Detection and Treatment of Sublesional Osteoporosis Among Patients with Chronic Spinal Cord Injury: Proposed Paradigms

B.C. Craven, L.A. Robertson, C.F. McGillivray, and J.D. Adachi

Low hip and knee region bone mineral density (BMD) after spinal cord injury (SCI) results in an increased risk of lower extremity fragility fractures or sublesional osteoporosis (SLOP). There are currently no guidelines for the identification and treatment of SLOP among patients with chronic SCI. A paradigm for identification (medical screening, fracture risk, and bone mineral density assessment) of persons with SLOP who warrant treatment and selection of appropriate SLOP treatment(s) (lifestyle/nutrition modifications, bisphosphonate/rehabilitation therapies) is proposed. Content is based on the authors' opinions/expertise and available published and unpublished literature and is intended for use by rehabilitation professionals.
Key words: *bone mineral density, fracture, osteoporosis, treatment, spinal cord injury*

Increased survival and increased life expectancy after SCI have shifted the emphasis of medical intervention from survival to minimizing secondary complications and maximizing quality of life.[1] Sublesional osteoporosis (SLOP) is a disease process unique to persons with SCI characterized by excessive bone resorption, deterioration in lower extremity bone architecture, and an increased propensity for lower extremity fragility fracture. Bone mineral density (BMD) of the hips, distal femur, and proximal tibia are 28%, 37%–43%, and 36%–50% below that of age-matched peers at 12–18 months post injury.[2–8] Prior studies suggested that hip and knee BMD stabilize 1–2 years post SCI, at 25%–50% below that of able-bodied peers.[9,10] Recent investiga-

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tions support a continual 3% per year BMD decline, indicating that lower extremity bone mineral homeostasis does not reach steady state after SCI.[8,9,11,12]

Twenty-five percent to 46% of persons living with chronic SCI will develop fragility fractures.[13–15] Fractures of the distal femur and proximal tibia predominate[14–18] and typically occur due to torsional stress on lower extremity bones during a transfer, or alternatively, compressive force at the knee during a low velocity fall. Fragility fractures often result in delayed union, nonunion, malunion, or, in extreme cases, lower extremity amputation.[18–20] A fragility fracture can initiate a cascade of events resulting in increased morbidity (i.e., heel pressure sore), decreased function (i.e., inability to do independent transfers), and increased nursing and attendant care requirements during fracture healing.

Although fracture reduction is the ultimate goal of SLOP detection and treatment, no treatment trial to date has been designed or adequately powered (sample size) to detect fracture reduction.[21] Most studies have used lower extremity BMD or bone resorption markers as proxy outcomes for fracture reduction. Methods are established for diagnosing SLOP via BMD testing. Health screening, fracture risk assessment, and determination of knee region BMD is needed to select patients for treatment. For the purposes of this discussion, chronic SCI refers to persons with C1-T12 American Spinal Injury Association Scale (AIS) A-D injury of ≥24 months duration. Treatments for SLOP include amelioration of secondary causes of osteoporosis, lifestyle modifications (smoking cessation, restricted alcohol and caffeine intake, mobility assessment, and counseling regarding sports participation), calcium and/or vitamin D supplements, rehabilitation interventions, and bisphosphonate therapy.

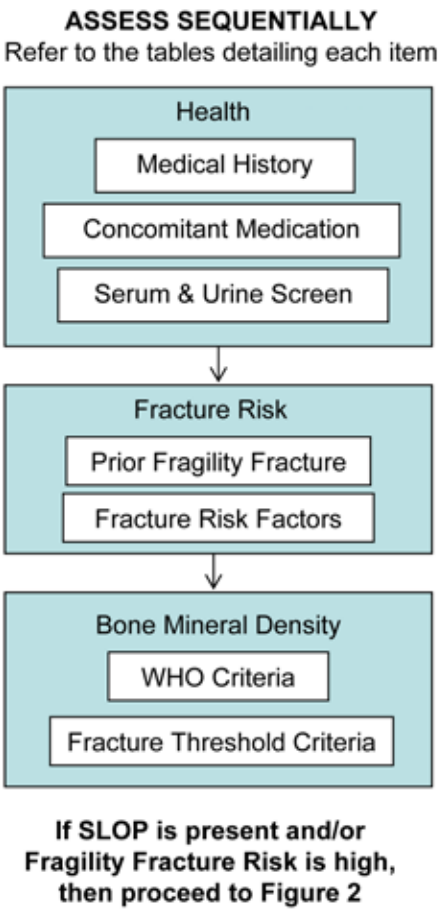

Figure 1. Paradigm for identification of patients with sublesional osteoporosis (SLOP) after SCI who require treatment.

Detection of SLOP

For ease of discussion and graphic representation, we have identified three categories of assessment a clinician should complete to identify patients with SLOP who warrant treatment: (1) health, (2) fracture risk, and (3) BMD (**Figure 1**).

Health

Does my patient have secondary causes of osteoporosis other than their SCI?

It is crucial for clinicians to identify secondary causes of osteoporosis that can exacerbate or mask SLOP. The health evaluation process includes (a) obtaining a detailed medical history to identify secondary causes of low BMD unrelated to SCI, (b) identifying past and current medications known to adversely affect BMD, and (c) screening serum and urine for secondary causes of osteoporosis amenable to medical intervention. The health evaluation is presented as a diagram (**Figure 1**), with three subsections: medical history, medications, and serum and urine screening.

Diseases or health conditions that adversely influence BMD include thyroid and parathyroid disease, hypogonadism, hypercalciuria, kidney stones, kidney failure, chronic liver disease, multiple myeloma, rheumatoid arthritis, mastocytosis, Crohn's and colitis (malabsorption), homocysteinuria, anorexia, osteogenesis imperfecta, Marfan's syndrome, prostate cancer, any type of cancer managed with chemotherapy or radiation therapy, as well as amenorrhea and menopause in women. Medications are also an important consideration, as prolonged use of corticosteroids (>7.5 mg for more than 3 months), anticonvulsants (carbemazapine or dilantin), lithium, inadequate or excessive thyroid replacement, loop diuretics, and blood thinners (heparin) have adverse affects on BMD.[22,23]

The 2002 Canadian Practice Guidelines for the diagnosis and management of osteoporosis, advise screening for secondary causes of osteoporosis not apparent during the typical history or physical examination.[24] Screening tests include serum thyroid stimulating hormone (TSH), parathyroid hormone (PTH), ionized calcium, bone-specific alkaline phosphatase, vitamin D (25–OH), protein electrophoresis, CBC, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (men) or estradiol (women), urea, creatinine clearance, and urinary calcium (**Table 1**). Patients who report unique secondary causes of osteoporosis (i.e., Marfan's syndrome or a history of anorexia) would need additional serum and urine screening. Although this process is time consuming, it has a high diagnostic yield, with about 30% of our patients having identifiable coexisting secondary etiologies of osteoporosis.

A recent retrospective cohort study completed at our centre, consisting of 133 men and premenopausal women with chronic SCI and low BMD (*T* scores < -2.0), identified 37 participants (28%) with a coexisting etiology of osteoporosis. Twenty-two subjects had serologic evidence of parathyroid disease, thyroid disease, vitamin D deficiency, hypogonadism, or chronic liver disease. Two subjects had hypercalciuria. Thirteen subjects had medical histories of alcoholism, Crohn's disease, or long-term anticonvulsant or loop diuretic usage. The results emphasize that not all decreases in BMD are due to SLOP; as many as 33% of individuals with chronic SCI have coexisting secondary etiologies of osteoporosis that can be identified.[23]

Fracture risk assessment

Does my patient have risk factors for fragility fracture?

The goal of SLOP treatment is to prevent fractures, therefore an assessment of fracture risk is essential to identify SCI patients with a high fracture risk. Assigning fracture risk

Table 1. Serum and urine screening for secondary causes of osteoporosis

Category	Test	Indication	Result normal
Serum	TSH	Thyroid disease	❑ Yes ❑ No
	FSH, LH, Testosterone (men), Estradiol (women)	Hypogonadism (men and women)	❑ Yes ❑ No
	25-OH vitamin D	Vitamin D deficiency	❑ Yes ❑ No
	Ionized calcium	If elevated, consider PTH, metastatic cancer, or multiple myeloma. If low, consider osteomalacia.	❑ Yes ❑ No
	Alkaline phosphatase	Screen for bone or liver disease	❑ Yes ❑ No
	Protein electrophoresis[a]	Multiple myeloma	❑ Yes ❑ No
	PSA[b]	Prostate cancer	❑ Yes ❑ No
	CBC		❑ Yes ❑ No
Urine	Creatinine clearance	Renal impairment	❑ Yes ❑ No
	Urinary calcium excretion	Hypercalciuria	❑ Yes ❑ No

Note: TSH = thyroid-stimulating hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PTH = parathyroid hormone; PSA= prostate specific antigen.

[a]Only in patients ≥65 years or with a prior history of prior vertebral fracture.

[b]Only in male patients ≥50 years or with a prior history of prior vertebral fracture.

Modified excerpt from Clinical practice guidelines for the diagnosis and management of osteoporosis. Scientific Advisory Board, Osteoporosis Society of Canada. *CMAJ.* 1996;155(8):1120.

involves a detailed history and limited physical examination (height, weight, and exam according to the International Standard for Neurological Classification of Spinal Cord Injury[25]).

Prior fragility fracture

Has my patient had a prior fragility fracture?

It is important to distinguish between an incident and fragility fracture. A fragility fracture is "caused by injury that would be insufficient to fracture normal bone: the result of reduced compressive and/or torsional strength of bone."[26(p59)] Most lower extremity fragility fractures after SCI are spiral fractures of the diaphysis or simple bending fractures of the distal femur or proximal

tibia epiphyses.[27–29] Common etiologies of fragility fracture after SCI include leg torsion during a car transfer or rolling in bed or falling to the floor from a wheelchair or commode on a flexed knee.[30] An incident fracture is caused by an injury sufficient to fracture normal bone (i.e., motor vehicle accident). Many patients with SCI have more than one fracture, with some reporting five or six, at different skeletal sites.[31] Incident fractures concurrent with the onset of SCI do not increase the future risk of fragility fracture, whereas postinjury fragility fracture(s) are a potent predictor of future fragility fracture(s).[32]

Prior fracture management (conservative vs. operative) does not help distinguish fragility fractures from incident fractures. In general, fractures that occur above the knee require an acute hospitalization and operative intervention, for nondisplaced and displaced femoral neck or intertrochanteric fractures, or fractures of the femoral or tibial shaft, while fractures which occur below the knee joint line tend to be managed nonoperatively with bivalve splints or casts.[33] Fractures can increase patient morbidity from concomitant cellulitis, osteomyelitis, deep venous thrombosis, femoral shortening, and, in rare cases, amputation.[34] The prevention of fractures is therefore a potent incentive to initiate SLOP screening and/or treatment.

Risk factors for fracture

How many risk factors does my patient have?

The prevalence of fragility fractures in persons with SCI is reported to be 25%–46%,[29] although this is likely an underestimate. Some individuals may be unaware of having sustained a minor fragility fracture and therefore did not seek medical attention or alternatively received treatment at local hospitals and were therefore not captured by published studies.[15,18] The incidence of fracture (fragility and incident) is 2%–6% per year,[13,35] and it increases with the duration of SCI: 14% incidence at 5 years post injury, 28% incidence at 10 years post injury, and 39% incidence at 15 years post injury in the United States.[36] The highest incidence of fragility fracture occurs in the following situations: SCI before age 16,[37] paraplegia versus tetraplegia,[17] BMI $\leq$ 19,[32] alcohol intake of more than five servings per day,[38] complete versus incomplete SCI,[39] and female versus male.[14,40] **Table 2** provides a list of common risk factors reported in the literature; we propose that the presence of three or more risk factors implies a moderate risk for fracture, while five or more risk factors implies a high risk.

Bone mineral density

Does my patient have SLOP? Is their BMD an independent risk factor for fracture?

In other populations with osteoporosis, combining BMD with clinical risk factors provides a better estimate of fracture risk than BMD or risk factors alone. For this article, we make a similar assumption for patients with SLOP. Following the diagram in **Figure 1** (Part III), BMD results are interpreted using the WHO criteria (**Table 3**) and fracture threshold criteria (**Table 4**) to identify patients at greatest risk of fracture.

Areal and volumetric measures of BMD are available using dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (p-QCT). DXA is the standard tool for measuring areal BMD (aBMD) and is used to diagnose osteoporo-

Table 2. Risk factors for lower extremity fragility fracture after SCI

Yes	No	Risk factors
❑	❑	Age at injury <16 years[a]
❑	❑	Alcohol intake >5 servings/day[b]
❑	❑	BMI <19[c]
❑	❑	Duration of SCI ≥10 years[d]
❑	❑	Female[d,e]
❑	❑	Motor complete (AIS A-B)[f]
❑	❑	Paraplegia[g]
❑	❑	Prior fragility fracture
❑	❑	Family history of fracture[h]

Note: BMI = body mass index; AIS = ASIA Impairment Scale.

[a]Parsons K, Lammertse D. Epidemiology, prevention and system of care of spinal cord disorders. *Arch Phys Med Rehabil*. 1991;72(4S):S293–294.

[b]Morse LR., Battaglino RA. et al. Osteoporotic fracture and hospitalization risk in chronic spinal cord injury. *Osteoporos Int.* 2009;20(3):385–392.

[c]Garland DE, Adkins RH, Kushwaha V, Stewart C. Risk factors for osteoporosis in the spinal cord injury population. *J Spinal Cord Med*. 2004;27(3):212–213.

[d]Garland DE, Atkins RH. Fracture threshold and risk for osteoporosis and pathological fracture in individuals with spinal cord injury. *Top Spinal Cord Inj Rehabil.* 2005;11(1):61–69.

[e]Slade JM, Bickel SC, et al. Trabecular is more deteriorated in spinal cord injured women versus estrogen free women. *Osteoporos Int.* 2005;16(3):263–272.

[f]Ragnarson K, Sell G. Lower extremity fractures after spinal cord injury: A retrospective study. *Arch. Phys. Med. Rehabil*. 1981;62:418–423.

[g]Freehafer, AA, Limb fractures in patients with spinal cord injury. *Arch Phys Med Rehabil.* 1995;76(9):823–827.

[h]Vestergaard P, Krogh K, Rejnmark L, Mosekilde L. Fracture rates and risk factors for fractures in patients with spinal cord injury. *Spinal Cord.* 1998;36(11):790–796.

Table 3. Diagnostic categories for osteoporosis based on WHO criteria

Category	Definition by BMD
Normal	A value for BMD that is not more than 1.0 *SD* below the young adults mean value
Low bone mass (osteopenia)	A value for BMD that lies between 1.0 and 2.5 *SD* below the young adults mean value
Osteoporosis	A value for BMD that is more than 2.5 *SD* below the young adults mean

Note: BMD = bone mineral density; *SD* = standard deviation; WHO = World Health Organization.

sis and/or monitor treatment effectiveness. During a DXA scan, the densitometer emits pencil or fan beam X-rays of different energy levels and records the differences in attenuation to distinguish bone from surrounding soft tissue.[41] Areal BMD (aBMD) in g/cm^2 is calculated as the measured bone mineral content (g)/area (cm^2).

To validly detect a clinically important change, changes in aBMD from serial scans must be equivalent to or exceed the least significant change of the densitometer.[42–44] Follow-up BMD testing is typically done when the expected change in BMD equals or exceeds the least significant change of the densitometer (about 12–18 months depending on the site measured).[45,46] The current recommendation of the International Society of Clinical Densitometry (ISCD) is to monitor response to treatment every 1–2 years at the same facility, with the same densitometer, using the same acquisition and analysis protocols.[47] DXA protocols are available for measuring multiple skeletal sites including the whole body, spine, hip, wrist, and heel.[48] The choice of measurement site is based on the distribution of BMD decline and the ability of the DXA measure to predict regional fracture risk. Measurements of spine and

Table 4. Fracture thresholds and fracture breakpoints for knee region BMD among patients with SCI

Name	Value	Definition
Fracture threshold[a]	≤ 0.78 g/cm^2 (aBMD)[b] <114 mg/cm^3 (vBMD-femur) <72 mg/cm^3 (vBMD-tibia)[c]	Knee region BMD values below which fragility fracture occur
Fracture breakpoint[a]	<0.49 g/cm^{2b}	Knee region BMD values at which the majority of fragility fracture occur

Note: BMD = bone mineral density; aBMD = areal BMD (DXA); vBMD = volumetric BMD (p-QCT).

SOURCE:

[a]Mazess R. Bone densitometry of the axial skeleton. *Orthop Clin North Am.* 1990;21(1):53–63.

[b]Garland DE. Fracture threshold and fragility fracture risk after SCI. *Topics Spinal Cord Inj Rehabil.* 2005;11:61–69.

[c]Eser P, Frotzler A, et al. Assessment of anthropometric, systemic and lifestyle factors influencing bone status in the legs of spinal cord injured individuals. *Osteoporosis Int.* 2005;16(1):26–34.

hip aBMD are commonly used due to ease of measurement and their ability to predict regional fracture risk for postmenopausal women.[49] The authors advocate measurement of lumbar spine, hip, and knee (distal femur and proximal tibia) BMD for persons with chronic SCI.[50]

Volumetric BMD (vBMD) in g/cm^3 is calculated as the measured bone mineral content (g)/volume (cm^3). p-QCT scans allow assessment of bone architecture, specifically cortical thickness, trabecular volume, and bone cross-sectional area in addition to vBMD. Currently, p-QCT is predominantly a research tool and is not routinely available in clinical settings. However, p-QCT has been used to study changes in vBMD after SCI in Europe, Australia, and Canada.[51,52] Regardless of the methodology, it is crucial that knee region BMD be assessed as it is the best predictor of knee fracture risk after SCI.[32,53] For individuals with chronic SCI, below average aBMD or vBMD is typically due to low peak bone mass or excessive resorption.[30]

WHO criteria

Does my patient meet the WHO criteria for osteoporosis?

Using World Health Organization (WHO) criteria, the diagnosis of osteoporosis among able-bodied postmenopausal women is based on an aBMD T score, which is ≥ 2.5 *SD* below the young adult mean (**Table 3**).[54] The *T* score is the number of standard deviations BMD is above or below gender-specific young adult mean peak bone mass. WHO diagnostic thresholds for osteopenia and osteoporosis have been widely adopted for identifying postmenopausal women with osteoporosis and identifying men/women with substantial fracture risk.[55] However, WHO diagnostic criteria are often confused with treatment thresholds or inappropriately applied to other patient groups including patients with chronic SCI.

The WHO diagnostic criteria for osteoporosis were intended for postmenopausal women. There remains uncertainty in os-

teoporosis literature as to how to diagnose osteoporosis or identify patients in other groups (e.g., men under age 50 and premenopausal women) in need of treatment based on low BMD.[56] The majority of patients with chronic SCI fall into the group for whom there is uncertainty over both diagnostic criteria and rational intervention thresholds.

The ISCD has recommended a *Z* score of ≤ -2.0 *SD* as a rational threshold for initiation of therapy in men under age 50 and premenopausal women.[56] *Z* scores indicate how an individual's BMD compares to age-matched peers. The National Osteoporosis Foundation (USA) recommends the initiation of "therapy to reduce fracture risk in postmenopausal women with BMD *T*-scores by DXA below -2.0 in the absence of risk factors and in postmenopausal women with *T*-scores below -1.5 if one or more risk factors are present."[57(p22)] An association between SLOP (i.e., low BMD of the hips and knee region) and fracture risk post SCI has been consistently described.[58] For men with SCI, Lazo et al demonstrated a 2.8 increase in relative risk of fracture for each 1 *SD* decrement in femoral neck BMD *T* score. After consideration of other confounding variables, including the subjects' age and time post injury, low BMD was found to be the strongest predictor of fracture risk.[59] Here, an intervention threshold of a hip or knee region *Z* score of ≤ -2.0 is proposed after SCI for premenopausal women and young men with three or more risk factors for fracture. This intervention threshold is intended to have face validity among osteoporosis and SCI clinicians alike.

Fracture threshold

Does my patient have a knee region BMD below the fracture threshold?

Fracture thresholds are BMD values below which fractures begin to occur, whereas *fracture breakpoints* are values at which the majority of fractures occur.[60] The concept of a fracture threshold has been rejected for postmenopausal osteoporosis based on recent meta-analyses,[49] which demonstrated a linear relationship between BMD and fracture risk. In contrast, use of a fracture threshold appears to be gathering support among SCI clinicians and researchers, based on data from recent studies that identify aBMD and vBMD threshold values below which there are significant increases in the incidence of lower extremity fragility fractures. aBMD values of the distal femur and proximal tibia are able to distinguish SCI patients at increased risk for lower extremity fragility fracture.

Among male SCI patients, Garland and colleagues reported fracture thresholds at the knee of 0.78 g/cm^2 and a fracture breakpoint of 0.49 g/cm^2.[32] In another study, fracture thresholds for the femur and tibia were identified as a distal femoral epiphysis trabecular vBMD <114 mg/cm^3 and proximal tibia epiphysis trabecular vBMD <72 mg/cm^3 among patients with motor complete SCI.[53] These vBMD values correspond to 46% of mean femur aBMD and 29% of mean tibia aBMD, respectively, for their reference group without SCI. Distal femur BMD below the fracture threshold and fracture breakpoint results in moderate and high fracture risk, respectively. Increases in BMD may be a suitable surrogate outcome measure for fracture reduction when assessing the effectiveness of SLOP therapy, with "optimal therapy" resulting in an increase in knee region BMD above the fracture threshold. We advocate treatment of SLOP among persons with chronic SCI based on the criteria proposed in **Table 5**.

Table 5. Definition of sublesional osteoporosis (SLOP)

Age range	Definition
Men ≥ 60 years or postmenopausal women	Hip or knee region T score ≤-2.5
Men <59 years or premenopausal women	Hip or knee region Z score <-2.0 with ≥3 risk factors for fracture
Men or women age 16–90	Prior fragility fracture and no identifiable etiology of osteoporosis other than SCI

Treatment

Should I offer treatment to my patient?

Having identified a patient with low BMD of the hip or knee region (*Z* score ≤ -2.0) and an increased risk of lower extremity fragility fracture (≥3 risk factors), the clinician must then consider treatment. **Figure 2** presents a diagram outlining a four-step process for treatment: health status, lifestyle, nutrition, and bone factors.

Health

Does my patient have causes of low BMD amenable to treatment?

Health status treatments focus on treating the identified condition, decreasing dosages or changing to an alternate medication, and longitudinal monitoring of the condition if warranted. Identifying and targeting a single secondary cause of osteoporosis is relatively simple, however, multiple etiologies are often identified. For example, a 52-year-old male with T10 paraplegia is identified as having hypogonadism and neuropathic pain for which he takes carbamazepine. Treatment of his hypogonadism will result in substantial BMD accrual; switching from carbamazepine to pregabalin for treatment of his neuropathic pain may prevent further declines in BMD. An alternate example is a 42-year-old premenopausal woman with C6 tetraplegia, hypothyroidism, and vitamin D deficiency. Her vitamin D deficiency has resulted in secondary hyperparathyroidism, and she has been taking excessive doses of her thyroid replacement because of the associated fatigue. Correcting her vitamin D deficiency will reduce her serum calcium level and perceived fatigue and, provided she is eucalcemic, allow her thyroid replacement to be titrated to within the normal reference range with serial monitoring. There are many published guidelines for the treatment of non-SCI causes of osteoporosis. The reader is advised to visit the appropriate osteoporosis society websites for links to these guidelines.[61–63]

Lifestyle

Are there lifestyle factors that, if targeted, would improve my patient's BMD or reduce his or her fracture risk?

The second area to consider when initiating treatment for SLOP is the influence of lifestyle factors, in particular, the effects of

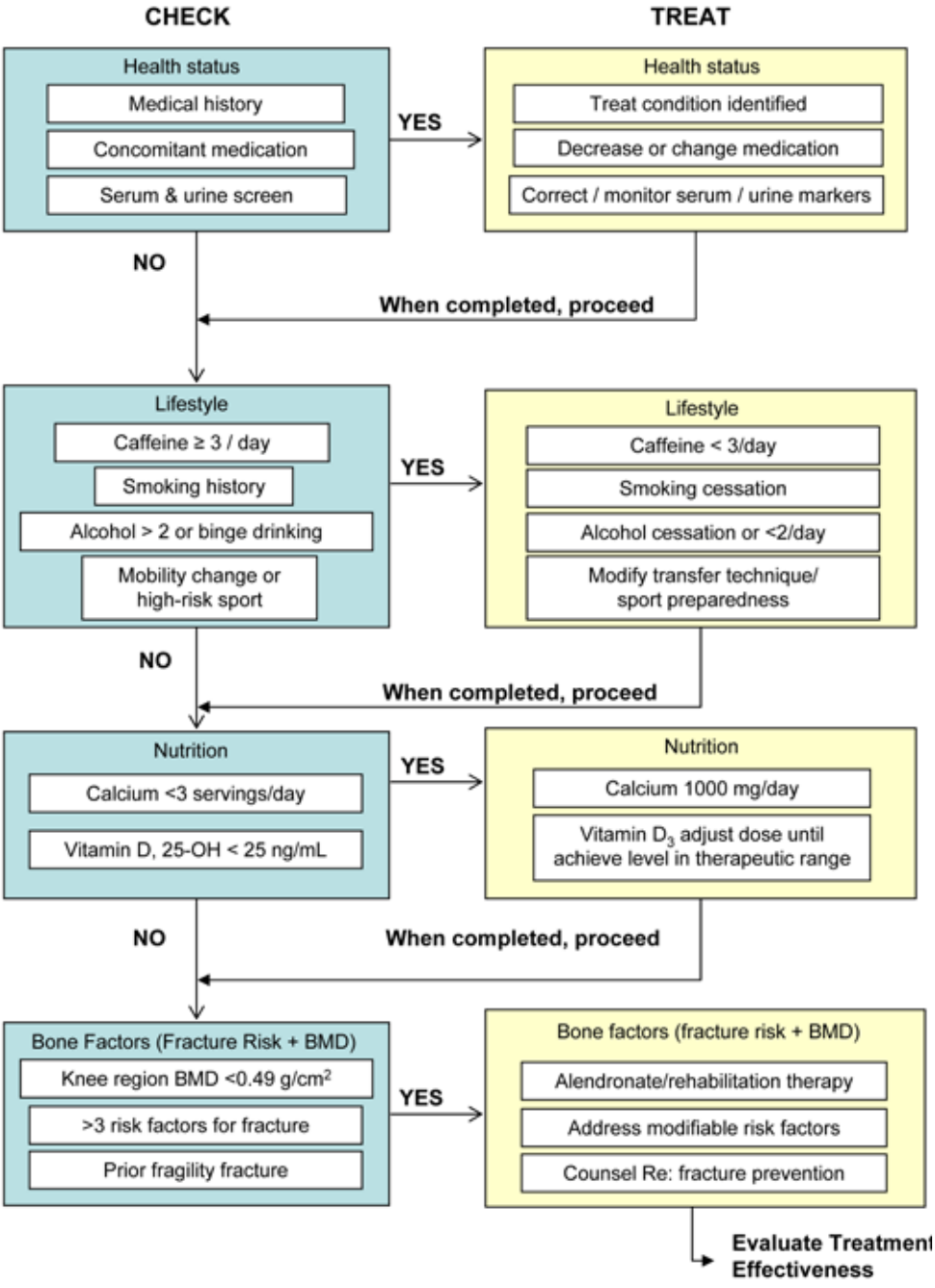

Figure 2. Paradigm for treatment of sublesional osteoporosis (SLOP) and/or fragility fracture risk after SCI.

alcohol, smoking, and caffeine consumption on BMD and the effects of aging and mobility on fracture risk. The intake of each of these substances can be determined with formal standardized assessment tools or by asking the patient about current and past alcohol consumption, smoking, and caffeine intake. Although no longitudinal studies have prospectively evaluated the relationship between smoking, caffeine, alcohol, and BMD among persons with SCI, their effects on global health and the weight of evidence from meta-analyses of their influence on BMD in able-bodied persons suggest they are prudent behavioral targets.[49,64]

Alcohol intake

Does my patient consume excessive amounts of alcohol?

Alcohol consumption is one of the most common risk factors for low BMD among able-bodied men.[65] This warrants significant attention given that 21% of patients post rehabilitation discharge fall in the "alcoholic range" or the "at risk range" on the Short Michigan Alcoholism Screening Test.[66,67] Canada's low-risk drinking guidelines recommend no more than 2 standard drinks per day, no more than 9 servings of alcohol per week for women, and no more than 14 per week for men.[68,69] Our recent cohort study (previously discussed) assessed alcohol consumption among study subjects (bottles per week, glasses of wine per week, and ounces of liquor per week). Thirty-one percent of the cohort reported alcohol intake in excess of 17 servings per week, a clear target for SLOP intervention.[30]

Smoking

Which smoking cessation strategy would be best to recommend?

Several studies from the United States have reported that a simple history of smoking duration is as good (in terms of validity) as trying to obtain detailed smoking information.[70] There are sufficient data from able-bodied osteoporosis studies to identify a causal relationship between smoking and low BMD. BMD is lower in smokers versus nonsmokers, and the difference increases linearly with age.[71] Longitudinal studies have demonstrated higher rates of decline in BMD among male smokers versus nonsmokers. Smoking cessation may slow or partially reverse the influence of longitudinal smoking on BMD. The prevalence of smoking in patients with chronic SCI is 31%–35%.[72,73] The National Health Interview Study in the United States revealed that smoking among young women with disabilities is nearly double the rate of smoking among young women in the general population.[74] The reader is directed to several guidelines for assisting patients with smoking cessation. Interventions include, but are not limited to, counseling strategies and seven medications that have been shown to be efficacious in facilitating smoking cessation.[75,76] There are no published contraindications to current smoking cessation programs for persons with SCI.

Caffeine

Is my patient's caffeine intake excessive?

In our cohort study, many subjects (51.5%, $n = 33$) were current caffeine drinkers, with a mean intake of two cups per day (range 0–6). A caffeine intake greater than three servings per day increases urinary calcium excretion, potentially exacerbating bone resorption. Because the amount of caffeine in a single serving of cola, coffee, and tea varies significantly, the reader should famil-

iarize himself or herself with a caffeine equivalence calculator.[77] It is also important to consider the compounding effects alcohol, caffeine, and smoking history may have in a single individual with SLOP.

Sports

Does my patient participate in high risk activities or contact sports?

Many individuals with SCI participate in contact or high-risk sports that have numerous physical and psychological benefits.[78] As a result, patients should be counseled regarding (a) their choice of sport or high-risk activity (i.e., parachuting); (b) the role of protective equipment (helmet, shin guards, wrist guards, and wheelchair modifications); and (c) the need for a high index of suspicion when they note regional swelling or visible deformity or after a collision/fall. These strategies may reduce the incidence of sports-related fractures and increase the detection of fragility fractures.

Mobility and aging

Has there been an interim decline in my patient's mobility or transfers?

Not infrequently, individuals aging with SCI develop functional declines in their mobility that manifest as changes in gait, use of mobility aids, and deteriorating transfers.[79,80] A careful review of functional abilities and transfer technique may prevent future fragility fractures. For individuals who walk, a discussion of strategies to reduce the risk of falls in the home is suggested.[81]

Nutrition

Does my patient's nutrition status contribute to their SLOP?

Ensuring SCI patients with SLOP receive sufficient calcium and vitamin D, either from diet or supplements, is essential; however, there are currently no evidence-based recommendations or consensus statements addressing optimal calcium intake after SCI. What follows is a discussion of calcium metabolism, assessment of dietary adequacy, and treatment recommendations based on our experience and the able-bodied literature.

Calcium

Does my patient have an adequate, but not excessive, calcium intake?

Given that calcium is required for mineralization of bone and vitamin D promotes calcium absorption,[82] concurrent supplementation has been an important adjunct to osteoporosis therapy.[24] The current Canadian treatment guidelines for osteoporosis recommend "routine supplementation with calcium (1000 mg/d) and vitamin D3 (800 IU/d) as a mandatory adjunct therapy to the main pharmacologic interventions (antiresorptive medications)."[83(pS95)] Osteoporosis Canada recommends a dietary calcium intake of 1000 mg daily for men and women age 10–50 years and 1500 mg per day for men and women over 50 years of age.[84]

Individuals with SCI have dietary calcium intakes that are less than or equivalent to age-matched peers.[30,85,86] After SCI, Levine et al reported mean calcium intake to be 550.0 ± 268.3 mg and 525.0 ± 262.9 mg per day for men and women, respectively. Tomey reported a mean calcium intake of 755 ± 268.3 mg per day for men with chronic SCI; 43% did not meet the recommended minimum calcium requirements of 670 mg/day.[85,87] We found that the mean calcium intake of patients with SCI (n = 87) was 870–1087 mg for men and 848–1087 mg per day for

women, based on 24-hour dietary recall data. The majority of men ingested less than two thirds of the Osteoporosis Canada guideline, with the most deficient group being men and women 51 to 68 years old.[30]

Factors that decrease calcium absorption include dietary fiber, phytates, oxalate found in vegetables (spinach, okra, celery), fruit (berries, currants), nuts (peanuts, pecans), caffeinated beverages (tea, cocoa), free fatty acids, magnesium, and phosphorous. Calcium absorption is increased by 1,25 hydroxyvitamin D levels and lactose. Some medications including but not limited to glucocorticoids, anticonvulsants, and aluminum-containing antacids decrease calcium absorption. Excessive dietary calcium intake can precipitate renal or bladder stones post SCI in persons with hypercalciuria[88–91] or can exacerbate constipation. Asymptomatic renal and bladder stones are frequently identified during routine renal and bladder ultrasounds or cystoscopy in patients with SCI. Symptomatic stones present as shale or blood in the urine or as urosepsis and renal failure in the event of ureter obstruction.[92]

Current calcium intake can be quantified during a patient encounter via a food frequency questionnaire or food record. Dietary adequacy is determined by adding the total dietary intake (mg) to any supplements. We generally recommend a dietary calcium intake of 1000 mg per day for patients with SCI and SLOP and no premorbid or post-SCI history of renal or bladder calculi. This calcium recommendation is equivalent to the Osteoporosis Canada guideline[84] for the treatment of osteoporosis in men and women 19 to 49 years old. This level of intake is intended to promote increases in BMD while minimizing the risk of renal and bladder stone formation. SCI patients with a history of recurrent calcium oxalate or calcium citrate stones or with significant renal impairment should be advised to lower their calcium intake to 500—666 mg and start a low oxalate diet; however, the instructions to the patient depend on the severity of renal impairment and stone type. There is a small subset of SCI patients for whom 1500 mg per day of calcium is recommended. These include young men or women who have not achieved peak bone mass, pregnant or breast-feeding women, and elderly patients with insufficient dietary intakes.

For patients with insufficient calcium intake, calcium absorption can be enhanced by taking supplements in divided doses, no more than 400–500 mg at a time. Absorption is maximized when calcium is ingested concurrently with a meal, while avoiding co-ingestion of oxalate and phytates. Optimal calcium intake refers to the level of consumption necessary for an individual with SLOP to (a) maximize peak adult BMD, (b) maintain BMD, and (c) minimize decline in BMD with aging. No prior study has demonstrated that adequate calcium intake alone will maintain BMD; however an adequate intake is an essential adjunct to oral alendronate in patients with SCI and SLOP.[83]

Vitamin D

Does my patient have an adequate but not excessive vitamin D intake?

Adequate, but not excessive, dietary calcium intake is important for maintaining BMD after SCI, but adequate vitamin D intake is also necessary to facilitate calcium absorption. Adequate doses of vitamin D have been shown to augment BMD as well as reduce coronary artery disease and cancer risk among able-bodied persons.[93,94] Osteoporosis Canada recommendations and

regional practices suggest a daily supplement of 800–1000 IU of vitamin D_3 daily.[84] Others advocate a sliding scale for vitamin D_3 supplementation: <30 years of age, 4,000 IU/day; 30–40 years of age, 3,000 IU/day; 41–50 years of age, 2,000 IU/day; and 51–75 years of age, 1,000 IU/day.

Most individuals with SCI have inadequate dietary vitamin D intake and require supplements to ensure optimal intake.[95] Although many persons with SCI take supplements, optimal vitamin D intake should be established via repeated measurement of serum levels to ensure they are within the therapeutic range.[96] A 32% prevalence of vitamin D deficiency (25-hydroxyvitamin D serum levels) and 24% prevalence of associated mild secondary hyperparathyroidism was reported in a cohort of 100 subjects with chronic SCI.[97,98] A more recent study reported a 100% prevalence of vitamin D deficiency among subjects with chronic SCI living in Chicago and 67% of subjects with chronic SCI living in Alabama.[99] In Canada, exposure to sunlight is often inadequate and compounded by lifestyle or environment-imposed mobility restrictions. Other etiologies of vitamin D deficiency include sunscreen, lactose intolerance, and altered vitamin D metabolism due to prescription medications.[100]

Vitamin D_3 (cholecalciferol) is synthesized in the skin from dehydrocholesterol in response to ultraviolet light exposure (UV B). Vitamin D_2 (ergocalciferol) is found in plants. Dietary sources of vitamin D are rare but include fortified milk, margarine, eggs, and fish oils. Carbamazepine and valproic acid are medications commonly used for the treatment of neuropathic pain post SCI that may accelerate vitamin D metabolism.[101,102] Baumann and colleagues studied the relative potency of vitamin D_2 versus vitamin D_3 in SCI subjects and reported that vitamin D_3 was 9.5 times as potent as vitamin D_2. The etiology of the difference in potency between vitamin D_2 and D_3 post SCI, as opposed to the general population, is unclear. Baumann et al recommended a minimum daily intake of 800 IU vitamin D_3 in the first 0–24 months after SCI.[103] This recommended vitamin D_3 intake is consistent with the Osteoporosis Canada recommendations. In summary, calcium 1000 mg/day and vitamin D_3 800–1000 IU/day are recommended routinely for chronic SCI, provided there is no history of renal or bladder stones, renal impairment, or heterotopic ossification. For SCI patients with these impairments, vitamin D_3 doses should be adjusted to maintain serum levels in the lower limits of the normal range. Optimal vitamin D intake should be confirmed with serial measurements of vitamin D (1,25 and 25-OH) levels. Once optimal intake is achieved, interim monitoring of adherence is recommended.

Bone factors

Is my patient's BMD low enough or fracture risk high enough to warrant treatment?

After implementing diet and lifestyle modifications, clinicians must consider rehabilitation and/or drug treatments for SLOP. In addition, we advocate addressing any modifiable risk factors for fracture and counseling the patient regarding common mechanisms of fracture and how to reduce fracture risk during transfers. Despite the high prevalence of lower extremity fragility fractures and associated morbidity, no guidelines currently exist regarding the treatment of SLOP after SCI. The following is a brief review of the current SLOP treatment literature and the clinical implications.

Rehabilitation interventions

Will my patient benefit from rehabilitation interventions?

There are 18 published studies that have examined the treatment of SLOP after SCI.[104] Two evaluate the efficacy of oral bisphosphonate therapy and are discussed in detail in the section on bisphosphonate trials. Sixteen are rehabilitation intervention studies: seven evaluate the efficacy of weight-bearing exercise, one evaluates vibration, and eight evaluate different forms of functional electrical stimulation (FES). Evaluated weight-bearing activities include passive standing, tilt table, reciprocating gait orthoses, and body weight–supported treadmill training. To date, none of the weight-bearing studies have demonstrated a significant or sustained increase in BMD of the hip or knee region.[105–109] One study evaluated vibration with modest results.[110] FES refers to a group of therapies in which an electrical current is applied to muscle(s) via an implanted or surface electrode to stimulate weak or paralyzed muscles to contract. Microprocessors can generate contractions in controlled sequences thereby facilitating the performance of functional activities such as walking, standing, and bicycling— activities that would not be possible otherwise.[111] Of the eight FES studies, five evaluated FES-cycle ergometry[112–116] and three evaluated FES of the quadriceps.[112,117,118] Belanger and colleagues reported increased lower extremity BMD in paraplegic men following 6 months of FES-cycle ergometry, but the increase in BMD was not sustained following discontinuation of FES.[117]

In summary, none of the 16 rehabilitation interventions led to sustained increases in hip or knee region BMD in subjects with SCI and SLOP. A recent systematic review by Biering-Sorensen et al provides a detailed evaluation of the nonpharmacological interventions for prevention of bone loss after spinal cord injury and further highlights the lack of efficacy of rehabilitation interventions.[119] In persons with chronic SCI and SLOP, rehabilitation interventions may be ineffective due to prolonged suppression of osteocyte and osteoblast activity.[120] It is also plausible that short durations of treatment, small sample sizes, or insufficient mechanical stress may have resulted in the lack of treatment effect to date. Relative contraindications for these therapies include a subluxed or dislocated hip, hip and knee flexion contractures >30 degrees (combined hip and knee angle), nonunion of lower extremity fractures, and a strong hip flexor synergy. Rehabilitation interventions may be offered as an SLOP treatment option, provided the limitations of the current literature and limited efficacy are discussed with the patient prior to initiation.

Bisphosphonate trials

Will my patient benefit from oral alendronate?

Alendronate inhibits osteoclast-mediated bone resorption and binds to hydroxyapatite in bone.[121] To date, two trials ($n = 84$ subjects in total)[122,123] have evaluated the efficacy of alendronate for treatment of SLOP in men and premenopausal women. Using a randomized open-label design, Zehnder et al evaluated the effectiveness of alendronate 10 mg daily and elemental calcium 500 mg daily versus elemental calcium 500 mg daily (alone) for 24 months on BMD after SCI. The study cohort consisted of 55 men with motor complete SCI (para/tetraplegia, AIS A or B) living in Switzerland. Injury duration ranged from 1 month to 29 years post SCI,

with group means of 10 years post injury. The primary outcome was change in tibia epiphysis BMD from baseline measured using DXA. Secondary outcomes included changes in BMD at the wrist, spine, and total hip region and changes in biochemical markers of bone turnover (i.e., osteocalcin). The key findings included an 8.0% decline in tibia epiphysis BMD in the control group and relative maintenance of tibia epiphysis BMD (-2.0%) in the treatment group ($p < .001$). Changes in total hip BMD were similar to the tibia, lumbar spine BMD increased in both groups, and there were no significant changes in wrist BMD. Limitations of this trial included the lack of blinding, failure to stratify/randomize by duration of injury or present subgroup analysis (e.g., separate acute from chronic SCI), lack of an objective evaluation of subject adherence to treatment (self-report as opposed to pill counts), and lack of concurrent treatment with vitamin D supplements.

Moran de Brito et al[123] conducted a 6-month randomized control clinical trial ($n = 19$) of men age < 50 and women age < 35, with paraplegia/tetraplegia, AIS A, B or C, 13–255 months post SCI in Sao Paulo, Brazil. The treatment group ($n = 10$) received alendronate 10 mg daily and calcium 1000 mg daily, while the placebo group received calcium 1000 mg daily. The outcomes of interest were change in aBMD at 6 months, as assessed by *T* and *Z* scores of the whole body and upper and lower extremities measured via DXA. The mean increase in wrist BMD was greater in the alendronate-treated group. There were no significant between-group differences in the mean change of lower extremity *T* scores or lower extremity BMD. Strengths of this study include the randomization and blinding procedures and inclusion of a representative sample. Limitations include the short duration of follow-up, lack of a single primary outcome measure, and failure to include biochemical markers to assist in discerning whether a Type II error had occurred. Although it is easy to find fault with trial data, these two opposing studies are seminal in nature and should not be discounted.

Based on the Zehnder data, we recommend that patients with SLOP[122] (**Table 5**) and motor complete injuries (AIS A, B) be treated with alendronate (10 mg daily or 70 mg weekly) and calcium (1000 mg daily in divided doses). We also advocate titration of vitamin D supplements to ensure a therapeutic serum level. As with all medications, there are side effects and contraindications to consider. Side effects of alendronate include hypocalcemia (>10%)[124]; gastrointestinal side effects (1%–10%), including abdominal pain and dyspepsia,[125] reflux, flatulence, and diarrhea; and rare but serious events including osteonecrosis of the jaw, atrial fibrillation (1.5%),[126] and hepatotoxicity.[127] Alendronate should be used with caution in premenopausal women due to the unknown teratogenic effects of these medications; patients with a prior history of cancer or radiotherapy due to the risk of osteonecrosis of the jaw; and patients taking acetylsalicylic acid, corticosteroids, or nonsteroidal anti-inflammatory drugs (NSAIDS) as concurrent use increases the relative risk of developing a gastric ulcer or bleeding. Periodic assessment of adherence to alendronate is indicated as >20% of the general population stops treatment during the initial 6 months of therapy due to gastrointestinal side effects and cost. Alendronate may be taken safely for 10–13 years after which a drug holiday and/or discontinuation of therapy should be considered.[128] Data from postmenopausal non-SCI women suggest BMD should be

monitored at least alternate years in patients who stop taking oral bisphosphonates. Those with a rapid decline in BMD of >10% in 2 years or >5% from initial baseline should be switched to alternate treatment or resume bisphosphonate therapy.[129]

There are no clinical trials evaluating drug treatments of SLOP among patients with motor incomplete injuries (AIS C and D). Recent p-QCT data from Frotzler describing longitudinal changes in lower extremity cortical and trabecular vBMD over time suggest there is a therapeutic window (2–8 years post injury) during which antiresorptive therapies are most likely to be effective for SCI patients; after which they propose that therapies which target bone formation or osteoblast activity would be more appropriate (i.e., recombinant PTH, whole body vibration, FES-cycle ergometry).[52] To further complicate the decision making, no study has identified or evaluated the impact of any intervention on fracture reduction, the primary impetus for the detection and treatment of SLOP.

The paradigms presented for the detection and treatment of SLOP are based on our opinions/expertise and interpretation of available published and unpublished literature and are intended to guide clinician decision making while highlighting the controversies and gaps in the current SLOP literature. We welcome discussion and dialogue regarding the proposed paradigms.

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