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Case Report

Insights on accelerated skeletal repair in Cushing's disease

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ABSTRACT

Cushing's disease with prolonged exposure to high circulating levels of glucocorticoids is associated with deterioration of the structural integrity of bone, resulting in increased skeletal fragility and fractures. The mechanism of bone repair following successful surgical treatment is poorly understood.

A 34-year-old man presented with a tibial fracture and severely low BMD, elevated AM serum cortisol, ACTH, and 24 h urinary free cortisol, which did not suppress with 2 days of high dose dexamethasone. Following transphenoidal resection of a pituitary microadenoma, serum cortisol and ACTH normalized. A repeat DXA at 8 months post-resection showed no change in BMD, however the Trabecular Bone Score (TBS), which reported severe deterioration of trabecular bone architecture at diagnosis, improved to normal. At that time, teriparatide (TPTD) was given for 2 years, which resulted in a 53.9% increase in BMD with only a small improvement in TBS. In this patient, spontaneous recovery of trabecular bone architecture was reflected by the early correction in TBS. Subsequent TPTD treatment was associated with marked improvement in BMD, presumably due to enhanced mineralization. Complete skeletal repair was achieved by this two-step mechanism in a very short time following successful surgical treatment for Cushing's disease.

1. Introduction

Cushing's disease with prolonged exposure to high serum cortisol results in muscle atrophy, skeletal fragility and failure with fracture. There is progressive bone degradation, primarily of trabecular bone, resulting in fractures of the vertebral bodies, and regions of bones with high trabecular content, such as the tibial and femoral metaphyses.

Histologically, one finds decreased trabecular volume and increased bone resorption with an increase in osteoclast number and activity, along with decreased bone formation and mineralization rate (Hermus et al., 1995; Di Somma et al., 2003). The consequences of this weakened bone are pathologic vertebral compression fractures, subchondral bone failure occasionally with osteonecrosis of weight bearing or stressed bone sites. At tissue level, excess cortisol has been shown to impair osteoblastogenic differentiation, decrease osteoblast function and increase osteoblast apoptosis, resulting in decreased bone formation (Canalis et al., 2007). At the cellular level, excess steroids have been shown to induce caspase-3 activation, which increases osteocyte apoptosis and therefore also increases remodeling at the bone surface (Rochefort et al., 2010).

The progression of skeletal catabolism to fracture is generally understood. However, the components and progression of bone repair following successful treatment and resolution of Cushing's disease is less well understood. This lack of understanding of bone repair during recovery impedes the rational selection of agents and their sequence of application to accelerate bone repair in order to rapidly reduce fracture risk. We present the first case of Cushing's disease induced osteoporosis in a young male patient demonstrating spontaneous normalization of trabecular bone score (TBS) 8 months after surgical cure, followed by accelerated bone mineralization with Teriparatide (TPTD).

2. Material and methods

Bone density (DXA) scans were obtained on the same Lunar Prodigy densitometer and the anonymized scan data were sent to the University of Lausanne, Switzerland for the calculation of spine TBS using the medimaps TBS iNsight®-2.1 software for texture analysis. A tighter/fuller trabecular network produces an image with many gray level variations of small amplitudes, which translates into a steep slope and a high TBS value (Hans et al., 2011). Blood tests were processed at the Quest lab.

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3. The case

A 34-year-old man was referred to Hospital for Special Surgery for metabolic bone disease evaluation after suffering a non-traumatic tibial stress fracture and subsequent development of avascular necrosis of the left femoral head.

On physical exam, he had truncal obesity with a slightly protuberant abdomen and large purple striae. Initial labs revealed elevated AM cortisol (21.6 ug/dl, nl 8–19 ug/dl) and urinary free cortisol (561 ug/24 h, nl <250 ug/24 h). After 1 mg dexamethasone, AM Cortisol remained elevated (27.2 ug/dl, nl <1.8 ug/dl) and ACTH did not suppress (84 pg/ml, nl < 48 pg/ml). Patient also had increased bone resorption evidenced by elevated NTX (65 nM BCE/mM, nl 3–51 nM BCE/mM), and had low vitamin D 25(OH) (24.8 ng/ml, nl 30–100 ng/ml) with intact PTH (54 pg/ml, nl 15–65 pg/ml). Bone formation markers such as P1NP or osteocalcin were not measured at this time.

Bone densitometry showed severely low BMD at lumbar spine (L-spine) 0.763 g/cm^2 with a Z-score of −3.0, and at total right hip 0.588 g/cm^2 with a Z-score of −2.8. The TBS displayed also a very low value, 1.16 compatible with highly degraded microarchitecture. Pituitary MRI revealed a focal lesion in the sella turcica consistent with microadenoma. The patient underwent transphenoidal resection of the microadenoma.

One-year post-resection, AM cortisol and ACTH had normalized (9.3 ug/dl and 21 pg/ml respectively). TBS improved to the normal range (from 1.16 to 1.377, an 18.7% increase), and NTX returned to normal. However, a repeat DXA obtained 8-months post-surgery showed no significant change in BMD at L-spine 0.753 g/cm^2 (Z-score −3.1); a 15% improvement in BMD at the right total hip, 0.686 g/cm^2 (Z-score −2.3) (Figs. 1–2). The BMD remained severely low, and the patient was started on Teriparatide (TPTD). During teriparatide therapy, patient's bone specific alkaline phosphatase (BSAP) and bone resorptive NTX appropriately increased, consistent with bone re-modeling and anabolic formation, peaking at 59.1 (0–20 ug/L) and 367 BCE/mM (nl 3–51 nM BCE/mM) respectively at 4 months of therapy.

After 2 years of TPTD, a repeat DXA revealed a 53.9% increase in BMD at L-spine (1.154 g/cm^2, Z-score 0.7); 50% increase at the total right hip (0.977 g/cm^2, Z-score −0.2) (Figs. 1–2). Trabecular bone score analyses at the start of TPTD and at completion showed an 11.9% increase, less than the change between surgery and the start of TPTD (18.7% increase) and far less than the percent change in BMD after TPTD (Fig. 3). The patient received an infusion of zoledronate upon completion of TPTD. Repeat DXA 3 years later showed BMD that continued to improve at spine and hip while the TBS remained stable as previously reported after bisphosphonate (Silva et al., 2014).

Seven-years post-surgical cure, free cortisol and ACTH remained normal 0.15 mcg/dl (nl 0.07–0.93 mcg/dl) and 27 (nl 6–50 pg/dl) respectively. In addition, other pituitary hormones remained normal with prolactin 5.6 ng/ml (nl 2–18 ng/ml), TSH 1.24 mIU/L (nl 0.4–4.5 mIU/L) and LH 2 mIU/ml (1.5–9.3 mIU/ml).

4. Discussion

Prior studies report a slow, progressive recovery of bone mass taking up to 10 years in adolescents and adults "cured" of Cushing's disease (Di Somma et al., 2003). In the current case, the patient's initial TBS of 1.16 met the criteria for having degraded microarchitecture of the trabecular bone in the spine. TBS is classified into normal (>1.350); partially degraded (1.2–1.35); and degraded microarchitecture (<1.2) (Silva et al., 2014). This patient's degraded microarchitecture prior to surgery is in agreement with the current literature, which demonstrated progressive demineralization and degradation, primarily of trabecular bone as a result of cortisol excess (Dalle Carbonare et al., 2005). Remarkably, the patient's TBS improved to normal range from 1.16 to 1.377 within 8 months post-surgical cure on calcium and vitamin D supplementation alone.

While we cannot completely exclude the possibility that changes in body composition in the marrow and visceral fat may have impacted the TBS, several factors argue against that possibility. First, the TBS was calculated using the updated TBS iNsight®-2.1 software, which corrects for increased BMI and truncal adiposity in men (Leslie et al., 2014). Second, the patient had BMI and abdominal thickness values that did not significantly change over the course of his illness and recovery (Table 1). Third, in spite of the increase in abdominal thickness from 17 cm to 18.5 cm from start to completion of TPTD, which would be

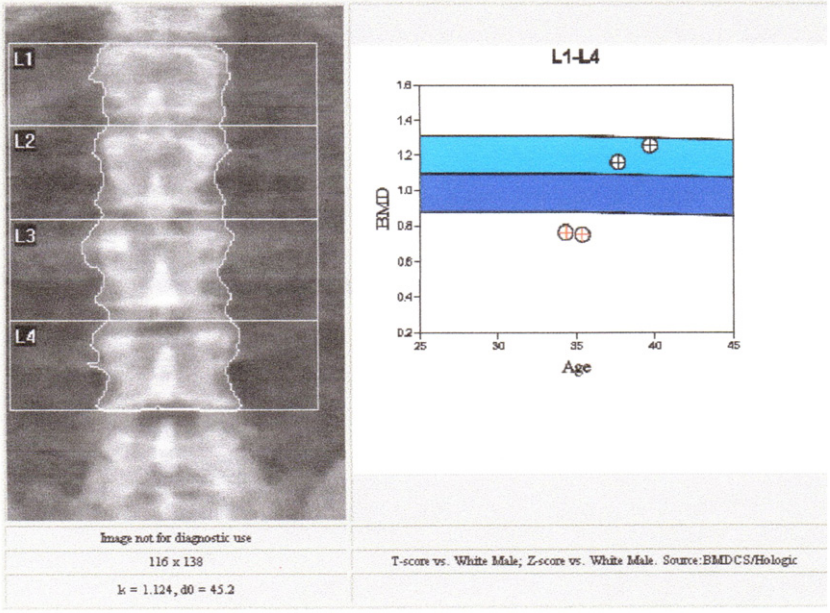

Fig. 1. DXA summary for changes in lumbar spine BMD from pre-operative to 5 years post-surgery: initially to 8 months post-surgery treatment with calcium and vitamin D alone, then TPTD for the next 2 years then one infusion with zoledronate.