Measuring Bone Mineral Density in Individuals with Spinal Cord Injuries: Evaluating the Validity of Quantitative Ultrasound

April Saval, MS, PAC
University of Michigan
Ann Arbor, MI
Disclosures

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At the conclusion of this activity, the participants will be able to:

1. Evaluate utility of QUS as a valid measure for screening BMD in SCI
2. Identify multiply barriers involved in utilizing DEXA scans for individuals with SCI as a clinical tool to assess BMD
3. Develop a clinical model or protocol for measuring BMD after SCI in the acute and chronic phase to be utilized in the clinic setting with the goal of early intervention to improve/maintain BMD for individuals with SCI
4. Design protocol for assessment of osteoporosis
5. Implement appropriate management plan for treatment of osteoporosis and reduction of fracture risk
* World Health Organization definition
  * Bone mineral density (BMD) greater than 2.5 standard deviations (sd) below the young adult mean with the fracture risk doubling for each decrease by 1 sd in BMD
  * DEXA used as tool for screening, assessing risk fracture and monitoring response to treatment
  * Endorsed by FDA, CMS, WHO (population dependent)
Osteoporosis is a common sequela of spinal cord injury (SCI)

* Increases with years of injury and aging of individual
* Occurs primarily in sites below the level of injury in cortical or trabecular rich sites where there is normally more active bone turnover
* The most commonly affected areas are the lower extremities, specifically the femur and tibia

Jiang et al., 2006; Zehnder et. al, 2004; Biering-Sorensen et al., 2009
Rate of Bone Loss

* Decline in BMD and bone mineral content (BMC) can start as early as 3-6 weeks after an SCI
* Decreasing in the initial months by as much as 2% a week in the lower extremities
* Peaking around 4-6 months
* Plateau between 1 and 3 years after SCI with BMD decreasing by 50%-70% overall

Jiang et al., 2006; Vestergaard et al., 1998; Garland et al., 1992; Giangregorio L. 2006; Mamoun et al., 2009
Femur is most affected by the immobilization osteoporosis of SCI patients, therefore the BMD measurements in these patients should be performed at the lower limb. The problem of the immobilization osteoporosis in SCI patients is the striking increase of bone resorption and the missing reaction of the bone formation.
Fracture Rates

* Double that of able-bodied individuals
* Increasing after beginning of chronic phase from 3rd year of injury out
* Low energy fractures considerably more common 19% compared to 1.5% specifically of lower limbs with femurs most common

Vestergaard et al., 1998
Pathophysiology of Bone Loss After SCI

* 3 Phases

1. **Acute Phase/6 months** - Rapid bone loss with elevation of bone resorption markers with osteoclastic response

2. **Sub-acute (Adaptation) Phase/1 year** – Bone resorption and endocrine markers return to baseline

3. **Chronic (Impairment) Phase/Beginning at 1.5 – 2 years**

Garland et al., 2008
Factors Affecting Pathophysiology of Bone Loss After SCI

* Exact etiology still unknown
* Osteoblastic/osteoclastic activity
* Immobilization vs neurologic
* Age at time of injury
* Affect of vitamin D deficiency
* Traumatic vs non-traumatic
• Initial loss of BMD at lumbar spine (LS), regained following injury has been observed
• Significantly differs from able-bodied population
• Mechanism of Action (MOA)
  • Though LS consists of mainly trabecular bone, the relatively unaffected and usually improved BMD has been linked with body weight-bearing associated with use of wheelchair required for mobility
Bone mass measurement may be reimbursed no more frequently than every two years unless as part of follow up BMD testing to assess FDA-approved osteoporosis drug therapy until a response to such therapy has been documented over time usually annually.

A confirmatory baseline BMD is only covered when it is performed with a dual-energy x-ray absorptiometry system (axial skeleton) and the initial BMM was not performed by a dual-energy x-ray absorptiometry system (axial skeleton).

For an individual being monitored to assess the response to, or efficacy of, an FDA-approved osteoporosis drug therapy, the test is only covered if it is performed with a dual-energy x-ray absorptiometry system (axial skeleton) except for women with osteoporosis over age of 50 (QUA covered).
* Loss of BMD at the femur is commonality of both able-bodied and SCI
* Tibia BMD is not commonly used to diagnose osteoporosis in the able-bodied population
* Different pathophysiology of osteoporosis in SCI vs those used to construct WHO guidelines
BMD is considered the single most important predictor of fracture risk

* Increase risk of development as individual ages¹
  * Bone density is most reliable in predicting fracture risk in the early stages of osteoporosis. With advancing age and progressive bone loss, other factors begin to increasingly influence fracture risk

* Vestergaard et al. (1998) reported individuals with SCI had double the fracture risk of able-bodied individuals over a lifetime

¹ McKinley et al., 1999
The FRAX tool was developed by the World Health Organization to help predict risk of having a fracture related to osteoporosis in the next 10 years.

- Based on WHO population criteria and lacking in SCI.
Diagnosis of Osteoporosis in SCI

* Review of osteoporosis in SCI literature revealed variety of articles providing descriptions of the physiopathology of the condition, the most frequently affected sites and the factors influencing bone loss, as well as treatment protocols.

* Less abundant were authors evaluating the diagnostic protocol itself.

Charmetant et al., 2010
Problems with Diagnostic Protocols and SCI

- Reliability of methods: Need for clearly defined procedure as part of measurement
- Reproducibility
- DEXA – Variability in sites used
- QUS – Region of Interest (ROI)
- Peripheral quantitative computed tomography (PQCT)
  - Expensive, used predominantly in research
- Longitudinal assessment
In our clinic, we do not systematically monitor BMD via a protocol including:
- Level of activity or inactivity
- Certain time parameters after SCI (6 weeks, six months or three years)
  - Is BMD even detectable with DEXA or other measures at these time frames?
- Few researchers proposed screening of BMD based on time since injury starting at 1 year and then every six months and drug treatment starting at 1 year
- Femur (proximal/distal), tibia

Biering-Sorensen et al., 2009; Szoller et al., 1998
Management: Non-pharmacologic treatments

* Standing- No significant effect though slight effect was observed at proximal femur in group standing > 1 hour for average period of 4 years¹
* Meta-analysis
  * Weight bearing via standing and walking on SCI injured more than 1 year vs during the first year after injury vs exercise vs. functional electrical stimulation early after injury vs after more chronic injury vs spasticity²
* Low-intensity pulsed ultrasound- Not effective³

Goktepe et al., 2008¹; Biering-Sorensen et al., 2009²; Warden et al., 2001³
Pharmacological Treatment

* Bisphosphonates (Strong inhibitors of bone resorption and soft tissue calcification)
  * Time limited treatment efficacy
  * No correlation with long term treatment outcomes¹
  * Cost benefit of use
* Calcitonin with anti-osteoclastic activity
  * Not used due to lack of therapeutic effect²
* Recombinant human parathyroid hormone
* Nitroglycerin ointment- Modest affect in post-menopausal women over 24 months³
* Vitamin D and Calcium (Found to improve BMD)
  * Dosing 2000IU Daily

Gilchrist et al., 2007¹; Charmetant et al., 2010²; Jamal et al., 2011³
### Recent Studies with Bisphosphonates

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Time since injury</th>
<th>Compound used</th>
<th>Dose</th>
<th>Treatment duration</th>
<th>BMD/other markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minaire et al. (1980)</td>
<td>21 SCI controls</td>
<td>Mean: 17.6 days (5-29 days)</td>
<td>Clodronate</td>
<td>400 or 1600 mg/d</td>
<td>3.5 months</td>
<td>BMD: increased after 3 months Histomorphometry: a drop in the osteoclast count after 3 months</td>
</tr>
<tr>
<td>Chappard et al. (1995)</td>
<td>20 SCI controls</td>
<td>4-19 days</td>
<td>Tilludronate</td>
<td>400 mg/d or 200 mg/d</td>
<td>3 months</td>
<td>Histomorphometry: a slight increase in bone volume in subjects having received 400 mg/d; a decrease in the osteoclast count</td>
</tr>
<tr>
<td>Pearson et al. (1997)</td>
<td>13 SCI controls</td>
<td>6 weeks</td>
<td>Etidronate</td>
<td>800 mg/d</td>
<td>2 cycles of 2 weeks</td>
<td>BMD: decreased in tetraplegics and was stable in paraplegics</td>
</tr>
<tr>
<td>Nance et al. (1999)</td>
<td>24 SCI controls</td>
<td>6 weeks</td>
<td>Pamidronate</td>
<td>30 mg/4 weeks</td>
<td>6 months</td>
<td>BMD: increased in lumbar and femoral areas (neck and metaphysis)</td>
</tr>
<tr>
<td>Luethi et al. (2001)</td>
<td>60 SCI controls</td>
<td>10.6 years</td>
<td>Alendronate</td>
<td>10 mg/d</td>
<td>18 months</td>
<td>BMD: increased in lumbar region and stable at the hip and the tibia</td>
</tr>
<tr>
<td>Sniger et al. (2002)</td>
<td>1 SCI control</td>
<td>27 years</td>
<td>Alendronate</td>
<td>10 mg/d</td>
<td>2 years</td>
<td>BMD: increased for the lumbar region and the hips</td>
</tr>
<tr>
<td>Bubbear et al. (2004)</td>
<td>4 SCI controls</td>
<td>12.75 years (2-30 years)</td>
<td>Alendronate</td>
<td>10 mg/d</td>
<td>2 years</td>
<td>BMD: increased in the lumbar region; the neck of the femur and the hips as a whole</td>
</tr>
<tr>
<td>Bauman et al. (2005)</td>
<td>6 SCI controls</td>
<td>22-65 days</td>
<td>Pamidronate</td>
<td>60 mg at 0, 1, 2, 3, 6, 9, 12 mths</td>
<td>12 months</td>
<td>BMD: same decrease as in control subjects</td>
</tr>
<tr>
<td>Gilchrist et al. (2007)</td>
<td>31 SCI controls</td>
<td>10 days</td>
<td>Alendronate</td>
<td>70 mg per week</td>
<td>12 months</td>
<td>BMD: smaller decrease in treated subjects</td>
</tr>
<tr>
<td>Shapiro et al. (2007)</td>
<td>8 SCI controls</td>
<td>10-12 weeks</td>
<td>Zoledronate</td>
<td>4 mg (n = 4) or 5 mg (n = 4) IV</td>
<td>Single dose</td>
<td>BMD: At 6 months: increased BMD at all doses At 12 months: lower for the neck of the femur</td>
</tr>
</tbody>
</table>

**Charmetant et al., 2010; Bryson et al., 2009**
Problems with Treatment Protocols

* Adequately assessing change in BMD
* Treatment preferences
* Monitoring changes over time
* There are no protocols
Risk Factors for Osteoporosis
Common to SCI

* Low Testosterone
* Usage of Anti-Epileptic Drugs
  * or anticonvulsants, such as carbamazepine (Tegretol), phenytoin (Dilantin), or gabapentin (Neurontin) for pain or seizures.
* Low Vitamin D/Calcium
* Smoking
Measuring BMD in SCI

- It is difficult for many spinal cord individuals to access equipment needed to evaluate for osteoporosis
- Barriers to use of dual energy x-ray absorptometry (DEXA)
  - Equipment design and increased time for scanning
  - Less accurate at assessing structural changes in bone
- Use of QUS
  - Quicker scanning, less safety risk, performed in an office setting
  - Warden et al. (2002) demonstrated QUS as a useful measure for acute changes in BMD in SCI (Validated in certain populations though not SCI)
Peripheral CT
DEXA
QUS: Mechanisms of Action

* QUS provides a measurement of the physical properties of bone
* Two common measures:
  * Speed of sound wave in m/sec (SOS) and broadband ultrasound attenuation in dB/MHz (BUA) of a sound wave as it travels through bone
  * SOS and BUA combined produce Stiffness Index (SI)
* Portable QUS of the calcaneous has been used as a means to screen for fracture risks in certain populations including postmenopausal women and men over the age of 40
* WHO Statement
* FDA
Typical QUS
Region of Interest

* Darker areas represent
Achilles Express
Lunar Corporation

ID  39
DATE  11/29/2000
TIME  10:39 AM

STIFFNESS INDEX  67 ±2

AGE  64
SEX  Female
FOOT  Right

REFERENCE  USA

% YOUNG ADULT  67
T SCORE  -2.1

% AGE MATCHED  90
Z SCORE  -0.5

STIFFNESS INDEX  T

![Graph showing stiffness index over age range]
Fracture Risk
The purpose of this study is to evaluate the validity of QUS parameters as a measure of BMD as compared to DEXA in individuals with chronic spinal cord injuries.
Design

* 30 individuals with SCI who will undergo QUS of the calcaneus during a clinic visit (each 1 minute in duration, 3 assessments) and within a week undergo a DEXA performed by a trained technician assessing lumbar spine and femurs
30 individuals with SCI from 19 years and older, classified as either ASIA A or B SCI, with injury levels from C4-T12 will

Exclusion criteria include individuals on anti-osteoporotic treatment or hormone replacement therapy, diseases that may predispose individuals to bone loss e.g. diabetes, thyroid disease, hyperparathyroidism, >3 + pitting edema or significant anatomical variation of the calcaneus such that it will not fit in the QUS device

Participants will be recruited through the SCI outpatient clinic and through the University of Michigan SCI Research Registry
QUS-Parameters collected will consist of broadband ultrasound attenuation (BUA) measured by dB/MHz and Stiffness Index (SI) measurements of the calcaneus.

- DEXA- LS and bilateral femurs
- T-scores produced by DEXA and QUS devices were used to compare BMD values.
  - Normative data for LS and bilateral femurs were used to obtain DEXA T-scores. BUA and SOS were used to obtain SI measures, which were then converted to T-scores.
- Individuals with T-scores less than -1 were grouped in the osteopenic range and individuals with T-scores less than 2.5 were grouped in the osteoporotic range.
For each individual:

1. Age
2. Gender
3. Body mass index (BMI), height and weight
4. Previous fracture history
5. Level of injury
6. Time since injury
Similar to other authors, we found stable or increased BMD in the lumbar spine of subjects based on results from the DEXA.

- Loading of lumbar spine
Level of Injury

![Bar Chart]

- C4/5/6: Count
- C7-T1: Count
- T2-T6: Count
- T8-T12: Count
Years Since Injury
Results

* There was a significant correlation between calculated threshold scores using QUS and DEXA with Pearson’s correlation coefficient of 0.85 with p-value of 0.001
* Unlike Warden, we were able to establish a correlation of scores, however our study focused on chronic SCI
* QUS may be better early predictor of change in BMD after early SCI than DEXA
Establishing cut scores for classification as normal, osteopenic or osteoporotic
Limitations of the Study

* QUS - There is decreased precision and less sensitivity than DEXA for detecting changes in bone density over time and diagnosis of osteoporosis in an individual
  * Positioning of the calcaneus/anatomical variation resulting in measurement variability
  * Inconsistent ability of the QUS to work due to readings of bone density too low with SCI individuals
Limitations of DEXA

* Though DEXA is “gold standard” is the assessment of trained DEXA technicians appropriate to use as a reliable for evaluating individuals with SCI?
  * protocol operationally defined ROI
  * Limited in terms of ability to evaluate structural aspects of bone
Future Direction

* Examine BMD overtime using biomechanical markers of bone loss
* Further investigating pharmacologic methods to reduce fracture risk and bone loss clinically with use of QUS
* Further validate QUS for use as monitoring device of treatment and as part of future models of measuring BMD after SCI in the acute, sub-acute and chronic phase
* Improve BMD predictors to allow for earlier intervention
* Studies designed to evaluate treatment effect on fracture risk
Protocol?

Postmenopausal women *

CRFs +
Heel QUS assessments

Low probability of fracture
Medium probability of fracture
High probability of fracture

Central DXA assessment according to WHO criteria

Primary prevention
Treatment initiation

*With no evidence for secondary osteoporosis or clinical evidence of vertebral fractures
Do you order a clinical work-up to look for SCI-induced bone loss?

When do you typically order the clinical work-up for SCI-induced bone loss?
- During acute rehab.
- After acute rehab in the outpatient setting.
- At any time after a fracture occurs.

Which of the following tests do you order as part of your diagnostic workup for SCI-induced bone loss? Please check all that apply.
- Bone turnover markers: C-telopeptide, N-telopeptide, osteocalcin
- Serum screening: PTH, calcium, Vit D OH25
- Urinalysis
- Bone mineral density by DEXA scan
- Other (please specify)

Please indicate the sites that you scan for BMD
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