related change and actual efficacy the efficacy of an intervention. Despite the varying degrees of bone loss reported among these reports, it is essential for clinicians to understand the precipitous loss in the sublesional skeleton that results from the abrupt onset of paralysis, as well as the likely accelerated continued loss over a

lifetime of immobilization, and to have an appreciation that the longevity of those with SCI approaches that of the able-bodied population. Thus, there exists the obvious need for safe and efficacious prescription of rehabilitative or pharmacological interventions once they become available to preserve or reverse osteoporosis in the SCI population. A comprehensive summary of descriptive studies that documented the bone loss at the DF and PT after SCI using DXA has been provided (Table 1).

#### DXA software for the knee region

Previous investigations using DXA technology to quantify aBMD at the knee ROI have used software applications that were nonspecific to the region and were adapted from forearm or lumbar spine software packages to measure BMD [38–40]. The adaptation and application of nonspecific software programs of the DF and PT were performed out of necessity because validated software programs to measure aBMD of the knee ROI had not been commercially offered by the DXA manufacturers. Using nonspecific software (e.g., forearm software), McPherson et al. [41] reported in a cross-sectional validation study in 12 persons with acute and 34 persons with chronic SCI that the root mean square coefficient of variation percent (RMS-CV%) for the aBMD by DXA was more precise in the acute SCI cohort than in the chronic SCI cohort at the DF epiphyses ( $1.7$  vs.  $3.1\%$ ), DF metaphysis ( $1.4$  vs.  $4.7\%$ ), and PT epiphysis ( $1.7$  vs.  $3.4\%$ ), respectively; all custom ROIs by DXA were highly correlated to these same image sites measured by QCT for volumetric BMD (vBMD) ( $r = 0.93$ ). The DXA regions created corresponded to a method previously developed using QCT, as described by Edwards et al. [28] (Fig. 1), and also corresponded to pQCT-derived 4 % limb length image regions that define the DF and the 96 % limb length image region that defines the PT, as measured from distal to proximal. The intra- and inter-rater reliability estimates (two raters) were also determined in the groups with acute and chronic SCI, with high intra-class correlation coefficients (ICCs;  $0.97$ – $0.98$ ). McPherson et al. concluded that the improved precision in the acute SCI cohort may be attributed to a higher mean absolute BMD than that in the chronic cohort, rather than a systematic difference in precision between the two groups.

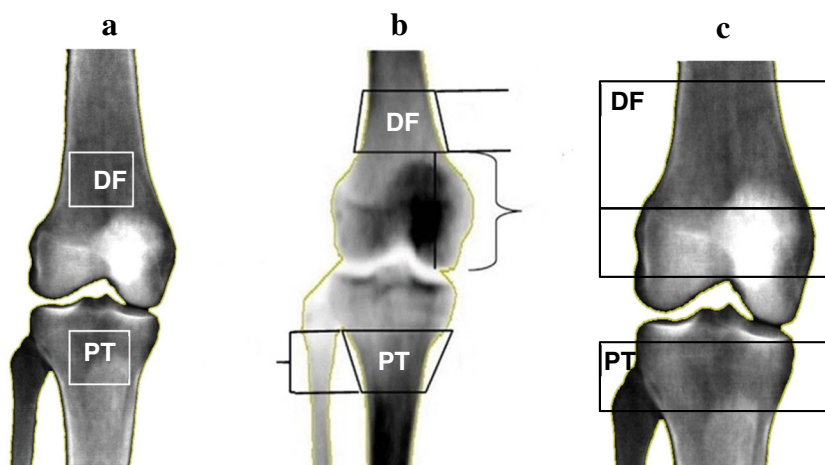
An orthopedic knee software program was developed to monitor BMD in patients after knee arthroplasty, and this software application has been recently approved by the Food and Drug Administration for commercial use; this software application is currently being used in rehabilitation [42] and pharmacological [43] clinical trials in persons with SCI. Bakkum et al. demonstrated excellent inter- and intra-rater reliability (ICCs between  $0.97$  and  $0.98$ ) using this software in an able-bodied cohort [44]. The precision of knee-specific software in 20 able-bodied adult patients who received unilateral knee

prosthesis was provided by Gilchrist et al. [45]; DXA scans were performed on both knees and aBMD from seven custom ROIs obtained. The CV% at the knee with the implant ranged between 0.55 and 4.04 %, and no significant differences in precision were found in comparisons between the implanted and non-implanted knee [45]. In a cohort of subjects with chronic SCI, Morse et al. [46] tested the precision (e.g., RMS-CV%) of the orthopedic knee software using a custom ROI and found that the precision of the DF (3.01 %) had better reproducibility than that of the PT (5.91 %) (Fig. 2a). A precision error at the DF of 3.01 % and PT of 5.91 % would mean that a change in BMD of less than 6 % from a clinical intervention could not be detected. Furthermore, this study performed repeat scans on 20 SCI participants and not the 30 required by the ISCD guidelines to calculate LSC [36]. However, given the same precision error, if an additional 10 scans were completed, the LSC would have been 8.4 and 16.4 % [3.01 and 5.91 % (RMS-CV%)  $\times$  2.77 (multiplier at 95 % CI) = LSC], a margin of error that would not capture even a fairly robust effect of an efficacious clinical intervention. Because only a few studies in persons with SCI have reported the precision error (RMS-CV%) from repeat scans using different DXA acquisition and analysis protocols [41, 46–48], none to date have completed the 30 scans necessary to have the statistical power to report the LSC at a 95 % CI [37]. As previously stated, the decreased precision in persons with SCI can be partly attributed to increased spasticity and contractures that can limit the internal rotation needed to standardize the amount of overlap between the tibia and fibula and, ultimately, the location of the ROI box. The placement of the DF ROI can also be confounded by movement of the patella into the ROI area that was used at the baseline assessment, forcing a shift in the placement of the ROI box more distal along the femoral distal metaphysis when analyzing the follow-up DXA scan of the knee region.

Standard ROIs, regrettably, have not been uniformly developed and adopted by clinicians and investigators, which has

created a variability and uncertainty in the effort to compare BMD findings at the knee among reports. Using non-knee-specific software, Shields et al. [32] developed a widely used method to isolate the DF and PT regions of interest, an approach which has been demonstrated to be highly reliable between multiple raters with ICC values for the DF of 0.98 and for the PT of 0.89 [32] (Fig. 2b); this methodology has been applied in subsequent studies of the knee in persons with SCI [47, 49]. However, this method obtains more of the metaphysis of the DF and PT, which does not correspond with the femoral 4 % (DF) and tibia 96 % (PT) regions captured when performing pQCT which have ROIs in the epiphysis, an important point to take into consideration if pQCT-derived images for regions of the DF and PT will be considered the reference in future validation studies. Slightly different custom ROIs that capture more of the epiphyseal region have been reported, and they have also proven to be highly reliable [41]. At the present time, there is no standardized method to capture the DXA-derived ROIs for the DF and PT and no study to date has prospectively compared the methods commonly reported in the literature. From the current body of literature, it would be logical for investigators to adopt the analysis method utilized by McPherson et al. as the best method to capture the DF and PT in prospective clinical trials [41] (Fig. 2c) because this method has been demonstrated to be both precise and accurate as determined by the strong relationship to measures of “true” vBMD, determined by CT technology. As previously mentioned, this method obtains vBMD of the distal femoral epiphysis, distal femoral metaphysis, and the proximal tibia epiphysis; epiphyseal ROIs that also correspond to commonly performed pQCT-derived images of the 4 % limb length reported as the DF and the 96 % limb length reported as the PT, as measured from distal to proximal. Future studies that perform repeat DXA scans of the knee using “on and off the table” and “different test days” methodologies, as well as validation studies comparing the different methodologies to capture QCT and pQCT, are necessary to

**Fig. 2** Commonly used methods using a custom region of interest to capture the DF and PT of the knee using dual energy X-ray absorptiometry (DXA) adapted from **a** Morse et al. [32], **b** Shields et al. [46], and **c** Edwards et al. [28]



understand the optimal method that should be utilized to perform DXA scans of the knee in persons with SCI.

Despite its obvious clinical feasibility, the use of DXA to evaluate BMD has appreciated drawbacks when applied to identify risk of fracture in the able-bodied population due to the confounding effects of bone size on aBMD [50], differences between manufacturer-derived algorithms to calculate aBMD [51], and DXA intra/inter-unit problems with accuracy and linearity [52]. Standardized scores for DXA (e.g., Z- and T-scores) at the knee have not yet been established. Thus, identification of a low bone mass that defines an increased risk for fracture at the knee is not currently available. As such, assessment of aBMD of the DF and PT alone without clinical risk factors for fracture is of limited use to guide exercise prescription and to reduce the possibility of fracture. At this time, the available evidence supports that the best use of knee software in clinical investigations is to monitor potential changes from mechanical and/or pharmacological interventions. Along with SCI-specific clinical risk factors [53], this information can guide clinical treatment options and/or research interventions associated with the application of substantial mechanical forces during supervised therapeutic sessions or exercise training routines. Because of the scarcity of literature that defines a given DXA-derived aBMD value, as well as the absence of a well-validated fracture threshold at the DF and PT, clinicians should consider collecting, if feasible, additional trabecular microarchitecture and bone geometry measures from CT or magnetic resonance imaging (MRI) to better identify persons who are at heightened risk of fragility fracture. Future research that establishes normative data generated from applying knee software from different manufacturers and ROIs to capture the DF and PT are needed to accurately and reproducibly identify the diagnostic threshold to predict increased risk of fracture at the DF and PT.

### Advanced bone imaging: CT and MRI

Computed tomography (CT) is a photon absorptiometric technique similar to DXA with the unique ability to provide vBMD of a bone region. Quantitative CT (QCT) is a 3-D imaging technique that can acquire trabecular and cortical vBMD as well as geometry parameters, such as the polar stress strain index ( $SSI_{pol}$  = surrogate measure of bone strength from the CSA) and the polar moment of inertia (IP = bone's ability to resist torsional loads) but cannot obtain bone microarchitecture. The use of this methodology has direct relevance to the SCI population because there is evidence supporting severe trabecular vBMD loss at the DF and PT epiphysis in the period shortly after injury, with a corresponding thinning of the endocortical envelope at the diaphysis [18, 54]. The change in the endocortical envelope temporally occurred with no significant decrease in cortical vBMD. Thus, it would appear that loss of vBMD of the diaphysial

endocortical envelope and cortical regions occurs at vastly different rates after acute SCI; however, a recent report suggests the deterioration of these two bony regions occurs at a similar rate and magnitude [55]. Thus, in contrast to DXA, where the specified DF and PT regions represent surrogate measures of trabecular bone, pQCT obtains actual trabecular and cortical vBMD of the epiphysis, metaphysis, and diaphysis at the DF and PT in persons with SCI (Fig. 1) [28]. Currently, multidetector CT (MDCT) devices produced by a number of manufacturers are readily available in most diagnostic imaging centers [56]. The advantage of this clinical technique is that central (spine and proximal femur) and peripheral (distal femur, proximal and distal tibia) skeletal sites and high-resolution microarchitecture parameters can be acquired. MDCT has shown to have moderate to strong correlations in vitro when compared to that of micro-CT ( $\mu$ CT) for vBMD and microarchitecture (app.BV.TV:  $r = 0.979$ ,  $p < 0.005$ ) [57], and it has recently been validated against DXA for all central aBMD sites as an accurate and reliable screening tool to diagnose osteoporosis in older men and women [58]. However, studies using MDCT are limited due to an effective radiation dose of approximately 3 mSv (approximately 1.5 years of background radiation). This is significantly higher than the effective radiation dose from DXA and pQCT, which ranges from 0.01 to 0.05 mSv (normal daily background radiation exposure). Bone imaging by pQCT also has the benefit of limiting direct radiation exposure to the extremities and does not expose radiosensitive organs to radiation [56].

Over the last decade, pQCT has been regularly used as a dedicated extremity imaging modality in the clinical research environment. This methodology is commonly used in clinical investigations to quantify bone changes in persons with SCI, with a recent review from an experienced research team detailing the challenges inherent when performing pQCT imaging in persons with SCI [59]. The two commercially available devices come with either a fixed gantry for the distal tibia (Xtreme CT; Scanco Medical AG, Brüttisellen, Switzerland) or with a sliding gantry that can obtain slices along the femur and tibia metaphysis and epiphysis, as well as at sites along the tibia diaphysis (XCT 2000/3000 scanner; Orthometrix/Stratec, White Plains, NY) [60]. The pQCT method has a relatively low resolution which is insufficient to obtain the trabecular microarchitecture, but it can acquire vBMD and geometry parameters of the cortical and trabecular regions. The Stratec pQCT scanner can obtain images at the 96 % tibia region (tibia epiphysis = PT) and the 4 % femoral region (femoral epiphyses = DF), with additional slices at the 38 % tibia region obtained for cortical bone density and thickness and the 66 % region to obtain muscle and fat volumes. A standardized protocol has been employed for both pQCT devices [59, 61, 62], with the starting point determined by a single scout projection required to assess the tomographic



region of the talocrural joint to be able to place a reference line at the distal tibia plateau when using a sliding gantry (XCT 2000/3000 scanner). Using this reference line at the distal end of the tibia, the standard measurement site using pQCT is the distal tibia epiphysis measured at 4 % of the tibia length, moving distal to proximal. Using the fixed gantry scanner, high-resolution peripheral quantitative computed tomography (HR-pQCT) images can quantify the trabecular microarchitecture at the 4 % distal tibia region but not at the DF and PT epiphyseal sites [56]. HR-pQCT can be used to calculate trabecular microarchitecture parameters such as the bone volume/total volume ratio (BV/TV = ratio of the segmented bone volume to the total volume of the region of interest), trabecular number (Tb.N = measure of the average number of trabeculae per unit length), trabecular spacing (Tb.Sp = mean distance between trabeculae, assessed using direct 3-D methods), and trabecular thickness (Tb.Th = mean thickness of trabeculae, assessed using direct 3-D methods) [63, 64]. The 4 % distal tibia region has been widely studied in both the AB and SCI populations but may not have equivalent clinical utility in persons with SCI as that of the 96 % tibia region and the 4 % femoral region. To obtain an image of the proximal tibial epiphysis using this same reference line as the starting point, the scanner obtains an image at 96 % of the tibia length, moving distal to proximal. Similar to identification of the tibia region, the femoral epiphyseal region is palpated and a single scout projection is used to identify and place a reference line at the most distal point at the end of the lateral femoral condyle. Using this reference line at the distal femur, the scanner obtains an image at 4 % of the femur length, moving distal to proximal [56, 58, 65, 66].

While it is appreciated that bone loss occurs throughout the entire lower extremity, the trabecular area above the knee (DF) and below the knee (PT) is a ROI commonly studied because these areas have the highest prevalence of fracture [67], because wheelchair-related accidents are the most common events that make the DF and PT vulnerable to impact and fracture in person with SCI [13, 28, 33, 68]. Although DXA is the most affordable and accessible method to measure BMD at the DF and PT, pQCT is regarded as the more informative and sensitive method. In recent years, the general availability of pQCT has increased, permitting investigators to differentiate between trabecular and cortical bone compartments and changes in bone microarchitecture. As a result, there have been several cross-sectional reports comparing vBMD in persons with SCI to an age- and gender-matched able-bodied cohort. In 12 chronic SCI and 21 able-bodied participants, Giangregorio et al. [69] found total vBMD at the DF and PT was, as expected, significantly lower in the SCI group than that of able-bodied controls. In a cross-sectional study to assess bone loss in separate compartments of trabecular and cortical bone, Eser et al. [18] used pQCT to measure the epiphyses of the DF and PT in 89 men with motor-complete SCI (24 tetraplegia and 65 paraplegia with

a duration of injury between 2 months and 50 years); the loss of bone mass in the epiphyses was ~50 % in the DF and ~60 % in the PT. In a cross-sectional study, Rittweger and colleagues [54] obtained serial slices of the tibia along its length in nine chronic SCI and nine able-bodied men and found those with SCI had 47 % lower BMC at the 95 % slice (PT). In addition to the cross-sectional reports described above, a few prospective studies have employed pQCT to capture the intra-patient loss of bone after SCI. A longitudinal study confirmed previous reports that a new steady-state for bone is reached in the paralyzed limbs several years after acute SCI. Frotzler et al. [17] used pQCT to measure vBMD at the DF at baseline and then at 15 and 30 months after the initial scan in 39 subjects with motor-complete acute and chronic SCI (duration of injury between 0.9 and 34 years) [18]. The authors observed a new steady state 3 to 8 years after SCI, with the onset of the steady-state condition dependent on the bone region and the specific pQCT densitometric variable; the femur reached steady-state more quickly than the tibia and the epiphyses more quickly than the diaphyses. In a report by Edwards et al. [28], QCT was used to quantify changes in vBMD and bone geometry and torsional stiffness at the trabecular and cortical region at the epiphyseal and metaphyseal region of the DF and PT in 13 SCI subjects soon after injury (mean measurement, 3.8 months after acute injury). The authors observed dramatic rates of monthly decline for BMC (–3 % to –4 %) and vBMD (–3 % to –5 %) at the epiphyseal trabecular region, as well as cortical diaphyseal BMC (–4 % to –5 %), with significantly smaller reductions in cortical vBMD of (–0.6 % to –0.8 %). The authors suggested that the loss of cortical bone was due to the thinning of the endocortical envelope. From these measurements, computation of bone strength and stiffness was performed and a two-fold greater reduction in these parameters was found when compared to reductions in BMD. These observations highlight the need for efficacious pharmacological or mechanical interventions shortly after injury to attenuate the skeletal losses in an effort to reduce the risk of fragility fracture [70]. Coupaud et al. [55] performed serial pQCT scans at the 96 % tibial region (PT) and 4 % femoral region (DF) at 4, 8, and 12 months after the initial scan on 26 acute subjects with SCI and noted a 20 % decrease in tibial and a 15 % decrease in femoral trabecular vBMD, with similar changes occurring at the tibial and femoral diaphysis cortical regions. This work suggested that absolute bone loss in the cortical diaphysis, where the predominant bone mass is located, occurs at approximately the same rate as trabecular bone in the epiphysis, findings that contradict previous reports that cortical vBMD is lost at a slower rate during this period. With the advent of clinical trials investigating advanced rehabilitation programs and new pharmacological treatments for bone loss after SCI, pQCT has become recognized as a method to monitor changes in trabecular and cortical vBMD compartments (Table 2) which DXA cannot capture.

MRI is an evolving high-resolution imaging methodology that is more readily available in the clinical environment than

HR-pQCT. The use of MRI in the clinical setting has several benefits: it does not utilize ionizing radiation while maintaining excellent soft tissue contrast and yields geometry measures that are highly correlated with bone variables from  $\mu$ CT [71]. Contrary to HR-pQCT that can only obtain high-resolution measurements at the ultradistal tibia, MRI can acquire high-resolution images of cortical and trabecular bone and can acquire variables such as BV/TV, Tb.Th, Tb.Sp, and Tb.N [64] at the distal femur and proximal tibia. Improvements in MRI acquisition methods and image post-processing have made quantitative MRI a viable clinical option to differentiate small changes in trabecular microarchitecture after interventions to treat osteoporosis in able-bodied postmenopausal women [72, 73]. A small number of cross-sectional investigations have been performed using MRI to quantify changes in trabecular microarchitecture at the DF and PT in persons with SCI. In a study investigating the deterioration of bone microarchitecture by MRI at the DF and PT in 10 SCI men with chronic motor-complete SCI and 8 age-matched AB control participants, Modlesky et al. [20] found the DF in the SCI group had a 27 % lower apparent (app) BV/TV, 21 % lower app.Tb.N, and 44 % higher app.Tb.Sp, with an 8 % thinner app.Tb.Th. At the proximal tibia, the group with SCI had 20 % lower app.BV/TV and app.Tb.N, 33 % higher app.Tb.Sp, with no difference in app.Tb.Th between the groups. Assessment of aBMD of the PT by DXA revealed a significant positive correlation with app.BV/TV ( $r = 0.62$ ) and app.Tb.N ( $r = 0.78$ ) and an inverse correlation with app.Tb.Sp in both the SCI and AB control groups combined ( $r = 0.78$ ). In another study by Slade et al. [74], the effect of menopause and immobilization from SCI on trabecular bone at the DF and PT was compared in pre- and postmenopausal ambulatory women, SCI younger (<30 years old) and SCI older (>35 years old) premenopausal women, and SCI postmenopausal women. Women with SCI had 30.9 % lower app.BV/TV, 61.7 % higher app.Tb.Sp, and app.Tb.Th that was 6.8 % thinner at the DF compared to the ambulatory group with no significant differences at the DF in any microarchitecture variable between the three groups of SCI women. At the PT, the SCI group had 23 % less app.BV/TV and 5.8 % lower app.Tb.Th compared to the ambulatory groups. Furthermore, an interaction effect was observed between app.Tb.Sp and ambulatory status with significantly greater spacing observed in the SCI groups compared to the ambulatory groups (Table 2). The degree of structural deterioration in these studies is similar to that reported when using pQCT. However, high-resolution microarchitecture parameters using pQCT are only possible at the ultradistal tibia; as such, direct comparison between pQCT and MRI of the DF and PT is not possible at this time. Furthermore, contrary to studies using pQCT, MRI cannot assess vBMD at the DF and PT, an essential component of fracture prediction and an essential variable to understand the effectiveness of any

intervention. In the research setting, pQCT, HR-pQCT, and MRI imaging methodologies can be essential tools to assess changes in cortical and trabecular vBMD, bone geometry, and microarchitecture as a means to understand and test the effect of loading from advanced rehabilitation strategies and pharmacological interventions. In addition to serial measurements before and after intervention, additional descriptive studies are required to understand the change in the endocortical envelope during the acute stage of SCI with progression into the chronic stage of SCI, where measures of cortical porosity and thickness are essential outcome measurements [55]. This technology may provide researchers greater insight with regard to the efficacy of clinical interventions not possible using DXA alone with the anticipated increase in the availability of these measurements in the clinical environment.

### Low BMD and fragility fracture in SCI

In persons with SCI, the severity of demineralization that occurs during the first 2 years following acute injury makes absolute BMD the primary risk factor for the prediction of future fracture [75], with other non-modifiable clinical risk factors to improve the estimate of fracture risk [30, 76]. In a review of proposed paradigms to diagnose and treat sublesional osteoporosis, Craven et al. [53] summarized the risk factors associated with fragility fracture based on the available literature as follows: SCI occurred <16 years of age [77], paraplegia [78], excessive alcohol consumption after SCI (>5 servings per day) [9], completeness of injury (American Spinal Injury Association Impairment Scale (AIS) A and B) [11], family history of fragility fracture [76], female [30], previous fragility fracture [30], low BMI (<19 kg/m<sup>2</sup>) [79], and duration of injury  $\geq 10$  years [30]. While it is true that larger prospective cohort studies are needed to identify the extent to which these risk factors are independent of aBMD, physicians and therapists should utilize these SCI-specific clinical risk factors along with aBMD of the DF and PT to guide treatment throughout the chronic phase of injury. Contrary to the occurrence of fractures in postmenopausal osteoporosis, a condition in which fractures predominantly occur at the femoral neck, hip, lumbar spine, and distal ulnar/radius, in persons with chronic SCI, the epiphyses of the DF and PT are the regions that are most vulnerable to fracture [10, 11, 80]. Fragility fractures tend to occur after minor trauma, such as bending, transfers, and physical therapy exercises [81]. These fractures typically occur as a result of torsional stress on the bones of the lower extremity when transferring or when compressive forces occur from a low velocity fall with the load applied to the knee region. The studies documenting fracture in SCI are limited to small cross-sectional reports, with a few prospective cohort studies that have evaluated persons with SCI in close proximity to the

time of fracture. As first described by Comarr et al. [82] in a cohort of 1363 SCI participants, fragility fractures were observed in 119 participants, of which 97 (82 %) occurred at the knee. The incidence of fracture increases with time after SCI, with a mean yearly fracture incidence of 1 % during the first year after SCI, with the incidence increasing to 4.6 % per year at 20–29 years after acute SCI [83]. More recently, in a retrospective study by Frotzler et al. [67], long-bone extremity fractures were assessed in 107 primarily motor-complete persons with SCI. Patients' medical charts revealed a total of 156 long-bone fractures exclusive to the lower extremity with the highest prevalence in the femur (60.9 %) compared to that of the tibia and fibula (39.1 %). The authors found a significant difference in fracture location between the upper and lower femur with a higher prevalence of fracture occurring distally (44.7 %). At the tibia, the greatest prevalence of fracture was reported proximally (41.9 %), compared to the distal (38.7 %), diaphyseal (14.5 %), and malleolar (4.8 %) regions. In a recent retrospective cohort study in which the risk for fracture was determined, Gifre and colleagues [81] reviewed the medical records of 63 patients with traumatic SCI at the time of injury and at a follow-up visit 10 years following injury; a total of 18 fractures were found in 10 patients (25 %), a fracture rate of 2.9 fractures per 100 patient-years, and 80 % of these fractures were in persons with SCI with motor-complete injuries. In another prospective cohort study, Morse et al. [9] addressed if sociodemographic and health-related factors predict hospitalization due to low impact fracture in 328 veterans with SCI; the most common fracture that required hospitalization was a tibia/fibula fracture (47.5 %), followed by the distal femoral metaphysis (20 %), and then the proximal femur (15 %). A fall from a wheelchair was identified as the most common cause of fracture, followed by transfers, and striking the lower extremity during wheelchair propulsion [83]. In a recent retrospective cohort investigation [13], a medical record review was conducted in 7590 male veterans with chronic traumatic SCI to identify lower extremity fragility fracture. The authors found 155 fractures in 140 persons with SCI with the majority of fractures occurring at the femur ( $n = 52$ ; 33 %) and tibia/fibula ( $n = 83$ ; 54 %), with the primary cause related to activities performed from the wheelchair. A high prevalence of fractures at the knee has been reported by other investigators in cross-sectional and retrospective investigations, with the majority of fractures occurring at the supracondylar femur, femoral shaft, and tibia [1, 9–11, 33, 84] (Table 3).

If fracture thresholds were defined and validated, they would be of great clinical relevance to guide therapeutic approaches. In a cohort of 70 SCI individuals, LaLa et al. [33] completed a retrospective analysis of baseline data from a 2-year prospective longitudinal study. The results of DXA and pQCT imaging (19 with history of fracture) found that participants who had a prior history of fragility fracture had significantly lower aBMD by DXA compared to individuals

**Table 3** Sites and prevalence of femur and tibia fractures in individuals with spinal cord injury

Author, Year	Supracondylar/ condylar femur (%)	Femoral shaft (%)	Tibia (%)	Total (%)
Eser et al. [87]	16	4	31	51
Ragnarsson et al. [11]	33	30	18	81
Ingram et al. [10]	27	15	42	84
Minaire et al. [1]	19	8	46	73
Zehnder et al. [83]	20	12	52	72
Morse et al. [9]	20	NP	48	68
LaLa et al. [33]	NP	42	29	71
Comarr et al. [82]	37	6	7	50
Frotzler et al. [67]	45	26	39	97
Akhigbe et al. [13]		33 <sup>a</sup>	54 <sup>b</sup>	87

Prevalence of fracture for each skeletal site (supracondylar/condylar, femoral shaft, and tibia)

NP not presented

Total percentage of fractures for these three sites vs. all other sites of fracture, based on data from references cited

<sup>a</sup> Femur supracondylar/condylar and shaft results combined

<sup>b</sup> Tibia and fibula results combined

without a history of fracture; furthermore, there was an increasing risk of fracture for every unit of standard deviation decrease in aBMD by DXA or in vBMD by pQCT. In a study of 10 able-bodied controls, 18 SCI persons with SCI with recent LE fracture, and 10 randomly selected individuals with motor-complete SCI, Garland and colleagues [85] found the net mean aBMD at the knee (mean of the DF and PT) was 0.592 g/cm<sup>2</sup> in participants with a recent history of LE fracture; the authors concluded the breakpoint for fracture at the knee was 0.6 g/cm<sup>2</sup>. In another observational study by this group [80], aBMD of the knee was assessed in 168 SCI participants with the cohort stratified into those with and without a history of fracture post-SCI (27 with LE fractures post-injury and 141 with no LE fracture). In those participants with no history of fracture, the mean aBMD was 0.6287 g/cm<sup>2</sup> (95 % CI 0.5988 to 0.6586 g/cm<sup>2</sup>) and in those participants with a history of fracture the aBMD was 0.5279 g/cm<sup>2</sup> (95 % CI 0.4802 to 0.5755 g/cm<sup>2</sup>), with the authors concluding that the findings from this larger cohort support the earlier finding that the breakpoint for fracture at the knee is 0.6 g/cm<sup>2</sup>. Using the methods to define the cutoff value for fracture in the AB population [86], data from this same cohort was reanalyzed in a later report; using this approach, the authors defined the fracture threshold as 0.78 g/cm<sup>2</sup> and the fracture breakpoint as 0.49/cm<sup>2</sup>, which demonstrated... (the “2’s” should be superscripted, as they appear in the text) the variability in defining a fracture threshold solely dependent upon the method used to calculate the cutoff value [30]. Utilizing similar methodology, Eser et al. [87] found that determination of

trabecular BMD by pQCT of the femur and tibia distal epiphyses was effective in identifying subjects with a history of fracture and that subjects with a history of fracture had trabecular BMD values that were  $<114$  and  $<72$   $\text{mg}/\text{cm}^3$  for the DF and PT, respectively. The aforementioned studies by Garland et al. and Eser et al. have provided guidance on fracture threshold by DXA and pQCT in the SCI population but, to date, no longitudinal studies in persons with SCI have been performed that have acquired BMD of the DF and PT at or near the time of fracture occurrence. Thus, a fracture threshold has not been accepted for the knee by any imaging modality. It must also be recognized that the primary reason why a BMD fracture threshold cutoff value has not been established in persons with SCI is because BMD alone is a less than satisfactory predictor of fracture risk, accounting for approximately 50 % of the variance in strength, with measures of mechanical structure (bone geometry and microarchitecture) accounting for the remaining variance in this predictive model [60, 72]. Future prospective cohort studies in persons with SCI will be essential to determine a validated fracture threshold that will enable clinicians to diagnose osteoporosis at the knee and to safely prescribe conventional physical training and emerging technologies for rehabilitative care.

### **Treatment of lower extremity bone loss: rehabilitation and pharmacological interventions**

The clinical aspiration is for rehabilitation professionals to have the ability to identify persons with SCI who have low BMD of the DF and PT and an increased risk of fracture from rehabilitation and/or exercise training modalities that stress tissues in the lower extremities, which currently includes robotic approaches for ambulation. The mechanostat theory, a derivative of Wolff's law, states that there are strains within bone that are kept within certain limits by adding and removing bone tissue, resulting in improved bone strength according to the particular forces that are imposed [88]. However, if force is applied below a certain set point (i.e., due to immobilization secondary to paralysis), bone tissue will ultimately be lost [89]. Over the last two decades, several rehabilitation initiatives have implemented various types of ambulation and electrical stimulation (ES) and functional electrical stimulation (FES) programs in an attempt to improve bone mass and strength in persons with SCI [90–92]. In persons with SCI who have had severe bone loss at the DF and PT, there is an increased risk of fracture by participation in rehabilitation interventions, albeit this level of risk has not been described in the literature for specific interventions.

Locomotor training using body weight-supported treadmill training to activate the neuromuscular system below the level of lesion is a clinically available rehabilitation program. The primary purpose of the program is to optimize the recovery of

function in persons with SCI with clinically motor-incomplete neurological injuries [93], with the potential endpoint of preservation of BMD in the lower extremities. While these programs have proven effective in strengthening the neural circuitry responsible for locomotion in those with motor-incomplete SCI, there is emerging evidence that this therapy alone is largely ineffective in attenuating the rapid bone loss at the DF and PT [94, 95]. There is considerable evidence that the use of cyclical muscle contraction induced by FES is at least partially effective in preserving BMD at the DF and PT soon after SCI, with FES cycle ergometry being the primary modality utilized to date. Preservation of site-specific bone tissue from FES cycling has also been documented in cohorts of individuals with chronic SCI. Using DXA as the imaging modality to assess aBMD of the DF and PT, Bloomfield and colleagues [96] conducted a 9-month FES cycling program in nine individuals with motor-complete SCI. The authors found that in a subset of subjects who achieved high power outputs ( $\geq 18$  W) after 6 months of FES training, aBMD of the DF and PT was significantly increased [96]. In a longitudinal intervention using high volume FES cycling, Frotzler et al. [97] examined the change in vBMD at the DF and PT in 12 motor-complete individuals with chronic SCI who completed 180 min/week of FES cycling for 12 months. The final pQCT measurement revealed a significant increase in cross-sectional area (1.2 %), trabecular vBMD (14.4 %), and total vBMD (7.0 %) at the DF epiphyses, but no significant change was observed at the proximal tibia.

The evidence previously presented which supports the use of FES in those with SCI should be balanced with a brief review of studies that have found FES exercise to have limited therapeutic value in the preservation of bone at the DF and PT. Of clinical relevance, preservation of bone after acute SCI [98, 99], or any reversal of bone after chronic SCI [100, 101], is rapidly lost once FES exercise is discontinued. Furthermore, a degree of controversy persists with regard to the ability of FES cycle training (30 min sessions performed three times a week) to attenuate vBMD loss at the tibial diaphysis in persons with SCI after acute traumatic motor-complete SCI [99]. In a study by Lai et al. [98], aBMD of the DF was assessed in 24 acutely injured (26–52 days post-injury) patients with motor-complete SCI to that of 12 participants receiving FES cycling and 12 age- and gender-matched participants in the control group; the rate of bone loss at the DF in the FES cycling group was significantly less than that of the control group, with the bone-sparing effect of FES completely lost once FES cycling was discontinued. These findings were supported in a study by Chen et al. [102] in which 15 participants with chronic SCI performed FES cycling 30 min a day, five times a week, for 6 months. At baseline, the DF and PT aBMD were 39 and 47 % lower compared to 15 age-matched able-bodied control participants. After 6 months of FES cycling, aBMD of the DF and PT increased by 11 and 13 %, respectively, with the aBMD of both

regions decreasing significantly 6 months after FES was discontinued. Furthermore, in a study by Mohr et al. [103], 12 months of FES cycling on average 2.3 times a week increased aBMD of the PT by 10 %. However, a reduced training exercise prescription of 0.9 times per week was insufficient to maintain these positive changes in aBMD. In a larger cohort of acutely injured patients (4–5 weeks after SCI), 19 patients completed FES cycling three times a week for 6 months and 19 patients served as controls; a small, nonsignificant increase in tibia shaft vBMD in the FES group was observed compared to the control group, with the authors concluding that FES cycling immediately after SCI did not attenuate bone loss [99]. A possible explanation for these contradictory findings previous studies may have been that the mid-shaft of the tibia, which was the site imaged for changes in vBMD, is composed primarily of cortical bone, whereas in prior studies that showed FES to be effective, the DF and PT were the sites imaged, which are sites rich in trabecular bone. The negative findings should serve as an example that a given bone imaging modality, specific outcome variables [e.g., aBMD or vBMD, microarchitecture (Tb.N, Tb.Sp, Tb.Th), and/or geometry measures (CSA, PI, SSI<sub>pol</sub>)] should be sufficiently sensitive to detect a change in the primary objective of the intervention being tested.

In recent years, the effect of ES on sublesional bone in persons with SCI has been studied with increased load delivered to the bone, against resistance (e.g., resistance training), performed in the standing position, or a combination of these approaches applied to improve BMD. In a pilot study of four chronically injured persons with SCI, Shields et al. [104] studied the effect of 6 to 11 months of an FES training intervention on the soleus muscle using plantar flexion ES to deliver a mean estimated load to the tibia of 110 % of body weight to one leg while using the other leg as a control limb. The authors found that aBMD of the PT in three of the participants increased by 19 and 31 % at months 3 and 4, respectively, with no additional increases noted for two participants who continued 11 months into the training program. In addition to this early pilot work, in a study in 28 individuals with motor-complete SCI with varying durations of injury (0.2 to 24.3 years since date of injury), Dudley-Javoroski et al. [100] compared the effect of bone compressive loads using 0 % body weight (no standing), 40 % body weight (passive standing), and 150 % body weight (ES of the quadriceps delivered compressive loads) on the change in vBMD at the DF and PT; the slope of BMD loss in the high-dose group was three-times lower at the DF and 25.1 % lower at the PT than that of the low-dose or control groups. In addition to the DF and PT sites, generating 150 % of body weight using standing ES of the quadriceps increased vBMD at the 12 % femoral length region [105]. In persons with chronic SCI (mean duration of injury ~10 years), Belanger et al. found a ~30 % restoration in BMD of the DF and PT with stimulation of the

quadriceps against an isokinetic load (1 h/day, 5 days a week for 24 weeks) compared to stimulation against gravity alone [101], with a report in preparation suggesting that ES of the upper and lower leg muscles combined with standing has a greater effect on aBMD of the DF and PT than did standing or ES alone [106]. This preliminary evidence supports the hypothesis that a combination of loading and intense cyclic muscle contractions against resistance in the upright position may be sufficient to elicit the minimum essential strain required to stimulate positive bone tissue adaptations at the DF and PT in persons with SCI, suggesting the value of the application of this approach in the clinic to ameliorate bone loss. Additional interventions have examined the effect of regular standing in a supportive frame, pulsed ultrasound at specific bone regions, and low-magnitude whole body vibration therapies on the preservation of BMD in the lower extremities [107–109], with none of these approaches demonstrating efficacy in the treatment of immobilization osteoporosis.

Bisphosphonates belong to a class of anti-resorptive compounds that are widely used in the treatment of postmenopausal, glucocorticoid-induced, and senile osteoporosis [110]. Investigators who have reported the administration of bisphosphonate preparations have had varying degrees of success in preventing sublesional bone loss in the SCI population [111–114]. The main confounding variable in these studies has been that persons with SCI had varying degrees of completeness of motor lesion and that the differences in weight-bearing activities/ambulation were not quantified over the course of the study. In a small randomized study investigating the effect of cyclical etidronate on preservation of bone within 6 weeks of acute SCI, Pearson et al. [112] found that persons with SCI who became ambulatory and received etidronate treatment ( $n = 2$ ) had preservation of bone density compared to ambulatory SCI participants who did not receive drug ( $n = 3$ ) and non-ambulatory SCI participants who received etidronate ( $n = 3$ ), which supports the need for further work to evaluate the efficacy of bisphosphonates or other anti-resorptive agents to prevent bone loss in a larger sample of individuals who are capable of weight-bearing activities and/or ambulation after acute SCI. In a double-blinded, randomized, placebo-controlled study by Bauman et al., despite repeated administration of pamidronate (60 mg intravenously administered at baseline, 1, 3, 6, 9, and 12 months) after acute SCI, BMD was not significantly different at 1 year from the placebo group at the hip and knee [115]. The administration of zoledronic acid (ZA) shortly after SCI has been demonstrated to have a bone-sparing effect at the spine and hip regions in reports by Bubbear et al. and Shapiro et al. [116, 117], but in these reports, BMD at the DF and PT was not evaluated. Bubbear and colleagues [116] administered ZA in an

open label study to 14 patients with acute SCI, 7 treated with ZA and 7 receiving placebo; these investigators noted significant benefit to BMD after 12 months at the lumbar spine (~3 %), total hip (~12 %), and greater trochanter (~13 %), but no significant benefit was observed at the femoral neck. In 17 persons with acute SCI, Shapiro et al. [117] administered ZA and observed a benefit at 6 months post-therapy at the hip, a transient positive result which was almost totally lost by 12 months for BMD, cross-sectional area, and measures of predicted bone strength (i.e., section modulus and buckling ratio) by DXA. In a more recent report by Bauman and colleagues [43], ZA was administered in an open label study to 13 patients with SCI, 6 treated with ZA and 7 receiving no treatment. Compared to the treatment group, the control group lost a significantly greater percentage of BMD at the total hip at month 6 (-3.2 vs. -13.9 %) and at month 12 (-7.5 vs. -20.1 %). However, contrary to the findings at the hip, the treatment group had a greater loss in BMD compared to the control group at the DF and PT at month 6 (-7.9 vs. -2.7 % and -10.5 vs. -4.8 %) and at month 12 (-18.5 vs. -8.4 % and -20.4 vs. -7.9 %). The authors concluded that it would not be prudent at the present time to recommend the use of ZA in an effort to reduce bone loss after acute SCI due to this lack of efficacy at the knee region and the fact that patients with chronic SCI fracture more at the DF and PT than at the hip. Similar to these findings, Schnitzer et al. [48] administered ZA at baseline in a double-blinded, randomized, placebo-controlled trial to 12 patients with SCI, 6 treated with ZA and 6 receiving placebo, with 6 months being the primary time point for drug efficacy after drug administration. Compared to the treatment group, the placebo group lost a significantly greater percentage of aBMD at the total hip (right, -2.2 vs. -8.6 %; left, -3.7 vs. -12.3 %). However, contrary to the report by Bauman et al. [47], the placebo group had a greater percentage of aBMD loss at the DF, but this loss was not significant compared to the treatment group 6 months after BL drug administration. Until adequately powered, well-designed, randomized control trials have been completed, the safety and efficacy of prescribing ZA shortly after SCI remain questionable. A recent single arm investigation looking at the effectiveness of denosumab (60 mg every 6 months) to ameliorate bone loss in 14 patients with acute SCI found this treatment was highly effective at preventing aBMD loss at the lumbar spine and total hip, but aBMD of the DF and PT was not measured, as such, the efficacy of denosumab at these ROI, and comparison to trials using ZA cannot be made at this time [118]. Given the small size of the cohorts to date and the limitations inherent when performing a bone loss intervention clinical trial

shortly after SCI [e.g., corticosteroid administration, individual variation in bone loss after SCI, and limited access to advanced imaging methods (CT and/or MRI)], future randomized control trials are warranted that compare multiple anti-resorptive agents with appropriate imaging modalities to more fully understand the drug with the greatest efficacy to preserve bone mass and architecture at the knee region.

### Future directions

While the use of pQCT to obtain vBMD and microarchitecture of the DF and PT is well appreciated by clinicians and researchers, the fact remains that pQCT is not widely available and the possibility of third party reimbursement in the USA is, to date, not a tenable option when one considers that even reimbursement for DXA imaging has diminished to a great extent over the past decade [119, 120]. Over the past three decades, the success of bone densitometry to diagnose osteoporosis in the clinical environment is largely due to the accumulation of normative data at the hip, lumbar spine, and forearm regions. There is ample evidence that activities while seated in a wheelchair place a person with SCI at greatest risk for low impact fragility fracture at the DF and PT. The future of routine densitometry in the SCI population is dependent on the development of normative databases and improved cutoff values for fracture at the DF and PT using both DXA and advanced imaging methods. Furthermore, future prospective cohort studies are required that employ a multiple component model that accounts for BMD and bone geometry at the DF and PT, as well as risk factors for fracture [e.g., completeness of lesion (motor and/or sensory), age at injury (<18 years of age), duration of injury, etc.] to permit the development of SCI-appropriate algorithms validated in the clinical environment that predict fracture. The successful evaluation of any novel intervention to prevent sublesional osteoporosis is contingent upon obtaining accurate, reproducible, and high quality imaging of the DF and PT. This imaging technology is currently available to clinical investigators and should provide the ability to properly address questions of the efficacy of newer interventions to prevent bone loss at the knee.

Future clinical trials in persons with SCI that are designed to test emerging pharmacological therapies to more potently suppress osteoclast activity by RANKL inhibition [anti-RANKL antibody (denosumab)], to promote osteoblast activity by physical means or by the use of anabolic agents (e.g., testosterone, teriparatide, or its analogs), or to be both anti-resorptive and anabolic [e.g., rehabilitation interventions with or without the administration of anti-resorptive pharmacological therapies or, perhaps, anti-

sclerostin antibody (romosozumab)] are needed to determine the efficacy of such therapeutic approaches at the knee in persons with SCI. Of great interest, preclinical studies from our group have shown the efficacy of sclerostin antagonism or SOST deletion in preventing loss of aBMD at the DF and PT by DXA and the relative preservation of vBMD and bone architecture by  $\mu$ CT after motor-complete SCI [121, 122]. This work suggests that pharmacological antagonism of inhibitors of the Wnt signaling pathway (e.g., sclerostin and/or DKK1), when these agents become commercially available, holds promise as a therapeutic approach to reduce the marked deterioration that occurs to the sublesional skeleton in individuals after the most neurologically complete forms of SCI and in other forms of extreme immobilization osteoporosis.

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