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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

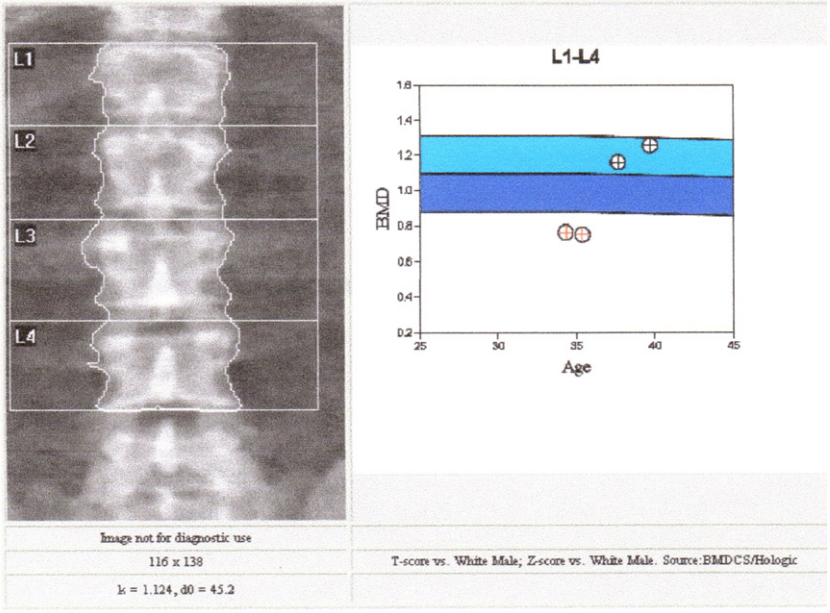

Fig. 1. DXA summary for changes in lumbar spine BMD from pre-operative to 5 years post-surgery: initially to 8 months post-surgery treatment with calcium and vitamin D alone, then TPTD for the next 2 years then one infusion with zoledronate.

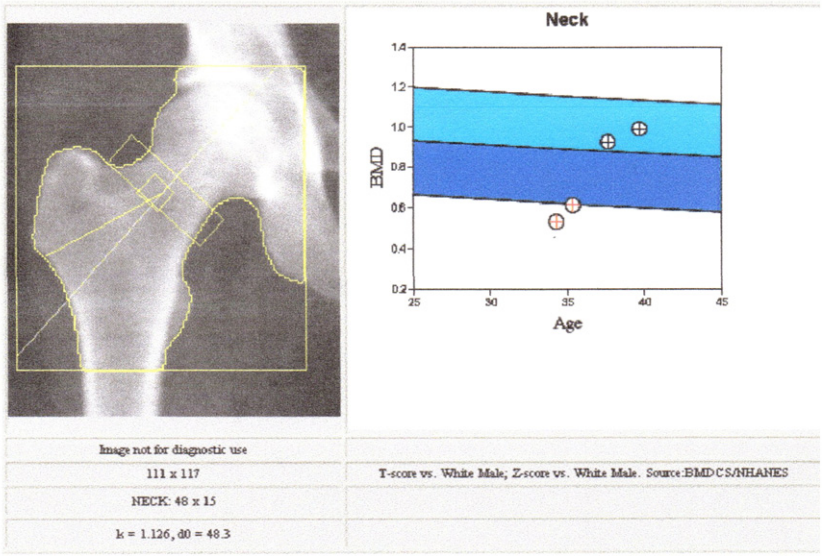

Fig. 2. DXA summary for changes in femoral neck BMD from pre-operative to 5 years post-surgery: initially to 8 months post-surgery treatment with calcium and vitamin D alone, then TPTD for the next 2 years then one infusion with zoledronate.

expected to attenuate the TBS change, the patient showed a significant increase in TBS from 1.377 to 1.541.

Despite spontaneous normalization of TBS 8 months post-surgical cure, BMD remained severely low. A clinical decision was made to treat this presented patient with teriparatide for several reasons. First, patient already suffered non-traumatic fragility fracture in setting of very low BMD and also suffered from avascular necrosis of the hip. Second, despite normalized cortisol and ACTH, patient's BMD remained severely low 1-year post-surgical cure, which still placed the patient at high risk for more fragility fractures. After 2 years of TPTD, patient's BMD improved to normal Z-scores at the spine and femoral neck. This is a significantly more rapid correction of BMD compared to prior studies, which reported slow recovery of bone loss, taking up to 2–10 years for complete recovery post-surgical cure (Di Somma et al., 2003). Although the improvement of BMD to normal range could have been achieved eventually over time post-surgery for the described patient, TPTD appears to have significantly accelerated mineralization resulting in complete normalization of BMD within two years.

It has previously been reported that the time and sequence of BMD recovery in Cushing's patients post-surgery varies within the different skeletal compartments. Earlier improvement was reported to occur at the lumbar spine (mainly trabecular bone) and femoral neck (a mix of trabecular and cortical bone) as compared to the whole body (80% cortical bone) (Kristo et al., 2006), which is consistent with the findings in the current study.

Further research is needed to better understand and identify the mechanisms of bone repair in patients cured of Cushing's disease. One can hypothesize that once the excess cortisol is removed by surgical

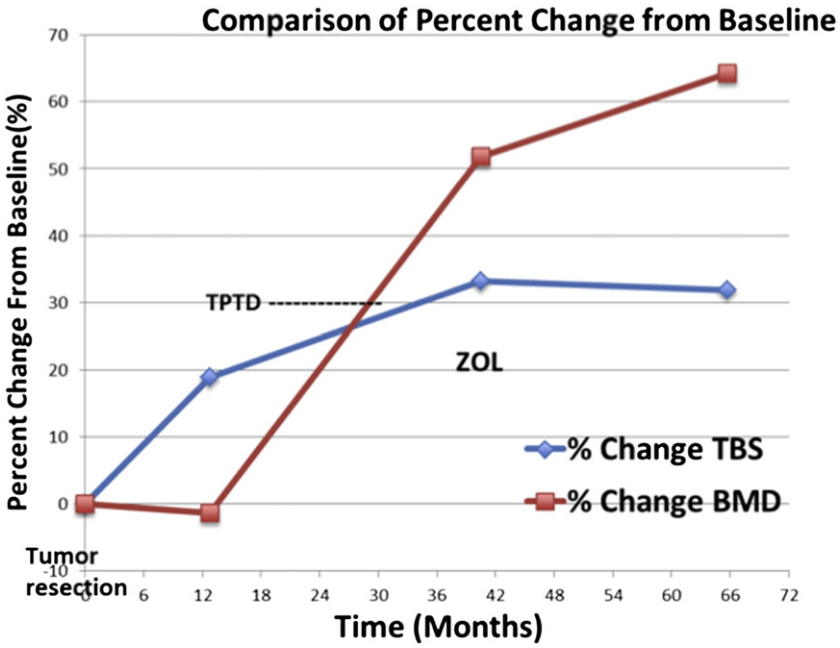

Fig. 3. Plotted percent changes in spinal BMD and TBS for the lumbar spine. TBS improved to normal range, with an 18.7% increase 8-months post-surgery. During this same period there was a slight decrease in bone density of −1.4%. After 2-years of teriparatide, bone density increased by 57.1% in the lumbar spine. TBS was further increased by 11.9%. BMD continued to rise slowly after zoledronate, no change was seen in the TBS.

Table 1
Physical parameters, TBS and BMD during clinical course.

Date	Weight (kg)	BMI (kg/m^2)	Body thickness (cm)*	TBS	BMD g/cm^2	BMD % change from baseline
8/2007 (Pre-surgery)	73	24.3	20.4	1.16	0.863	
9/2008 (8 months post-surgery)	69	24.1	17	1.377	0.753	−1.4%
12/2010 (Upon completion of TPTD for 2 years)	73	25	18.5	1.541	1.158	+57.1
1/2013 (25 months after ZOL)	77	26.2	19.5	1.525	1.253	+64.1%

resection, the once impaired osteoblastogenic differentiation will regain its function to normalize osteoblast function, increasing bone formation. Furthermore, the increased caspase-3 activation from excess cortisol will normalize, which will slow down osteocyte apoptosis (Rochefort et al., 2010). However, it is still unclear how long it takes for the osteoblast to regain its function and its correlation with clinical improvement in bone strength, measured by BMD.

As presented in this case, the removal of excess cortisol allowed for recovery of normal trabecular bone structure 8 months post-surgical cure. However, the BMD remained very low, which improved to normal after 2 years of teriparatide. Teriparatide, a recombinant parathyroid hormone (PTH) works by providing intermittent exposure to PTH, which is the primary regulator of calcium and phosphate metabolism in bone and kidney. Intermittent exposure to teriparatide with once a day injection results in activation of osteoblast more than osteoclast, leading to net anabolic bone formation. In the presented case, teriparatide likely accelerated normalization of BMD by increased activation of osteoblasts, which in turn mineralized the recovered trabecular bone architecture post-surgical cure.

On literature review, there are only two published case reports of patients with Cushing's disease treated with TPTD. Both patients were pre-menopausal women, treated for 24 and 6 months respectively, and they showed a modest increase in LS BMD of 18% and 4.5% respectively, far less impressive than the increase in BMD of 53.9% seen in our case (Medina et al., 2013; Han et al., 2012). Both patients were started on TPTD immediately after surgical resection without a waiting period to assess spontaneous recovery of BMD. It is difficult to determine whether that 1-year delay in the treatment with teriparatide after the surgical cure of Cushing's disease allowed for more rapid increase in BMD with TPTD. However, the finding of complete recovery of TBS post-surgical cure provides insight into the bone recovery process that starts with trabecular bone repair, followed by mineralization, which in this case likely was accelerated with TPTD.

To our knowledge, this is the first case of TPTD use in a young male patient with Cushing's induced osteoporosis that has successfully normalized BMD after 2 years of therapy. It is also the first case demonstrating spontaneous recovery of TBS 8-months post-curative surgical resection without pharmacologic therapy in a patient with Cushing's disease. This finding provides more insight into the process and sequence of bone repair in Cushing's disease post-surgery. Once the endogenous excess cortisol is removed, the bone recovery seems to start with trabecular bone structure, as evidenced by rapid, spontaneous normalization of TBS. The bone mineralization seems to begin once trabecular structure has been restored. This finding may explain the delayed improvement seen on DXA, which only measures mineralization of the bone. Therefore, TBS measurement may be a helpful tool in monitoring bone recovery in addition to DXA in patients with Cushing's disease induced osteoporosis post-surgery.

5. Conclusion

In Cushing's induced osteoporosis, a nearly complete restoration of the TBS was seen within 8 months of curative surgery on calcium plus vitamin D supplementation alone. Restoration of BMD was delayed and most evident after trabecular microstructure repair, which can be accelerated on anabolic therapy with TPTD. The principle deficits in trabecular bone (i.e., trabecular microstructure and BMD) appeared to correct quickly with time and treatment but in a discordant fashion. Therefore, TBS measurement can be a helpful marker in monitoring bone recovery in Cushing's patients post-surgery in addition to DXA to guide clinicians in timing and choice of therapy such as bisphosphonates or teriparatide.

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Disclosure: S.K., O.D., and R.B. have nothing to disclose. D.H. is a co-owner of the patent for TBS.

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