Case report

High bone density masks architectural deficiencies in an individual with spinal cord injury

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Context: Spinal cord injury (SCI) causes a decline of bone mineral density (BMD) in the paralyzed extremities via the gradual degradation and resorption of trabecular elements. Clinical tools that report BMD may not offer insight into trabecular architecture flaws that could affect bone's ability to withstand loading. We present a case of a woman with a 30-year history of SCI and abnormally high distal femur BMD.

Findings: Peripheral quantitative-computed tomography-based BMD for this subject was ~20% higher than previously published non-SCI values. Computed tomography (CT) revealed evidence of sclerotic bone deposition in the trabecular envelope, most likely due to glucocorticoid-induced osteonecrosis. Volumetric topologic analysis of trabecular architecture indicated that the majority of the bone mineral was organized into thick, plate-like structures rather than a multi-branched trabecular network. Visual analysis of the CT stack confirmed that the sclerotic bone regions were continuous with the cortex at only a handful of points.

Conclusions: Conventional clinical BMD analysis could have led to erroneous assumptions about this subject's bone quality. CT-based analysis revealed that this subject's high BMD masked underlying architectural flaws. For patients who received prolonged glucocorticoid therapy, excessively high BMD should be viewed with caution. The ability of this subject's bone to resist fracture is, in our view, extremely suspect. A better understanding of the mechanical competency of this very dense, but architecturally flawed bone would be desirable before this subject engaged in activities that load the limbs.

Keywords: Osteonecrosis, Osteoporosis, Spinal cord injuries

Introduction

The disruption of normal mechanical, neural, and hormonal factors after spinal cord injury (SCI) precipitates a dramatic loss of bone mineral density (BMD) in paralyzed extremities. BMD of the femur and tibia fall by 50–80% within the first 4 years post-injury,¹ leading to a substantial increase in fracture risk.² Most previous studies of BMD after SCI have used dual X-ray absorptiometry (DXA), a standard clinical assessment tool. DXA is accurate and reliable for measuring bone status at the hip and lumbar spine, but lacks specific

protocols and established normative values to measure distal sites in the lower extremity.³ Three-dimensional measurement techniques such as peripheral quantitative-computed tomography (pQCT) and multi-detector computed tomography (CT) are more suitable for these high-risk locations and allow separate analysis of the cortical and trabecular envelopes. This is of key importance to the study of post-SCI osteoporosis because post-SCI bone loss is most severe in the center of the bone's cross-section.^{4,5} A second advantage of three-dimensional imaging is the opportunity to scrutinize interventions designed to preserve bone architecture. High-resolution CT captures trabecular architecture features that may reveal the fundamental

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workings of bone adaptation to anti-osteoporosis interventions. Changes in the thickness and connectivity of the trabecular lattice offer a window into the architectural mechanisms contributing to bone adaptation.

We present a case of a woman with chronic SCI and unique evidence of bone architecture and density pathology observed during pQCT and CT scans. This subject's radiographic presentation is unique in the literature and illustrates several key advantages of three-dimensional bone imaging.

Case description

Case subject

The case subject is a 48-year-old Caucasian female, who sustained complete C6 quadriplegia at age 18. On the date of her SCI, she was admitted to our facility's trauma unit and received a total of 130 mg of dexamethasone in the first 48 hours post-injury. This was followed by tapering doses of dexamethasone until day 24 post-injury, with a total cumulative dose of 532 mg. She underwent a standard course of inpatient and outpatient rehabilitation. She currently requires an assistant for transfers and daily activities, drives a van with hand controls, and uses a power wheelchair for mobility. She reports that she has not undergone menopause but underwent endometrial ablation approximately 5 years ago. The subject has never engaged in electrical stimulation training, ambulation, passive standing, or other weight-bearing activities.

For the first 20 years after SCI, the subject had an uncomplicated medical history with occasional treatment for urinary tract infections. In the last 10 years she has been diagnosed with type II diabetes and hyperlipidemia. Approximately 2 years ago she began to experience hair loss, weight loss, and hot flashes. She was diagnosed with a benign thyroid nodule which was treated with methimazole. She reports continued difficulty with achieving euthyroid status and has alternately been prescribed methimazole and levothyroxine.

The subject reports an approximately 12-year history of alendronate use, ending approximately 5 years ago. She stopped taking alendronate on the advice of her family practice physician, who cited research implicating chronic alendronate use in atypical fragility fractures.

Review of the subject's medical record indicates current or past use of the following medications: baclofen and tizanidine (anti-spasmodic agents), oxybutynin (bladder anti-spasmodic), dipyridamole (anticoagulant), fluconazole and nitrofurantoin macrocrystal (antibiotics), glimepiride and metformin (glucose regulators), and pravastatin (lipid regulator).

Comparison subjects

Four female comparison subjects were evaluated using pQCT and CT. Three of these subjects had SCI of >10 years duration and had performed no weight-bearing activities or electrical stimulation after SCI. Comparison subject #2 was post-menopausal. The fourth comparison subject was a 14-year-old female with a 3-month history of SCI, whom we present as an example of typical BMD immediately post-SCI. Demographic data for all subjects appear in Table 1. All the subjects signed an informed consent document approved by our institution's human subjects research review board.

pQCT aggregate dataset

To obtain a context for interpreting the pQCT results from the case subject, we utilized data from our previously published longitudinal pQCT image database.⁵⁻⁷ This database included 27 subjects with SCI duration ranging from 2 months to 23 years. We also compare the case subject's BMD to the non-SCI normative values from our database.

pQCT imaging

pQCT measurements were performed with a Stratec XCT3000 densitometer (Stratec Medical, Pforzheim, Germany). Accuracy of this device is 2% (to the COMAC phantom); precision is $\pm 3 \text{ mg/cm}^3$ for trabecular bone and $\pm 9 \text{ mg/cm}^3$ for cortical bone.⁸ pQCT images were obtained at 12% of femur length (measured from the distal end) using our previously reported method.^{1,5,9,10}

High-resolution CT

Subjects underwent high-resolution multi-detector CT imaging (Definition Flash, Siemens Healthcare, Erlangen, Germany) of both distal femora using our

Table 1 Subject demographics

Subject	Age	SCI duration	SCI level	Height (cm)	Weight (kg)
Case subject	48	30.5	C5-6	160	68.2
Comparison 1	44	23.1	C7	173	77.3
Comparison 2	65	10.3	T1	175	63.6
Comparison 3	32	10.9	T4	163	86.4
Comparison 4	14	0.26	T6	157	54.6

previously reported method.¹ Images were processed using volumetric topologic analysis (VTA).¹¹ VTA analysis has demonstrated good predictive ability of bone's elastic modulus and other mechanical properties.¹¹

The INTable™ Calibration Phantom Couch Pad was scanned together with the participant and used to convert CT Hounsfield units into volumetric BMD (mg/cm^3). We characterized trabecular architecture by calculating normalized network area (NNA), the summed surface area of trabecular elements in a region divided by the volume of the region. A low NNA indicates that trabecular surface area is low in a given trabecular bone volume. This can have two implications; first, that very little calcified tissue is present in the volume. Secondly, a low NNA can occur when the majority of calcified tissue is organized into a few, thick, plate-like structures, rather than as a web of individual trabecular elements. For a given quantity of calcified tissue, the surface area of a network of trabeculae will be higher than the surface area of a handful of thick plates.

Imaging findings

pQCT images from the case subject were noteworthy for densely calcified regions within the medullary cavities of the femur distal epiphyses (Fig. 1A). These regions had irregular sclerotic borders surrounding lower-density bone and appeared to share tenuous connections to the cortical wall via few trabeculae. This appearance was noteworthy for two reasons: first, an individual with SCI of 30 years duration would be expected to have almost no preserved bone in the trabecular envelope of the epiphyses (Fig. 1B).⁵ Secondly, the highly calcified regions did not appear similar to healthy non-SCI

bone, which would instead have a relatively uniform trabecular lattice. The presence of fully calcified bone within the trabecular envelope of the case subject yielded spuriously elevated trabecular BMD values: for example, 283 and 305 mg/cm^3 at the distal femur (Fig. 1C). No other femur BMD values in our pQCT database, including non-SCI subjects, exceeded 255 mg/cm^3 .

Fig. 2 displays representative distal femur CT images from the case subject and comparison images from a subject with acute SCI (3 months, Comparison subject 4) and a subject with chronic SCI (23 years, Comparison subject 1). The comparison subject with acute SCI demonstrates a relatively uniform trabecular network throughout the bone. The width of most of this subject's bone structures fell within the normal range for trabeculae (~ 0.05 – 0.3 mm) (red and orange regions). The comparison subject with chronic SCI demonstrates the destruction of the trabecular lattice that routinely occurs with long-term SCI. No structures for this subject exceed the dimensions of normal trabeculae.

The case subject's image in Fig. 2B is qualitatively different from either SCI example. The location of the two calcified regions appears to follow the medullary cavity of each femoral condyle and contains a preponderance of structures that exceed the normal dimensions of trabecular elements (green regions). We visually inspected a stack of CT cross-sectional images from this subject and concluded that the sclerotic central regions are connected to the cortex in only a handful of places.

CT-derived BMD was higher for the case subject than for three comparison females with chronic SCI (Fig. 3A). For all but the most proximal regions

Figure 1 pQCT images showing sclerotic bone regions in the distal femur of the case subject (A) and the typical appearance for chronic SCI bone (B: Comparison subject 1). Panel (C) depicts BMD from our previously published pQCT image database of SCI and non-SCI participants.^{1,9} The case subject's spurious BMD values are circled.

Figure 2 Reconstructed CT images of the distal femur for the case subject (C), a comparison subject with acute SCI (A) and a comparison subject with chronic SCI (B). Voxels are color coded according to the width of trabecular elements ("TB width"). Typical trabeculae in normal bone range from 0.05 to ~0.3 mm.

(where the marrow cavity emerges), the case subject's BMD was also higher than the comparison subject with acute SCI. Plotting BMD as a function of trabecular width confirmed that the majority of the case subject's bone mineral was organized into structures that exceed the width of normal trabecular elements (Fig. 3B). NNA values for the case subject were intermediate between the subject with acute SCI and the subject with chronic SCI (Fig. 3C).

Clinical interpretation

An experienced musculoskeletal radiologist (>30 years) examined the case subject's CT images. He interpreted that this subject experienced intramedullary bone infarcts and subsequent osteonecrosis consequent to high-dose corticosteroid administration at the time of her SCI. In this scenario, proliferation of fatty marrow in response to steroid treatment increased the femur intramedullary pressure, creating ischemic conditions.¹² Osteocyte death in the trabecular lattice was followed by remodeling and subsequent establishment of a sclerotic margin.

Discussion

While glucocorticoid administration can yield superior neurological outcomes after SCI,¹³ some authors have questioned whether this treatment approach could yield adverse consequences within the skeletal system.¹⁴ We located a single case report of a man with SCI who experienced osteonecrosis of bilateral humeral heads after high-dose, prolonged glucocorticoid administration.¹⁵ The total dose of dexamethasone that the patient received (797 mg) and duration of administration (26 days) was very similar to our case subject. Both of these individuals sustained SCI

several years before publication of the Second National Acute Spinal Cord Injury Study (NASCIS-II),¹⁶ which established guidelines supporting high-dose, short-duration (48 hours) glucocorticoid therapy. A prospective study of 29 patients receiving methylprednisone, according to that protocol, reported no instances of femoral head osteonecrosis.¹⁴ Interestingly, the total cumulative glucocorticoid dose received by the present case subject was equivalent to only a fraction of the dose prescribed by the NASCIS-II protocol.¹⁵ Others have suggested that the duration of sustained glucocorticoid therapy is more important than dosage¹⁷; this study's data support that theory.

Current studies support that 5–40% of patients, who receive long-term glucocorticoid therapy for various diseases develop osteonecrosis.¹⁸ The underlying factors separating individuals who do and do not develop the disease are uncertain. In addition to creating ischemic conditions in marrow,¹⁹ glucocorticoids strongly induce osteocyte apoptosis.²⁰ Glucocorticoids also exacerbate bone ischemia by decreasing the production of vascular endothelial growth factor, thereby limiting angiogenesis in affected bone.²¹ Individual genetic variations likely modulate both osteocyte apoptosis and vascular factors that determine susceptibility to osteonecrosis.²²

The ultimate issue in this case is whether the abundant, although senescent bone in this subject's femoral epiphysis affords her any protection from fracture. The imaging studies we carried out can help to shed light on this issue. This subject's high BMD would, at first glance, suggest that her bone strength is superior to her peers with chronic SCI. However, this observation is potentially misleading because a considerable portion of this subject's medullary space contains no bone whatsoever (Fig. 1A), a key hallmark of post-

Figure 3 CT-derived BMD and architecture analysis for the case subject and the comparison subjects. The x-axis origin for each panel corresponds to the distal end of the femur. Compared with her peers with chronic SCI, the case subject possessed abnormally high BMD (A). She demonstrated a preponderance of excessively large trabecular structures (B), suggesting that her abundant bone mineral was organized into plate-like structures, not a normal trabecular lattice (max width ~0.3 mm). Confirmation of this is provided in panel (C): the case subject has a lower NNA (bone surface area divided by bone volume) than the acute SCI comparison subject, despite having substantially higher BMD.

SCI osteoporosis. Her high BMD values belie this fact and may mislead an observer to the conclusion that this subject's bone is essentially "normal".

The architectural integrity of the distal femur is suspect because the sclerotic calcified regions appear to be only tenuously connected to the cortical shell. Mechanical loads experienced by the limb may or may not be transmitted from the cortex to these aberrant bone regions. Detailed finite element analysis of the case subject's bone epiphyses may shed light on the quality of load transmission within these atypical bone interfaces.

It is widely accepted that the orientation (architecture), and not just the quantity of bone (BMD) is a key factor in bone's ability to withstand applied loads.²³ The case subject offers an example of a bone with outstanding apparent BMD, but potentially critical architectural flaws. Instead of a healthy trabecular lattice capable of withstanding loads from a variety of vectors, this subject's abundant bone tissue is irregularly organized into thick plates. This is reflected in Fig. 3C: although the case subject's BMD was superior to the subject with acute SCI, her lower NNA reveals a loss of trabecular surface area. Importantly, these architectural abnormalities would have been wholly undetected by DXA imaging. Given these considerations, we would be hesitant to assume that this limb could withstand normal stresses associated with standing or muscle electrical stimulation.¹

Conclusion

This subject demonstrates an osteonecrosis consistent with a previous report of glucocorticoid-induced osteonecrosis after SCI.¹⁵ Conventional clinical imaging with DXA would have revealed high BMD, which could lead to erroneous assumptions about this subject's bone quality. CT-based analysis revealed that this subject's high BMD masked the underlying architectural flaws, supporting the fact that three-dimensional imaging may be superior to DXA for post-SCI bone assessment. For patients who sustained SCI prior to publication of the NASCIS-II guidelines, excessively high BMD should be viewed with caution. The ability of this subject's bone to resist fracture is, in our view, extremely suspect. A better understanding of the mechanical competency of this very dense, but architecturally flawed, bone would be desirable before this subject engaged in activities that load the limbs.

Acknowledgments

This study was supported by awards from the National Institutes of Health (R01NR010285, R01HD062507),

the Craig H. Neilsen Foundation, and the United States Department of Veterans Affairs. The authors thank Georges El Khoury MD, FACR for clinical interpretation of CT and pQCT images.

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