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Sublesional Osteoporosis Prevention, Detection, and Treatment: A Decision Guide for Rehabilitation Clinicians Treating Patients with Spinal Cord Injury

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ABSTRACT: *Background.* Sublesional osteoporosis (SLOP) is characterized by excessive bone resorption at the hip and knee region after spinal cord injury (SCI), resulting in a lifetime increased risk of lower extremity fracture. There are no consensus guidelines to aid clinicians in the prevention or treatment of SLOP. *Objectives.* (1) To review risk factors, skeletal distribution, pathophysiology, and diagnosis of SLOP; (2) familiarize clinicians with the tools available to inform clinical decisions regarding the prevention and treatment of SLOP; and (3) synthesize results of relevant SLOP systematic reviews. *Methods.* We conducted a literature review by searching the MEDLINE/PubMed, CINAHL®, EMBASE, and PsycINFO databases for "SCI" and 14 other bone-related MeSH terms, including publications current to July 1, 2009. The incorporated articles were graded for rigor by using the 11-item Physiotherapy Evidence Database (PEDro) for randomized control trials and the 27-item Downs and Black tool for other intervention studies with scoring modifications. *Implications.* Rehabilitation clinicians can use tools to identify those acute and chronic SCI patients who will benefit from prevention or treatment of low bone mineral density in the hip or knee region, respectively. Therapy selection for SCI patients should stem from the best-available evidence, an understanding of literature limitations, and knowledge of the concurrent conditions that may influence the safety and efficacy of the intervention.

KEY WORDS: bone mineral density, therapy, bisphosphonates, systematic review, guideline, spinal cord injuries

I. INTRODUCTION

Sublesional osteoporosis (SLOP) is a disease process that is characterized by excessive bone resorption and regional declines in bone mineral density (BMD) of the hips and knee regions early after traumatic spinal cord injury (SCI), which reduces bone quantity and quality resulting in a lifetime increased propensity for lower extremity fragility fracture. Twenty-five percent to 46% of persons living with chronic SCI develop fragility fractures secondary to SLOP,[1–3] with fractures of the distal femur and proximal tibia being the predominant types. A single fragility fracture results in a cascade of events that ultimately increases patient morbidity, caused by the complications of fracture immobilization (i.e., heel ulcer or deep venous thrombosis), and decreases patient

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functional abilities (i.e., new or increased need for attendant services as a result of immobilization devices). Fragility fractures after SCI frequently result in delayed union, nonunion, or malunion; in extreme cases, lower extremity amputation may result.[2–4] Fragility fractures are a potent impetus for SCI patients to want to initiate SLOP treatment. However, optimal care should focus on fracture prevention and the judicious use of therapy based on assessment of the patient's fracture risk.

There are two groups of SCI patients who require SLOP interventions; those newly injured for whom we wish to prevent excessive resorption of lower extremity BMD (*Prevention*) and those with established low BMD of the hips and knee regions and a significant risk of fragility fracture whom require therapy (*Treatment*). Because the decline in BMD after SCI is caused by an imbalance between bone resorption and bone formation, drugs and rehab therapies that primarily inhibit resorption, and/or stimulate formation are appealing SLOP therapies. Applying existing guidelines for the diagnosis and treatment of osteoporosis in the general population[5,6] to SLOP in individuals with SCI may not be appropriate, because there are distinct differences between postmenopausal osteoporosis (PMO) and SLOP. There are currently no consensus-based guidelines for the detection, prevention, or treatment of SLOP, which has resulted in diverse SLOP screening, prevention, and treatment practices among SCI clinicians.[7,8]

During rehabilitation, clinicians are asked to make judicious decisions regarding a SCI patient's need for therapy, including the type (if indicated), duration and dosing regimen, criteria for determining treatment efficacy, and the need to change or stop therapy. This article aims to provide the best available evidence regarding the diagnosis and management of SLOP, to assist SCI rehabilitation providers in caring for the bone health of patients with SCI in a manner that optimizes patient outcome and minimizes risk of adverse sequelae.[9] The specific objectives of this article are (1) to provide a succinct review of the risk factors, pathophysiology, and diagnosis of SLOP after SCI to assist clinicians in identifying patients with SLOP and a high risk of fragility fracture; (2) to familiarize clinicians with the tools (decision trees and diagnostic tests) available to inform clinical decision making related to the diagnosis, prevention, and treatment of SLOP; and (3) to present the results of systematic reviews regarding the prevention and treatment of SLOP in a format intended to facilitate evidence-based decision making for busy clinicians.

II. SUBLESIONAL OSTEOPOROSIS

A. Measurement of Bone Mineral Density

1. Areal Bone Mineral Density

Areal BMD (aBMD) can be used as a predictor of fracture risk.[10] Dual-energy X-ray absorptiometry (DXA) is the standard tool for measuring aBMD (g/cm^2), which is calculated as the measured bone mineral content (BMC) (g) per area (cm^2); thereby combining the influence of both density and geometry on bone strength.[11] DXA protocols are available for measuring multiple skeletal sites including the whole body, spine, hip, wrist, and heel.[11] BMC (g), aBMD (g/cm^2), and lean mass and fat mass (g) can also be determined for the whole body and subregions of the body by using DXA.[12] The choice of the DXA measurement site is based on the skeletal distribution of BMD decline and the ability to predict regional fracture risk. DXA is used primarily to diagnose osteoporosis and/or monitor treatment effectiveness at fracture-prone sites in the general population, typically the lumbar spine, hip (proximal femur), or wrist regions. There are many common DXA anomalies that preclude accurate DXA measures of the lumbar spine[13] and hip BMD after SCI[14] (Fig. 1). DXA protocols for the assessment of knee region BMD are available in some rehab settings.[15–17]

The radiation dose associated with DXA scanning is 0.1 μSv or about 1/10th to 1/30th of a chest X-ray.[18] DXA is limited by the projectional nature of the scan that precludes true volumetric measurements of bone density. Despite the widespread use of DXA, aBMD alone may be insufficient to predict fractures. Fracture risk assessments should ideally include measurement of both bone material and bone structural properties to improve fracture risk prediction.[19]

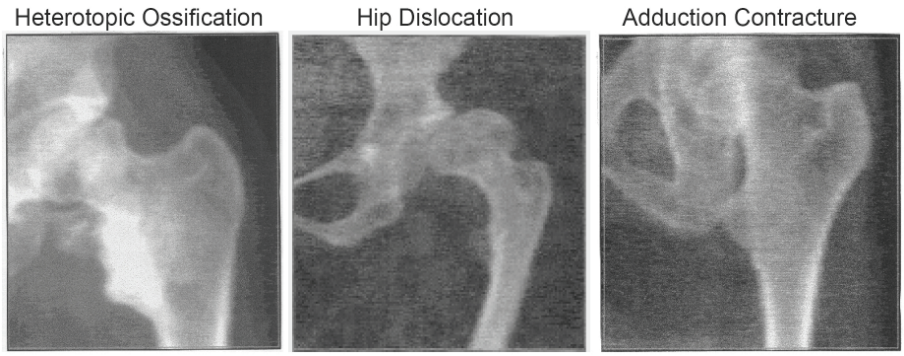

FIGURE 1. Common DXA anomalies that preclude accurate DXA measures of hip BMD after SCI.[14]

2. Volumetric Bone Mineral Density and Bone Quality

Bone quality is a concept that has emerged to describe other parameters of bone strength beyond aBMD. New technologies including quantitative computed tomography (pQCT), high-resolution peripheral quantitative computed tomography (HR-pQCT), and magnetic resonance imaging (MRI) enable the quantification of parameters, such as volumetric BMD (vBMD), bone geometry, cortical thickness, and trabecular bone structure. Volumetric BMD (g/cm^3) is calculated as the measured BMC (g) per volume (cm^3). Although bone quality indices may provide more information regarding bone fragility, assessments of these outcomes are predominantly done in research settings and are not yet routinely available in clinical settings in North America. The radiation exposure from pQCT is 1–2 μSV.

3. Detection of Significant Changes in Bone Mineral Density

Changes in aBMD (increases or decreases) from serial scans must be equivalent to or exceed the "least significant change" (LSC) of the densitometer to be valid.[20–22] LSC is calculated for a 95% confidence level by multiplying the precision error by 2.77.[23] Clinically meaningful increases in BMD should exceed the LSC of the densitometer and be sufficient to result in a reduction of fragility fracture risk. Although there is a linear relationship between BMD and fracture risk for PMO women,[10] increases in BMD are assumed to be a surrogate for fracture risk reduction among patients with SCI; however, no study has prospectively validated this assumption.

Follow-up BMD testing is typically done when the expected change in BMD equals or exceeds the LSC of the densitometer.[24] The current recommendation of the International Society of Clinical Densitometry (ISCD) is to monitor response to treatment among osteoporotic patients with aBMD measures every 1–2 years at the same facility with the same densitometer using the same acquisition and analysis protocols.[25] Serial aBMD or vBMD measures serve one of three purposes: (1) to identify untreated patients for whom therapy is indicated given an interim decline in BMD; (2) to monitor response to therapy among treated patients; and (3) to identify nonresponders to therapy (ongoing decreases in BMD) among treated patients whom require further investigations.[24]

B. DISTINGUISHING SUBLESIONAL OSTEOPOROSIS FROM POSTMENOPAUSAL OSTEOPOROSIS

1. Detection of Postmenopausal Osteoporosis

Osteoporosis is a disease that is characterized by "low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture."[26,27] A fragility fracture is defined as a "fracture caused by injury that would be insufficient to fracture normal bone; the result of reduced compressive and/or torsional strength of bone."[28] Among

TABLE 1
Risk Factors That Identify Who Should Be Assessed for Osteoporosis

Major risk factors	Minor risk factors
Age >65 y	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40 y	Chronic anticonvulsant use
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy for ≥3 months	Smoking
Malabsorption syndrome	Excessive alcohol intake
Primary hyperthyroidism	Excessive caffeine intake
Propensity to fall	Weight >57 kg
Osteopenia apparent on X-ray	Weight loss of 10% of body weight at age 25 y
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45 y)	

Source: Brown et al.[6]

postmenopausal women, osteoporosis manifests as hip and wrist fragility fractures secondary to falls from standing height[29] and vertebral fractures due to bending and lifting.[30]

Risk factors that should prompt clinicians to initiate screening for postmenopausal osteoporosis (PMO) have been identified.[6] Among the many factors identifying those whom require aBMD testing, age >65 years; prior wrist, spine, or hip fragility fracture after age 40; a family history of osteoporotic fracture; and >3 months of systemic glucocorticoid therapy are key (see Table 1). The World Health Organization (WHO)[26] has defined osteoporosis as having an aBMD T-score at the spine, proximal femur, or radius that is 2.5 standard deviations (SD) or greater below the mean of a gender-specific healthy young adult reference population (see Table 2). Osteoporosis may be diagnosed in postmenopausal women and men ≥50 years of age if the T-score of the lumbar spine, total hip, or femoral neck is ≤–2.5. These diagnostic criteria were intended for application to postmenopausal women, yet have been widely adopted. There remains uncertainty as to how to diagnose premenopausal women and men under age 50 with osteoporosis, or how to identify patients in these age groups in need of treatment.[31,32] The majority of patients with SCI fall into the group for whom there is uncertainty over diagnostic criteria.[33] Furthermore, aBMD alone is insufficient for predicting fragility fractures in the general population.[34] Recent osteoporosis risk assessment guidelines focus on the 10-year fracture risk, on the basis of an assessment of BMD *and* clinical risk factors including age and prior fracture independent of aBMD.[35,36]

TABLE 2
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 value

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

2. Osteoporosis Intervention Thresholds

The WHO diagnostic criteria are often confused with treatment thresholds and controversy exists regarding the selection of a rational intervention threshold for premenopausal women or young men with low BMD. The ISCD has recommended a Z-score of 2.0 SD below age-matched peers as a rational threshold for initiation of therapy in men under age 50 and premenopausal women.[32] The National Osteoporosis Foundation (NOF) in the United States recommends 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."[37] The latter intervention threshold, applied to premenopausal women and young men with SCI, is reflected in this article.

3. Sublesional Osteoporosis

SLOP after SCI is distinct from PMO in its rate of onset, microarchitecture of bone, rate and severity of decline in BMD, etiology, and associated regional fracture risk.[16,38–40] Patients with SCI develop SLOP throughout their lower extremities in the first year after injury. A 3%–4% per-month decline in aBMD of the hip and knee region for 12–18 months post injury, with relative preservation of lumbar spine aBMD, is characteristic for persons with traumatic SCI.[41,42] The rapid decline in aBMD throughout the lower extremities after SCI results in aBMD of the hip, distal femur, and proximal tibia being 28%, 37%–43%, and 36%–50% below that of age-matched peers, respectively, at 12–18 months postinjury.[43–49] The decline in vBMD of the hip and knee region is predominantly peri-articular, with reduced trabecular volume.[50,51]

After SCI, there is disruption and loss of trabecular struts (Fig. 2). A loss of trabecular struts and absence of a trabecular network results in an overall reduction in bone strength. Trabecular vBMD at epiphysial sites in the lower limbs is reduced in chronic SCI and there is endosteal resorption at cortical sites resulting in decreased cortical thickness.[52] Geometrical parameters of bone strength, such as second moment of inertia

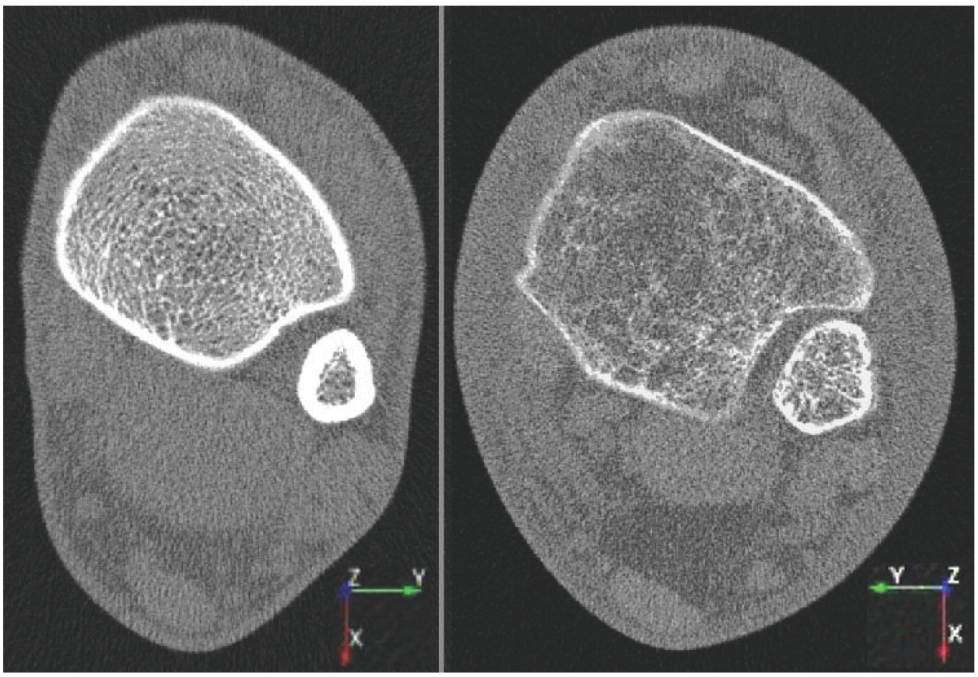

FIGURE 2. pQCT scans of the ultra-distal tibia of a 21-year-old healthy male participant (Left), and of the ultra-distal tibia of a 34-year-old male patient with T5 SCI, 3 years after injury with loss of trabecular struts (Right).

and section modulus, are also altered in the long bones of the legs after SCI, and may be associated with fracture risk.[49] Disruption of trabecular structure may also reduce the capacity for bone formation, because there are fewer structural units on which new bone can be deposited.[53] A prospective study of male patients with complete SCI revealed that there were no significant changes in vBMD and bone cross-sectional area of the femur and tibia among participants in the cohort over a 30-month period. However, in about 10% of scans, decreases in these variables were observed at the 95% confidence level, suggesting that a steady state in bone density and bone shape is achieved, after the initial acute phase of SCI, but there is a subset of patients whom continue to lose bone at an accelerated rate.[54]

A cross-sectional study of 89 men with motor complete SCI (24 tetraplegics, 65 paraplegics; 2 months to 50 years after injury) versus 18 healthy controls without SCI demonstrated greater regional declines in vBMD of the epiphyses (50%) versus the diaphysis (30%) of the femur and tibia in patients with SCI.[39] The process of endosteal resorption occurred at 0.25 mm/y for the first 5 years after SCI in the femur, and the first 7 years in the tibia. The BMD of the remaining cortical bone at the tibia decreased transiently with the initial SCI, but was found to be equivalent to age-matched peers at 5 years after injury.[55] In addition to regional changes in aBMD and vBMD after SCI, changes in the shape and structure of the long bones of the legs were observed.[56,57] Alterations in bone cross-sectional area and bone geometry after SCI have also been reported.[45,49]

4. Risk Factors for Sublesional Osteoporosis

On the basis of studies to date, the degree of decline in aBMD is greatest among women, and those with motor complete injuries [American Spinal Injury Association Impairment Scale (AIS) grades of A or B], SCI ≥10 years' duration, and reduced lower extremity muscle cross-sectional area.[58–60]

In cross-sectional studies, fracture rates have been reported to increase with time after SCI, from 1% per year in the first year to 4.6% per year in individuals >20 years after injury.[61] Furthermore, most individuals with SCI will have low bone mass at the hip, but not all will fracture, suggesting that the aBMD thresholds and clinical risk factors (see Table 3) used to define fracture risk may be different in patients with SCI than in postmenopausal women.[55] Finally, the common

TABLE 3
Risk Factors for Lower Extremity Fragility Fracture After SCI

Yes	No	Risk factors
☐	☐	Age at injury <16 y[64]
☐	☐	Alcohol intake >5 servings/d[65]
☐	☐	BMI <19[66]
☐	☐	Duration of SCI ≥10 y[67]
☐	☐	Female gender[57, 67]
☐	☐	Motor complete (AIS A–B)[68]
☐	☐	Paraplegia[69]
☐	☐	Prior fragility fracture

Note: SCI, spinal cord injury; BMI, body mass index; AIS, ASIA Impairment Scale. Note that reference numbers are given alongside the corresponding risk factor. (Reprinted from Topics in Spinal Cord Injury Rehabilitation, Vol. 14, Craven BC, Robertson LA, McGillivray CF, Adachi JD, Detection and treatment of sublesional osteoporosis among patients with chronic spinal cord injury: proposed paradigms, pp. 1–22, © 2009, p. 6. Reproduced with permission from Thomas Land Publishers, Inc. www.thomasland.com[70])

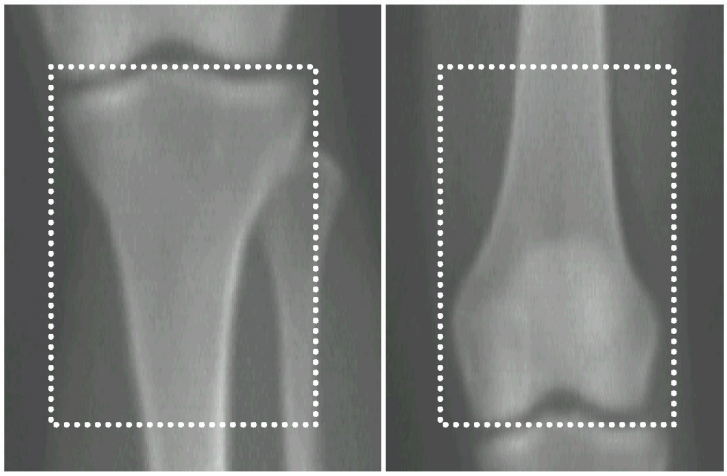

FIGURE 3. DXA scans of the proximal tibia (Left) and distal femur (Right) measurement sites.[17]

sites of fragility fracture in SCI (proximal tibia and distal femur) are not similar to those observed in the non-SCI population. To assess bone loss at fracture-prone sites in SCI, several protocols for measuring peripheral aBMD at the distal femur and proximal tibia have been reported (Figs. 2 and 3).[17] Fracture rates and thresholds for individuals with SCI have been proposed, but they are based on prevalent, not incident fractures.[16,55] Prior studies suggest that aBMD stabilizes by 1 to 2 years after SCI, at 25%–50% below that of able-bodied peers in the hips and knee regions.[41,62] However, recent investigations support the existence of a continual decline in aBMD with time after injury of 3% per year and that a steady state of lower extremity bone mineral homeostasis is not reached.[39,48,50,63]

5. Fracture Thresholds and Fracture Breakpoints

BMD fracture thresholds are values below which fractures begin to occur, whereas fracture breakpoints are values at which the majority of fractures occur.[71] The concept of a fracture threshold is one that has been rejected for PMO on the basis of a recent meta-analysis,[10] demonstrating a linear relationship between aBMD and fracture risk. Use of a fracture threshold has gathered considerable support among SCI clinicians and researchers, on the basis of data from recent studies that identified aBMD and vBMD threshold values below which there are significant increases in lower extremity fragility fracture among SCI patients. Low aBMD values of the distal femur and proximal tibia are able to distinguish SCI patients with and without lower extremity fragility fractures (see Table 4). Among male SCI patients, Garland and colleagues reported DXA-based aBMD fracture thresholds at the knee of 0.78 g/cm^2 and a fracture breakpoint of 0.49 g/cm^2.[67] Fracture thresholds for vBMD were identified as a femoral epiphysis trabecular vBMD <114 mg/cm^3 and a tibia epiphysis trabecular vBMD <72 mg/cm^3 among 21 of 99 patients with motor complete SCI.[55] These vBMD values corresponded to 46% of the mean femur aBMD and 29% of the mean tibia aBMD, respectively, for their reference group without SCI.

Increases in aBMD may be a suitable surrogate outcome measure for fracture reduction when assessing the effectiveness of therapy for SLOP, with "optimal therapy" resulting in an increase in aBMD or vBMD above the fracture threshold in the absence of fracture. However, there is limited evidence for the use of fracture thresholds to prospectively predict fracture occurrence or as a benchmark for treatment effectiveness. Because of the distinct contrasts between PMO and SLOP, it is inappropriate to apply fracture risk categories and intervention thresholds for the general population to individuals with SCI, as the risk factors important for fracture prediction are different, and the data used to derive algorithms for determining

TABLE 4
Fracture Thresholds and Fracture Breakpoints for Knee Region BMD Among Patients with SCI

Name	Value	Definition
Fracture threshold[71]	≤0.78 g/cm^2 (aBMD)[67] <114 mg/cm^3 (vBMD-femur)[55] <72 mg/cm^3 (vBMD-tibia)[55]	Knee region BMD values below which fragility fractures occur
Fracture breakpoint[71]	<0.49 g/cm^2[67]	Knee region BMD values at which the majority of fragility fractures occur

Note: SCI, spinal cord injury; BMD, bone mineral density; aBMD, areal BMD (DXA); vBMD, volumetric BMD (pQCT). Note that reference numbers are given alongside the corresponding name and value. (Reprinted from Topics in Spinal Cord Injury Rehabilitation, Vol. 14, Craven BC, Robertson LA, McGillivray CF, Adachi JD, Detection and treatment of sublesional osteoporosis among patients with chronic spinal cord injury: proposed paradigms, pp. 1–22, © 2009, p. 7. Reproduced with permission from Thomas Land Publishers, Inc. www.thomasland.com[70])

10-year fracture risk are based on epidemiologic data from non-SCI individuals.[35,36]

6. Physiology and Mechanisms for Declining Bone Mineral Density After Spinal Cord Injury

To understand SLOP, it is necessary to have a rudimentary understanding of bone metabolism.[72,73] Bone is the structural support of the human body; however, it is also a dynamic and specialized organ responsible for blood cell production and calcium storage. Unlike other organs, bone has an enormous capacity for growth, regeneration, and remodeling. Bone homeostasis is characterized by bone formation and resorption and is a continuous process in healthy human bones. The bone turnover process replaces old or damaged bone with new bone in order to maintain bone elasticity, strength, and function. *Osteoblasts* and *osteoclast*s are two cell types that are integral to the bone remodeling process. Osteoblasts originate from mesenchymal cells and are responsible for bone formation. Osteoblasts secrete osteoid, the protein that forms the bone matrix. Osteoblasts have vitamin D, parathyroid hormone (PTH), and estrogen receptors. When osteoblasts have filled the bone cavity with osteoid, they become lining cells that cover the bone surface. Osteoblasts may also differentiate into osteocytes, which function to maintain the bone, and lining cells.

Osteoclasts are large cells with many nuclei that originate from hematopoietic cells. They secrete the acids and enzymes responsible for bone resorption. Under normal or healthy conditions, the amount of bone formed by osteoblasts is equal to the amount of bone removed by osteoclasts.

The process of bone remodeling begins when the lining cells on the bone surface are activated by an osteocyte or stimulated by hormonal or growth factors. In response to stimulation, the lining cells on the bone surface secrete RANKL, a protein that activates the RANK receptor on pre-osteoclasts; RANKL is an acronym for Receptor for Activation of Nuclear Factor Kappa B Ligand. RANKL is expressed on the surface of osteoblast cells and binds to RANK. Binding of RANKL to RANK leads to the differentiation and maturation of osteoclast precursor cells into mature osteoclasts. The mature osteoclasts then dissolve the bone, creating a cavity, and several days later die in a process of programmed cell death called apoptosis. The signals for bone resorption to cease and for bone formation to begin to repair the bone cavity are poorly understood but appear to be related to tumour necrosis factor-α (TNF-α), insulin-like growth factors, and the interleukins.[74]

Remodeling continues with osteoblasts migrating to the bone cavity where they secrete osteoid. The osteoid starts to mineralize and gradually the resorption cavity is filled with newly mineralized bone over 2 to 3 months. The osteoblasts will then undergo apoptosis and turn

into osteocytes or lining cells. The new bone is more densely mineralized for up to 3 years and the process of remodeling is complete.

In healthy bone, the process of bone formation and resorption are closely coupled. However, when the level of mechanical strain on bone is below a specific threshold, the amount of loading produces insufficient strains on bone to maintain BMD.[75,76] Disuse-mode remodeling is enhanced bone resorption with little or no bone formation and bone tissue is lost until a level of BMD is reached that is insufficient to withstand the imposed strain.[75] The key problem with bone remodeling for patients with SCI is increased bone resorption and little or no bone formation.[77]

In the first 4 months after SCI, there is an acute period of excessive bone resorption, during which specific metabolic alterations occur. These alterations include increased urinary calcium, nitrogen, hydroxyproline, and zinc excretion, and depression of osteocalcin, a serum marker of bone formation.[78] A contusion model of SCI revealed a rapid increase in osteoclastic bone resorption and mineralization defects in the femoral epiphyses of growing rats only 10 days after injury, with associated losses of trabecular and cortical bone.[79] Maimoun and colleagues have also reported modifications in the osteoprotegerin/RANKL system after SCI, suggesting that T cells and lymphocytes may regulate the differentiation of osteocytes early after SCI via immune-mediated mechanisms that are unique to patients with SCI.[80]

Factors other than impairment that may contribute to the predictable curve of declining BMD in the first year after SCI include increased renal calcium excretion and reduced intestinal absorption of calcium; hormonal and metabolic changes including transient pituitary suppression of thyroid stimulating hormone (TSH) or increased insulin resistance; decreases in the mechanical forces applied to the bone due to paralysis; vitamin D deficiency; alterations in blood flow induced by the SCI; and alterations in the immune system including high serum osteoprotegerin (OPG) and low serum RANKL levels.[80–83] OPG is an inhibitor of osteoclast activity, and individuals with cervical SCI (AIS A–C) had lower OPG levels.[84] The relative importance of each of these factors has not been clearly established. However, Jiang et al. have described it as, "an oversupply of osteoclasts relative to the requirement for bone resorption and/or an undersupply of osteoblasts relative to the requirement for cavity repair."[81]

7. Biochemical Markers

Biochemical markers of bone turnover can be used as an adjunct to DXA in the assessment of bone health among patients with SCI. Serum and urine markers provide useful insight into bone metabolism at specific time points after injury and are an effective tool for monitoring response to therapy. The current therapeutic utility of bone turnover markers is limited by day-to-day, diurnal, inter-individual, and inter-assay variability. For urine markers, results need to be corrected for creatinine.[77] Also, because bone turnover may not return to normal levels after SCI, SCI-specific normative data are needed to establish whether there is utility in using bone markers to determine fracture risk. Serum markers of bone resorption may demonstrate reduced variability compared to urine markers.[85] Comprehensive review articles regarding their use among non-SCI individuals are available and provide direction regarding analytic methods, inter-individual and inter-assay measurement variability, and non-SCI reference ranges.[86,87] For a bone marker to be useful in assessing the rate of bone turnover and/or monitoring therapy effectiveness, the difference in the rate of bone turnover before and after SCI, as well as the early period versus the late period after SCI, needs to be discernable. Significant changes in response to treatment, and the ability to measure clinically important changes in short time frames (i.e., months vs. years) are needed. Biochemical markers of bone turnover are generally divided into three subclasses: bone formation markers, bone resorption markers, and markers of calcium homeostasis. Bone turnover markers can be used as an adjunct to DXA by providing insight into bone metabolism and/or to monitor early response to therapy

a. Markers of Bone Formation

The bone formation markers include bone-specific alkaline phosphatase (BALP), osteocalcin (OC),

N-terminal propeptide of type I collagen (PINP), and C-terminal propeptide of type I collagen (PICP). These markers reflect bone matrix mineralization (BALP, OC) and type 1 collagen synthesis (PINP, PICP).[86] Although PICP levels have previously been reported in studies of individuals with SCI, PINP is now preferred to PICP as a marker of bone formation.[86,87] Commercial assays for OC and BALP are often routinely available, and there are more SCI-specific data available using these markers. OC levels are low or normal in the first month following SCI, increasing to a peak several months later but often remaining within normal ranges.[88,89] PICP levels within normal ranges have been reported up to 3 months after SCI.[89] Levels of BALP in acute SCI approximately 3 months after injury were not significantly different from controls.[90] However, high levels of ALP have been reported during the first year after injury in individuals with SCI.[91] Among male patients with chronic, complete SCI, serum OC and BALP decreased compared to controls after 24 months of alendronate therapy.[92] BALP was not significantly different among male patients with acute SCI who received zoledronic acid for 12 months compared to controls.[93]

b. Markers of Bone Resorption

Markers of bone resorption include urinary free and total pyridinoline (Pyr) and deoxypyridinoline (DPD) crosslinks, type 1 collagen C-telopeptide (CTX), and N-telopeptide (NTX). Pyr and DPD are molecules that provide stability to collagen and, along with CTX and NTX, are released when collagen is degraded during bone resorption.[86] Commercial assays for serum CTX are routinely available, and may demonstrate reduced variability compared to urinary Pyr, DPD, and NTX, but should be taken in the morning during the fasting state.[86] Notable increases in bone resorption markers have been reported to occur as early as 2 weeks following SCI, reaching peak values 2 to 4 months after injury onset.[78,89,90,94] Values did not return to baseline levels at 6 months after injury, indicating that bone loss is ongoing.[94] Elevated levels of DPD and NTX have been reported in individuals greater than 5 years after SCI but were lower than the levels observed in individuals less than 1 year after SCI, suggesting that elevated bone resorption may continue in chronic SCI, although at a reduced rate compared to the acute stages.[77] Increasing age has been positively associated with CTX levels among individuals with SCI.[84]

There are SCI-specific data showing that bone resorption markers demonstrate responsiveness to bisphosphonate therapy in male patients with acute[93] and chronic SCI[92]; markers of bone resorption were reduced in those patients receiving bisphosphonate therapy compared to controls after 12 and 24 months of therapy in acute and chronic SCI, respectively. Interestingly, bone resorption markers also declined compared to baseline after 24 months of calcium supplementation alone among individuals with chronic SCI in the control group; however, the between-group difference was still significant.[92]

c. Markers of Calcium Homeostasis

Systemic factors known to regulate bone and calcium homeostasis are frequently altered after SCI. A cross-sectional study of 40 men with long-standing SCI revealed that PTH levels were significantly lower than in a group of able-bodied controls and negatively correlated with injury level.[95] In contrast, a large cross-sectional study of 176 individuals with SCI found depressed PTH levels only during the first year after SCI.[96] A smaller study also demonstrated that PTH was not significantly different from the reference range in individuals with long-standing SCI.[46] In the first 4 months to the first year after injury, PTH levels have been reported to be low, eventually returning to normal levels,[78,90] whereas 1,25-dihydroxyvitamin D (1,25-(OH)2 D), which is also a regulator of calcium metabolism, may decrease during bed rest and after SCI.[90,94,97,98] Depressed levels of 1,25-(OH)2 D have been demonstrated in individuals with long-standing SCI.[95]

Hypercalciuria is often reported after SCI and may be reduced with re-ambulation.[99,100] Serum ionized calcium has been demonstrated to increase into the hypercalcemic range after SCI, remaining there for 6 months with a parallel increase in urinary calcium excretion.[94] Predisposing factors for hypercalcemia in acute SCI include age ≤21 years, higher injury level, complete injury, and

prolonged immobilization.[101] In individuals with long-standing SCI, ionized calcium levels were not different from non-SCI controls.[95] A study of bone and calcium metabolism in 28 patients demonstrated enhanced bone remodeling during the first year after injury, with maximal values occurring between 3 months and 10 months after injury. In addition, the rate of bone calcium turnover was greater in the nonparalyzed areas than in the paralyzed areas during the first 2 months after injury.[91] There was no appreciable loss of BMC at an upper limb site (radius).

The impact of alterations in systemic factors regulating bone and calcium homeostasis is reflected in the bone loss that occurs after an SCI. The removal of weightbearing may initiate alterations in calcium metabolism via decreased PTH and 1,25-(OH)2 D synthesis, resulting ultimately in bone loss. Conversely, given that unloading-induced bone loss occurs to a greater extent in the lower extremities, the bone loss may not be solely a result of changes in systemic regulation of calcium metabolism. The slight decreases in PTH and 1,25-(OH)2 D may be a result of increasing calcium concentrations in serum because of increased bone resorption that is initiated via alternate means. The bone response to reduced weightbearing may be modulated by systemic factors, such as PTH and 1,25-(OH)2 D, but it is likely that local factors are primarily responsible for bone changes.[102]

III. DIAGNOSIS OF SUBLESIONAL OSTEOPOROSIS

A. Identifying Patients with Sublesional Osteoporosis and High Fracture Risk

Identification of patients with SLOP and high fracture risk entails aBMD testing (Fig. 3) with a polycarbonate positioning device (Fig. 4) and a review of fracture risk factors (Table 3). Fragility fracture risk factors after SCI include SCI before the age of 16 years,[64] duration of SCI >10 years,[64] paraplegia,[69] body mass index (BMI) ≤19,[67] alcohol intake of >5 servings per day,[65] motor complete SCI,[68] female gender,[2,40] prior history of fracture, and maternal family history of fracture.[1] The presence of ≥3 risk factors implies a moderate fracture risk, whereas ≥5 risk factors imply a high fracture risk.

DXA is the clinical tool used for diagnosing SLOP. Based on hip or knee region BMD results

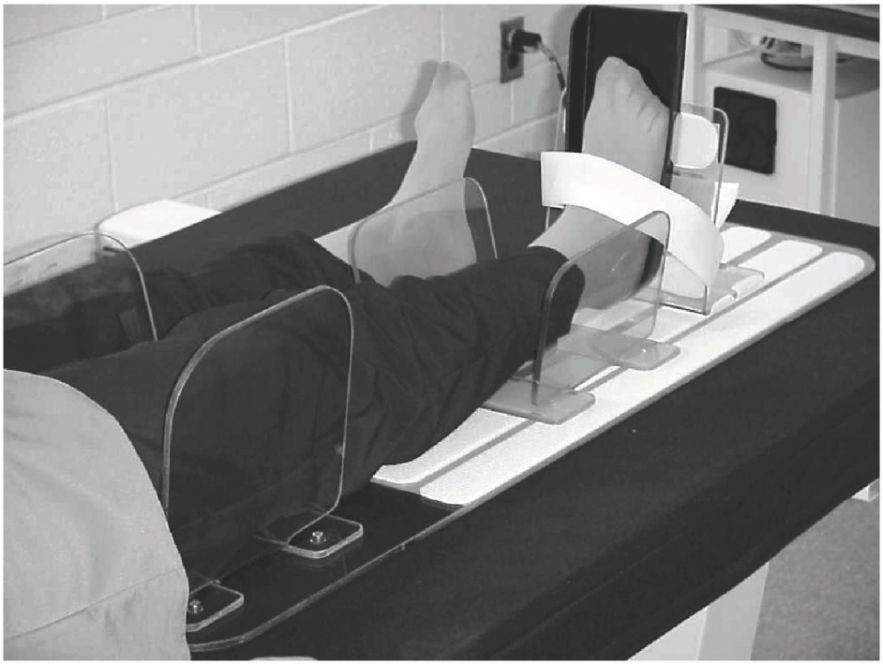

FIGURE 4. A polycarbonate positioning device used for knee DXA scan acquisition.

(T-scores or Z-scores), clinicians may identify patients with SLOP on the basis of their gender and age at the time of scan acquisition (see Table 5). There are several established methods for measuring knee region BMD.[15–17,39,45,103,104] Regardless of the methodology chosen, it is crucial that knee region BMD be assessed because it is the best predictor of knee fracture risk after SCI.[16,55,67] Knee region aBMD and vBMD thresholds for fracture and breakpoint have been identified[59,67] and are shown in Table 4. Patients diagnosed with SLOP (Fig. 5) and a high fracture risk (>5 risk factors) or low BMD of the hip or knee region (Z-score ≤–2.0) and a moderate fracture risk (≥3 risk factors) require treatment.

IV. THERAPEUTIC DECISION MAKING

A. Principles

We propose that multimodal therapy for the prevention or treatment of SLOP should include the following principles: (1) treatment of secondary and lifestyle causes of low or declining BMD unrelated to SCI; (2) ensuring adequate but not excessive intake of calcium and vitamin D; (3) selection of appropriate drug or rehab therapy based on the likelihood of the therapy to benefit the patient without associated adverse effects; and (4) routine monitoring of therapy adherence and assessment of treatment effectiveness. Figure 6 provides an overview of the process of working through these aforementioned principles, and these decision-making processes were also described in greater detail in a recent publication.[70]

B. Treatment of Secondary Causes of Low or Declining Bone Mineral Density

Identification of treatment targets, specifically lifestyle behaviors and secondary metabolic causes of low or declining BMD unrelated to SCI, can be accomplished via a detailed medical history (see Tables 6 and 7), serum screening (see Table 8), and simple questions regarding daily or weekly caffeine and alcohol intake and smoking history.[70] Hypercalcemia,[101] vitamin D deficiency,[105] and hypogonadism[106] are common among acute SCI patients. Hypothyroidism, secondary hyperparathyroidism, renal insufficiency, hypogonadism (men), and amenorrhea (women) are frequently identified treatment targets among chronic SCI patients.[107] Smoking cessation, reduced caffeine intake (<3 servings per day), and restricted alcohol intake (<2 servings per day) are rational behavior intervention targets.[108] We have previously presented paradigms to assist clinicians in identifying secondary causes of osteoporosis amenable to treatment and initiating appropriate lifestyle interventions.[70]

C. Ensuring Adequate Calcium and Vitamin D Intake

Assessment of the patient's dietary adequacy is necessary to ensure sufficient but not excessive

TABLE 5
Definition of SLOP

Age and gender	BMD and clinical criteria
Men ≥60 y or postmenopausal women	Hip or knee region BMD T-score ≤–2.5[26]
Men < age 59 y and premenopausal women	Hip or knee kegion BMD Z-score ≤–2.0 with at least 3 risk factors or ≥5 risk factors
Men or women age 16–90 y	Prior lower extremity fragility fracture and no identifiable etiologies of osteoporosis other than SCI

Note: Reprinted from Topics in Spinal Cord Injury Rehabilitation, Vol. 14, Craven BC, Robertson LA, McGillivray CF, Adachi JD, Detection and treatment of sublesional osteoporosis among patients with chronic spinal cord injury: proposed paradigms, pp. 1–22, © 2009, p. 9. Reproduced with permission from Thomas Land Publishers, Inc. www.thomasland.com[70]

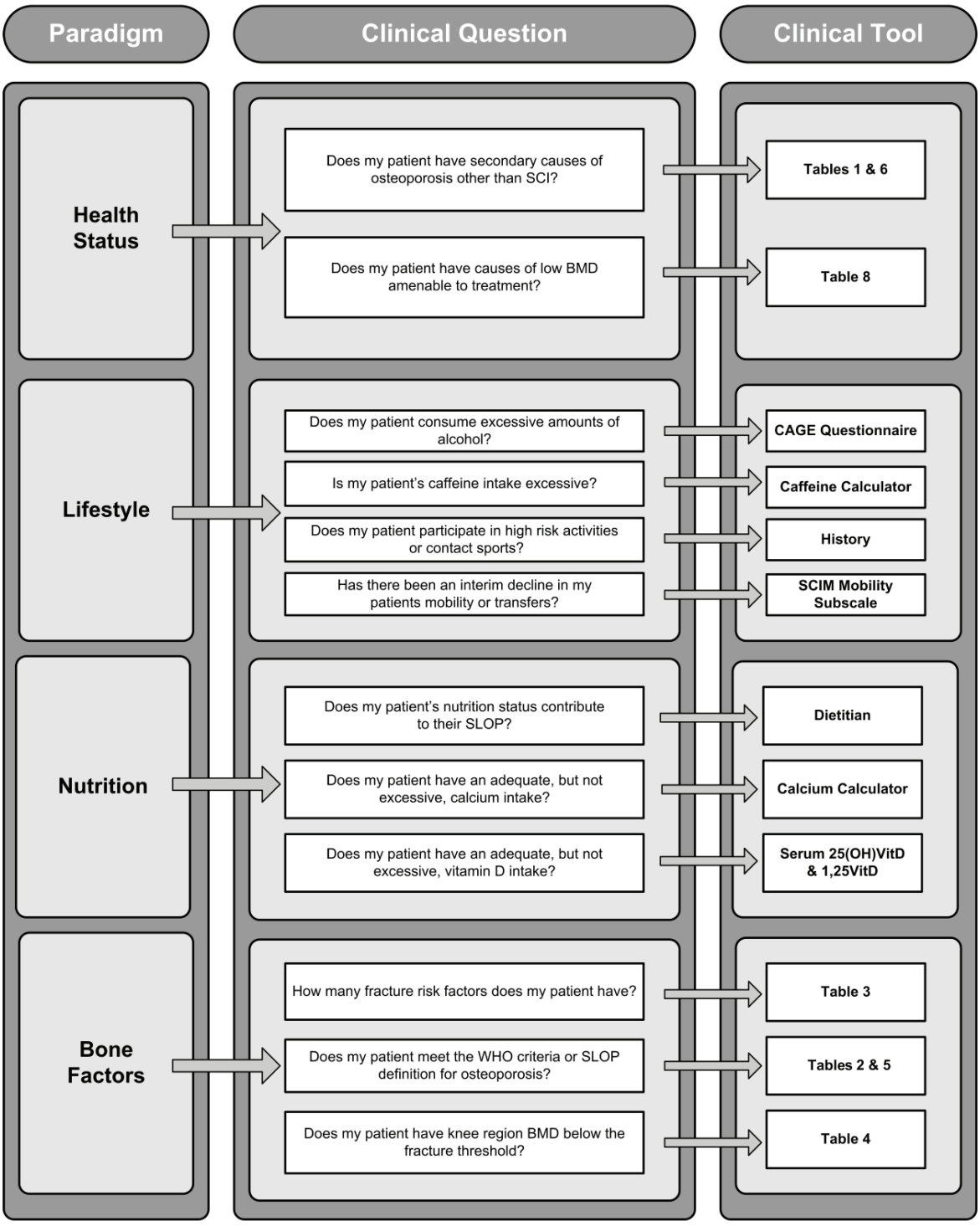

FIGURE 5. The paradigm and clinical tools used for the diagnosis of SLOP.

calcium and vitamin D intakes via diet or supplements. Prudence is indicated when prescribing supplements because an excessive calcium intake may precipitate stones in the bladder or kidney, whereas excessive vitamin D intakes may precipitate heterotopic ossification. Although optimal vitamin D intake has been shown to prevent fractures in patients with PMO,[111] a similar effect has yet to be established among patients with SCI and SLOP.

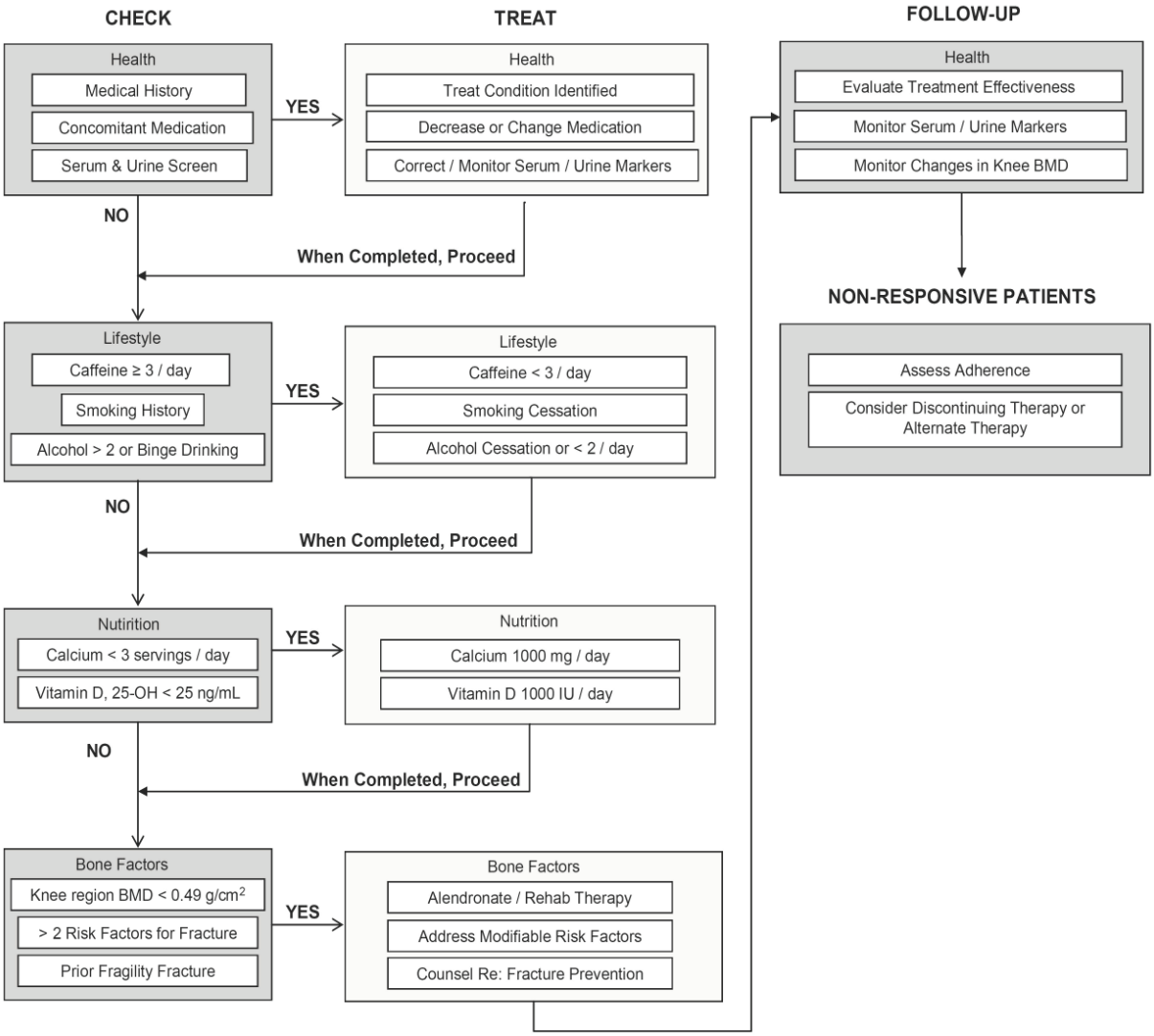

FIGURE 6. The protocol for the diagnosis, initiation, and evaluation of treatment effectiveness for SLOP.

Clothing, medications, sunscreens, hours of sun exposure, and skin pigment all influence vitamin D absorption.[112] There is a 30% prevalence of vitamin D deficiency reported among persons with SCI.[113] Bauman 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 after SCI is unclear.[114] Bauman et al.[113] recommended a minimum daily intake of 800 IU vitamin D_3 in the first 24 months after SCI. We concur, provided that there is no prior or current history of renal or bladder stones, renal impairment, or heterotopic ossification. Monitoring of serum 25(OH) vitamin D and 1,25-$(OH)_2$ vitamin D levels is needed to detect vitamin D deficiency and ensure serum levels are within a therapeutic range after initiation of therapy with supplements.[115]

Calcium absorption is influenced by the patient's dietary intake of fiber, oxalates in green leafy vegetables (spinach), fruits (berries, currants), nuts (peanuts, pecans), and caffeinated beverages (tea, cocoa).[116] SCI patients, especially elderly men, have been reported to have insufficient dietary calcium intakes[117–119] and require supplements to achieve optimal intakes. Daily routines, family and personal factors, food preference, and perceived lactose intolerance affect adherence to dietary calcium recommendations among young Canadian women[120] and persons with SCI.[119] The current

TABLE 6
Secondary Causes of Low BMD Unrelated to SCI

Yes	No	Category	Medical history
☐	☐	Inherited	Osteogenesis imperfecta
☐	☐		Homocysteinemia
☐	☐		Marfan's syndrome
☐	☐	Nutritional	Malabsorption—Crohn's or colitis
☐	☐		Chronic liver disease
☐	☐		Alcoholism
☐	☐		Calcium deficiency
☐	☐		Vitamin D deficiency
☐	☐	Endocrine	Hypogonadism (men and women)
☐	☐		Hyperthyroidism
☐	☐		Hyperparathyroidism
☐	☐		Anorexia nervosa
☐	☐		Hypercalciuria or kidney stones
☐	☐	Other	Renal failure
☐	☐		Multiple myeloma
☐	☐		Rheumatoid arthritis
☐	☐		Anorexia
☐	☐		Mastocytosis
☐	☐		Prostate cancer
☐	☐		Breast cancer
☐	☐		Prior chemotherapy or radiotherapy

Source: Modified excerpt from Lewiecki.[109]

Canadian treatment guidelines for osteoporosis recommend "routine supplementation with calcium (1000 mg/d) and vitamin D_3 (800 IU/d) as a mandatory adjunct therapy to the main pharmacologic interventions (antiresorptive medications)."[5] The National Osteoporosis Foundation in the United States recommends a dietary calcium intake of at least 1200 mg/d including supplements and a vitamin D intake of 800–1000 IU/d for adults over 50 years of age.[37] The safe upper limit for

TABLE 7
Concurrent Medications That Adversely Effect BMD

Yes	No	Concurrent medications
☐	☐	Prednisone (>7.5 mg × 3/12)
☐	☐	Anticonvulsants (i.e., Dilantin and Tegretol)
☐	☐	Excess thyroid replacement
☐	☐	Diuretics (i.e., hydrochlorothiazide)
☐	☐	Heparin
☐	☐	Other, *specify:*

TABLE 8
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*	Multiple myeloma	☐ Yes ☐ No
	PSA†	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. (Reprinted from Topics in Spinal Cord Injury Rehabilitation, Vol. 14, Craven BC, Robertson LA, McGillivray CF, Adachi JD, Detection and treatment of sublesional osteoporosis among patients with chronic spinal cord injury: proposed paradigms, pp. 1–22, © 2009, p. 4. Reproduced with permission from Thomas Land Publishers, Inc. www.thomasland.com[70])

* Only in patients ≥65 y or with a prior history of prior vertebral fracture.

† Only in male patients ≥50 y or with a history of prior vertebral fracture.

Source: Modified excerpt from Table 1 of the "Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis."[110]

vitamin D for the general population is generally recommended to be 2000 IU/d. However, recent evidence suggests that higher levels may be required to obtain therapeutic 25(OH) D levels. We advocate a dietary calcium intake of 1000 mg daily for patients with SCI and SLOP who have no premorbid history of renal or bladder stones. Calcium absorption can be enhanced by taking supplements in divided doses, no more than 400–500 mg at a time, concurrently with a meal. Once optimal intakes are achieved, interim monitoring of adherence is required.

D. Offering Appropriate Therapy

Appropriate SLOP treatments are those deemed to be relatively safe and likely effective. A recent systematic review summarizes the drug and rehabilitation interventions available for SLOP prevention and treatment based on the strength of evidence.[121]

1. Decision Making and Grades of Evidence

The therapy recommendations presented in the subsequent sections of this article were derived from a literature review by using the MEDLINE/PubMed, CINAHL®, EMBASE, and PsycINFO databases to identify all relevant SLOP literature published from 1980 to July 2009, and searching using "spinal cord injuries" and 14 bone-related MeSH terms. Identified articles were graded for the rigor of the study design (see Table 9) by two independent raters. The Physiotherapy Evidence Database (PEDro) tool, an 11-item scale with a maximum score of 10, was used to assess the randomized controlled trials. The first item on

TABLE 9
Levels of Evidence Based on Rigor of Study Methods

Level	Research design	Description
1	RCT	RCT, PEDro score ≥ 6; includes within-subjects comparison with randomized conditions and crossover designs
2	RCT	RCT, PEDro score < 6
	PCT	PCT, Level 2 (not randomized)
	Cohort	Prospective longitudinal study using at least 2 similar groups with one exposed to a particular condition
3	Case control	A retrospective study comparing conditions, including historical controls
4	Pre–post	A prospective trial with a baseline measure, intervention, and a post-test using a single group of participants
	Post-test	A prospective post-test with 2 or more groups—intervention, then post-test (no pretest or baseline measurement) using a single group of participants
	Case series	A retrospective study usually collecting variables from a chart review
5	Observational	Study using cross-sectional analysis to interpret relations

Note: RCT, randomized controlled trial; PEDro, Physiotherapy Evidence Database; PCT, prospective controlled trial.
Source: Eng et al.[123]

the scale relates to external validity whereas the remaining 10 items assess the internal validity of the trial.[122] One point was given for each satisfied criterion (except for the first item, which was given a YES or NO). The higher the score (out of 10 points), the better the quality of the study; a point for a particular criterion was awarded only if the article explicitly reported the criterion. The scoring system is detailed in Table 10. Two independent raters reviewed each article; scoring discrepancies were resolved through discussion. All other study designs included in this review that used a nonexperimental or uncontrolled design (nonrandomized comparative trials, cohort studies, or retrospective studies) could not be assigned a PEDro score.

Relevant intervention studies (cohort, case control, and observational) were assessed with the Downs and Black Tool, comprised of 27 questions with a maximum score of 28 points.[124] This tool consists of the following subsections: reporting, external validity, internal validity–bias, and internal validity–confounding (selection bias). The original scoring range was from 0 to 32. However, we modified the last question from a scale of 0–5 to a scale of 0–1, where 1 was scored if a power calculation or sample size calculation was provided, and 0 was scored if none was present. Thus, the modified Downs and Black tool[123] was scored from 0 to 28 points, with a higher score indicating better methodological quality (Table 11).

Results of the systematic reviews are summarized in tables ranking the study methods and, by association, the strength of the inferences obtained. In addition, results of the systematic reviews are shown in SCIRE format tables,[123,125] which provide greater detail regarding the study methods and outcomes. Data were abstracted from the articles to create tables ranking study rigor, and outlining sample size, study population, nature of the therapy or intervention, type of outcome (BMD or biochemical markers), and a sign indicating the overall outcome of the study (where a plus sign [+] represents a positive outcome in the treatment group, and a minus sign [–] represents a negative outcome in the treatment group) as it relates to the study objectives.

E. Bisphosphonate Therapy

Bisphosphonates are a group of medications that are used to prevent declines in bone mass or to treat low BMD by slowing down the rate of bone resorption via early osteoclast apoptosis. There are two types of bisphosphonates, those that contain

TABLE 10
PEDro Scoring

Criteria	Description
Yes/No	Eligibility criteria were specified.
1	Participants were randomly allocated to groups (in a crossover study, participants were randomly allocated in the order in which treatments were received).
2	Allocation was concealed (the individuals responsible for determining if participants were eligible for inclusion were blinded to the allocation of a participant or future participants).
3	The groups were similar at baseline regarding the most important prognostic indicators.
4	There was blinding of all participants.
5	There was blinding of all therapists who administered the therapy.
6	There was blinding of all assessors who measured at least one key outcome.
7	Measures of at least one key outcome were obtained from more than 85% of the participants initially allocated to groups.
8	All participants for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by "intention to treat."
9	The results of between-group statistical comparisons are reported for at least one key outcome.
10	The study provides both point measures and measures of variability for at least one key outcome.
SCORING	9–10: excellent 6–8: good 4–5: fair <4: poor

Source: Eng et al.[123]

nitrogen (pamidronate, alendronate, ibandronate, risedronate, and zoledronate) and those that do not (etidronate, clodronate and tiludronate). Etidronate (Didrocal), alendronate (Fosamax), and risedronate (Actonel) are oral bisphosphonates that are currently approved for treatment of PMO in North America.[6] Clodronate (Benefos or Ostac) is available in intravenous and oral formulations, whereas tiludronate (Skelid) is only available in an oral form, and zoledronic acid (zoledronate) via intravenous formulation. Concurrent supplementation with calcium and vitamin D have been important additions to bisphosphonate therapy for non-SCI–related osteoporosis[6] and should be considered when prescribing oral bisphosphonates, although concurrent administration has had limited prospective evaluation among persons with SCI.

1. Bisphosphonate Prevention Therapy

Studies investigating the prevention of SLOP onset with bisphosphonates include 7 randomized controlled trials (n = 138 total participants; with sample sizes varying from 13 to 31) and 1 non-randomized trial (n = 24) (see Table 12). These studies, as a group, are difficult to interpret because of the variability in methodologic rigor (only 3 of 7 studies scored ≥8), the timing and choice of the intervention, primary outcome measure, durations of follow-up, sample sizes, and lack of stratification based on AIS (see Table 13).

Preventing a decline in BMD early after SCI is challenging given the rapid rate of resorption in AIS A patients and the relatively unknown rate and severity of decline of BMD in AIS C–D patients. The majority of studies favored the bisphosphonate-treated group relative to the control group. However, the treatment efficacy appears to be strongly influenced by the time of introduction of therapy and the degree of impairment. Greater treatment efficacy was observed if bisphosphonates were introduced early after SCI, and AIS D patients demonstrated less bone loss than AIS A patients. Two studies reporting that first-generation bisphosphonates (i.e., clodronate) can maintain BMD were short in duration (3-month intervention) and the participants had less-severe impairments.[126,129,133] In the studies by Pearson et al.[128] and Nance et al.,[131]

TABLE 11
Modified Downs & Black Scoring

Criteria		Description
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?
	3	Are the characteristics of the patients included in the study clearly described?
	4	Are the interventions of interest clearly described?
	5	Are the distributions of principal confounders in each group of participants to be compared clearly described?
	6	Are the main findings of the study clearly described?
	7	Does the study provide estimates of the random variability in the data for the main outcomes?
	8	Have all important adverse events that may be a consequence of the intervention been reported?
	9	Have the characteristics of patients lost to follow-up been described?
	10	Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is <0.001?
	11	Were the individuals asked to participate in the study representative of the entire population?
	12	Were those individuals who were prepared to participate representative of the entire population from which they were recruited?
	13	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?
Internal validity—bias	14	Was an attempt made to blind study participants to the intervention they have received?
	15	Was an attempt made to blind those measuring the main outcomes of the intervention?
	16	If any of the results of the study were based on “data dredging,” was this made clear?
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
	18	Were the statistical tests used to assess the main outcomes appropriate?
	19	Was compliance with the intervention/s reliable?
	20	Were the main outcome measures used accurate (valid and reliable)?
Internal validity—confounding	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
	22	Were study participants in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
	23	Were study participants randomized to intervention groups?
	24	Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
	26	Were losses of patients to follow-up taken into account?
	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

TABLE 12
Research Evidence for Prevention of SLOP Using Drug Interventions

Study type and scoring tool								Study duration (mos)	Outcome measures (see descriptors below)		
PEDro (RCT)	Downs & Black (non-RCT)	Author	Year	Intervention	Study design	Sample size (N)	Gender and impairment		BMD	Biomarkers of bone turnover	Other
10		Bauman[132]	2005	Pamidronate-2	RCT	14	Men and women, motor complete paraplegia and tetraplegia	12	– BMD (total leg, pelvis, femur, tibia)	– N-Tx and P1NP	– 24-h urinary calcium
10		Minaire[126]	1981	Clodronate-1	RCT	21	Men and women, motor complete paraplegia	3.5	+ BMD and BMC (femur and tibia) Tx	– Plc	
9		Chappard[127]	1995	Tiludronate-2	RCT	20	Men and women, C5–T12	3	+ Bone Volume Tx	+ Resorption Tx and Plc	
8		Pearson[128]	1997	Etidronate-1	RCT	13	Men and women, C5–T12 AIS A or D	4.5	+ BMD for AIS D participants Tx		+ Safety and tolerability Tx
7		Minaire[129]	1987	Clodronate-1	RCT	21	Men and women, motor complete paraplegia	3.5	+ BMD Tx	– Turnover Tx + Resorption Plc	
7		Shapiro[93]	2007	Zoledronate-3	RCT	18	Men and women, paraplegia and tetraplegia, AIS A–B	12	+ BMD (hip)		+ Bone outcomes, buckling ratio, Tx
7		Gilchrist[130]	2007	Alendronate-2	RCT	31	Men and women, AIS A–C	12	+ BMD (hip)		– Urinary calcium and serum C-telopeptide, Tx
	13	Nance[131]	1999	Pamidronate-2	PCT	24	Men and women, C5–T12 AIS A–D	6	+ BMD		

Note: BMD, bone mineral density; RCT, randomized controlled trial; PCT, prospective controlled trial (nonrandomized); Tx, treatment group; Plc, placebo group; +, increase or positive effect; –, decrease or negative effect; neutral, maintenance of BMD or insignificant effect; no effect, no change as a result of the intervention.

both groups continued to have a decline in BMD with the exception of AIS D participants who were taking bisphosphonates. Participants with AIS A had the greatest declines in both studies. A prior study that used a second-generation version of the bisphosphonate, pamidronate, and a longer intervention period, found no significant differences between groups after 1 year.[132] In contrast, Gilchrist and colleagues noted a significant difference in BMD at the hip with once-weekly alendronate administered within 10 days of injury.[130] After 12 months, there was a 5.3% difference ($p < .001$) in total body BMD and a 17.6% difference ($p < .001$) in the total hip BMD between the two groups. Shapiro and colleagues[93] determined the effect of once-yearly intravenous zoledronate and noted significant improvements in BMD at the hip at 6 months that returned to baseline values at 12 months in the treatment group. In contrast, the placebo group lost bone during the 12-month intervention. There appears to be increasing evidence of the lack of efficacy of oral bisphosphonates for the prevention of SLOP, with the exception of alendronate, because more-recent studies have failed to demonstrate efficacy at 1 year, in contrast with prior shorter duration studies. The differences observed may be attributed to timing of the intervention, the choice of primary outcome measure, and the mechanism of action of nitrogen versus non-nitrogen containing bisphosphonates.

In summary, there is Level I evidence that alendronate 70 mg weekly with vitamin D initiated within 10 days of injury maintains whole body and hip region BMD among SCI patients with AIS A–D injuries.[130] There is similar evidence that oral etidronate may maintain BMD of the hip and knee region among AIS D patients who return to walking within 3 months of injury. There is conflicting Level I evidence demonstrating the lack of efficacy of IV pamidronate and zoledronate for preventing SLOP onset by maintaining hip and knee region BMD.

2. Bisphosphonate Treatment Therapy

Evidence for treatment of SLOP includes three randomized controlled trials ($n = 124$ total participants) (see Tables 14 and 15). There is Level I evidence supporting alendronate for SLOP treatment among patients with motor complete paraplegia. By 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.[92] Alendronate inhibits osteoclast-mediated bone resorption and binds to hydroxyapatite in bone. The study cohort consisted of 55 men with motor complete SCI (paraplegia/tetraplegia, AIS A–B) living in Switzerland. Injury duration ranged from 1 month to 29 years after SCI, with group means of 10 years after injury. The primary outcome was the change in tibia epiphysis aBMD from baseline. 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.

On the basis of the Zehnder et al.[92] data, we recommend that patients with SLOP and motor complete injury (AIS A–B) be treated with alendronate (10 mg daily or 70 mg weekly) and calcium (1000 mg daily in divided doses).[92] There are no clinical trials evaluating bisphosphonate therapy for treatment of SLOP among patients with motor incomplete injuries (AIS C–D). Recent pQCT data describing longitudinal changes in lower extremity cortical and trabecular vBMD over time suggest that there is a therapeutic window (2–8 years after injury) during which antiresorptive therapies are most likely to be effective for patients with SCI.[54]

3. Bisphosphonate Safety Considerations

Reported side effects of alendronate[134] in the general population include hypocalcemia (>10%)[136]; abdominal pain, reflux, flatulence, and dyspepsia (1%–19%)[137]; and rare but serious events including osteonecrosis of the jaw,[138] atrial fibrillation (1.5%),[139] and hepatotoxicity.[140] Alendronate should be used with caution in premenopausal women because of the unknown teratogenic effects; patients with a prior history of cancer or radiotherapy because of the risk of osteonecrosis of the jaw; and patients who are taking acetylsalicylic acid, corticosteroids, or nonsteroidal

TABLE 13
Prevention of SLOP Using Bisphosphonates (SCIRE Format)

Author, year[ref]; Country Score Research design Total sample size	Methods	Outcome
Bauman et al. (2005)[132]; USA PEDro = 10 RCT *N* = 14	Population: 14 men and women, ages 21–61, motor complete paraplegia/tetraplegia. Treatment: Pamidronate for 12 mos. Participants were randomized to (1) 60 mg IV (*n* = 6), or (2) placebo (*n* = 5) at baseline, 1, 2, 3, 6, 9, and 12 months after SCI. Outcome measures: BMD by DXA, bone turnover markers.	1. No significant between-group differences in BMD decline at 1 year. 2. The treatment group had significantly lower 24-h urinary calcium at 1 month versus the placebo group ($p < .05$) and there were no significant changes in markers of bone formation over the 12-month study.
Minaire et al. (1981)[126]; France PEDro = 10 RCT *N* = 21	Population: 21 men and women, ages 15–54, complete paraplegia. Treatment: Clodronate for 3.5 mos. Participants were randomized to (1) 400 mg/d (*n* = 7), (2) 1600 mg/d (*n* = 7), or (3) placebo (*n* = 7). Outcome measures: BMD by DPA, histomorphometry.	1. No reported adverse effects on bone mineralization with intervention. 2. Increase in serum and urine markers in the placebo group (indicative of increased bone turnover). 3. Effective for acute prevention of declining bone mass and a maintenance of BMC of the femur and tibia in the treatment groups.
Chappard et al. (1995)[127]; France PEDro = 9 RCT *N* = 20	Population: 20 men and women, ages 16–50, injuries between C5–T12 Treatment: Tiludronate for 3 mos. Participants were randomized to (1) 400 mg/d (*n* = 7), (2) 200 mg/d (*n* = 7), or (3) placebo (*n* = 6). Outcome measures: histomorphometry.	1. There was an increase in total bone volume in the treatment group 1 (400 mg/d) versus the treatment group 2 (200 mg/d) and placebo groups. 2. Increase bone resorption indicators in the placebo group versus the treatment groups.
Pearson et al. (1997)[128]; Canada PEDro = 8 RCT *N* = 13	Population: 13 men and women, ages 22–57, injuries between C5–T12, AIS A or D. Treatment: Etidronate for 30 wks. Participants were randomized to (1) 800 mg daily (*n* = 6), or (2) conventional rehab and calcium 1000 mg/day (*n* = 7). Outcome measures: DXA and adverse event rate.	1. BMD loss at the distal femur was 26% and 22% at the proximal tibia. The rate of decline in BMD was greatest among the AIS A patients. BMD of lower extremity for the etidronate-treated AIS D patients was preserved. 2. Oral etidronate was safe and well tolerated by participants.
Shapiro et al. (2007)[93]; USA PEDro = 7 RCT *N* = 18	Population: 14 men and 4 women, ages 18–60. Type of injury: tetraplegia (*n* = 5) or paraplegia (*n* = 13), AIS A (*n* = 14) or AIS B (*n* = 4). Treatment: Zoledronic acid. Participants were randomized to a (1) single dose IV solution either 4 mg (*n* = 4) or 5 mg (*n* = 4), or (2) the placebo group, which received 50 mL of normal saline over 15 min (*n* = 10). Participants with low serum 25-hydroxyvitamin D received oral supplementation. Outcome measures: bone turnover markers, BMD by DXA.	1. In the treatment group: • Six months after zoledronic acid, BMD, cross-sectional area, and sectional modulus increased at the hip and the buckling ratio decreased consistent with improved bone outcomes. • At 12 mos, narrow-neck femur values declined and intertrochanteric and femoral shaft BMD was maintained. 2. The placebo group showed a decrease in bone outcomes and an increase in buckling ratio at the hip at 6 and 12 mos.

Gilchrist et al. (2007)[130]; New Zealand PEDro = 7 RCT *N* = 31	Population: 31 women and men ages 17–55. Type of injury at entry: 10 AIS A, 1 AIS B, and 3 AIS C. Treatment: Alendronate (oral) for 12 mos within 10 d of acute injury. Participants were randomized to (1) 70 mg once weekly, or (2) placebo. Outcome measures: BMD and body composition by DXA, ultrasound, bone turnover markers.	1. BMD at the femoral neck was maintained in the treatment group, and there was less BMD loss at other hip sites compared with the placebo group. 2. BMD at the hip in the placebo group declined steadily over the 18-month follow-up. 3. At 12 months, there was a 5.3% difference in total body BMD and a 17.6% difference in the percent change in total hip BMD between the 2 groups. 4. Alendronate compared with placebo-induced reductions in urinary calcium excretion and serum C-telopeptide at 3 mos only.
Minaire et al. (1987)[129]; France PEDro = 7 RCT *N* = 21	Population: 21 men and women, ages 15–54, complete paraplegia. Treatment: Clodronate for 100 days. Participants were randomized to (1) 400 mg/d (*n* = 7), (2) 1600 mg/d (*n* = 7), or (3) placebo (*n* = 7). Outcome measures: DXA, histomorphometry, bone turnover markers.	1. There was a greater increase in bone removal markers in the placebo group (48%) compared with the treatment groups (17%–27%). 2. BMD was maintained in treatment groups with a decrease in the placebo group. 3. Lower bone turnover markers in treatment groups.
Nance et al. (1999)[131]; Canada Downs & Black score = 13 Prospective controlled trial (nonrandomized) *N* = 24	Population: 24 men and women, ages 25–57, injuries between C5–T12, AIS A–D. Treatment: Pamidronate for 6 months. Participants randomized to (1) 30 mg IV every 4 wks x 6 doses (total 180 mg/participant) (*n* = 14), or (2) conventional rehab (*n* = 10). Outcome measures: BMD by DXA, urine biochemical bone markers.	1. There was a lower % decline in BMD in treatment versus control groups. The mean overall bone loss was 8.1% in the placebo group but only 2.7% in the treatment group ($p = .02$). The average loss of BMD was 3.1% in the AIS D group and 7.7% in the AIS A group.

Note: SLOP, sublesional osteoporosis; SCIRE, Spinal Cord Injury Rehabilitation Evidence; PEDro, Physiotherapy Evidence Database; RCT, randomized controlled trial; BMD, bone mineral density; aBMD, areal BMD (DXA); AIS, ASIA Impairment Scale, DPA, dual photon absorptiometry.

TABLE 14
Research Evidence for Treatment of SLOP Using Drug Interventions

Study type and scoring tool								Study duration (mos)	Outcome measures (see descriptors below)		
PEDro (RCT)	Downs & Black (non-RCT)	Author	Year	Intervention	Study design	Sample size (N)	Gender and impairment		BMD	Biomarkers of bone turnover	Other
10		Bauman[113]	2005	Vitamin D	RCT	40	39 men and 1 woman, motor complete paraplegia and tetraplegia	24	+ BMD (leg), Tx	– Resorption Tx	
7		Zehnder[92]	2004	Alendronate and calcium	RCT	65	Men, motor complete, T1–L3, AIS A–B	24	– BMD (hip, tibia), Ctl + BMD (hip, tibia), Tx	– Turnover, Tx	
6		Moran de Brito[135]	2005	Alendronate and calcium	RCT	19	Men and women, paraplegia and tetraplegia, AIS A–C		+ BMD, Tx		

Note: BMD, bone mineral density; RCT, randomized controlled trial; Tx, treatment group; Ctl, control group; +, increase or positive effect; –, decrease or negative effect.

TABLE 15
SLOP Treatment Studies Using Drug Therapy (SCIRE Format)

Author year[ref]; Country Score Research design Total sample size	Methods	Outcome
Bauman et al. (2005)[113]; USA PEDro = 10 RCT *N* = 40	Population: 40 participants with complete motor injuries: 17 participants with tetraplegia and 23 participants with paraplegia. Treatment: Vitamin D analog, 24 mos. (1) Vitamin D: 4 µg 1-alpha D(2) (*n* = 19); (2) placebo (*n* = 21) was administered daily for 24 months; or (3) both groups received calcium and vitamin D. Outcome measures: BMD by DXA, biomarkers at 6, 12, 18, and 24 mos.	1. Significant changes noted in leg BMD only in the vitamin D group at 6, 12, 18, and 24 mos. There was significant interaction for group by time. 2. In the vitamin D group, smoking had a negative effect on increase in percent change of BMD. 3. In the vitamin D group, urinary marker of bone resorption was significantly reduced, but markers of bone formation were not changed.
Zehnder et al. (2004)[92]; Switzerland PEDro = 7 RCT *N* = 65	Population: 65 men, ages 18–60, complete injuries between T1–L3, AIS A–B. Treatment: Alendronate for 24 mos. (1) 10 mg/d plus 500 mg calcium per day (*n* = 33) or (2) calcium alone (500 mg per day) (*n* = 32). Outcome measures: BMD by DXA and bone turnover markers.	1. Decrease in BMD of the tibia in the calcium-alone group but remained stable in the treatment group (group difference, $p = .017$). There was no change in wrist BMD and a significant increase in lumbar spine BMD in both groups. BMD of the mid-shaft tibia and hip were maintained in the treatment group and decreased in the calcium-alone group. 2. Biochemical markers of bone absorption significantly decreased from baseline in the treatment group.
Moran de Brito et al. (2005)[135]; Brazil PEDro = 6 RCT *N* = 19	Population: 19 men (<50 y) and women (<35 y), para/tetraplegia, AIS A–C. Treatment: Alendronate for 6 months. (1) 10 mg and calcium 1000 mg bid (*n* = 10), or (2) calcium 1000 mg bid (*n* = 9). Outcome measures: BMD by DXA.	1. There was a mean increase in upper extremity BMD that was greater in the treatment group versus the calcium group although not statistically significant. There were significant differences for total T-index and BMD.

Note: SLOP, sublesional osteoporosis; SCIRE, Spinal Cord Injury Rehabilitation Evidence; PEDro, Physiotherapy Evidence Database; RCT, randomized controlled trial; PCT, prospective controlled trial (nonrandomized); BMD, bone mineral density; aBMD, areal BMD (DXA); AIS, ASIA Impairment Scale.

anti-inflammatory drugs because concurrent use increases the relative risk of developing a gastric ulcer or bleeding.[141] Alendronate may be taken safely for 10–13 years, after which a drug holiday and/or discontinuation of therapy should be considered.[142] Many questions remain regarding the safety of these medications among people with SCI and the optimal duration of therapy. Zoledronate, an IV bisphosphonate, has been reported to increase the incidence of serious atrial fibrillation resulting in hospitalization or disability among 1%–3% of elderly non-SCI patients.[143] Zoledronate should be used with caution in elderly persons with SCI, and with patients who have premorbid atrial fibrillation or ventricular arrhythmia secondary to autonomic dysfunction after SCI. The risk of osteonecrosis of the jaw is highest among people with a prior history of cancer or radiotherapy. Both osteonecrosis of the jaw and arrhythmia should be discussed during consent for oral bisphosphonate therapy.

4. Nonresponse to Bisphosphonates

Sebba recently reviewed clinical studies from 1990 to October 2007 that investigated BMD response and bone loss during treatment with bisphosphonates.[144] His review highlights that maintenance or an increase in BMD from baseline is considered indicative of a positive treatment response. A decline in BMD is indicative of nonresponse to bisphosphonate therapy. Key areas to consider when assessing an apparent decline in BMD include (1) the LSC of the densitometer in order to best estimate the true biological change in BMD; (2) how clinic patients differ from clinical trial participants in their adherence to bisphosphonate therapy, calcium, and vitamin D supplements; and (3) the patient comorbidities that may adversely affect bone metabolism. Therefore, although a decline in BMD in a clinical trial is considered as a "nonresponse to therapy," the same cannot be said for a patient in the clinical setting because many factors may contribute to an interim decline in BMD. In clinical trials of alendronate, risedronate, and ibandronate among PMO women, Sebba reported that those who experienced a decline in BMD had a higher baseline fracture risk compared with those whose BMD increased; however, the results showed that there was some fracture risk reduction (30%–60%) when compared to placebo-treated patients.[144]

5. Bisphosphonate Adherence

Adherence to therapy is defined as the percentage of prescribed medication taken. Persistence occurs when a patient continues to take the prescribed medication. Long-term adherence and persistence with any therapy is poor, with 1 in 4 patients having poor adherence (<50%).[145] Good adherence to treatment is key to treatment success and is associated with positive health outcomes.

Adherence to bisphosphonate therapy has been shown to be greater among postmenopausal women (n = 2471) taking the weekly (69.2%) versus daily (57.6%) bisphosphonate formulations.[146] Weekly postmenopausal bisphosphonate users persist with therapy significantly longer than daily users (44.2% weekly; 31.7% daily) and have higher retention rates on treatment at 1 year. About 20% of postmenopausal women discontinue bisphosphonate therapy in the first 6 months of treatment.[146] Etidronate may be given safely for at least 7 years,[147] risedronate for at least 5 years,[148] and alendronate for at least 10 years[149] without adverse effects on bone mineralization.

The adherence and persistence of patients with SCI who are taking oral bisphosphonates is unknown. The adherence to bisphosphonates in PMO trials was 75%–80%, among a group of meticulously screened, highly motivated subjects who participated in routine adherence assessments (pill counts and/or serum screening). A minimum 60% adherence and 18 months persistence in a clinical practice setting is desired.[119]

F. Rehab Therapy

Rehabilitation options for SLOP prevention and treatment after SCI focus on stimulating muscle contraction and/or weightbearing in the hopes of simulating the mechanical stresses to which bone is exposed in activities of daily living among healthy persons. In healthy bone, the process of bone formation and resorption are closely coupled. However, when the level of mechanical strain on

TABLE 16
Research Evidence for Prevention of SLOP Using Rehabilitation Intervention

Study type and scoring tool								Study duration (mos)	Outcome measures (see descriptors below)		
PEDro (RCT)	Downs & Black (non-RCT)	Author	Year	Intervention	Study design	Sample size (N)	Gender and impairment		BMD	Biomarkers of bone turnover	Other
11		Warden[150]	2001	Ultrasound	Within-group RCT	15	Men, C5–T10 AIS A–B	1.5			No effect, QUS
9		Ben[155]	2005	Standing	Within-participant RCT	20	Men and women, paraplegia and tetraplegia	3	No effect		+Ankle mobility
6		de Bruin[156]	1999	Standing/ walking	RCT	19	Men, C4–T12, AIS A–D	6	Neutral (tibia)		
	21	Clark[157]	2007	ES	PCT	33	Men and women, paraplegia and tetraplegia, AIS A–D	5	+ BMD, Tx		+ Safety and tolerability, Tx
	17	Frotzler[54]	2008	ES	Pre–post	11	Motor complete, T3–12, AIS A	9	+ BMD (distal femur), Tx – BMD (femoral shaft), Tx		
	15	Shields[152]	2006	ES	PCT	6	Men and women, C5–T10	36	+ BMD, Tx		
	15	Shields[158]	2006	ES	PCT	7	Men and women, C5–T10	24–36	+ BMD, Tx (distal tibia)		
	15	Shields[159]	2007	ES	Pre–post	4	Men, T1–7, AIS A	6–11	No effect		
	14	Eser[151]	2003	FES cycle-ergometry	PCT	38	Men and women, C5–T12	6	No effect		
	13	Giangregorio[60]	2005	Treadmill training	Pre–post	5	Men and women, C3–8, AIS B–C	6–8	– BMD, Tx	No effect	No effect, CT
	11	Frotzler[160]	2009	ES	Pre–post	5	Motor-sensory complete, T4–7, AIS A	12	Neutral		
	10	Dudley-Javoroski[161]	2008	ES	Case report	1	Man, T4, AIS A	36	+ BMD, Tx		
	14	Dudley-Javoroski[153]	2008	ES	Case control	21	12 SCI Men C5–T11 AIS A–B; 9 non-SCI Men	54–72	+ vBMD, Tx		

Note: SLOP, sublesional osteoporosis; BMD, bone mineral density; RCT, randomized controlled trial; PCT, prospective controlled trial (nonrandomized); Tx, treatment group; QUS; quantitative ultrasound; CT, computed tomography; +, increase or positive effect; –, decrease or negative effect; neutral, maintenance of BMD or insignificant effect; no effect, no change as a result of intervention.

TABLE 17
Prevention Studies Using Rehab Therapies (SCIRE Format)

Author year[ref]; Country Score Research design Total sample size	Methods	Outcome
FES-cycle ergometer		
Eser et al. (2003)[151]; Switzerland Downs & Black score = 14 PCT *N* = 38	Population: 38 men and women, mean age = 33, complete injuries between C5–T12 (19 participants, 19 controls). Treatment: FES-cycle ergometer. Progressive training sessions until able to cycle for 30 min. Then 3x/wk for 6 mos from this baseline. On the remaining 2 d of the week, there was passive standing. The control group performed 30 min of passive standing 5 d/wk. Outcome measures: CT.	1. Both groups had 0%–10% decrease in tibial cortical BMD. There was no difference between groups for BMD after the intervention.
Clark et al. (2007)[157]; Australia Downs & Black score = 21 PCT *N* = 33	Population: 33 men and women; 15 tetraplegia and 18 paraplegia; AIS A–D. Treatment: FES, 5 mos. Low-intensity stimulation to leg muscles, 15 min, 2x/day 5 days/wk, 5 months (*n* = 23); or control group (no treatment) (*n* = 10). Outcome measures: DXA at 3 wks, 3 and 6 mos after injury.	1. ES was safe and well tolerated, but there was only a minimal difference between groups for total body BMD only at 3 mos after injury ($p < .01$). Other DXA measures (hip and spine BMD) did not differ between groups at any time point.
Frotzler et al. (2008)[54]; UK/Switzerland Downs & Black score = 17 Pre–post *N* = 11	Population: motor complete T3–12; AIS A; >3 y after injury; aged >18 y; 9 men/ 2 women. Treatment: FES-cycle at gluteus quadriceps, hamstrings; (*n* = 5 also calf); conditioning: 30–60 min, 3–5x/wk until participant can FES-cycle; pretraining: 10–60 min, 3–4x/wk for 3 mos until FES-cycle for 60 min; training 60 min, 5x/wk for 9 mos. Outcome measures: pQCT at baseline, 6 mo, and 12 mo bilaterally in femur and tibia.	1. After 12 mos, increase 14% trabecular bone at distal femoral epiphysis. Increase 7% total BMD ($p = .05$). Increase 1.2% cross section at distal femoral epiphysis ($p = .001$).Decrease at femoral shaft: 0.4% cortical BMD ($p = .003$) and 1.8% BMC ($p = .037$).
Frotzler et al. (2009)[160]; UK/Switzerland Downs & Black score = 11 Pre–post *N* = 5	Population: motor-sensory complete T4–7; AIS A; >3 y after injury; aged 28–48 y; 4 men/1 woman. Treatment: 12 mos detraining following 12-mo high-volume FES-cycling, 4 participants stopped FES cycling and one reduced to 2–3, 30-min sessions per week (detraining). Outcome measures: tibia and femoral epiphysis pQCT after 12 mos detraining.	1. Twelve-month detraining in 4 participants: 59.4% preservation of total BMD gain in distal femur (73% total BMD); 3.6% decrease in femoral shaft cortical BMD (1.8% BMC). 2. Twelve-month reduced training in 1 subject: 92.6% preservation of total gain in distal femur total BMD (95% in trabecular BMD); 5.4% decrease in femoral shaft cortical BMD (7.3% BMC).

Electrical stimulation

Shields et al. (2006)[152]; USA Downs & Black score = 15 PCT *N* = 6	Population: 6 men with complete injuries from C5–T10; started study within 4.5 mos of injury. Within-participant design. Treatment: ES at 1.5x body weight for 3 y. Treatment leg only received a home program of ES to stimulate leg plantar flexors with 35-min protocol (4 bouts with 5-min rest between bouts) for 5x/wk. Outcome measures: DXA tibial analysis protocol.	1. There was a greater decline in bone mineral loss on the untrained limb compared with the trained limb (10% vs. 25%) ($p < .05$).
Shields and Dudley-Javoroski (2006)[158]; USA Downs & Black score = 15 PCT *N* = 7	Population: 7 men with complete injuries from C5–T10; started study within 4.5 mos of injury. Within-participant design. Treatment: ES at 1.5x body weight; 2–3 y. Treatment leg only received a home program of ES to stimulate leg plantar flexors with 35-min protocol (4 bouts/d with 5-min rest between bouts) for 5x/wk. Outcome measures: pQCT 4%, 38%, and 66% sites of bilateral tibiae.	1. No significant difference at the tibial midshaft but a 31% higher distal tibia trabecular BMD in trained limbs compared with untrained leg.
Shields and Dudley-Javoroski (2007)[159]; USA Downs & Black score=15 Pre–post *N* = 4	Population: 4 men with SCI; aged 52.3 ± 11.2 y; level of injury: T1–7 (AIS A); TSI: 8.9 ± 4.1 y. Treatment: Trained 1 leg using an isometric plantar ES protocol (the untrained limb serving as within subject control) for 30 min/d, 5 d/wk, for 6–11 mos. Mean estimated compressive loads delivered to the tibia were ~110% body weight. Outcome measures: BMD by DXA.	1. Untrained limb BMD did not differ from trained limb BMD either before or after training. 2. Unchanged BMD of proximal tibia before and after training for trained and untrained limb ($p > .05$). Trained limb of 2 participants had ~0.02 g/cm^2 gain in BMD but not statistically significant.
Dudley-Javoroski and Shields (2008)[161]; USA Downs & Black score = 14 *Case control* *N = 21 (12 SCI)*	Population: 12 men with SCI motor complete C5–T11, AIS A–B; 0.3–22.5 y after injury; ages 21–72; 3 in intervention arm, 9 SCI controls, and 9 non-SCI controls between ages 24–61. Treatment: Unilateral soleus ES 5x/wk 15 Hz every 2 s for 120 contractions (8000 contractions/mo). Outcome measures: pQCT (vBMD of distal tibia) of one leg versus the other leg ~annually for 4–6 years.	1. At 4.5–6 y, a sustained between-limb difference in posterior distal tibia vBMD of 7.61 mg/cm^3 ($p = .04$).
Dudley-Javoroski and Shields (2008)[161]; USA Downs & Black score = 10 Case report *N* = 1	Population: 1 man; T4 AIS A paraplegia; aged 21 y; 7 wks after injury. Treatment: Four bouts of 125 soleus contractions over 30 min, 5x/wk in one leg; actual 8000 contractions/mo. Outcome measures: pQCT of one leg versus the other leg after 1 y and 3 y.	1. After 1 y, no difference in trabecular architecture; 4.5% difference in trabecular BMD. 2. After 3 y, 15%/y BMD decline in untrained tibia and 7.6%/y BMD decline in trained limb. Lower decline attributed to posterior portion, which lost 2.59%/y.

Standing/walking

Ben et al. (2005)[155]; Australia PEDro = 9 Within-participant RCT *N* = 20	Population: 20 men and women (8 paraplegia, 12 tetraplegia), within-participant design. Treatment: Tilt-table standing, 12 wks. Treatment leg only received weightbearing on a tilt-table for 30 min, 3x/wk. Wedge applied to treatment leg to provide adequate dorsiflexion and weight bearing to the ankle. Control leg was not loaded in standing. Outcome measures: DXA proximal femur.	1. No clinically significant effect on proximal femur BMD in treatment group, but a 4° improvement in ankle mobility.

(continued on the following page)

TABLE 17 *(continued)*
Prevention Studies Using Rehab Therapies (SCIRE Format)

Author year[ref]; Country Score Research design Total sample size	Methods	Outcome
de Bruin et al. (1999)[156]; Switzerland PEDro = 6 RCT *N* = 19	Population: 19 men, ages 19–59, injuries between C4–T12, AIS A–D. Treatment: Standing/walking. Group 1 had 0–5 h/wk of loading exercises with standing frame. Group 2 had 5+ h of standing exercises per wk (standing). Group 3 had 5+ h of standing and treadmill (walking). Interventions lasted 25 wks. Outcome measures: BMD by pQCT.	1. Marked decrease in trabecular BMD at the left tibia for the immobilized group but minimal decrease in trabecular BMD in groups 2 and 3.
Treadmill training		
Giangregorio et al. (2005)[60]; Canada Downs & Black score = 13 Pre–post *N* = 5	Population: 2 men and 3 women, ages 19–40, injuries between C3–8, AIS B–C, no controls. Treatment: Body-weight supported treadmill training. Initial session started at 5 min and was increased gradually to 10–15 min in all but 1 participant during 48 sessions of 2x/wk-training over a period of 6–8 mos. Outcome measures: BMD by DXA and CT; bone turnover markers.	1. Decrease in BMD for all participants at almost all lower limb sites after training, ranging from –1.2% to –26.7%. 2. Lumbar spine BMD changes ranged from 0.2% to –7.4%. 3. No consistent changes in bone geometry at distal femur and proximal tibia. 4. Did not alter the expected pattern of change in bone biochemical markers over time.
Ultrasound		
Warden et al. (2001)[150]; Australia PEDro = 11 RCT *N* = 15	Population: 15 men, ages 17–40, injuries between C5–T10, AIS A–B, (within-group design). Treatment: Pulsed therapeutic ultrasound. Applied to both calcanei for each participant for 20 min/d, 5x/wk over a consecutive 6-wk period. Right and left calcaneus within each participant was randomized. Outcome measures: BMD by DXA and QUS.	1. For specified dose, no significant effect of QUS for any skeletal measurement parameter ($p > .05$).

Note: SLOP, sublesional osteoporosis; SCIRE, Spinal Cord Injury Rehabilitation Evidence; PEDro, Physiotherapy Evidence Database; RCT, randomized controlled trial; PCT, prospective controlled trial (nonrandomized); BMD, bone mineral density; aBMD, areal BMD (DXA); ES, electrical stimulation; QUS, quantitative ultrasound.

bone is below a specific threshold, as in AIS A paraplegia/tetraplegia, it is insufficient to maintain BMD.[75,76] Disuse-mode remodeling is enhanced bone resorption with little or no bone formation, which leads to bone tissue loss until a level of BMD is reached that is insufficient to withstand specific strains.[75] Recall that the key problem with bone remodeling for patients with SCI is increased bone resorption and little or no bone formation.[77] The rate of bone remodeling can be measured indirectly by measuring bone turnover markers in the blood or urine.

In total, this section reviews the efficacy of five rehab interventions including functional electrical stimulation (FES), electrical stimulation (ES), standing and walking, body weight support treadmill training (BWSTT), and ultrasound. FES involves the use of surface or implanted electrodes to stimulate regional lower extremity muscle contractions to facilitate standing, ambulation, or cycle ergometry with the goal of increasing regional BMD. FES cycle ergometry (FES-CE) requires a series of electrodes placed over the hamstrings, quadriceps, and gluteal muscles of the legs to simulate a cycling pattern. Weight-bearing activities include either passive standing (tilt-table or standing frame) or active standing with or without FES to assist with knee extension. Many rehab studies have enrolled participants with both acute and chronic injuries, and are therefore difficult to classify as pure prevention or treatment interventions. Increases in BMD may be a suitable surrogate outcome measure for fracture risk reduction when assessing the effectiveness of SLOP therapy, with increases in knee region BMD above the fracture threshold desired.

1. Rehab Therapy for Prevention of SLOP

The vast majority of the SLOP prevention therapies can currently be discounted because of their poor methodologic quality (PEDro scores ≤ 6/10, and Downs and Black scores ≤ 15/28) and small sample sizes (see Tables 16 and 17). There is Level I evidence that 6 weeks of ultrasound therapy is not effective for preventing SLOP after SCI.[150] There is Level II evidence that FES-CE 30 minutes 3 times weekly for 6 months did not maintain BMD of the tibia midshaft among patients with acute SCI.[151] In contrast, ES (without the bike) reduced the rate of decline in BMD in the trained limb compared to the untrained limb of study participants with acute SCI.[152] Sustained (4.5–6 years) of unilateral soleus training with ES resulted in between-limb difference in posterior distal tibia vBMD of 7.61 mg/cm^3 (p = .04).[153]

It is unfortunate that some of the shorter intervention studies did not measure biochemical markers of bone turnover in addition to BMD, because these measures are more likely to be sensitive to meaningful change with a short rehab intervention study. Overall, there is limited evidence for prevention of SLOP with rehab therapies. Future studies should (1) prospectively investigate the therapeutic potential of rehab therapies to stimulate bone formation concurrent with potent antiresorptive stimuli; (2) control for calcium and vitamin D intake because insufficient intakes may be a significant confounder in these intervention studies; and (3) extend the duration of the intervention to allow at least two cycles of bone turnover to occur (i.e., 6–8 months duration), ideally longer, in order to detect clinically meaningful changes in bone outcomes (i.e., biomarkers, vBMD, MRI). A recent systematic review by Biering-Sorensen et al.[154] provides a detailed evaluation of the nonpharmacological interventions for prevention of bone loss after SCI and further highlights the lack of efficacy of rehabilitation intervention studies.

2. Rehab Therapy for the Treatment of Sublesional Osteoporosis

Not unlike the SLOP prevention literature, the SLOP treatment literature suffers from some of the same limitations including few studies of poor methodologic quality (PEDro scores ≤ 6/10, and Downs and Black scores ≤ 15/28) and small sample sizes (≤10 in many studies; see Tables 18 and 19). Although there were no randomized controlled trials that assessed the effect of ES for treatment of SLOP, Bélanger et al.[162] produced impressive results with a Level II, nonrandomized trial that used one limb as the treatment limb and the other as the control limb; treatment included 24 weeks of stimulated leg extensions against

TABLE 18
Research Evidence for Treatment of SLOP Using Rehabilitation Intervention

Study type and scoring tool								Study duration (mos.)	Outcome measures (see descriptors below)		
PEDro (RCT)	Downs & Black (non-RCT)	Author	Year	Intervention	Study design	Sample size (N)	Gender and impairment		BMD	Biomarkers of bone turnover	Other
11		Belanger[162]	2000	ES	PCT	28	Men and women, C5–T6 (able-bodied controls)	6	+ BMD Tx		
	20	Giangregorio[176]	2006	Treadmill training	Pre–post	14	Men and women, motor incomplete, C4–T12, AIS B–C	12	No effect		
	16	Carvalho[164]	2006	ES and treadmill training	Pre–post	21	Men, C4–T1	6		+ Formation, Tx – Resorption, Tx	
	15	Melchiorri[165]	2007	Vibration	Pre–post	10	Men and women, T1–3	3	Neutral (whole body), Tx + BMD (arms), Tx		
	12	Leeds[166]	1990	FES-cycle ergometry	Pre–post	6	Men, tetraplegia	6	Neutral, Tx	+ Formation, Tx – Resorption, Tx	
	12	Kunkel[167]	1993	Standing	Pre–post	6	Men C5–T2	5	No effect (femur, spine), Tx		
	10	Rodgers[168]	1991	ES	Pre–post	12	Men and women, paraplegia and tetraplegia, motor complete and incomplete	3	Neutral, Tx		
	10	BeDell[169]	1996	FES-cycle ergometry	Pre–post	12	Men, C5–T12	?	+ BMD, Tx		
	10	Pacy[170]	1988	FES-cycle ergometry	Pre–post	4	Men, paraplegia	?	Neutral (spine, femur, tibia), Tx		

10	Needham-Shropshire[171]	1997	Standing/ walking	Pre–post	16	Men and women, motor complete, T4–11	2	No effect (hip)		
10	Kaplan[100]	1981	Standing	Pre–post	10	Men and women, motor incomplete, tetraplegia	6 or 12–18			+ Urinary calcium, Tx
9	Chen[172]	2005	FES-cycle ergometry	Pre–post	30	Men, motor complete, C6–T8 (able-bodied controls)	6	+ BMD (femur, tibia), Tx – BMD (hip), Tx		
9	Hangartner[173]	1994	FES-cycle ergometry	Pre–post	15	Men and women, motor complete and incomplete, C5–T10	6–8	Neutral (tibia), Tx		
9	Mohr[163]	1997	FES-cycle ergometry	Pre–post	10	Men and women, C6–T2	13	+ BMD (tibia), Tx	No effect	
8	Ogilvie[174]	1993	Walking	Pre–post	4	Men and women, paraplegia	avg. 5	+ BMD (hip), Tx No effect (spine)		
8	Thoumie[175]	1995	Walking	Pre–post	7	6 men and 1 woman, T2–10	3–14	No effect		

Note: SLOP, sublesional osteoporosis; BMD, bone mineral density; RCT, randomized controlled trial; PCT, prospective controlled trial (nonrandomized); Tx, treatment group; +, increase or positive effect; –, decrease or negative effect; neutral, maintenance of BMD or insignificant effect; no effect, no change as a result of intervention.

TABLE 19
Treatment of SLOP Using Rehabilitation Interventions (SCIRE Format)

Author year[ref]; Country Score Research design Total sample size	Methods	Outcome
Electrical stimulation		
Bélanger et al. (2000)[162]; Canada PEDro = 11 PCT *N* = 28	Population: 14 men and women, ages 23–42, complete and incomplete injuries between C5–T6, 14 able-bodied controls. Treatment: ES. Quadriceps training was conducted 5 d/wk for 24 wks. Participants trained for 1 h/d or until fatigue. The right quadriceps were stimulated with no resistance (but against gravity), whereas the left quadriceps were stimulated against a resistance. Outcome measures: BMD by DXA.	1. At baseline BMD from the experimental group was lower at the distal femur, proximal tibia, and mid-tibia (decreased range: 25.8% to 44.4%) than able-bodied controls. 2. Increased BMD with training ($p < .05$) for both sides of SCI participants, but the type of training had no effect (resistance vs. no resistance). There was a significant increase in the BMD of the distal femur and proximal tibia, but not in the mid-tibia.
Rodgers et al. (1991)[168]; USA Downs & Black score = 10 Pre–post *N* = 12	Population: 12 men and women, ages 19–63, para/tetraplegia, complete/incomplete, no controls (only 9 participants had BMD). Treatment: ES. Each participant trained for a total of 36 sessions (3x/wk for 12 wks) using a progressive intensity protocol for PES-stimulated knee extension. This progression was continued to a maximum 15-kg load. Outcome measures: BMD by DXA.	1. Tibial BMD was not significantly changed after ES protocol ($p > .05$), but BMD was better than predicted values.
Vibration		
Melchiorri et al. (2007)[165]; Italy Downs & Black score = 15 Pre–post *N* = 10	Population: 10 men with mean age 34 ± 4 yr; level of injury: between T8–10; TSI: 8 ± 3 y. Treatment: Vibration using handlebars and 4 series of maximal speed arm curls with the load being increased with each series to 5%, 8%, 10%, and 15% of the individual's body weight (handlebar and extra load together) at a frequency of 30 Hz. Participants were exposed to vibrations for 12 weeks, 5x/wk, 5 min/session. Outcome measures: BMC and BMD by DXA (total body).	1. Total DXA measurements corresponding to BMC and BMD showed no statistically significant differences between 3 time points. Segmental analysis showed a nonsignificant increase in BMD for both arms.
FES-cycle ergometry		
Leeds et al. (1990)[166]; USA Downs & Black score = 12 Pre–post *N* = 6	Population: 6 men, ages 18–17, tetraplegia, no controls. Treatment: FES + FES-cycle ergometer. quads strengthening exercise for 1 mo, followed by 6 mos CE. Knee extension sessions were 45 lifts/leg, 3x/wk for 1 mo. CE sessions were 3x/wk up to 30 min for 6 mos. Outcome measures: BMD by DXA.	1. The BMD of the proximal femurs were below normal before commencing exercise intervention (compared with matched able-bodied individuals). 2. After 7 months of exercise training, there was no significant difference in BMD for any of the sites of the proximal femurs.

BeDell et al. (1996)[169]; USA Downs & Black score = 10 Pre–post *N* = 12	Population: 12 men, ages 23–46, complete injuries between C5–T12, no controls. Treatment: FES + FES-cycle ergometer. Participants participated in a 3-phase training program of FES-CE. Phase 1: quads strengthening. Phase 2: FES-CE progression for 30 min continuously. Phase 3a: 24 sessions of 30-min continuous exercise performed 3x/wk. Phase 3b: 24 additional 30-min sessions adding simultaneous arm ergometry (8 participants only). Outcome measure: BMD by DPA.	1. At baseline, SCI participants were not significantly different from age-matched able-bodied ambulatory men for lumbar-spine BMD. However, BMD was signficantly lower for participants at the hip ($p < .025$) for bilateral trochanters, Wards triangles, and femoral necks. 2. Only the L2–4 values demonstrated any positive training effects ($p = .056$). Further training (phase 3b) did not demonstrate further increase in BMD at any site.
Pacy et al. (1988)[170]; UK Downs & Black score = 10 Pre–post *N* = 4	Population: 4 men, ages 20–35, paraplegia, no controls. Treatment: FES + FES-CE. Part 1 was quads strengthening with increased load ranging from 1.4 to 11.4 kg bilaterally for 15 min for 5//wk (10 wks). Part 2 was FES-CE at 50 rpm with resistance (0–18.75 W). Performed for 15 min, 5x/wk (32 wks). Outcome measures: BMD by DXA.	1. No significant change in lumbar spine and femoral shaft and/or distal tibia trabecular BMD after the intervention.
Chen et al. (2005)[172]; Taiwan Downs & Black score = 9 Pre–post *N* = 30	Population: 15 men, ages 23–37, complete, C6–T8, 15 able-bodied controls. Treatment: FES-cycle ergometer. Participants performed FES-CE exercises with minimal resistance for 30 min/d, 5 d/wk for 6 mos. Follow-up 6 mos after intervention. Outcome measures: BMD by DXA.	1. At baseline, participants' BMD at the femoral neck, distal femur, and proximal tibia were lower than controls. 2. After 6 mos, BMD of the distal femur and proximal tibia increased significantly ($p < .05$). BMD in the distal femur, proximal tibia, and heel decreased significantly after 6 mos without intervention ($p < .05$). The BMD of the femoral neck decreased progressively throughout the treatment ($p > .05$).
Hangartner et al. (1994)[173]; USA Downs & Black score = 9 Pre–post *N* = 15	Population: 15 men and women, ages 17–46, complete and incomplete injury between C5–T10, no controls. Treatment: FES + FES-cycle ergometer. Either (1) FES knee extension exercises ($n = 3$), (2) FES-CE ($n = 9$), or (3) both ($n = 3$). Sessions were 3x/wk for 12 wks, except that group 3 had 24 wks. Outcome mesures: CT.	1. Participants in the exercise groups continued to lose bone at the distal and proximal end of the tibia, but it was less than expected from the regression lines.
Mohr et al. (1997)[163]; Denmark Downs & Black score = 9 Pre–post *N* = 10	Population: 10 men and women, ages 27–45, injuries either C6 or T2, no controls. Treatment: FES. Stimulated the legs for 30 min, 3x/wk for 6 mos. Followed by 1x/wk for 6 mos. Outcome measures: BMD by DXA, bone turnover markers.	1. After 12 mos of training, there was a significant (10%) increase in proximal tibia BMD ($p < .05$) but no change at the lumbar spine or femoral neck. 2. After 6 mos of reduced training, BMD for the proximal tibia returned to baseline. 3. Blood and urine markers were within normal limits at baseline, and there was no significant change with PES.
Standing		
Kunkel et al. (1993)[167]; USA Downs & Black score = 12 Pre–post *N* = 6	Population: 6 men, ages 36–65, complete and incomplete, C5–T12, no controls. Treatment: Passive standing frame. Increased gradually until able to "stand" 30 min, 3x/d. Progressed to 45 min, 2x/d. Participants then completed 45 min of standing, 2x/d for 5 mos. Outcome measure: BMD and fracture risk by DPA.	1. There was no significant change in fracture risk as measured with BMD for femoral neck or lumbar spine with "standing."

(*continued on the following page*)

TABLE 19 (*continued*)
Treatment of SLOP Using Rehabilitation Interventions (SCIRE Format)

Author year[ref]; Country Score Research design Total sample size	**Methods**	**Outcome**
Needham-Shropshire et al. (1997)[171]; USA Downs & Black score = 10 Pre–post *N* = 16	Population: 16 men and women, mean age = 29, T4–11, AIS A–B, no controls. Treatment: Standing and ambulation. After 32 sessions, participants then continued ambulation for 8 more wks. Outcome measures: BMD by DPA.	1. There were no significant changes in BMD in the femoral neck, Ward's triangle, or the trochanter.
Kaplan et al. (1981)[100]; USA Downs & Black score = 10 Pre–post *N* = 10	Population: 10 men and women, ages 19–56, incomplete tetraplegia, no controls. Treatment: Tilt-table weight-bearing and strengthening exercises. Each tilt-table session lasted at least 20 min, 1x/d, and the tilt-table angle attained was ≥45°. Two groups: (1) early (within 6 mos of SCI) and (2) late group (12–18 mos after SCI). Outcome measures: urinary calcium excretion.	1. Significant improvement ($P < .01$) in calcium excretion, urinary calcium, and calcium balance for the early group. 2. The late group had significant improvements for urinary calcium and calcium balance.
Walking		
Giangregorio et al. (2006)[176]; Canada Downs & Black score = 20 Pre–post *N* = 14	Population: 14 men and women, ages 22–53, C4–T12, AIS B–C, reference control group. Treatment: Body-weight-supported treadmill training, 12 mos. Completed protocol 3x/wk for 144 sessions; intensity increased as tolerated. Outcome measures: BMD by DXA, bone markers.	1. There were no significant changes in bone density or bone geometry at axial or peripheral sites with the exception of a small but significant decrease in whole-body BMD. 2. No significant difference in bone markers.
Carvalho et al. (2006)[164]; Brazil Downs & Black score = 16 PCT *N* = 21	Population: 21 men with mean age 31.95 ± 8.01 y; C4–8, TSI: mean 66.42 ± 48.23 mos, range 25–180 mos. Two groups: In the treatment group, all individuals had a complete lesion; in the control group, individuals had an incomplete lesion (AIS B). Treatment: Treadmill gait training provided NMES. Quadriceps and tibialis anterior stimulated for <5 mos before beginning gait training (2x/wk) in order to walk for 20 min and support <50% of body weight (pre-gait training). Participants received either (1) NMES for 6 mos, 20 min/session, 2x/wk (*n* = 11), or (2) no training (*n* = 10). Outcome measures: BMD by DXA, bone markers.	1. Increase in bone formation markers after gait training occurred in 81.8% (9/11) of the participants, and 66.7% (8/11) had a decrease in bone resorption markers. 2. In the control group, no changes were observed in 3 participants; 2 individuals had an increase in bone formation markers; and 3 people had a decrease in bone resorption markers.

Ogilvie et al. (1993)[174]; England Downs & Black score = 8 Pre–post *N* = 4	Population: Bone assessment with 2 men and 2 women, ages 16–42, paraplegia, no controls. Treatment: RGO. No protocol provided. QCT repeated every 6 mos from the first referral, orthotic fitting and training, to independent and regulator ambulation (mean = 5 mos). The RGO was used daily on average for 3 h. Outcome measures: BMD by QCT.	1. Three of 4 participants increased or maintained femoral neck BMD but had no change in lumbar spine.
Thoumie et al. (1995)[175]; France Downs & Black score = 8 Pre–post *N* = 7	Population: For bone assessment, there were 6 men and 1 woman, ages 26–33, T2–10; no controls. Treatment: RGO-II hybrid orthosis. Completed the protocol within 3–14 mos (2-h sessions 2x/wk). Outcome measures: BMD by DPA.	1. At baseline, participants (compared with age-matched Z-score) had no significant change in L-spine BMD but a decrease in femoral neck BMD. 2. After the training program (16 mos), no consistent changes at the femoral neck BMD among participants (4 participants decreased BMD, 1 participant increased BMD, and there was no change in 2 participants).

Note: SLOP, sublesional osteoporosis; SCIRE, Spinal Cord Injury Rehabilitation Evidence; PEDro, Physiotherapy Evidence Database; RCT, randomized controlled trial; PCT, prospective controlled trial (nonrandomized); BMD, bone mineral density; aBMD, areal BMD (DXA); ES, electrical stimulation; CE, cycle ergometry; QUS, quantitative ultrasound; NMES, neuromuscular electrical stimulation; RGO, reciprocal gate orthosis; QCT, quantitative computed tomography; DPA, dual photon absorptiometry; TSI, time since injury.

resistance 5 times per week, whereas the control limb performed stimulated leg extensions against no resistance. Following training, BMD recovered about 30% of bone loss when compared with the results of the able-bodied participants. Unfortunately, the therapeutic effects of stimulation seem to be isolated to the area stimulated and return to baseline within months of therapy cessation.[163]

For FES-CE, there are mixed results for SLOP treatment. Two studies reported an increase in BMD at the proximal tibia or distal femur,[163,172] whereas there was no significant within-participant BMD change at the hip in 3 pre–post studies, where no hip region stimuli were applied.[166,169,170] The FES-CE study reported positive effects on bone parameters when used thrice weekly as a training stimulus for 6 months, and increases in the bone parameters directly over the knee region or the stimulated area were observed. FES-CE treatment needed to be maintained, otherwise the BMD gains were lost.[172] FES-CE shows promise as an effective treatment for BMD around the knee; however, there is limited availability of cycle ergometry for home use because of cost and resource issues. FES-CE will not be routinely available unless there are dramatic changes in social policy and funding for these pursuits.

Evaluated weightbearing devices and activities include passive standing in a standing frame, tilt tables, reciprocating gait orthoses, and body weight–supported treadmill training. To date, none of the weightbearing studies have demonstrated a significant *and* sustained increase in BMD of the hip or knee region.[100,167,171,174–176] One study evaluated vibration with modest results.[165,177]

In persons with chronic SCI and SLOP, rehabilitation interventions may be ineffective because of prolonged suppression of osteocyte and osteoblast activity.[75] It is also plausible that short durations of treatment, small sample sizes, or insufficient mechanical stress may have resulted in the lack of treatment effects reported to date. Rehabilitation interventions may be offered as SLOP treatment to patients with contraindications to drug therapy, provided that limitations of the current literature and their limited efficacy are discussed prior to initiation.

The quality of the rehab study designs and inadequate details regarding the intervention and study methods also limit the conclusions that can be drawn from the available research. Limitations of the generalizability of the current SLOP studies include the exclusion of women and propensity to study those with motor complete paraplegia.[52,104,178,179]

3. Rehab Therapy Precautions

FES and ES should be used with caution in patients with combined hip and knee flexion contractures of >30°, a prior lower extremity fracture, severe lower extremity spasticity, and/or significant ankle plantar flexion contractures. FES, ES, and passive and active standing therapies are contraindicated in patients with untreated orthostatic hypotension, hip dislocation, and nonunion fractures. Several anecdotes describing lower extremity fractures among patients with SCI after quadriceps stimulation are noted in the literature.[114] Most rehab therapies are considered to be safe; however, few studies have prospectively reported adverse sequelae related to FES or ES protocols. We reported frequent ankle swelling, pressure sores on the feet and ankles, and infrequent autonomic dysreflexia and orthostatic hypotension in a cohort of patients with chronic SCI who participated in a regular program of passive standing.[180] There is no lower extremity BMD value that should preclude patients from participating in rehab interventions; however, activities that result in torsion of the distal lower extremity with an anchored foot and/or ankle present an undue falling risk and should be avoided.

V. KEY MESSAGES

In summary, sublesional osteoporosis is characterized by excessive bone resorption at the hips and knee regions after SCI, resulting in a lifetime increased risk of lower extremity fracture.

- The lack of consensus guidelines does not preclude physicians from identifying patients with low BMD and high fracture risk of the lower extremities.
- Fracture risk can be ascertained with DXA measurements of aBMD of the knee region and screening for fracture risk factors.

- The primary purpose of SLOP prevention and treatment is to identify patients with a high fracture risk and ameliorate fractures before they occur.

The rate and severity of decline in hip and knee region BMD are predictable among patients with acute motor complete injuries.

- Research is needed to describe changes in aBMD of the hip and knee region among patients with AIS C–D impairments.
- There are no published studies adequately powered to prospectively evaluate fracture risk reduction among patients with SCI; increases in BMD are assumed to be an appropriate surrogate for fracture risk reduction.
- We recommend a daily calcium intake of at least 1000 mg per day and vitamin D 1000 IU daily.
- Bisphosphonates, particularly oral alendronate with calcium and vitamin D supplements, remain the mainstay for prevention and treatment of SLOP pending outcomes from ongoing drug and rehab intervention studies (www.clinicaltrials.gov). Poor study quality and the lack of methodologic rigor precludes generalization of the rehab intervention studies.
- Maintenance of knee region BMD, in the absence of a fragility fracture, is likely an effective therapy.

Optimal therapy should increase BMD of the distal femur and proximal tibia above the fracture threshold.

- Biochemical markers and BMD values may be used to identify responders and nonresponders to SLOP therapy.
- Prospective multimodal intervention studies involving a representative sample of SCI subjects and appropriate controls using established outcome measures are needed.

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Evidence-Informed Management of Chronic Low Back Pain with Lumbar Strengthening and McKenzie Exercise

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ABSTRACT: There are basically two ways to change the structure in the painful spine, which include the use of strengthening exercises or repeat movements, which are guided by pain response. In this article, we take the position that strength training can only rationally be achieved by using exercise equipment that enables the knowledge of range, resistance, and number of repetitions on each exercise occasion. Without translating exercise into numbers, information that is available when using exercise equipment, progress is very difficult to define. The same is true with repeated movements, which can alter the location of pain. Such is the case with McKenzie testing, wherein centralization of the pain is the goal of the repeated movements. Adverse movements are defined those that cause peripheralization of the pain radiating into the extremities. Changing the internal status of the disc is the assumed function of repeated movements. The justification of these maneuvers is demonstrated by definable endpoints of improved function.

KEY WORDS: progressive resistance exercise, muscle isolation, progressive overload, mechanical diagnosis and therapy, repeated motion

I. INTRODUCTION

In this article, we take the position that exercise is the only noninvasive treatment that is able to change the structure in individuals who suffer from chronic back pain. However, the very diverse passive treatment methods for this common, often disabling condition are a very significant aspect of the treatment problem. The varied approaches were recently summarized in a supplement of the *Spine* journal, titled "Evidence-Informed Management of Chronic Low Back Pain without Surgery."[1] Twenty-four different interventions were profiled, with each article required to present evidence of their benefit. In the summary of this extensive review, the editors indicated that the only methodology with consistent supportive scientific evidence was exercise.

Resistance exercise and stretching with directional preference are the focus of this article, and both have good physiologic justification and a rationale of support in the literature. In an effort to gain more insight into the development of the rationale for these forms of treatment, we will devote a portion of our discussion to the history of the concepts.

II. JUSTIFICATION FOR STRENGTH TRAINING

Is muscle weakness the cause of back pain? It is unlikely; no one has ever defined atrophic muscles as painful. Does weakness of the vastus medialis cause knee pain? Of course not; there must be some underlying structural damage within the knee. The same is true for low back problems. Diminishing the effects of the structural abnormalities causing symptoms is the goal of exercise.

Back pain is extremely common. It is also clear that once back pain has occurred, approximately 90% of patients suffering from the first episode of

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acute low back pain will be asymptomatic within 3 months.[2] However, there is a very high recurrence rate of 40%–60% among those patients who are suffering from low back pain for the first time.[3]

In addition, there are morphological changes in the lumbar extensor muscles that exist in those patients suffering from low back pain.[3] This fact, of course, leads us to question whether or not muscle weakness is the cause of the first onset of back pain, which seems unlikely because there are no studies to support that concept. We completed a study of shipyard workers, in which strength testing of the lumbar spine was performed with a large group of experienced workers who did not previously have back pain.[4] We followed the study participants for 2 years, and there were 12 claims for work-related back pain. Ten of these individuals tested as average or slightly above average in isolated isometric testing over the full range of motion; only two workers were slightly below average.[4]

On the other hand, there is a discrepancy between claims of back pain in the workplace and the incidence of back pain. In another study that we conducted at a strip mine, about one third of the workers had complaints of back pain, although, at the time of the study, they were not making claims.[5] In an effort to reduce significant rates of back injury claims, a specific once-a-week training program for lumbar extensor strengthening was instituted. Only about one half of the workers volunteered for this program, but 80% of this group had some back pain in the past. These workers tested weaker than those without past back pain, and this deficit was correctable with training. The incidence of back injuries at the mine fell from 1.5 per month to a total of 1 day off during the whole next year for those workers who participated in the training. These results demonstrate that a strengthening program can be successful in reducing injuries.

A similar experience has been demonstrated with airline employees. An injury prevention program was conducted with two major airlines in the United States (airline A and airline B). Voluntary participants included ramp workers (baggage handlers), flight attendants, and pilots. The study participants exercised their isolated lumbar extensors once per week, and their low back strength increased 80%. Both airlines demonstrated similar savings. Although the data acquisition time (airline A: 20 months; airline B: 6 months) and number of workers were different (airline A: n = 622; airline B: n = 373) for these data sets, both demonstrated significant back strength gains, decreased injury rates, and cost reduction against large control groups (airline A = 2937; airline B = 2219). Participants from airline A showed a 78.5% increase in strength and those from airline B showed an 80% increase. Annualized injury rates for the exercising employees were 5.7 and 7.9 per year in airline A and airline B groups, and 179 and 256 in the control groups, respectively. The nonexercising control groups were 6.6 (airline A) and 5.5 (airline B) times more likely to be injured than the exercising workers. When the annualized cost savings (work comp direct + indirect costs) per employee per year for the exercisers versus the control group were considered, the costs per injury were $206 for airline A and $63 for airline B, contrasted with $4883 and $1223 in the nonexercising groups. These data led to a return on investment of 10/1 and 6.4/1, respectively, for airline A and airline B. In addition, when the employees were surveyed, all of them rated the program as either good or excellent.[6]

Where is the weak link? For many years, it was thought to be in the abdominal musculature. In the 1960s, Williams crystallized the common concept regarding the cause of recurrence and the appropriate focus of training.[7] His opinion was that the reversal of lumbar lordosis would yield more room in the neural foramen. Williams also suggested that abdominal strengthening would increase intra-abdominal pressure, which is necessary for torso control. Even now, a significant number of clinicians regard abdominal strengthening as the main exercise mode. Thus, the continued prescription of so-called Williams's flexion exercises is common.

Despite considerable data identifying the weak link as being in the lumbar extensors, the erroneous concept of the abdominal musculature as the weak link persists.

A. Documenting the Weak Link

As radiographic techniques such as computed tomography (CT) and magnetic resonance imaging

(MRI) became available, they made it possible to create axial views of the lumbar area. It became clear that the lumbar extensors, and especially the multifidus, were atrophic associated with back pain when compared to other muscles in the torso. Alaranta et al. made this observation by using CT scanning; the more severe the back pain, the greater the atrophy observed in only the lumbar extensor muscles.[8] Parkkola et al. reported similar findings in that the lumbar extensors of patients with chronic low back pain had a greater amount of fatty infiltration as noted by MRI.[9] Mayer et al. used CT technology and showed a significant amount of atrophy in the extensors in postoperative patients.[10] Investigators have noted similar findings by investigators using electromyography (EMG) techniques. Studies have demonstrated that inhibition existed in the lumbar extensors, whereas the lumbar flexors functioned normally.[11–13] Our research has revealed similar findings. In a prospective study of a series of patients with chronic low back pain compared to healthy individuals, we found that there was considerable muscle atrophy with fatty infiltration in patients with chronic back pain.[14] This was quite specific in that other torso musculature as well as the iliopsoas showed no fatty infiltration or muscle atrophy. When tested, the individuals in this series with back pain averaged 35% below the expected normal strength during isometric testing of extension over the full range of motion. With training, muscle strength was able to return to normal; however, the inhibited surface EMG scans for the extensors showed considerable modification as the muscles strengthened. At the conclusion of treatment, the total amount of myoelectric activity was reduced for the same initial resistance with strength training, resulting in clinical improvement.

Hodges and Richardson conducted one of the most sophisticated myoelectric studies to date by using fine wire electrodes that were placed in the torso musculature under ultrasound visualization, resulting in some significant observations.[15–17] These studies highlighted that, in the case of low back, the activation of the multifidus and transversus abdominis was delayed by approximately 200 milliseconds compared to healthy individuals. Therefore, stabilization of the torso was slightly delayed when upper extremity activity was initiated. This also was true for lumbar activity such as flexion and rotation, which seem to make the trunk more vulnerable to physical stress in the case of an unguarded moment.

Hides and colleagues also made a significant observation regarding the atrophy of the multifidus muscles. The researchers used real-time ultrasound technology to study patients with first-time onset of unilateral back pain, and followed them with ultrasound measurements of the lumbar extensor musculature. The results showed that atrophy occurred rapidly, sometimes within weeks, in the multifidus on the symptomatic side. Moreover, this atrophy persisted even after there was spontaneous resolution of the symptoms.[18,19] A recent study indicates that the unilateral atrophy, which occurs only in the once-symptomatic side, persists even when it is no longer symptomatic, largely in the shorter, deeper multifidus fibers.[20]

B. The Physiologic Justification of Early Atrophy

Although the findings of unilateral atrophy on the symptomatic side may be surprising and even suspect, this is not a unique physiologic phenomenon. All clinicians are aware of the rapid atrophy of the vastus medialis soon after a knee injury. This atrophy can even be created by the painful stimuli that emerge simply from knee effusion. The atrophy is caused by the reduced neural drive to the musculature based on inhibitory processes. The specific area of atrophy cannot be caused by some disuse phenomenon, otherwise it would be much more generalized. Hodges et al. recently explored this phenomenon in an animal study, in which they used pigs to conduct a comparative study of muscle mass after three experimental conditions.[21] One condition was merely a sham incision but created no structural damage; another condition was a medial branch transection of the L3 dorsal ramus; and, finally, the last condition was an incision of the L3–4 disc with laceration of the annulus. As a result, rapid atrophy occurred at the L4 disc level of the multifidus muscles; however, no change occurred from the sham incision. The multifidus muscle has three fascicles from deep to superficial, and range in various levels of attachment to the spinal segment. With

the injury to the L3–4 disc, however, the atrophy only occurred at the L4 level, which suggests that there is a specific inhibition of the musculature. Atrophy persisted in the pigs that were examined in the study of Hodges et al. These results, of course, reflect the same observation in humans, which noted that after an acute episode of low back pain, the multifidus cross-sectional area did not resolve spontaneously and was present to the same degree when retested 4 weeks after the onset of symptoms.[22] After transection of the dorsal ramus of the L3 nerve root, the cross-sectional area was reduced over three segments rather than merely at the level of damage (L4). At present, the mechanism is unclear in terms of how some structural damage to the disc in humans creates this phenomenon; however, it is apparent that some reflex feedback to the central nervous system must be an important phenomenon that later leads to the inhibition of neuromotor activity.

In summary, it is clear from the discussion above that lumbar extensor function, specifically in the multifidus musculature, is reduced on the occasion of symptomatic back injury. Neurologic inhibitory factors are important because atrophy of the extensors occurs rapidly in individuals with symptoms of back pain.

Multiple studies have described multifidus function as a deficiency in chronic low back pain by multiple studies. This deficiency is particularly notable in the abdominal flexors, which remain normal.[23] An important aspect of multifidus function is the more rapid fatigability of this muscle.[12] In a unique study using specialized MRI analysis, Flicker et al. demonstrated that the multifidus fatigued more rapidly than any other torso musculature, which was true in both normal healthy persons as well as patients with chronic back pain.[24]

III. SHORT HISTORY OF THE DEVELOPMENT OF THERAPEUTIC SPINAL EXERCISE

Therapeutic exercise, in general, is a rather recent form of therapy in medical care. The medical applications of exercise likely began with the Central Institute of Gymnastics in Stockholm, established in 1813 by Per Henrik Ling. Ling was appointed as a fencing master at the University of Uppsala in 1805 and developed a series of exercises originating from the craft of fencing. He then elaborated a system of gymnastics exercises and maneuvers divided into various categories such as pedagogical and medical, military, and aesthetic. The Royal Gymnastics Central Institute was established in 1813 by a grant from the Swedish government. Over time, Ling made claims of being able to cure diseases, such as arthritis and scoliosis, and to hasten delivery in obstetrical care, by using exercise. Ling was elected a member of the Swedish General Medical Association in 1831.[25]

Gustav Zander, a Swedish physician, was a student who was initially in the Ling curriculum and was impressed by the concepts. Ling had coined the terms *eccentric* and *concentric* exercise and had developed a protocol of progressive resistance exercises. However, the progressive exercises were performed against the manual, hands-on resistance methods that were used by therapists; thus, the amount of exercises was variable, based on the fatigue of the therapist. In an effort to be more consistent and offer a more specific method of muscle group-isolated strengthening, Zander developed what he called *medical mechanical therapy system*. Eventually, Zander went on to create 40 different pieces of equipment that allowed variable resistance exercises based on a series of weights, levels, and gears.[26]

Although the medical community did not initially accept the claims of potential medical benefits from these new techniques, demonstration of their efficacy was documented by the fact that Ling was elected to the Swedish General Medical Association in 1831. Zander opened up the Medical Mechanical Institute in 1857, and he was elected to the Swedish Institute 10 years later. Zander's equipment spread around the world and, by the turn of the century, there were 200 facilities in locations ranging from Australia to New York City. The system faded, however, as hospitals emerged with their insistence on sterility and with the therapeutic philosophy of proper hygiene, appropriate nutrition, and prolonged rest. As late as the 1930s, women delivering babies in the hospital tended to stay for a week to 10 days. Therapeutic exercise was not considered of medical interest. The concept of rest as applied to back pain persisted until the 1990s. Bedrest and traction were certainly the main themes of the

training programs. For many of the older physicians today, these concepts remain.

It took perhaps a war to rediscover the benefits of progressive resistance exercise, as developed by Zander and Ling. Dr. Thomas DeLorme transferred the concepts he had learned as a world-class weightlifter to the treatment of injured joints. At the beginning of World War II, before the importance of rehabilitation systems emerged in the medical community, troops who required knee surgery for a torn meniscus while in training were discharged with what was then assumed to be a permanently injured joint. DeLorme, however, documented that progressive resistance exercise to the knee and other joints by using weights and progressive repetition could restore normal function.[27] The injured or postsurgical troops did not have to be discharged. However, after World War II, the concepts of rehabilitation by using progressive exercises slowly faded in favor of electronic systems including ultrasound, massage, heat, cold, and so forth. Incidentally, the concepts of Ling and Zander were completely unknown to DeLorme. He first became aware of Zander equipment when, as an orthopedic surgeon at Harvard with an interest in rehabilitation, he was approached by an administrator about what he should do with the dusty, unused equipment (Zander's) in the basement of Massachusetts General Hospital.

The value of muscle isolation, progressive overload, and documentation of progress by using exercise equipment were once again discovered, this time for sports, by Arthur Jones. Jones invented Nautilus equipment.[28] The fact that he published all of his findings and experiences in *Iron Man* magazine indicated that the earlier interest in this exercise system was focused at the health enthusiast, and not to the medical context community. Jones, too, was completely unaware of Zander and Ling, and only became aware of their work in conversations with Dr. DeLorme. Because the concepts of lumbar extensor deficiency were gradually emerging, the value of isolation and progressive resistance exercise related to low back deficiencies became apparent. On the basis of these findings, Jones proceeded to develop MedX equipment for the specific application as therapeutic exercise to the spine (Fig. 1). This equipment was developed in the academic environment of the University of Florida. Thus, specific protocols based on extensive human testing were developed.[29]

The next section of this review focuses on the clinical application of strength training.

IV. THE FUTURE OF THERAPEUTIC STRENGTH TRAINING FOR LOW BACK PAIN

The impact of therapeutic strength training for low back pain is quite minimal, as documented in a recent review of nonoperative care for chronic low back pain, in which there were 24 chapters written by various experts in this field, but only one focused on lumbar extensor training.[30] This minor visibility in the broad array of back treatments demonstrates a current and perhaps future application for treatment. This is despite the fact that one of the few solid scientific observations concerning back pain is the recognized delay in activation of the multifidus in individuals with back pain compared to those without back pain. This delay was associated with a delay of the transversus abdominis.[16] Other authors have also noted the atrophy of the multifidus,[31] and therefore it seems quite reasonable that strengthening of this musculature would be appropriate. Atrophy was observed in patients who had complaints of persistent back pain with an unknown cause.

Of course, in chronic back pain, there are no pathognomonic signs for this problem on physical examination and even on standard imaging studies. Radiographs and MRI and CT scans do not define the back pain problem.[32] Defining back pain is extremely difficult because of the lack of pathognomonic findings during a regular physical examination. For that reason, we focus on the McKenzie rationale later in this article, which discriminates different types of back pain and their associated treatment.

Back pain has led to an abundant use of diagnostic and therapeutic procedures.[32] For example, there was a 543% increase in facet injections from 1997 to 2006 in Medicare beneficiaries. There was also a 518% increase in discography and a 159% increase in epidural procedures. Because of the limited scientific basis for these procedures, there is a 14-fold difference in the application of these procedures across the United States.

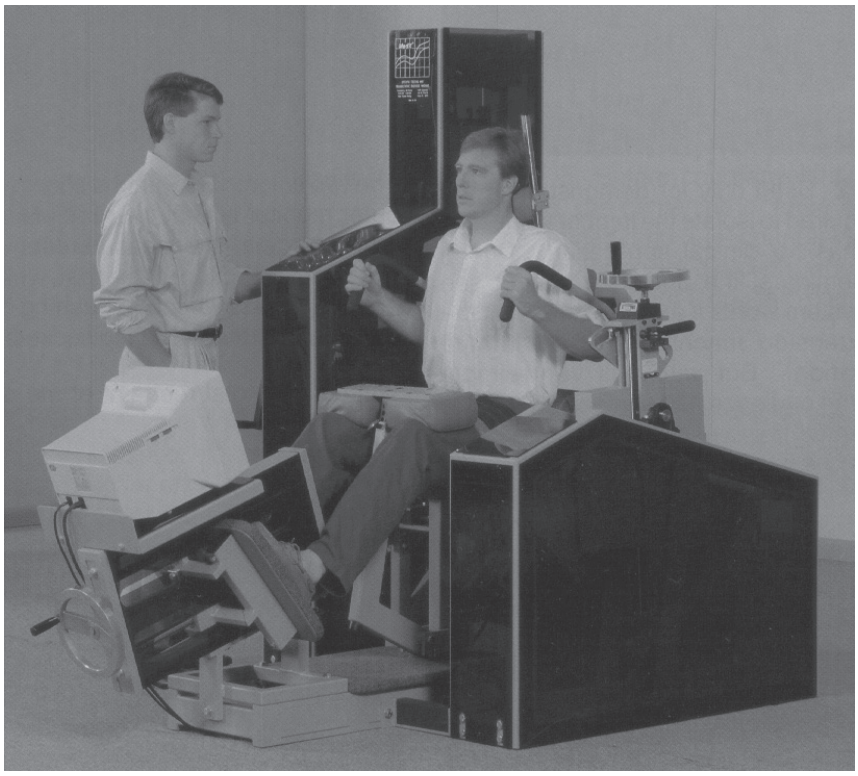


FIGURE 1. A testing device for measurement of strength and range of motion of the lumbar spine. (Reproduced with permission from MEDX LIMITED, Ocala, FL.)

Nonetheless, there is rationale for strength training, which was well identified in a recent article by Mayer et al. published in *The Spine Journal.*[30] The American College of Sports Medicine notes that there are guidelines for strength training that are focused on frequency, intensity, volume, duration, and mode.[33]

A. Current Justification for Strength Training Rationale

Strength training should have the opportunity for overload.[34] Science has demonstrated that intensity must be increased to produce strength training. However, progressive overload should be gradual in intensity and volume, particularly in treating patients with chronic low back pain. Also, the strength training should be specific to isolate the weak link; in the case of chronic back pain, the weak link is the lumbar extensors. It therefore is necessary to use a specific piece of equipment to create the specificity and gradual overload.[30] It is extremely difficult to create a gradual increase in overload and specific muscle strengthening by using calisthenics or floor exercises.

Exercises should be continued if they are necessary from a therapeutic standpoint. Atrophy of unused tissues occurs physiologically. Nonetheless, once strengthening has been achieved, strength training can be reduced to at least once per month.[34]

If the exercise is specific, it can be carried out in one set twice per week to achieve ultimate improvement.[14,33] With the use of specific equipment, high intensity and short duration of exercise are possible. To obtain the most significant effect, each repetition of a particular exercise should be performed in slow, controlled fashion through the full range of motion.[35] These exercises should not be performed at a rapid rate on multiple occasions. Ideally, a single set with 15–20 repetitions is as effective as any other method of strength training.[29] Hypertrophy and more-efficient bioelectric activity of the lumbar extensors have been documented after performing a single set of exercises twice per week. However, to achieve the maximum benefit, the exercise program must be carried

out for 10–12 weeks when it is performed twice per week. Functional gains will be made earlier in the program, but the ultimate benefit will not be reached until there is a plateau, essentially at 2½ to 3 months.[34]

Although the extension dynamometer is not necessary to achieve appropriate isolation and specificity of function, similar levels of specific training can be achieved with the Roman chair.[36] The Roman chair has a disadvantage of engaging the hip extensors, which can substitute for the deficient lumbar extensors. Nonetheless, it is a low-tech option and can be used in most fitness facilities or even in a home program.

The point of these programs is that the universal weak link in persistent back pain is the lumbar extensors.[37] The theme for these treatment programs is that, in chronic low back pain, lumbar extensors are weak, highly fatigable, atrophied, and demonstrate excessive fatty infiltration.[38] To achieve the best results in recovery of these weak links, isolation and progressive overlay of the lumbar extensors is necessary. The better isolated the musculature is, the more efficient the strength training is.

There is literature to support the benefits of progressive isolated strength training of the lumbar extensors. In an article by Manniche et al.,[39] high-intensity exercise demonstrated a significant improvement in low back pain and reduced disability. In another article by Risch et al.,[40] individuals with low back pain were treated in a specific strength training program as described above. Treatment was delayed for the group of control participants and upon testing of their strength and psychological function, it was determined that the delayed group had significant defects. However, when participants in the delayed group were placed on the strength training program, they had resolution of their psychological strength problems. Even after surgery, strength training has benefits in range, strength, and return to function, as compared to no strength training.[41] In a randomized, controlled trial by Kankaanpaa et al.,[42] twice-per-week strength training for 12 weeks compared to no intervention resulted in improved pain intensity and disability rating. The 3- and 12-month improvements for each outcome were significantly greater for the strength training group.

Progressive strength training has been shown to have significant potential in reducing the need for spine surgery. In a study by Nelson et al.[43] of a group of 38 patients who had been recommended to have elective spine surgery, only 3 patients required surgery after a progressive exercise program.

A significant problem in treating persistent back pain is the inability to measure baseline and results. As the discussion above indicates, strength training performed on equipment can have a specific measurement of deficit improvement. On the other hand, individuals are more concerned with function. There are many functional questionnaires available to patient populations. However, in common practice today, less than 50% of therapy facilities use any form of outcome measure such as the standard questionnaires.[44] This is likely one of the reasons why so many methods of care for persistent back pain have been advocated. Because of the lacking of any methodology in measurement, it is difficult for a scientifically based treatment system to be identified. For this reason, strength training, with its reasonable rationale and specific measurement capacity, seems to be quite an appropriate system of treatment to advocate for persistent back pain.

Unfortunately, the rationale and evidence described above have not become persuasive to either the medical profession or to patients. In a recent study in North Carolina, Carey et al. noted that there is a substantial underuse of therapeutic exercise and structured rehabilitation, whereas there is an overuse of muscle relaxants and imaging studies and physical modalities.[45]

V. MECHANICAL DIAGNOSIS AND THERAPY: THE MCKENZIE METHOD

Although we have discussed the value of strengthening exercises in the spine, mechanical management of spinal pain has also been shown to demonstrate successful management and a reduction in symptoms. Mechanical management in this context refers to a two-fold process. First, a provocative assessment permits clinicians to divide patients into the subgroups of mechanical responders and mechanical nonresponders. A mechanical responder is one who has intermittent symptoms. Intermit-

tent symptoms suggest that there are positions that cause symptoms to get better or worse. It is these patients for whom movement patterns may be discovered that are able to increase or decrease symptoms. When a movement pattern is discovered that reduces the patient's symptoms, it is termed the "directional preference"—meaning that a preferred direction of movement has been found to make the patient's symptoms consistently better. This provides important compatibility to strength training in that a reduction of symptoms makes strengthening easier to accomplish. The value of mechanical assessment and directed treatment are discussed in the following section of this article.

A. Mechanical, Nonspecific Low Back Pain

Mechanical, nonspecific low back pain is one of the most ubiquitous presenting symptoms for health care professionals, second only to that of the common cold. One of the reasons that low back pain remains difficult to treat is that there is no consistently accepted method of assessment that directs treatment. Each clinician follows the methods in which he or she was trained, very few of which have a common thread. This is best reflected by the educator Maslow, who said, "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail."[46]

In general, health care practitioners assess, diagnose via exotic and expensive testing, and treat back pain in legions of ways, depending on their training. Primary care physicians often treat with anti-inflammatory medications, and some specialists treat with injections and exotic medications ranging from the fairly benign to the potentially dangerous, whereas physical therapists have a broad variety of manual approaches depending on the school of thought in which they have trained. Many of these providers also have different vocabularies and mechanical diagnoses that they use to describe their treatments.

Herein lies the problem in the world of back pain management and, in particular for this discussion, physical therapy. Like other health care providers, physical therapy treatment of spinal pain has many different approaches. Manual therapy gurus are many and each have their own sense of how spinal pain should be treated. Although treatments and rationales for these methods abound, they often have little in common from a clinical standpoint. Because much of this treatment relies on the therapist's intuition, years of experience, and belief in their specific approach, there is little common ground among purveyors of treatment. In addition, each has a vocabulary for describing the importance of the way they treat, which makes communication regarding the different methods difficult. Furthermore, there are lengthy courses that teach therapists how to "feel" pathology in muscle and other spinal anatomical areas in order for successful treatment to occur; for example, it could be a bilateral muscle imbalance, misalignment of the vertebrae of facets, some proprioceptive imbalance in the lower extremities, or tightness of connective tissue in some critical area. The lack of common thought is pervasive and, for each different approach, an almost evangelical zeal exists in their promotion and defense. There are, however, at least two striking commonalities in the manual therapy treatment of back pain. First, there is little or no objective measurement involved in the assessment and treatment, which is a problem because without measurement, one cannot assess patient improvement or, at the very least, link improvement to treatment beyond some unknown psychosocial phenomenon or natural history. Second, manual therapy approaches do not have as much evidence published in the scientific literature to support their methods. In some ways, manual therapy could be described as charismatic treatment in the sense of unmeasured laying on of the hands.

B. Mechanical Diagnosis: Subgrouping Patients

Once manual assessment is performed, treatments become surprisingly generic. Most medical treatments flow from the ADTO model (i.e., assess—diagnose—treat—outcome) as previously described, where the assessment informs the diagnosis and treatment.[47] There seems to be little linking of assessment to mechanical diagnosis, hence treatment in manual therapy. It is almost as if the treatment and outcome are distinctly separate from the assessment and diagnosis process. Making matters more difficult are the plethora

of manual diagnoses, most of which do not have any relationship to an approximated pathology. Even more interesting is that the generic standard programs that are typically given to patients most frequently involve palliative activities on the basis of time exposure. That is to say, hot/cold packs are applied for certain periods of time. TENS (transcutaneous electrical nerve stimulation) units or electrical stimulation are applied for certain periods of time. Stretches are assigned, performed, and held for certain periods of time. Some of these treatments are intended to increase blood flow or diminish pain, whereas others are intended to create adaptive changes in connective tissue. Most of these treatments are subjectively applied at best, or passed on through some unsubstantiated theory at worst. Few activities are performed on the basis of physiology or mechanical responses of soft tissue, and success is almost always reported by the patient's reflected feelings. This fairly amorphous approach has been labeled as the standard of care for nonspecific back pain.

This "one-size-fits-all" approach has been the hallmark of back pain treatment. As a result, the literature has been equivocal regarding the efficacy of one treatment over another.[48] As previously noted in this article, the one approach that seems to consistently work for patients is exercise, but which form of exercise is best? How does one determine which exercises are most valuable in their armamentarium for mechanical nonspecific back pain?

One of the foundations of medicine is the differential diagnosis. For example, a patient arrives at his or her doctor's office with a complaint of nonspecific chest pain. How does the physician determine the course of treatment? It could be:

- intercostal chondritis from a lifting strain or other inflammatory source
- anterior wall chest pain related to muscle
- esophagitis from acid reflux, or
- myocardial pain from an ischemic change in the heart

Diagnosing the source of the pain would lead to the appropriate treatment pathway. In effect, the source of the pain would become more clear with a good history and possibly some provocative testing. The differential diagnosis is a method of subgrouping the patient. Once the subgroup has been identified (e.g., esophagitis), the appropriate treatment (i.e., antacids) would be applied.

A standard, reproducible assessment then, leading to a mechanical differential diagnosis, might be the place to start in the case of a patient who presents with nonspecific back pain. A standard evaluation would help health care providers to identify categories (i.e., subgroups) of back pain in the patients they see. For example, in the patient who presents with nonspecific intermittent back pain, are there specific movements that make their symptoms better or worse? If a directional preference were to be discovered (i.e., a repeated movement pattern relieving symptoms), treatment based on that movement preference would enhance the patient's potential for recovery. The question is: How does one subgroup patients with back pain?

The idea of subgrouping in spinal patients began to find its way into the clinical arena several decades ago.[49] As is often the case with discoveries, its presence made a slow and arduous journey into the world of spinal care. It began with an observation, which led to trial and error, which led to an assessment methodology. This methodology, directly informed by patient response to provocative movements, led to the development of a reproducible clinical evaluation. Tracking patient responses over a long period of time led to an understanding that a large percentage of patients with back and neck pain could be predictably and successfully treated. This approach to spinal pain has been called mechanical diagnosis and therapy (MDT) or, in more recognizable terms, the McKenzie method.

C. A Brief History of Mechanical Diagnosis and Therapy

To appreciate this method, it may be helpful to see how categorizing and subgrouping patients came to be understood. Like most discoveries, it was a chance event in the furthest place from the study of back pain. It began in 1956 in a small clinic in Wellington, New Zealand, in the hands of a physiotherapist named Robin McKenzie. Like therapists before and after him, he used many different approaches to the management of patients

with back pain. In that day, treatments ranged from galvanic stimulation to Williams flexion exercises,[7] as previously described. McKenzie's experience and results, like therapists before and after him, were singularly unsuccessful in the consistent treatment of patients with back pain. If there was a method that actually helped, it was either serendipitous or the tincture of time combined with benevolent neglect.

As is often the case with discovery, it was an accidental observation that began a clinical dialogue that continues to enlighten the treatment of back pain to this day.

While treating a patient with a knee problem, McKenzie had elevated his treatment table to an upward angle so that the patient could sit up while being treated. In a busy practice, often attention is not paid to everything in the course of the daily clinical flow. And so, by chance, the next patient to be sent to this treatment room was one with low back pain. McKenzie told him to go in, lie down, and he would be back in a few minutes. When McKenzie entered the treatment area, he was alarmed to note the patient was laying face down on the table with his back in an extreme arched position, and had been there for about 10 minutes! As McKenzie fumbled for the appropriate words, the patient exclaimed it was the best his back pain had felt in a considerably long time. Not only was this confusing, but it flew in the face of everything that McKenzie had been taught. This event created a curiosity, one that would irrevocably change both his life and the treatment of back pain.

Over the course of subsequent years, McKenzie experimented with variations of this early experience, treated many patients, and organized his thoughts. Initially, he tried extending all of his patients and found that this method did produce consistent results. Through trial and error, he discovered many patients' symptoms were made better or worse depending upon specific movement patterns that were produced during physical examination. Gradually, a standardized assessment of provocative movements emerged. This assessment revealed that patients with back pain could be classified into different categories. The key to the discovery of a directional preference in patients was repeated end-range movement. A single flexion or extension motion would reveal little, but repeated flexion or extension (both in standing and lying) movements, provided a clear directional preference with a number of patients. Exercises that were adapted by the directional preference found during the assessment proved to afford much better results in McKenzie's patients.

D. A Mechanical Differential Diagnosis

While experimenting, McKenzie also discovered that some back pain got better simply by correcting poor posture, others got better by challenging shortened connective tissue, and some did not respond to any movements. From these observations, he developed a system of assessment, leading to a level of predictable success as yet unknown in the management of back pain. This codification of a repeatable and consistent assessment that was meant to inform treatment became known as the McKenzie method. This codification was separated into three basic syndromes: postural, dysfunction. and derangement.[50]

Postural syndrome. Postural pain typically comes from prolonged static postures or positions that can affect joint surfaces, muscles, and tendons, leading to discomfort and pain. The pain is generally local and reproduced when the patient slouches for extended periods of time at end-range positions. Repeated movements during assessment do not affect symptoms. The hallmark of postural syndrome is that the pain is intermittent and simple corrections in seated or standing posture relieve symptoms immediately.

Dysfunction syndrome. It became clear to McKenzie that some patients had limited end-range motion, meaning that connective tissue had gone through some sort of adaptive shortening, scarring, or adherence that caused discomfort or pain. Patients with this syndrome may have chronic or intermittent symptoms but, in all cases, its hallmark is loss of motion and pain at the end-range of movement. When the patient moves away from the pain, it subsides and reveals itself as an "on-off" phenomenon during assessment. Treatment for this syndrome takes time because it requires tissue remodeling—meaning a plastic change (permanent adaptation) in connective tissue (tendon or ligament). In order for a plastic change to occur, end-range stretching must occur

and it takes time for remodeling to take place. This syndrome is not a common finding, but it occurs frequently enough that it has been observed and defined.

Derangement syndrome. This is the most common clinical presentation of patients with low back pain. The hallmark of this syndrome is symptom sensitivity to provocative movements. Repeated flexion-extension exercises on assessment cause symptoms to become more central or more peripheral—meaning that, in the case of the low back, repeated flexion or extension causes the symptoms to move. It is not uncommon for a patient to experience a rapid reduction of his or her symptoms immediately during the assessment. That is to say, if the pain were in the right calf, it might move more centrally into the right buttock. When symptoms become more central, the patient's directional preference has been found and treatment is informed by this preference. Any central movement of symptoms is key to understanding the derangement syndrome.

Nonresponders. As important as it was to find suitably treatable patients, it was equally valuable to discover patients for whom mechanical exercise would not work. These patients were referred to as nonresponders and were quickly moved to some treatment other than MDT.

It is a common mistake to think of the MDT method as a series of exercises. Indeed, there are no MDT exercises, per se. As demonstrated above, there is an assessment and that assessment drives the treatment. Without the assessment, there are simply generic exercises. Studies conducted by therapists who were either not trained or minimally trained in the McKenzie method have effectively demonstrated that indicated extension exercises were better than flexion exercises, but that neither one of them were particularly meaningful in the treatment of acute back pain. In these studies, assessment did not drive the exercises. In one study, patients presenting with nonspecific back pain were randomly assigned to one of three groups: (1) bed rest, (2) mobilization exercises (extension and side bending), and (3) usual life activities as tolerated (the control group). The results were equivocal related to the extension and side-bending exercises.[51] In another one of these studies, patients with nonspecific low back pain were randomly assigned to three groups: (1) McKenzie physical therapy, (2) chiropractic manipulation, and (3) an educational booklet. Although there was a trend toward the McKenzie exercises being more effective, all three groups showed improvement with no significant differences when followed over 2 years.[52] It is no surprise, therefore, that the results were equivocal. Assessment is the key.

E. McKenzie Exercises

Once movement patterns are found that make the patient's symptoms better, exercises are given that support the reduction of patient symptoms. The discovery of directional preference seems simple and straightforward, but it had escaped the attention of the spine-care community and was the first clinical insight to standardizing an approach to the management of low back pain.

Although other manual approaches to the management of low back pain provide a vague view of causation, the MDT method confronts the disc head on. Although the model does not require a pathoanatomic diagnosis and explanation for causation, it does focus on the disc as the pain generator. McKenzie[49] published his methodology in a text in the early 1980s and hypothesized that repeated movements, particularly in the derangement syndrome, caused migration of the nucleus of the disc. When the patient's symptoms moved more centrally, he suggested that the nucleus moved away from the posterior elements of the disc, leading to a relief of pressure and therefore symptoms. A reduction of or increase in symptoms with repeated motions, the method contended, suggested that there was migration of nuclear material in the disc that may aggravate or relieve symptoms. Clinical experience seemed to suggest this, but there was little evidence at the time. As is often the case with keen observation and hypothesizing, discoveries stand or fail the test of time.

F. Standardized Training: A Key to Success

In the 1980s, McKenzie understood the importance of educating the physical therapy world to his discovery.[49] This led to an educational initiative

and ultimately to an institute dedicated to teaching the assessment and treatment to physical therapy professionals. Eventually, for the spine, it became a four-part education program, which consisted of courses for the lumbar and cervical spine in addition to two further-advanced problem-solving courses. This series of structured training modules was intended both to teach the assessment in a standardized method and to ensure a certain quality of training that would permit similar results to be found among trained health care professionals.

It is beyond the scope of this article to provide a comprehensive review of the MDT method, which has been done by previous authors.[53,54] However, it is interesting to note how this insight of nuclear movement with repeated motion has played out in the scientific and clinical literature.

G. Brief Clinical Review

Although the MDT method was standardized and taught to interested physiotherapists, it was not clearly described in the scientific literature until 1990 when Donelson et al. showed that directional preference was an observable and quantifiable phenomenon.[55] Donelson and colleagues' work was a retrospective chart review of 87 patients presenting to an orthopedic practice. All of the patients had been evaluated by using the MDT assessment, and the authors, on initial evaluation, looked for patients with the presence or absence of centralizing symptoms. In Donelson's study, 87% of patients showed signs of centralization, suggesting that directional preference was identifiable in clinical practice. Outcomes included a return to normal activity, pain relief, and patient satisfaction. The authors concluded that assessment and treatment of patients by using the MDT method was a good predictor of successful outcomes, as described. The following year, Donelson et al. performed a prospective study that examined the effects of flexion and extension exercises on patients with low back pain. The majority of patients showed a centralization response to extension exercises (39%), whereas 8% demonstrated a centralization response to flexion exercises. Although this was an exercise study, it suggested that patients do not demonstrate a directional preference with a "one-size-fits-all" exercise approach.[56]

An early cadaver study suggested that there was nuclear migration with repeated motion,[57] but the number of subjects was very small and the study was poorly designed. In more recent years, however, Alexander and others have shown significant anterior and posterior nuclear movement through static loading of the lumbar spine in either the flexed or extended positions.[58] MRI scans were performed on 11 healthy volunteers in a variety of positions (i.e., standing, sitting, supine, and prone extension). This method differed from other MRI studies in that the patients were functionally loaded in several of the measured positions. None of the patients had back symptoms or a history of having had treatment for back pain. The participants held their positions for approximately 10 minutes per scan in an upright MRI machine that could image in the supine, erect, and seated positions. The authors demonstrated that the greatest sagittal migration of the disc nucleus was at the L4-L5 and L5-S1 levels. They further suggested that their results were in alignment with the ". . . theoretical model of posterior migration, leading to disc bulging and ultimately pathology . . ."[58] It was noted that prone extension induced less posterior migration than the sitting positions, suggesting that standing or sitting extension may be preferable for better nuclear movement. However, it should be noted that these participants were held in static positions, whereas the MDT method is based upon repeated motion.[58]

Although the previous study[58] showed nuclear migration, it was done under static conditions. By using a cervical porcine cadaver model, Scannell and McGill demonstrated a reduction of the cervical nucleus through repeated movements in the cervical spine.[59] The authors noted that the porcine cervical spine resembles the human lumbar spine, allowing for some comparative thought. The specimens were frozen immediately postmortem and then thawed just prior to the experiment. The work by Scannell and McGill is not the first study to show repeated movements to influence nuclear movement,[59] but it is the best-designed study with resultant migration. The specimens were repeatedly flexed under axial compression. Four specimens were exposed to sagittal flexion only, whereas 14 were subjected to combined sagittal and lateral flexion

loads, leading to disc prolapse. Five of the discs failed and 11 prolapsed. Once prolapse had been accomplished, those that had prolapsed were exposed immediately to repeated extensions or a combination of extension and lateral flexion. The specimens that had only moderate disc height loss all responded by centralizing (n = 5). Six of the 11 specimens had severe disc height loss and did not respond. The data demonstrated a 45% response rate and a 55% nonresponse rate. The discs that demonstrated centralization of the nuclear material did so with opposite movements (same plane) to those that had caused the prolapse in the first place. The cadaver specimens were controlled for diet, exercise level, and age, but obviously did not appear with the same comorbidities of the chronic spine patient. Nonetheless, Scannell and McGill's study demonstrated that nuclear positioning can be influenced by repeated motion. As is the case with patients presenting clinically, not all nuclei moved as a result of repeated motion—meaning that some patients respond and others are nonresponders.

The strongest clinical suggestion for the data of Scannell and McGill appeared earlier in the literature. It had been assumed that for there to be nuclear migration, the annulus would need to be competent. Patients who did not respond with a directional preference were theorized to have an incompetent annulus. Donelson et al. tested this hypothesis by subjecting 63 patients with low back pain to repeated movements using a discogram to determine the integrity of the annular wall.[60] All of the patients underwent a McKenzie repeated end-range motion evaluation in both the loaded (standing) and unloaded (lying down) positions. Patients were classified as (1) centralizers, meaning that symptoms moved more centrally; (2) peripheralizers, meaning that symptoms moved more peripherally; and (3) nonresponders, meaning that there was no change in symptoms. Immediately following the evaluation, the patients underwent a lumbar discogram to determine integrity of the annular wall. Thirty-one of the patients (49%) centralized, 25% peripheralized, and the remainder experienced no change. Ninety-one percent of the patients who demonstrated centralizing symptoms had intact annuli, suggesting that the centralization phenomenon requires an intact annulus. This study further suggested that an MDT mechanical evaluation was as successful in indicating an intact annulus as the provocative discogram.[60]

These studies substantiated the observational theory of nuclear migration put forth by McKenzie in the early 1980s, from both the scientific and clinical standpoints.

The other major thrust of the MDT thought process was whether the method could be taught with reproducible results. In other words, would training in the method produce consistent results between trained therapists across patient populations? Furthermore, would how well therapists were trained in the method make a difference? Finally, if patients were determined to have a directional preference by using the assessment process, what would happen if they were given exercises that were contraindicated—meaning, if their directional preference was repeated extension exercise, what would happen if repeated flexion exercises were prescribed? As is often the case in health care, what works in one facility in the hands of one provider, does not always translate into the same result in the hands of another provider in a different facility. To address this issue, the MDT method requires 98 hours of postgraduate training, followed by both written and practical examinations. Passage of these examinations is necessary to be credentialed in this method.

A number of studies have been performed to determine inter-rater reliability for subgrouping patients with back pain.[61–65] Riddle and Rothstein examined intertester reliability in patients with low back pain by therapists who were trained in the McKenzie method.[63] The study authors were interested in looking at the effects of McKenzie training on the ability of therapists to provide consistent classifications. Therapists were given written descriptions of the McKenzie method and classification criteria. Three hundred sixty-three patients were evaluated by 49 physical therapists in eight clinics. The therapists agreed on only 39% of patient classifications. One of the limitations of Riddle and Rothstein's study is that only 16 of the therapists had attended one postgraduate McKenzie training course, whereas the remaining 33 therapists relied on the written descriptions of the method. Only the outcome was reported with no comment on the consistency of assessment, making the case that inconsistently trained therapists produce inconsistent results. On

the other hand, Clare et al.[66] performed a study with 50 MDT credentialed therapists in different locations to see whether they would consistently be able to classify patients solely on the basis of a completed assessment form. The participants were presented with 50 completed patient assessment forms that had been performed by other highly trained MDT therapists. They were then asked to classify the patients into the McKenzie syndromes based on the assessment presented to them. The authors found there was a 91% agreement of the physical therapy raters when it came to selecting the major MDT syndromes. The authors showed that reliability of patient classification could be adequately determined between raters when presented with a completed McKenzie assessment form. The clinical implication is that proper training provides common-enough language and techniques that enable different clinicians to communicate about their patients.

Kilpikoski et al.[67] tested interexaminer reliability among MDT-trained physiotherapists to determine the effectiveness of a standard education and assessment process. Two different physiotherapists evaluated 39 patients who presented with nonspecific back symptoms. These physiotherapists had a " . . . high level of training . . ." and an average of 5 years of clinical experience in the MDT method. Both examiners were present for the patient history and subjective findings; they then examined the patients separately. Among the 34 patients whose pain was described as centralizing, there was a 95% agreement and a 90% agreement on the directional preference. The authors concluded that there is a high level of interexaminer reliability among therapists who have been trained in the MDT method. The study further emphasizes the importance of a deliberate training methodology to ensure consistency in clinical management, as well as communication in a common language to other trained physiotherapists.[67]

Once an assessment has been performed and a directional preference established, it is then possible for the patient to perform the appropriate exercises. Exercises directed by the assessment generally guide repeated movements that the patient can do on a defined schedule until symptoms are either significantly reduced or completely abated. Once the patient's symptoms have been successfully treated, emphasis is placed on returning to function that includes exercises in all directions.

Clearly, good posture is important in any treatment mode. Patients are educated in good standing and sitting postures (Figs. 2A and 2B).[68]

Recommended exercises for the patient with an extension directional preference could include laying prone, progressing to supported elbow and full press-up exercises (Figs. 3A–3C).[68] Recommended exercises for patients with a flexion

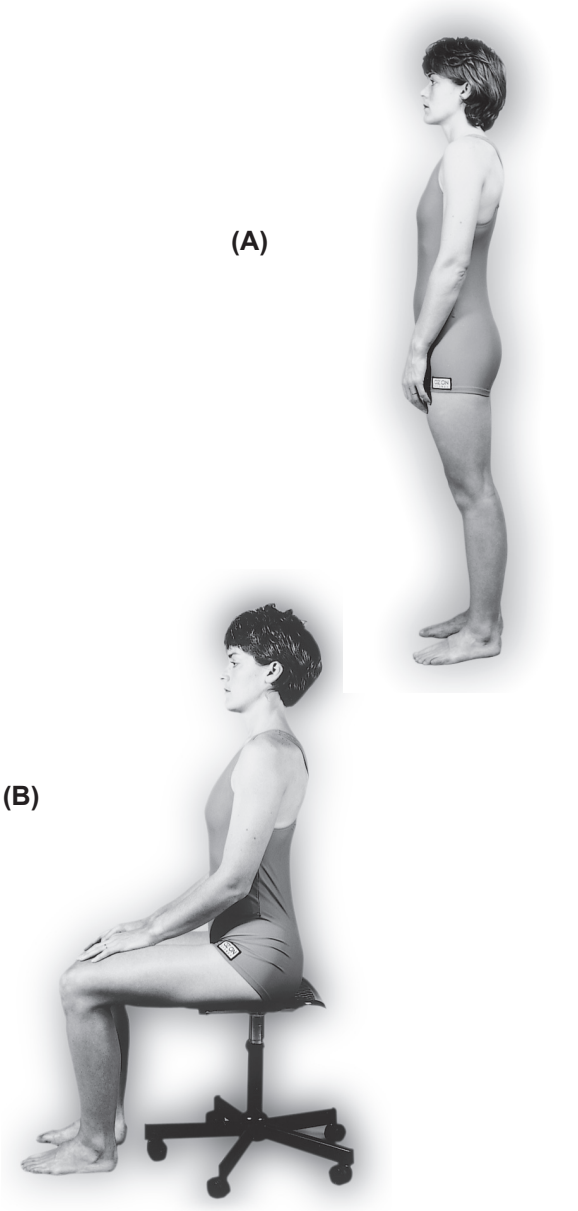


FIGURE 2. Proper standing (**A**) and sitting (**B**) positions. (Reprinted from McKenzie R, Treat your own back, © 2008. Reproduced with permission from Spinal Publications, New Zealand.[68])

directional preference could include laying supine, progressing to bent knee and then knees to chest (Figs. 4A–4C).[68] In addition, seated or standing flexion exercises might also be recommended (Figs. 5A and 5B).[68]

As previously discussed, most physical therapy has mostly been a "one-size-fits-all" approach, with little ability to know what is or is not successful. Long et al.[69] specifically tested the question as to whether it really matters which exercises are given to patients. In other words, was there clinical and, more importantly, prognostic value in performing a consistent assessment that directed treatment?[69] The authors performed a multicenter, randomized controlled trial, to determine how the effect of assessment-directed exercises would affect patient outcome. Therapists who were experts in the method administered the MDT assessment to 312 consecutive patients. This study used an intention-to-treat model, so any patients who did not show a directional preference were excluded from the study. The results revealed that 230 patients (74%) showed a directional preference and were included in the study, whereas 82 patients (26%) were nonresponders and were excluded from the study. Participating patients were randomly assigned into one of three groups: (1) exercises in line with the directional preference, (2) exercises in opposition to the directional preference, and (3) standard exercise as usual, expressed by evidence-based standards. Results demonstrated that patients who exercised in compliance with their directional preference on assessment had significantly more successful

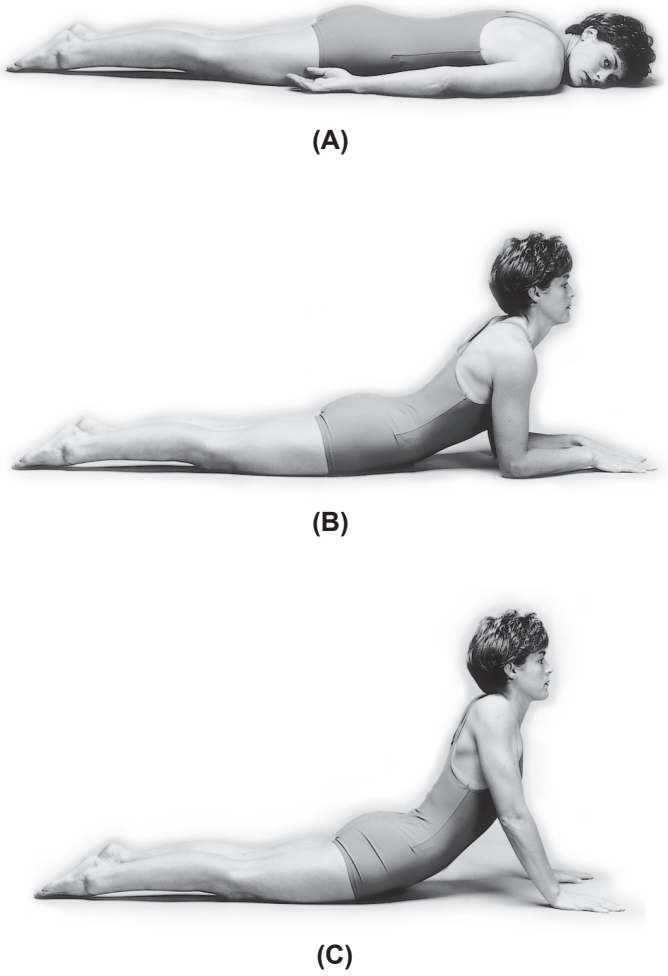
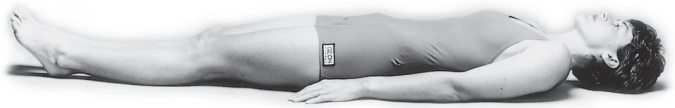


FIGURE 3. The progression of exercises for patients with an extension preference (**A–C**). (Reprinted from McKenzie R, Treat your own back, © 2008. Reproduced with permission from Spinal Publications, New Zealand.[68])

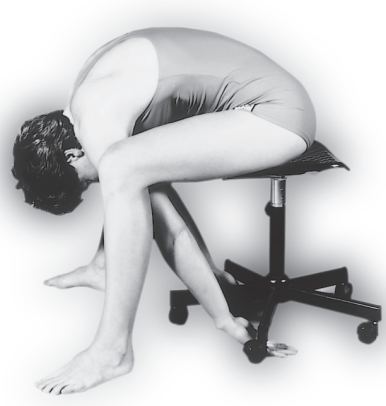


(A)

(B)

(C)

FIGURE 4. The progression of exercises for patients with a flexion preference. (Reprinted from McKenzie R, Treat your own back, © 2008. Reproduced with permission from Spinal Publications, New Zealand.[68])



(A)

(B)

FIGURE 5. Additional seated and standing flexion exercises. (Reprinted from McKenzie R, Treat your own back, © 2008. Reproduced with permission from Spinal Publications, New Zealand.[68])

results. Indeed, patients assigned to exercises that were opposite of those suggested by the assessment developed worsening symptoms. These data refuted earlier systematic reviews that suggested specific exercises were not warranted. What was the defining difference? The key to this finding was a consistent and reproducible assessment method, permitting the subgrouping of patients.

H. Summary

The key to effective treatment of any kind is being able to know where the process begins and, more importantly, to measure it. It is an initial and reproducible measurement, in this case a consistent assessment process, followed by treatment and examination of results, that leads to a better understanding of any process. In the world of physical therapy and its treatment of back pain, the McKenzie method stands out for its methodology and leadership in the arena of better patient classification.

VI. CONCLUSIONS

Two different forms of exercise have been detailed in the preceding paragraphs. Both have their place in treatment of spine pain, and both have a distinctive rationale that is supported in the literature. Unfortunately, their effectiveness depends upon the eagerness of a pained individual to participate in a regular and repeated manner. The desire to take control of one's own health matters is not a universal human trait. The failure of these two exercise methods to gain more traction in the clinical world is partly because of a lack of physician enthusiasm and patient enthusiasm for participation in persistent effort. As stated above, the impact of these two exercise regimens likely will be limited in the future because of the desire of all of us for a quick fix and magic. There is no magic in human reconditioning.

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Research on Myofascial Pain Syndrome

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ABSTRACT: Myofascial trigger point (MTrP) is the major cause of myofascial pain syndrome. On the basis of recent studies on both human and animal subjects, the pathophysiology of MTrP has been better understood. There are multiple sensitive loci in an MTrP region that are sensitized nociceptors in the vicinity of dysfunctional endplates. The irritability of an MTrP depends on the amount of sensitized nociceptors in the MTrP region. Stimulation of the sensitive locus can cause pain, referred pain, and local twitch response. As a result of excessive leakage of acetylcholine in the dysfunctional endplate, sarcomeres in this endplate region become shortened, which can cause taut band formation and elicit an energy crisis that perpetuates the vicious cycle train of "excessive acetylcholine leakage"-"increase of tension in taut band"-"release of sensitizing painful substance." Interruption of this cycle can inactivate the MTrP. However, the most important strategy to treat myofascial pain is to identify and treat the underlying etiological lesion that activates the MTrP. Effective methods that can inactivate an MTrP include stretching, deep-pressure massage, laser therapy, and needling.

KEY WORDS: energy crisis, myofascial trigger points, needling, nociceptors, referred pain, sensitization

I. MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome (MPS) has been defined as a regional pain syndrome characterized by muscle pain that is caused by myofascial trigger points (MTrPs).[1–11] In a broader sense, however, MPS includes a regional muscle pain syndrome of any soft tissue origin that is associated with MTrP.[4,7]

There is significant evidence indicating that MPS is frequently caused by or related to a lesion in another soft tissue. In clinical observation, myofascial pain can be suppressed by an effective MTrP injection, but the pain often recurs shortly afterward if the related pathological lesion is not eliminated.[1,12] When the underlying etiological lesion is completely eliminated, the pain caused by MTrPs can be "permanently" suppressed unless it is reinjured.[13,14] A study by Wu et al. indicated that the number and pain intensity of MTrPs were significantly reduced after physical therapy or surgery for lumbar disc herniation.[15] Other studies have also suggested that active MTrPs are associated with a multitude of conditions such as chronic tension-type headache,[16] cervical disc lesions,[17] cervical radiculopathy,[18] lumbar disc lesions,[19] osteoarthritis of the knee,[20] teres minor tendinitis,[21] lateral epicondylitis,[22] muscle strain,[23,24] floating kidney,[25] septic arthritis,[26] or herpes zoster.[27] Spinal manipulation of a cervical facet joint could effectively relieve the shoulder pain caused by MTrPs in the upper trapezius muscle.[28] Local steroid injections into a cervical facet region could suppress the shoulder pain caused by MTrPs in the upper trapezius muscle for a significantly long period of time.[29,30] Similarly, local steroid injections to the lumbar facet joint could relieve the gluteal pain because of MTrPs in the piriformis muscles, which was caused by a lumbar facet lesion.[31] The similarities of referred pain patterns between MTrPs and a cervical facet lesion at a certain level have been documented.[32] It is likely that many cases of myofascial pain are related to the facet joint lesion. An MTrP occurs less frequently as a consequence of a primary muscle lesion.[2,3,33] In clinical practice, muscle pain

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caused by overloading of the involved muscle can be observed, but the pain may be controlled easily after a few days of rest. Therefore, in most of cases, we deal with the chronic myofascial pain secondary to other soft tissue lesions.

II. THE NATURE OF THE MYOFASCIAL TRIGGER POINT

A. Definition

1. Active Versus Latent MTrPs

An MTrP has been defined as the most tender (hyperirritable) circumscribed spot in a palpable taut band of skeletal muscle fibers.[9,11] High-pressure stimulation of an MTrP can elicit pain, referred pain (ReP), and local twitch response (LTR, a brisk contraction of the muscle fibers in its taut band). The pain elicited by compression of this spot is similar to the usual pain complaint (pain recognition).[34] A *latent MTrP* is tender but not spontaneously painful,[11] and can be found in most normal adult skeletal muscles, but not in newborns or babies under 1 year of age.[35] An *active MTrP* is painful spontaneously or in response to movement of the involved muscle. A latent MTrP can be activated into an active MTrP, and an active MTrP can be suppressed with appropriate treatment and become a latent one. The important characteristics of latent and active MTrPs are listed in Table 1. Depending on the severity of an MTrP, it can be further classified into a few categories. However, there are no clear-cut distinctions between the different categories except for a latent MTrP and an active one. The separation of active MTrPs into three categories (mildly, moderately, and severely active MTrPs, as listed in Table 1) is artificial. In a mildly active MTrP, pain is present but ReP and LTR are not obvious. In a moderately active MTrP, ReP frequently develops and LTR can frequently be elicited. In a severe case, motor dysfunction can frequently be observed and autonomic phenomena can also sometimes develop. It has been suggested that the amount and severity of sensitized nociceptors in an MTrP region is the most important factor in determining the degree of MTrP severity.[2]

2. Primary Versus Secondary MTrPs

A patient with MPS can have many active MTrPs. However, in most cases, only one active MTrP in the affected muscle secondary to a soft tissue lesion can be identified in the beginning. If this MTrP is not appropriately treated or the associated

TABLE 1
Clinical Characteristics of Latent and Active Myofascial Trigger Points (MTrPs)

	Latent MTrPs		Active MTrPs	
Characteristics of MTrP	**Mild**	**Moderate**	**Severe**	
Taut band	Mild tension	Moderate tension	Strong tension	Very strong tension
Tenderness	Mild	Moderate	Severe	Extreme
Referred tenderness	Occasionally	Sometimes	Usually	Always
Local twitch response	Occasionally	Sometimes	Frequently	Usually
Restricted range of stretch	Sometimes	Usually	Usually	Always
Pain (spontaneous)	No	Mild	Moderate	Severe
Referred pain (spontaneous)	No	Sometimes	Frequently	Usually
Motor dysfunction	No	Rarely	Sometimes	Frequently
Autonomic phenomena	No	No	Rarely	Sometimes

underlying pathological lesion is not eliminated, the pain region can expand to other regions and develop additional active MTrPs as a consequence of central sensitization.[7] The original MTrP is defined as the *primary MTrP* or *key MTrP*, and those that develop later are defined as *secondary MTrPs* or *satellite MTrPs*.[9] Inactivation of a key MTrP can subsequently eliminate the satellite MTrPs.[1,9]

3. Central Versus Attachment MTrPs

MTrPs are usually located within the endplate zone. Endplate noise (EPN) can usually be recorded electromyographically in an MTrP region, but rarely is recorded in the non-MTrP region in the endplate zone and never in the muscle tissues outside the endplate zone.[9,34,36,37] The typical MTrP in the endplate zone has been defined as a *central MTrP*, and the trigger points in other locations in the muscle or tendon attachment region have been defined as *attachment trigger points*.[9,38,39] These attachment trigger points are located at the end of a taut band. Compression of an attachment trigger point of a certain muscle can elicit pain locally and referred pain in the central MTrP of the muscle.[38] LTR can sometimes be elicited by compression of an attachment trigger point; however, EPN can not usually be recorded from an attachment trigger point region of muscle.

B. Clinical Characteristics of Myofascial Trigger Points

1. Painful or Tender Spot

The essential characteristic of an MTrP is a circumscribed spot in the muscle with pain or tenderness. This spot can be identified in approximately the same region in different persons.[11,40] The exact location of the MTrP in almost every skeletal muscle has been demonstrated in the *Trigger Point Manual*.[9,11]

2. Taut Band

Simons et al. have suggested that a taut band is the precursor of an MTrP and an MTrP is always located in a taut band of skeletal muscle fibers.[9,34] A taut band is also an essential component for defining an MTrP,[9,11,34,40] because it can cause the restriction of stretch with a reduced range of motion. In electromyographic (EMG) examination of the taut band, no action potential could be recorded from the muscle fibers in a taut band, but EPNs (nonpropagated potentials) could be recorded in only the MTrP region.[7,9,34] EPNs are different from muscle shortening due to active contraction or electrically induced contractions associated with the generation of action potentials.

3. Referred Tenderness and Referred Pain

Referred tenderness is the spread of pain from an MTrP to a distant muscle when this MTrP is compressed, and ReP occurs spontaneously from an active MTrP to other distant sites.[9] The occurrence of referred tenderness depends on two factors: the irritability of the MTrP and the pressure of compression.[41–43] The spontaneous ReP usually occurs in relatively severe cases of MPS (Table 1).[41] Each muscle has almost the same area of referred pain in different persons.[11,40]

4. Local Twitch Responses

A local twitch response (LTR) is a sudden brisk contraction of a group of muscle fibers in the taut band in response to snapping palpation (quick compression across the muscle fibers perpendicularly) of the MTrP or a needle insertion into the MTrP region.[1,9,11,12,43–45] The occurrence of the LTR also depends on two factors: the irritability of the MTrP and the pressure applied for eliciting LTR.[43] In a slightly irritable MTrP, high pressure is required to elicit an LTR. However, in a highly irritable MTrP, even a low-pressure stimulation can elicit LTR. A needle tip can be used to provide high-pressure stimulation to the MTrP and can elicit LTR much easier than by using finger palpation.[43,46]

5. Motor Dysfunction

Motor dysfunction associated with an MTrP includes weakness of the muscle containing

that MTrP, muscle spasm (hyperactivity) of the involved muscle, reflex muscle spasm of the remote muscles, inhibition of hyperactivity in the remote muscles, delayed relaxation of the involved muscle, and increased fatigability of the involved muscle.[7,9,47] The clinically observed reduced muscle strength (weakness) due to an MTrP is actually a pain-induced weakness, neither a true neurogenic nor a myogenic weakness. It usually occurs only in severe cases of myofascial pain. However, disuse muscle atrophy rarely occurs except for in very severe and chronic cases of MPS.[9] Muscle spasm (hyperactivity) is defined as the involuntary contraction (with EMG activity) of a muscle that is not dependent on posture.[7]

6. Autonomic Phenomena

Autonomic phenomena (including abnormal sweating, abnormal tearing, abnormal salivation, increased vasomotor response, and increased pilomotor response) can be observed in extremely severe cases of MPS.[9] Clinically, it is similar to the autonomic reaction that is observed in complex regional pain syndrome (reflex sympathetic dystrophy).

III. CLINICAL STUDIES OF MYOFASCIAL TRIGGER POINTS

A. Diagnostic Criteria for the Myofascial Trigger Point

Classically, the diagnosis of MTrPs depends on manual palpation and clinical judgment.[9] However, manual palpation has been considered to be an unreliable technique.[48] Previous studies by 3 different groups (Wolfe et al. in 1992,[49] Nice et al. in 1992,[50] and Njoo et al. in 1994[51]) could not obtain conclusive diagnostic criteria for MTrP. In a study on the interrater reliability after special training of the examiners, it has been suggested that spot tenderness, taut band, and pain recognition are the three most important criteria for the diagnosis of MTrP.[52] An exquisitely tender spot in a taut band, with pain in response to digital compression that can induce or aggravate the patient's usual clinical complaint, is the MTrP responsible for the clinical symptoms. Referred pain and local twitch responses can be confirmatory signs of an MTrP diagnosis.[52] It seems that the examiners should be experienced and well trained to perform reproducible examinations.[7]

B. Studies of MTrP Pain

Numerical rating scales, based on either subjective verbal report, or visual analog scales (VAS) are generally used to assess objective pain intensity. The scales usually range from *0* to *10*, with *0* representing no pain and *10* indicating the worst pain that could be experienced. The pressure algometer, developed by Fischer, can be used for a semi-objective assessment of MTrP irritability.[41,53,54] A scale on the pressure algometer can be used to read the pressure applied on the MTrP as soon as the patient reports pain. Because the patient cannot see the scale on the algometer, three consecutive measurements with reading values on the scale can be considered to be reliable. It has been demonstrated that the pressure algometer is a reliable and valid device for the assessment of myofascial pain.[55] The pressure algometer is also useful in assessing the effectiveness of MTrP therapy.[45,56–59]

Recent studies have suggested that the irritability of an MTrP is proportional to the prevalence[60] and the amplitude[61] of EPNs recorded from the MTrP region, which is an objective assessment of the MTrP irritability. MTrPs can also be used to assess the effectiveness of certain therapeutic methods.[62–68]

C. Studies on Referred Pain

In human studies, referred tenderness could be elicited not only from an active MTrP, but also from a latent MTrP region or even normal muscle tissues, if a strong pressure was applied.[42,69] In a study on the ReP elicited by palpation (with a constant pressure about 4 kg/cm^2) before MTrP injection and by needling during MTrP injection, it was found that patients who had occurrences of ReP had significantly higher mean pain intensity than those without occurrences of ReP; the ReP was either elicited by palpation or by needling.[43]

Based on the above findings, it seems that the occurrence of ReP is related to the degree of MTrP irritability. It was also found that the pressure required to elicit ReP from a compressed site is reversibly proportional to the degree of irritability at that site.[41,42]

D. Studies on Local Twitch Response

Local twitch responses (LTRs) can be elicited either by snapping palpation[11] or by needling when the needle encounters a sensitive locus.[1,12,45] However, LTR could be elicited much more easily with needling of the MTrP than with finger palpation, which is because the needle stimulation could provide higher-pressure stimulation than finger palpation (pressure = force/area). During needle stimulation, LTR could be elicited only when the needle encountered a sensitive tiny spot (locus). Many sensitive loci could usually be encountered by the needle tip in an MTrP region, especially a very active one. In a study on the LTRs elicited by palpation and by needling, it was found that all patients had occurrences of LTR during MTrP injection, but only 39% of patients had LTR elicited by snapping palpation. Patients with elicited LTRs by palpation had significantly higher mean pain intensity than those without LTRs.[43] Therefore, similar to the ReP occurrence, LTR occurrence is also related to the MTrP irritability. Based on the above findings in the studies of both ReP and LTR, it was hypothesized that the degree of MTrP irritability is directly proportionate to the amount of sensitive loci (sensitized nociceptors).[2,70]

Fricton et al. first reported that EMG activity of an LTR elicited by stimulation of an MTrP could be recorded in the taut band containing that MTrP.[44] It was found that the EMG characteristics of the LTRs elicited by needle insertion and those elicited by snapping palpation were not significantly different in the mean number of discharges per LTR, mean duration, or discharge density.[46] In a human study, EMG activity of an LTR in the MTrP of the extensor digitorum communis muscle diminished gradually during ischemic compression of the ipsilateral arm with a sphygmomanometer, and finally disappeared completely 30–40 minutes later when the radial nerve of the arm was completely blocked.[71] However, it recovered to the original level 5 minutes after relief of the pressure.[71] In one case study, the EMG activity of LTR could not be recorded from the extensor digitorum communis muscle in a patient who had a brachial plexus injury with a complete block of the posterior cord, as confirmed by electrodiagnostic tests.[72] The injured nerve partially recovered 6 months later, and the LTR could then be partially recorded.[72] It seems that an intact innervation of the involved muscle is required to elicit an LTR.

LTR can also be observed with diagnostic ultrasound.[73] However, it seems to be a difficult procedure and the actual MTrP cannot be visualized with sonographic study.[73,74]

E. Thermographic Studies of MTrP

Previous thermographic studies demonstrated that a thermographic hot spot (region with hyperthermia) could be found over the MTrP area.[54,75,76] However, finding a hot spot on the thermogram is not sufficient to make a diagnosis of an MTrP.[7,9] In a study on the sensitivity and specificity of thermography for use in MTrP diagnosis, Swerdlow and Dieter found a 40% false positive rate and a 20% false negative rate among 139 patients with MTrPs of the trapezius muscles.[77] The use of thermography for the assessment of MTrP is still controversial.[7,9,77]

F. Study of MTrP in Early Life and the Formation of MTrPs

In a study of latent MTrPs in the brachioradialis muscles, Kao could not identify latent MTrPs in children less than 1 year of age.[35] It seems that latent MTrPs develop as a child grows. However, it is still unclear when and how the nociceptors in the MTrP region become sensitized in later life. Further studies on populations of children older than 1 year of age are required. Because the brachioradialis muscle does not have a high incidence of active MTrP in an adult population, it is necessary to investigate other muscles with a high incidence of active MTrPs, such as the upper trapezius, extensor carpi radialis, or extensor digitorum communis muscles. Gunn suggested

that the formation of MTrP is caused by minor lesions in the peripheral nerve, especially in the nerve root.[78,79] This hypothesis cannot be accepted for all types of MTrPs because many of them are related to a lesion other than in a nerve.[3,13,80] However, it is still possible that the formation of a latent MTrP in early life is caused by a minor peripheral nerve injury during the growing-up period.[80]

G. Concept of Multiple Sensitive Loci in an MTrP region

In 1993, Hong first described the concept of multiple sensitive loci in an MTrP, based on clinical observations during MTrP injections and studies on LTRs with needle stimulation.[12] Travell's traditional technique for MTrP injection was performed by using multiple needle insertions into the MTrP region slowly, in an attempt to encounter a tiny sensitive locus for procaine injection. A drop of procaine was injected when the patient expressed pain with facial expression or slight muscle contraction at the injected site. The patients sometimes described referred pain, and occasionally, an LTR could be elicited if the MTrP was extremely irritable. Hong has suggested a new injection technique that involves rapidly moving the needle in and out in a straight track to avoid damage to the muscle fibers that is caused by side movement of the sharp-edged needle or the grabbing of the needle by an elicited LTR.[1,9,12,45] By using this method, ReP and LTR, in addition to pain sensation, can be easily elicited during rapid needle insertion (high pressure stimulation because pressure = force/area, and force = mass × acceleration) when the needle tip encounters a tiny sensitive site (Fig. 1). Many LTRs can be elicited from various sites during the injection of a very painful MTrP, but only a few LTRs can be elicited from a low-grade MTrP. The tiny sensitive site has been initially defined as a the *sensitive locus*,[12] and was later defined as an *LTR locus* because an LTR can be elicited by a strong pressure stimulation.[3] Hong has suggested that more sensitive loci (sensitized nociceptors) are located in the MTrP with high irritability than with low irritability.[2]

IV. BASIC RESEARCH ON MYOFASCIAL TRIGGER POINTS

A. Animal Models for MTrP Studies

Prior to the development of an animal model, the pathogenesis of MTrP remained unclear. In 1976, Simons and Stolov developed the first animal model for morphological study of MTrP in the skeletal muscle of a dog.[81] However, this model is no longer in use. In 1994, Hong and Torigoe developed another animal model for MTrP study that used the rabbit.[82] When a certain sensitive

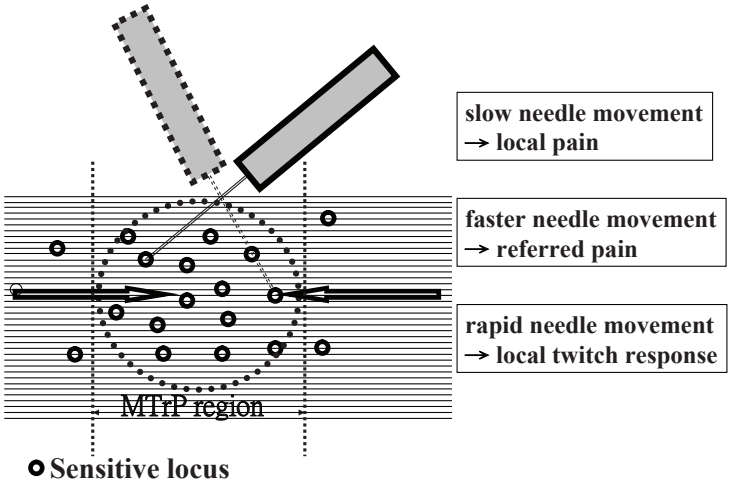

FIGURE 1. Pain, referred pain (ReP), and local twitch response (LTR) are elicited during an myofascial trigger point (MTrP) injection; multiple sensitive loci (sensitized nociceptors) in a MTrP region.

spot in the biceps femoris muscle was compressed before anesthesia, the rabbit kicked and exhibited signs of pain. This spot was marked before anesthesia, and then was mechanically stimulated with an EMG needle under anesthesia. A brisk muscle twitch, which was similar to LTRs elicited in human skeletal muscle, could be elicited when the needle tip encountered a sensitive locus. LTRs rarely occurred in other unmarked spots.[82] Similar to human studies, spontaneous electrical activity (SEA), including endplate noise (EPN) and endplate spike (EPS), could be frequently recorded within this sensitive spot, but very rarely from other sites in the endplate zone and never in the non-endplate zone.[36,37] To distinguish it from human MTrP, this sensitive spot in the rabbit was defined as a myofascial trigger spot (MTrS).[82] The rabbit model of MTrP can provide at least three important characteristics that are similar to human MTrP: pain, LTR, and SEA.[3]

B. Morphological Studies

1. Studies on the Sensitive Locus

By using the traditional technique of iron deposit to mark the sensitive locus (LTR locus or where LTR was elicited), a histological study revealed a nerve ending (nociceptor) at the LTR locus.[83] Another recent study showed that the injection of certain dyes (horseradish peroxidase) into the area of the nociceptors (LTR loci) can cause the dye to spread to the sensory neurons[84]; these results further supported the fact that the LTR loci are actually nociceptors.

2. Studies on the Taut Band and Contraction Nodule

In a light-microscopic study that used trichrome stain of canine muscles, Simons and Stolov demonstrated the taut band and contraction knot.[81] Sarcomere shortening occurred only in the endplate zone, but the sarcomeres outside the endplate zone in either direction became somewhat elongated (because the muscle fiber length was unchanged). In this way, the central portion of the taut band in the endplate zone became thicker (shortened) and formed a nodule, but the other portion became thinner (elongated). The length of the muscle fibers in the taut band was unchanged, but the tension was increased.

The existence of the taut band has also been demonstrated in a light-microscopic study of rat muscles,[85] an ultrasonic study of human muscles,[73] a vibration sonoelastography (VES) of human upper trapezius muscles,[86] an electromicroscopic study of human muscles,[87] and a magnetic resonance elastography (MRE) study of human muscles.[88]

C. Electrophysiological Studies

1. Studies on Referred Pain

In their studies of rats, Mense et al. have shown the referred pain from a muscle to other distant muscles.[85,89–94] The receptive field of the skin corresponding to a certain dorsal horn neuron of the spinal cord could be confirmed if action potentials could be recorded or intensified when this receptive field was stimulated. In a study by Hoheisel et al.,[95] the original receptive field could be expanded to other sites 5 minutes after the injection of bradykinin into another distant muscle. By using this method, the brain could perceive pain at other sites in addition to the originally stimulated site (referred muscle pain). Fifteen minutes after the injection, an innocuous stimulation to the original receptive field could also induce a response in the dorsal horn neuron (allodynia). Both phenomena are related to central sensitization. However, this expansion of the receptive field in this study[95] could not be simply explained by the traditional convergence-projection theory (synaptic connections of a dorsal horn neuron with two separate innervation areas), because the size, number, and nature (high threshold or low threshold) of the receptive fields for a dorsal horn neuron were changed rapidly after noxious stimuli.[7,91,96] Mense et al. have explained that this mechanism is caused by the unmasking of formerly ineffective synaptic connections among neurons corresponding to different receptive fields under the influence of certain conditions, such as a long-standing painful stimulus or a particularly strong painful stimulus.[7,91–93] A strong noxious stimulus

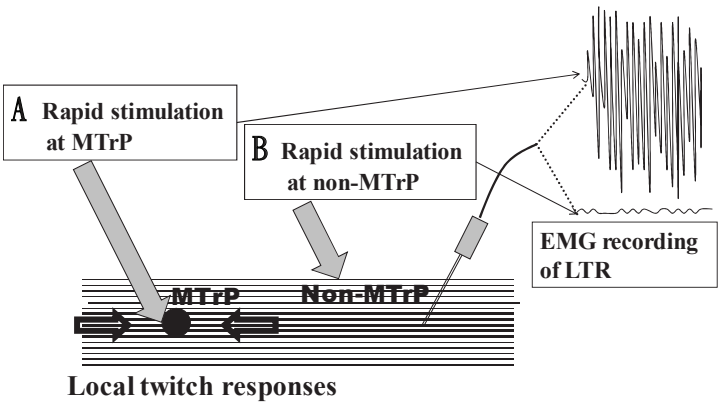

FIGURE 2. The local twitch response (LTR) can only be recorded when the myofascial trigger point (MTrP) is stimulated.

can send the impulse to the corresponding dorsal horn neuron and induce it to release substance P and calcitonin gene-related peptide (CGRP), which diffuse to other dorsal horn neurons and promote silent synaptic connections.[94]

2. Studies on Local Twitch Response

By using the rabbit model, Hong and Torigoe found the specificity of LTR.[82] A typical LTR could be elicited only when the MTrS (equivalent to MTrP in humans), but not any other site, was stimulated (Fig. 2). The LTR was best recorded electromyographically in the taut band, but not outside the taut band (Fig. 3).[82] Similar to previous human studies, these animal studies also demonstrated that LTRs could be elicited and their EMG activity could be recorded from a muscle only if the innervated nerve was intact with a complete connection to the spinal cord.[82] Immediately after a complete transection of the spinal cord at a level higher than that providing innervation to the investigated muscle, the EMG activity of LTR recorded from that muscle was completely suppressed. However, it recovered gradually later and was almost completely recovered after the spinal shock period (Fig. 4).[97] The above findings suggest that LTR is mediated by a spinal cord reflex, but is rarely related to a central nervous center above the spinal cord.[3,97]

3. Studies on Motor Dysfunction by Using Surface Electromyography

Muscle spasms (hyperactivity) can be demonstrated in surface EMG studies of the muscles with

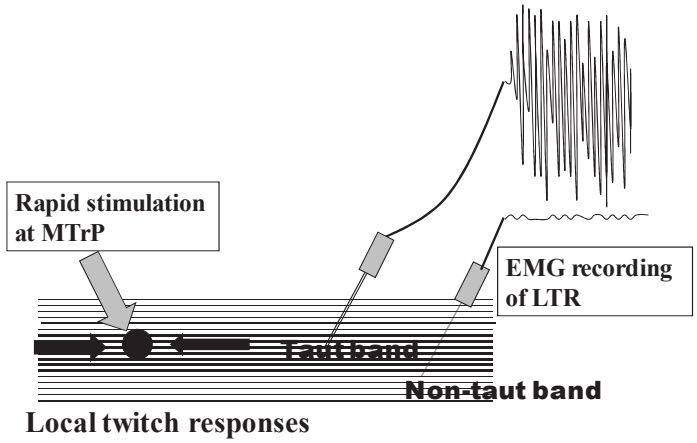

FIGURE 3. The local twitch response (LTR) can only be best recorded in the taut band.

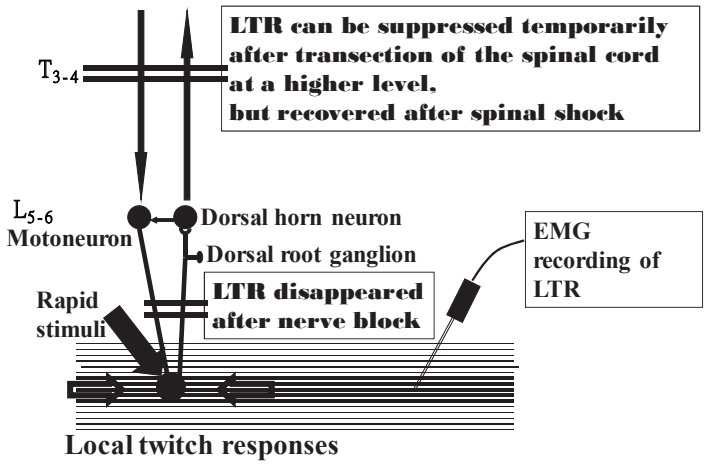

FIGURE 4. The local twitch response (LTR) in a spinal cord reflex.

MTrPs.[98–101] The surface EMG amplitude recorded over a muscle with MTrP could be 20% greater than that of the asymptomatic muscle. Headley further demonstrated that when pressure was applied on the MTrP of the supraspinatus muscle, a referred muscle spasm in a distant muscle could also be recorded with surface EMG.[100] Carlson et al. found a significant reduction in surface EMG activity of the masseter muscle after MTrP injection of the trapezius muscle.[102] However, Headley found that the hyperactive gluteal muscles, which were caused by spasms induced by active MTrPs and demonstrated in surface EMG, could be suppressed by an active MTrP in the quadratus lumborum.[101] In their studies of experimental acute muscle pain, Arendt-Nielsen et al. frequently observed reduced activation (muscle contraction) of an artificially induced painful muscle.[47,103–106] However, it is unclear whether the artificially induced muscle pain was actually an MTrP.

A muscle with an active MTrP could have delayed relaxation during a repetitive exercise (alternative contraction and relaxation), and could have loss of relaxation at each end of the contraction.[7,107] Surface EMG studies have also shown that muscles with MTrPs could fatigue easily (acceleration fatigability) and recover slowly (delayed recovery) in response to exercise for long periods of time.[7,107,108] A work tolerance study of the upper trapezius muscle with painful MTrPs also showed evidence of initial fatigue (increased amplitude and reduced median power frequency of surface EMG activity), as compared to the contralateral pain-free muscle.[108]

4. Studies on Spontaneous Electrical Activity Recorded in the MTrP region.

Spontaneous electrical activity (SEA) that was recorded from an active MTrP region of the upper trapezius muscle was first reported by Hubbard and Berkoff in 1993.[109] Originally, the authors considered SEA as potentials that were recorded from a muscle spindle.[110] In EMG studies, SEA could be recorded only in the endplate zone, more frequently from an MTrP region than from other regions including normal muscle tissues.[9,36,37,38,111–113] When the SEA was recorded by an EMG needle, the patient always complained of a sharp pain sensation.[37] The painful locus in which SEA is recorded was originally defined as an active locus,[36] and later as an SEA locus,[3] or an EPN locus.[67]

There are two components in the SEA that is recorded from the MTrP region, including the low-grade continuous electrical activity and a few sharp spikes with much higher amplitude (Fig. 5). The waveforms of the low-amplitude continuous electrical activity correspond closely to previously published records and descriptions of endplate noise (EPN), and the spikes correspond to the endplate spikes (EPS), as described in Kimura's authoritative EMG text.[114] EPN is an accumulation

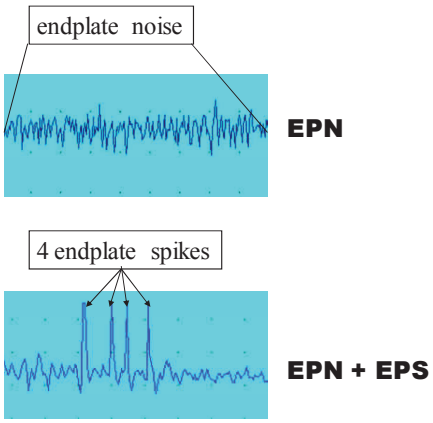

FIGURE 5. Spontaneous electrical activity (SEA), including endplate noise (EPN) and endplate spikes (EPS), recorded in a myofascial trigger point region.

of nonpropagated miniature endplate potentials (MEPPs), and EPS are propagated action potentials that are generated from the endplate of extrafusal muscle fibers.[34,113]

In a study on the skeletal muscle of rabbits, Wiederholt recorded electric activity that was similar to the low-amplitude component of SEA as endplate noise on the basis of histologic and pharmacologic studies.[115] Liley illustrated the conversion of the normal discrete negative monophasic potentials (miniature endplate potentials) to abnormal continuous noise-like action potentials, similar to the low-amplitude component of SEA, by applying mild mechanical stimulation to the terminal nerve fiber or the endplate region.[116] Ito et al. also suggested that these abnormal patterns of endplate potentials occurred as a consequence of the excessive release of acetylcholine packets.[117] Wiederholt found that the intra-arterial injection of tubocurarine (0.5 mg) produced a rapid decline of the muscle-action potential, and of frequency, amplitude, and rise time of potentials in endplate noise.[115] A recent study also demonstrated that EPN can be suppressed by botulinum toxin A, a presynaptic neuromuscular blocking agent.[67] Therefore, Simons has suggested that EPN recorded in the MTrP region is caused by the excessive leakage of acetylcholine (ACh) in the endplate region.[34]

EPS recorded from the MTrP region is likely elicited by a strong irritation of the recording needle on the hyperirritable endplate, because it occurs more frequently in hyperirritable active MTrPs than in latent ones.[34,37,60,113]

The excessive leakage of ACh molecules can cause calcium release from the T tubules of the sarcomeres in only the endplate zone, but not in other portions of muscle fibers. However, EPN potentials are not propagated action potentials (no action potential can be recorded from a taut band) because ACh molecules do not emerge simultaneously to cause action potentials; consequently, ACh molecules can cause focal contractures of sarcomeres in only the endplate zone. This focal contracture of sarcomeres can produce a contraction knot in the endplate zone as mentioned above.[81] Based on this finding, Simons and Travell have developed an "energy crisis" hypothesis to explain the formation of a taut band (Fig. 6).[118] The focal contracture of sarcomeres in the endplate zone can cause an increase in metabolism and a decrease in local circulation; thus, the sarcomeres cannot relax due to the inadequate energy supply. The persistent contracture of sarcomeres further impairs focal circulation and increases energy demand. In this way, a vicious cycle of "energy

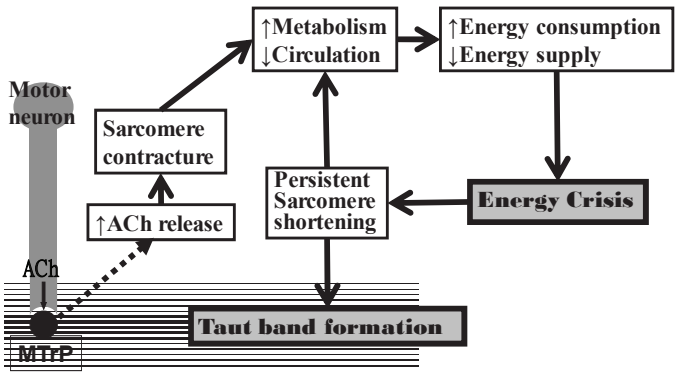

FIGURE 6. Excessive acetylcholine (ACh) leakage to cause energy crisis and taut band formation.

crisis" can develop because the muscle tension in the endplate region remains persistently high to form a taut band.

In a study using a rabbit model, SEA persisted after transection of a peripheral nerve or a high-level spinal cord.[119] These results seemed to indicate that ACh leakage in the endplate region was not under the immediate control of the nervous system. In another rabbit study that used single-fiber EMG recordings, it was found that the neuromuscular jitter in the MTrS region was not increased.[120] Therefore, the neuromuscular transmission itself is not impaired in the MTrS (equivalent to MTrP in humans) region, and the excessive ACh leakage is a secondary phenomenon rather than an abnormality in neuromuscular transmission. These findings can support the theory that energy crisis itself in the MTrP region is a focal reaction and is not related to neural controls. However, in a recent single-fiber EMG study, Chang et al. found evidence of degeneration in motor nerve endings in the MTrP region.[121] Additional research is required to clarify if any motor-axon loss is involved in the pathogenesis of MTrP.

D. Studies of the Biochemicals Associated with Pain and Inflammation in an MTrP Region

Shah et al. have performed a very important biochemical study of the MTrP of upper trapezius muscle.[122,123] By using a microanalytic technique, the researchers measured pain- and inflammation-related biochemicals (including substance P [SP], calcitonin gene-related peptide [CGRP], bradykinin, 5-hydroxytryptamin/serotonin, norepinephrine, tumor necrosis factor-α, and interleukin-1β) at the MTrP of the upper trapezius muscle (corresponding to an acupuncture point GB-21) in patients with active MTrPs and/or latent MTrPs, and normal participants with no neck pain and no MTrPs. The results showed that active patients had significantly higher concentrations of all analyzed biochemical substances than those patients in the latent or normal groups.[122,123] Shah et al. also found that the biochemicals mentioned above were remarkably elevated in the MTrP region during the occurrence of LTR, followed by a slow, variable return to baseline. However, SP and CGRP were the only two biochemicals for which concentrations during the recovery period after the LTR were significantly below the baseline concentrations.[122] These findings likely explain the immediate pain relief (reduced SP and CGRP) after eliciting LTRs during MTrP injection.

V. HYPOTHESES FOR MYOFASCIAL TRIGGER POINTS

A. The MTrP Locus as a Basic Unit of MTrP

On the basis of clinical and basic studies of MTrPs, Hong and Simons have hypothesized that there are multiple MTrP loci in an MTrP region (Fig. 7).[3]

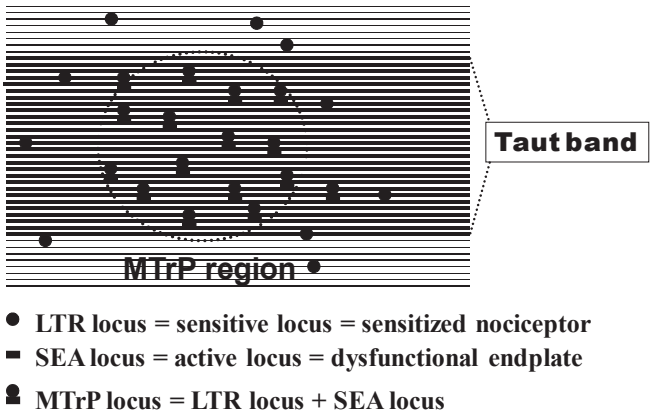

FIGURE 7. Multiple myofascial trigger point (MTrP) loci in a MTrP region. LTR = local twitch response; SEA = spontaneous electrical activity recorded from an endplate.

The sensory component of the MTrP locus is the sensitive locus or LTR locus,[12] and the motor component is the active locus,[36] which is later defined as the SEA locus[13] or EPN locus.[67] An LTR locus is a sensitized nociceptor (free nerve ending)[83] and an EPN locus is a dysfunctional endplate.[34,113] An SEA locus is in close proximity to an LTR locus, and both interact to form the taut band and to facilitate the formation of MTrP (see Section B below for Simons's integrated hypothesis of MTrP).

B. Simons's Integrated Hypothesis of MTrP

Simons has developed an integrated hypothesis of MTrP, which takes into consideration the three essential features of MTrPs that include excessive ACh release, sarcomere shortening, and the release of sensitizing substances.[9,124,125] ACh leakage in the motor endplates can cause an increase in the muscle-fiber tension (taut band of the MTrP), which can subsequently cause an energy crisis with increased metabolism and impaired local circulation. Tissue ischemia and hypoxia can then induce the secretion of sensitizing substances to cause pain. The sensitizing substances can further cause abnormal ACh release, thereby activating a vicious cycle. These three essential features relate to one another in a positive feedback cycle (Fig. 8) that is self-perpetuating once it is started, but can be interrupted at several points in the cycle in a number of ways.[7,9,124,125] However, it is still uncertain whether the abnormal ACh release initially occurs to sensitize nociceptors via peripheral sensitization, or the inflammatory reaction initially causes the release of inflammatory and pain substances and then induces abnormal ACh release. In fact, the findings of Shah et al.[122,123] support either scenario because the inflammation reaction can also be elicited by the muscle ischemia in the contracture knot.

C. The MTrP Circuit in the Spinal Cord: Spinal Cord Mechanisms of Pain, Referred Pain, and Local Twitch Response

Hong has hypothesized the concept of an MTrP circuit to explain the spinal cord phenomena of MTrP including REP, LTR, motor dysfunction, and autonomic reaction (Fig. 9).[13] Nociceptors (sensitive loci) in an MTrP region connect to a group of dorsal horn sensory neurons in the spinal cord to mediate the ReP and LTR that are elicited by stimulation of this MTrP. These MTrP-related sensory neurons in the spinal cord are responsible for central sensitization and for transmission of pain information to the brain. The neural network with connections among these MTrP-related sensory neurons is defined as an *MTrP circuit*.[13,14] These MTrP-related sensory neuron" can also send nerve branches to connect with the other groups of dorsal horn neurons (other MTrP circuits) that correspond to other MTrPs. These connections are silent (ineffective synaptic connections) in

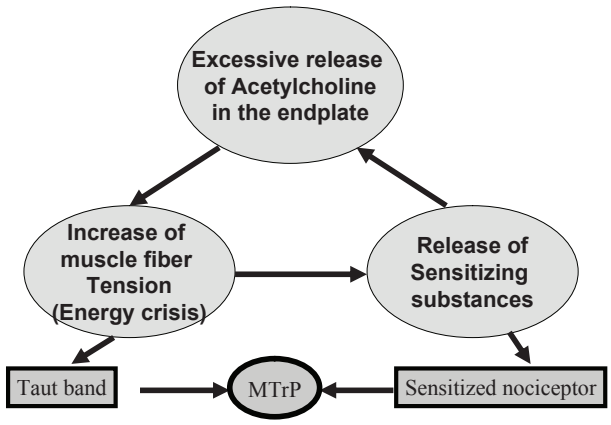

FIGURE 8. Simons's integrated hypothesis of the myofascial trigger point (MTrP).

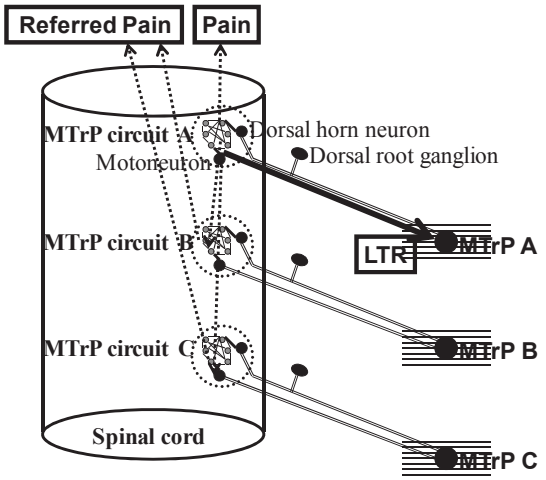

FIGURE 9. Connection of the myofascial trigger point circuit (MTrP circuit) in the spinal cord.

normal situations.[91] However, when nociceptors in the MTrP receive a strong stimulation, strong impulses can be transmitted to other MTrP circuits to cause ReP because these connections become synaptically effective as a result of the strong stimulation.[91] These impulses can also even spread to corresponding motor neurons in the anterior horn to elicit an LTR via the spinal cord reflex.

VI. EVIDENCE FOR THE EXISTENCE OF MYOFASCIAL TRIGGER POINTS

A. Controversies of MPS

The existence of MPS has been questioned.[126,127] However, research over the past 20 years has helped to clarify the nature of MTrPs.[2,3,7,9,70] Currently, the major controversy surrounds the lack of specific diagnostic criteria for clinicians to use to obtain a common agreement regarding the existence of MTrPs (interrater reliability).[48,128] The examiners require special training before performing the MTrP examination in order to reach a common agreement on the current criteria.[52]

Recently, the existence of MTrPs further has been confirmed on the basis of clinical observations and recent research studies, as described below and summarized in Table 2. However, the electrophysiological and morphological studies of MTrPs are also technically difficult and time-consuming; they cannot realistically be part of the criteria for the diagnosis of MTrPs.[9] Therefore, it is very important that inexpensive and simple devices to measure MTrP characteristics be developed in the near future.

TABLE 2
Evidence for the Existence of Myofascial Trigger Points

Clinical observations

1. Pain recognition only with compression at an MTrP region.
2. Consistent location of an MTrP in a certain muscle for different persons.
3. Consistent referred pain pattern for an MTrP in a certain muscle for different persons.
4. Multiple sensitive loci (nociceptors) in an MTrP region confirmed during MTrP injection.
5. Pain, referred pain, and local twitch response elicited by stimulation of a sensitive locus in the MTrP region (depending on the irritability of MTrP and the intensity of pressure stimulation)
6. Immediate pain relief after appropriate treatment of the involved MTrP

Experimental studies

1. SEA recorded near the sensitive locus of the MTrP
2. High concentration of biochemicals related to pain and inflammation in the active MTrP region, but low concentration of that in other regions
3. Nerve ending (nociceptor) found in the sensitive locus of MTrP
4. Connection between LTR locus and sensory neuron
5. Morphological evidence of the taut band and contracture knot in the MTrP region

B. Clinical Observations

1. Examination of MTrPs

Compression of the MTrP can reproduce or aggravate a patient's usual complaint (pain recognition).[34] For a certain muscle, one or more MTrPs can be identified in the same locations for different persons (consistent location).[11,40] Only the MTrP, but not other tender spots in the same muscle, can be responsible for the type of pain that is usually vocalized by a patient with myofascial pain. For different patients, the same referred pain patterns can be elicited by compressing the MTrP in each individual muscle (consistent ReP pattern).[11,40]

2. Treatment of MTrPs

Effective elimination of the MTrP (or more appropriately, inactivation of the MTrP) can relieve the pain and uncomfortable symptoms (effective MTrP therapy).[9,13,14,39,78,129–132] High-pressure stimulation (including deep-pressure massage and needling) to the MTrP can suppress the pain.[9,11,33,40] Needling to a tiny sensitive loci (nociceptors) in the MTrP region can induce pain, referred pain, and local twitch response, which can be recorded electromyographically.[3,44,46,71,72] Immediate relief of MTrP pain can be expected if LTRs are elicited during needling of the MTrP.[1,12,45,129] There are multiple sensitive loci in an MTrP region, as confirmed during an MTrP injection (Fig. 1).[1,45] The irritability of the MTrP is proportionate to the amount of such loci .[2,43,45]

C. Experimental Studies

All MTrPs are located within the endplate zone,[2,3,7,9,36,37,38,70,112,113,133] and SEA, including EPN and EPS, can be recorded more frequently from an MTrP region than a region with normal muscle tissue.[9,36,37,111,113] High concentrations of biochemicals that are associated with pain and inflammation can be found in the vicinity of an active MTrP.[122,123] A nerve ending (nociceptor) can be found at the locus of needle stimulation for eliciting an LTR.[71] The injection of certain dyes to an EPN locus can cause the dye to spread to the sensory neurons.[84] There is morphological evidence of the existence of taut bands and contraction knots (or locally shortened sarcomeres) in the MTrP region (endplate zone).[73,81,85,87,88]

RESEARCH STUDIES RELATED TO MYOFASCIAL PAIN THERAPY

A. General Principles for the Management of Myofascial Pain

It has been suggested that treating the underlying etiological lesions that cause the activation of MTrPs is the most important strategy in MPS therapy.[1,3,9,13,14,134] The underlying pathology should be appropriately and completely treated to avoid the reactivation of the MTrP. However, treatment of the active MTrP itself is still required in cases of severe intolerable pain, pain or discomfort that may interfere with functional activities (e.g., gait pattern[135]), persistent pain and tightness (which may interfere with the healing process of the injured tissue) even after the underlying etiological lesion is appropriately treated, difficulty in identifying the underlying pathology, or failure in treating the underlying pathology. Inactivation of active MTrPs can relive the muscle tightness caused by the taut band, and can subsequently improve the local circulation to facilitate the healing process of the underlying etiological lesion.[1,13,14] Conservative noninvasive treatment (e.g., physical therapy) should be performed prior to more aggressive therapy (e.g., needling) for treating either active MTrPs or their underlying pathology, especially for acute lesions or mild lesions.[13,14,130,136] Any perpetuating factor that might cause persistent existence or recurrence of active MTrPs should be corrected or treated, and adequate education and home-care programs should be provided to patients, in order to avoid recurrent or chronic pain.[9,137]

The management of myofascial pain caused by MTrPs has been extensively reviewed.[4,6,7–11,13,14,39,130,136–140] Table 3 lists the commonly used methods for inactivating MTrPs. Some of the conservative programs for MTrP therapy, as recommended by Travell and Simons, include spray and stretch, deep-pressure soft tissue massage, myotherapy, trigger-point pressure release,

TABLE 3
Commonly Used Methods for Treatment of Active Myofascial Trigger Points

A. Physical therapy modalities
   1. Thermotherapy: hydrocollator hot pack, and ultrasound
   2. Electrotherapy: interferential current, transcutaneous nerve stimulation
   3. Laser therapy: cold laser
   4. Others
B. Manual therapy
   1. Thermotherapy (adjunct procedure)
   2. Stretching: spray and stretch (intermittent cold and stretch)
   3. Deep-pressure soft tissue massage
   4. Myotherapy, ischemic compression, acupressure, Shiatzu
   5. Trigger-point pressure release (modified myotherapy)
   6. Manipulation and mobilization
   7. Voluntary contraction and release methods:
      a. Muscle energy technique
      b. Reciprocal inhibition
      c. Postisometric relaxation
   8. Others
C. Needling
   1. Traditional acupuncture to the acupuncture point
   2. Dry needling to the MTrP[78,142]
   3. Dry needling to the subcutaneous tissues above the MTrP; superficial dry needling[141,172,173]
   4. Modified dry needling to the MTrP with acupuncture technique[183]
   5. MTrP injection with local anesthetic solution[1,12]
   6. MTrP injection with additional preinjection block[138,174]
   7. MTrP injection with botulinum toxin A
D. Others: medication, exercise therapy, biofeedback, and hypnosis
E. Combination therapy

and postisometric relaxation.[9,11] Other procedures such as thermotherapy, electrotherapy, laser therapy, muscle energy technique (contract-relax), reciprocal inhibition, or mobilization and manipulation, have also been recommended by Simons as an adjunct for myofascial pain therapy.[1] MTrP needling procedures (e.g., MTrP injection, dry needling, or acupuncture) are very effective for pain control if they are applied appropriately and accurately.[1,11,12,13,45,53,78,129,131,138,141–145] A combination of various methods is frequently used for treating myofascial pain in clinical practice.[9,13,14]

Thermotherapy is the most frequently used modality in physical therapy practice, because it can improve local circulation directly or reflexively via vasodilatation.[146] Although local heat cannot relieve MTrP pain directly, it is an important adjunct procedure for combining other myofascial pain therapy programs.[9] It is also suggested that thermotherapy be applied before and after any manual therapy.[9,13]

In the literature, the most frequently recommended myofascial pain therapy modalities include ultrasound and electrotherapy.[9,12,14,58,59,136,139,147,148] It has been demonstrated that ultrasound can provide immediate pain relief[59,149] or an immediate increase of the pressure-pain threshold.[150] Recent reports, on the basis of clinical and electrophysiological studies, suggested that high-power threshold ultrasound was effective in treating active MTrPs.[151,152] It is possible that ultrasound might provide mechanical stimulation from the sound waves in addition to the thermal effect. Electrical stimulation to the nerve, such as transcutaneous nerve stimulation, can assist in pain control via the gate-control mechanism if low-intensity currents are given, or via counter-irritation (hyperstimulation analgesia) if high-intensity currents are applied.[153] In a controlled study, Tanrikut found that high-voltage galvanic stimulation could effectively relieve MTrP pain for up to 15 days, and attributed its effectiveness

to the gait control theory because only the large sensory fibers were stimulated by the generated currents (resulting in a tingling sensation during stimulation).[148] It has been demonstrated that electrical stimulation to the muscle can be used for the release of muscle tightness that is caused by taut bands.[58] Electrical stimulation to the muscle, such as interferential current therapy, can provide a massage effect from intermittent muscle contractions.[58] One study indicated that combined electrotherapy and ultrasound therapy can provide better effectiveness than when the methods are used separately.[59]

The application of a low-power laser in treating MTrPs has also been studied. Good results have been demonstrated in some studies,[154–159] but not in others.[160–162] This discrepancy could be caused by the different dosages that were applied in the different studies. The mechanism of laser therapy in treating MTrP is still unclear. In a recent animal study, Chen et al. showed that the prevalence of EPN (irritability) in the rabbit MTrS region was significantly reduced after the application of a low-power laser on the trigger spot (the animal equivalent to the human MTrP).[64]

Shockwave therapy is a newly developed device for treating active MTrPs.[163,164] However, further clarification of its efficacy and the mechanism are still required.

B. Manual Therapy for the Management of MTrPs

Manual therapy is one of the most effective techniques for the inactivation of MTrPs and has been described by various authors.[9,11,40,130,165] Commonly applied techniques include spray and stretch (stretch with intermittent cold spray),[11] deep-pressure massage,[149] ischemic compression,[56,66] trigger-point pressure release (modified myotherapy),[166] alternating contraction–relaxation techniques,[9] postisometric relaxation,[132,167] and manipulation.[28,57,166]

The traditional technique of spray and stretch, as recommended by Travell and Simons, can release the taut band immediately after stretch if it combines with cold spray to facilitate the effectiveness of stretch, because the cold can inhibit cutaneous nociceptors that may cause reflex muscle spasms during stretch.[11] Focal circulation in the MTrP region can be improved when the taut band is released.

Many of the commonly used myofascial release techniques are actually modified massage therapies. A controlled study by Hong et al. demonstrated that deep-pressure massage was the most effective treatment for the immediate relief of MTrP pain, as compared to the use of hot packs, ultrasound, and stretch with cold spray.[149] In that study, the described technique of deep-pressure massage involved a simultaneous stretch on the MTrP region to provide a focal stretch effect for improving the local circulation.[149] A pure ischemic compression may cause severe pain with local ecchymosis and may not be favorable for some patients.[9]

Simons has recommended some alternating contraction–relaxation techniques, including muscle energy techniques, postisometric relaxation, reciprocal inhibition, and some myofascial release techniques.[9] However, the scientific bases for those techniques are still limited and required further controlled studies. Lewit developed a postisometric relaxation technique for stretching the taut band and for pain relief[9,132,167] that combines alternating isometric contraction and relaxation of the involved muscle. The tight muscle fibers can be stretched easily immediately after an isometric contraction. The effectiveness of this technique can be enhanced if it is further combined with adjusted respiration and eyeball movement.[132]

Limited studies have demonstrated the effectiveness of spinal manipulation for the immediate relief of certain types of pain caused by MTrPs.[28,57,166] It is likely that the strong mechanical stimulation to the facet joint during a quick manipulative thrust provides an effect that is similar to needling (hyperstimulation analgesia).[153]

C. Needling for the Management of Myofascial Pain

The effectiveness of traditional acupuncture to the acupuncture point for the treatment of myofascial pain has been demonstrated. Ghia et al. have indicated the importance of eliciting the *De-Qui* effect during acupuncture therapy.[168] In fact, many acupuncture points for pain control are actually

MTrPs.[153,168,169] Gunn et al. used an acupuncture needle[78] and Chu used an EMG needle[142] to perform dry needling of an MTrP to avoid the tissue damage that is caused by the sharp edge of the regular injecting needle. Chu et al. further modified this technique by adding electrical stimulation during treatment (electrical twitch-obtaining intramuscular stimulation [ETOIMS]).[170,171] This modified technique is actually similar to electrical acupuncture. Baldry has recommended the technique of superficial dry needling (inserting the needle into the subcutaneous tissues, above the MTrP region, but not the muscle tissues) for treating myofascial pain.[141,172,173] This technique is similar to the superficial needle penetration used in traditional acupuncture.

The traditional MTrP injection technique described by Travell and Simons was a multiple-insertion procedure in an attempt to encounter the sensitive loci in an MTrP region.[1] Hong modified this technique into a "fast-in and fast-out" procedure for multiple needle insertions.[12] This new injection technique has been recommended by Simons et al.[9] and is described below. In this procedure, the exact location of the MTrP should be carefully located for needle penetration. The fingertip of the nondominant hand compresses the MTrP region firmly to direct the needle-tip placement. The syringe is held tightly by using the dominant hand with the thumb and long fingers, allowing the index finger to control the moving part of syringe. The needle is initially placed in the subcutaneous tissue layer in a direction toward the MTrP region under the site that is compressed by the directing fingertip. The needle is then moved quickly into the MTrP region to search for sensitive loci. When an LTR is elicited, a local anesthetic solution is then injected into the sensitive locus. As soon as a drop of solution is injected, the needle is then quickly pulled back to the subcutaneous layer. The needle is then turned into a different direction for another fast-in and fast-out movement to search for another sensitive locus. This procure is repeated many times to search for more sensitive loci as indicated by the elicited LTRs. If no LTRs can be elicited from several subsequent insertions in different sites (loci), the needle is pulled out of skin and the injection procedure is completed. Recently, Fischer suggested infiltrating into the entire taut band with local anesthetic, including the myotendinal junction, during MTrP injection.[138,174] Fischer has also developed a technique of using preinjection blocks to prevent the pain that could be caused by needle penetration of the sensitive tissue. The sensory nerves supplying the area to be injected were locally anesthetized prior to the MTrP injection.[138,174]

The therapeutic effectiveness of administering botulinum toxin A injections to the MTrP region has also been demonstrated.[175–179] Botulinum toxin A provided a presynaptic block of acetylcholine release in order to relieve the taut band in the MTrP region. In a controlled animal study, EPNs recorded in the MTrP region were suppressed after the injection of botulinum toxin A.[67] However, some studies suggested that the effectiveness of botulinum toxin A on myofascial pain relief was likely only caused by the needling effect, because no further benefits from botulinum toxin injections, compared to dry needling[180,181] or bupivacaine injections,[182] could be found.

Recently, Chou et al. combined the traditional acupuncture technique and the "fast-in and fast-out" MTrP injection technique into a new technique of dry needling, the "fast-screwed-in and fast-screwed-out" technique.[183] This technique is similar to MTrP dry needling with the insertion of the acupuncture needle into multiple sites of the MTrP region with a fast insertion speed (high pressure) to elicit LTRs. Simultaneous rotation of the needle was also performed to facilitate the needle movement and to avoid bending of the small-diameter acupuncture needle. Using a small-diameter acupuncture needle can reduce focal tissue damage and decrease postinjection pain or discomfort. This technique of dry needling with a small acupuncture needle is particularly useful for treating fibromyalgia patients with MTrPs, who usually have stronger postinjection discomfort from the penetration of big needles than patients with simple MPS.[184]

It seems that needling with or without the injection of any solution can provide effective relief of MTrP pain.[1,11–13,39,78,129,131,138,141–145,185] However, the injection of local anesthetic may reduce the intensity and duration of postinjection soreness or discomfort.[45] It has been strongly suggested by many authors that it is important to elicit LTRs during needling in order to obtain immediate and complete pain relief.[1,12,33,45,78,143,171] When an LTR

is elicited during needling, the patient usually can feel a sharp pain with referred pain and muscle twitching. Such a feeling is similar to that described when a *De-Qui* effect is obtained during acupuncture therapy. Eliciting an LTR indicates that a sensitive locus (nociceptor) is encountered by the needle tip. In an animal study, both LTR and SEA were suppressed after repeated needling on the same locus in the rabbit MTrS region.[63] This finding indicated that, after a sensitive locus was encountered and an LTR was elicited, the irritability of this sensitive locus (nociceptor) could be suppressed. Needling of a key MTrP could also inhibit the irritability of satellite MTrPs[186] that is caused by a central desensitization phenomenon. The mechanism of pain relief by needle stimulation was explained as hyperstimulation analgesia.[153] A strong pressure stimulation to the MTrP locus (nociceptor) can provide very strong neural impulses to the dorsal horn cells in the spinal cord, which may subsequently break the vicious cycle in the MTrP circuit.[13,14] Further studies are required to clarify this mechanism.

D. Summary of Myofascial Pain Therapy

The most important initial step to treat MTrP pain is identifying and treating the underlying pathological lesions that cause activation of MTrPs. Conservative treatments, including manual therapy combined with physical therapy modalities, should be tried prior to using aggressive procedures, such as needling, for either treating the underlying lesions or inactivating MTrPs. Thermotherapy should be given before and after any manual therapy. Needling is very effective for immediate and complete relief of MTrP pain if it is performed appropriately and accurately. Combined therapy programs are usually recommended for the inactivation of MTrPs. Selection of treatment procedures should be individualized based on the physician's wisdom and the patient's preference.

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