AACE Clinical Case Rep. 10 (2024) 152–155

Clinical Case Reports™
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Case Report

Acceleration of Preexisting Aortic Stenosis After Teriparatide Initiation

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ARTICLE INFO

Article history:
Received 28 February 2024
Received in revised form
16 April 2024
Accepted 22 April 2024
Available online 26 April 2024

Key words:
teriparatide
aortic stenosis
osteoporosis
valve calcification

ABSTRACT

Background/Objective: Teriparatide, an osteoanabolic agent similar to parathyroid hormone in properties, is used to manage severe osteoporosis. Aortic valve stenosis is a common valve condition observed in the elderly. Its natural history includes gradual progression toward severity. We present a case of a patient who had rapidly progressive aortic stenosis after teriparatide initiation.
Case Report: An 84-year-old woman who was diagnosed with osteoporosis was treated with oral bisphosphonates. When she had spinal compression fractures, she was found to have primary hyperparathyroidism. She underwent parathyroidectomy and was treated with denosumab infusions every 6 months. However, after she experienced bilateral atypical femoral fractures, she was switched to teriparatide daily injections. Her laboratory test results showed a calcium level of 10 mg/dL (reference range, 8.5-10.2 mg/dL), 25-hydroxyvitamin D level of 38.2 ng/mL (reference range, 31.0-80.0 ng/mL), and phosphorus level of 3.3 mg/dL (reference, range, 2.7-4.8 mg/dL). On reviewing echocardiograms before and after teriparatide initiation, we found a rapid progression of her aortic stenosis from moderate to severe based on the mean gradients (23 to 40 mm Hg) and peak velocities (3.09 to 4 m/s), over a span of 10 months. She eventually required valve replacement.
Discussion: Natural progression of mild to severe aortic stenosis typically occurs at the rate of 3 to 7 mm Hg per year over several years. Chronic exposure of human valvular endothelial cells to parathyroid hormone can trigger endothelial dysfunction and valvular calcification.
Conclusion: In patients with preexisting aortic stenosis, coordination of care with cardiology and echocardiographic monitoring while on therapy may be considered.

Introduction

Teriparatide belongs to the anabolic class of medications that is currently approved by the Food and Drug Administration to treat severe osteoporosis and patients at high risk of fracture. It is a form of parathyroid hormone (PTH), consisting of amino acids 1 to 34, but retains all biologic activities of full-length PTH noted in human beings. It binds to the same receptors on the bone and kidney as full-length PTH.[1] It is administered daily in the form of an injection via the subcutaneous route and has excellent bioavailability.

In the United States, aortic stenosis is one of the most common manifestations of heart valve disease.[2] Its prevalence increases with age, and mineral metabolism is thought to play a role in this process as well. Previously, in patients with classical primary hyperthyroidism, it was common to find calcified aortic valves with a prevalence as high as 46%.[3] Recently, this was shown even in mild primary hyperparathyroidism, where there is a significant correlation between PTH and aortic valve calcification area.[4] This is also particularly true in secondary hyperparathyroidism noted in renal insufficiency and low vitamin D status.[5] Although the mechanism is poorly understood, it is believed that calcified cardiac valves often contain osteoblast-like cells, which can potentially respond to PTH. Increased heart valve calcifications have not been commonly reported with the use of teriparatide. In fact, based on our extensive literature review, only 1 such case has previously been reported.[6]

We present a case of a patient who had rapid progression of preexisting aortic stenosis after teriparatide initiation.

Abbreviations: BMD, bone mineral density; DXA, dual x-ray absorptiometry; ECHO, echocardiogram; PTH, parathyroid hormone.

Funding Statement: No financial support received in the preparation of this article.

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https://doi.org/10.1016/j.aace.2024.04.006

Case Report

An 84-year-old woman was referred to the metabolic bone disease clinic for evaluation and management of long-standing osteoporosis complicated by bilateral atypical femoral fractures. Her past medical history included hypertension, hyperlipidemia, chronic kidney disease stage 3, and atrial fibrillation on anticoagulation. Osteoporosis was diagnosed 22 years before her presentation, and she was initially treated with alendronate for 14 consecutive years. She developed a spinal compression fracture while on therapy. On further investigation, primary hyperparathyroidism was diagnosed. She underwent parathyroidectomy with removal of the right superior gland. After surgery, she was not on any medication for osteoporosis for the subsequent 2 years. Denosumab, every 6 months, was started 3 years before her presentation because of the lack of improvement in bone mineral density (BMD) on the dual x-ray absorptiometry (DXA) scan. The lowest T-score of −5.3 in the left forearm corresponded to a BMD of 0.355 g/cm^2. While she was on denosumab for 3 consecutive years, her DXA showed a change in BMD with the T-score improving to −4.2 in the left forearm corresponding to a BMD of 0.443 g/cm^2 (Table). One month before her presentation, she had bilateral atypical femoral fractures and underwent intramedullary pinning of both femurs, and denosumab was stopped.

Her medication list at the time of presentation to the clinic included atorvastatin 10 mg, furosemide 20 mg, losartan 25 mg, spironolactone 25 mg, warfarin 5 mg, and trazodone 50 mg. She did not take any over-the-counter supplements including calcium.

At the time of her presentation, the physical examination result was positive for a pan systolic murmur in the aortic area and negative for shortening of her height, scoliosis, kyphosis, or tenderness in the spine. Her body mass index was 17.76 kg/m^2. Her basic metabolic panel demonstrated a calcium level of 10 mg/dL (reference range, 8.5-10.2 mg/dL), phosphorus level of 3.3 mg/dL (reference range, 2.7-4.8 mg/dL), albumin level of 4.6 g/dL (reference range, 3-4.9 g/dL), creatinine level of 1.02 mg/dL (reference range, 0.58-0.96 mg/dL), and glomerular filtration rate level of 54 mL/min/1.73 m^2 (reference range, 60 mL/min/1.73 m^2). Other laboratory test results included a 25-hydroxyvitamin D level of 38.2 ng/mL (reference range, 31.0-80.0 ng/mL), hemoglobin A1c level of 5.7% (reference range, 4.3%-5.6%), thyroid-stimulating hormone level of 2.52 μIU/mL (reference range, 0.27-4.2 μIU/mL), and PTH level of 44 pg/mL (reference range, 15-65 pg/mL).

After the fractures healed, she was started on 20-mcg teriparatide injections daily for severe osteoporosis. Her DXA scan 12 months after her presentation while on teriparatide showed a lumbar spine BMD (L1-L3) of 0.763 g/cm^2 and T-score of −2.3, which was a statistically significant increase from a previous BMD (2 years prior) of 0.719 g/cm^2 and T-score of −2.7. The left forearm BMD and T-score were 0.443 g/cm^2 and −4.2, respectively (Table).

Eighteen months after her presentation, we became aware of her upcoming plans for a transcatheter aortic valve replacement. On review of her previous echocardiograms (ECHOs), she had preexisting mild aortic stenosis. She had gradual progression to moderate aortic stenosis in 1 month before her presentation. An ECHO 14 months after presentation and 10 months after starting teriparatide demonstrated that the peak velocity had increased from 3.09 to 4 m/s (Fig. 1), along with an increase in the mean gradient from 23 to 40 mm Hg (Fig. 2). The calculated aortic valve area decreased from 1.02 to 0.6 cm^2 (Fig. 3) after treating the patient with teriparatide for 10 months.

After talking to the patient and the cardiology team, teriparatide was stopped. After transcatheter aortic valve replacement, the patient opted for conservative management of osteoporosis with calcium and vitamin D optimization along with resistance training.

Highlights

- Parathyroid hormone and aortic stenosis have a weakly positive correlation
- No randomized trials are available to show that teriparatide worsens aortic stenosis
- Cardiology follow-up in patients with aortic stenosis on teriparatide may be needed

Clinical Relevance

We present a case of rapid aortic stenosis progression in a woman after starting teriparatide for severe osteoporosis. This suggests a potential association between teriparatide and accelerated aortic calcification, possibly due to stimulation of valvular osteoblast-like cells. Close cardiology follow-up should be considered in patients with preexisting aortic stenosis.

Discussion

In this case, we present a patient who presented for management of severe osteoporosis initially treated with a prolonged course of oral and parenteral antiresorptive agents, complicated by atypical femoral fractures on whom we decided to start teriparatide as an alternative agent given severity of osteoporosis. Using an ECHO, we demonstrate a rapid progression and worsening of aortic stenosis in 10 months after initiating teriparatide. The American Heart Association in its 2014 update estimated the prevalence of aortic stenosis at 5%.[2] In another recent study in Norway, the prevalence varied from 3.9% to 9.8%, with a higher prevalence in those aged >80 years.[7] The most common etiology is calcification of the aortic valve. In patients with primary hyperparathyroidism, this prevalence is as high as 46%.[3] A case-control study in 2012 demonstrated that the aortic valve calcification area was significantly higher in patients with primary hyperparathyroidism than in controls.[4] In terms of progression of the disease in an aging population, the mean rate of increase in the mean gradient is usually 3 to 7 mm Hg per year, and the valve area usually declines at a mean

Table
Dual X-ray Absorptiometry Findings

Date (time in relation to the first office visit)	Location	BMD (g/cm^2)	T-score
March 2018 (3 y before office visit, before denosumab)	Left forearm	0.355	−5.3
March 2020 (1 y before office visit, on denosumab)	Lumbar spine (L1-L3)	0.719	−2.7
March 2021 (during the first office visit, denosumab paused)	Left forearm	0.443	−4.2
March 2022 (12 mo after presentation, on teriparatide)	Left forearm	0.443	−4.2
March 2022 (12 mo after presentation, on teriparatide)	Lumbar spine (L1-L3)	0.763	−2.3

Abbreviation: *BMD* = bone mineral density.

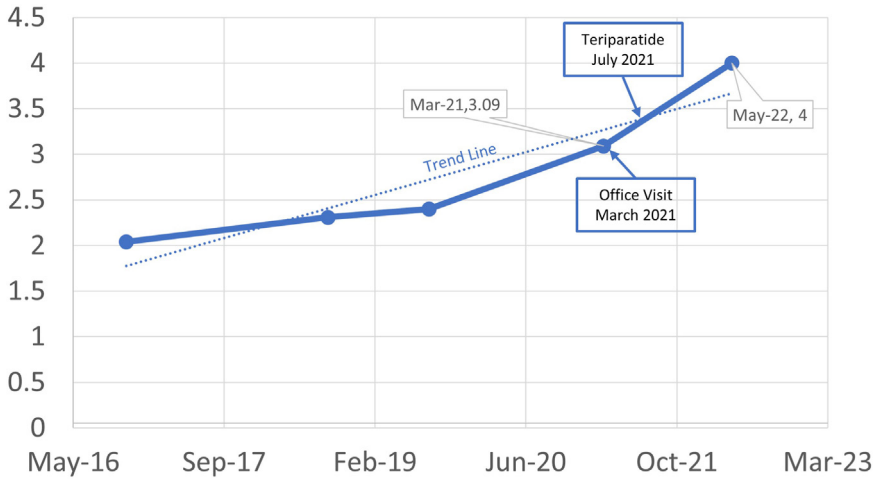

Fig. 1. Peak velocity (m/s) plotted against time.

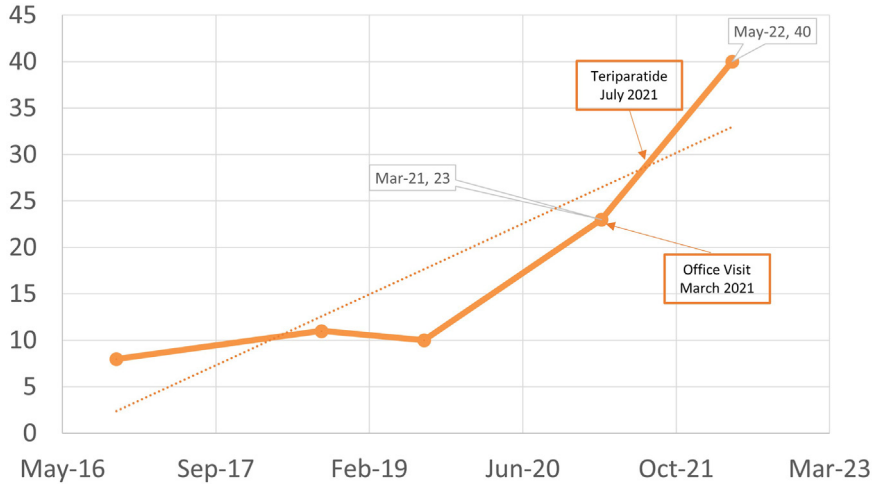

Fig. 2. Mean gradient (mmHg) plotted against time.

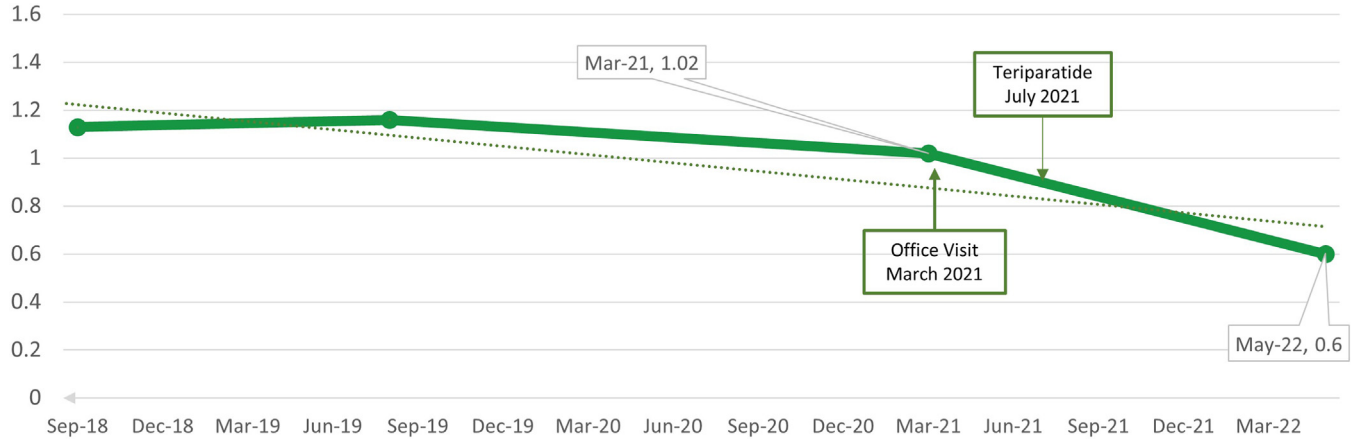

Fig. 3. Aortic valve area (cm^2) plotted against time.

rate of 0.1 cm^2 per year.[7] The accelerated deterioration in valvular function that was noted in our patient was unusual.

The COFRASA study established that serum PTH, CTX (cross-linked C-telopeptide of type I collagen)/osteocalcin ratio, and vitamin D status had significant, independent, weak positive association with aortic stenosis.[5] This association was strongest with low vitamin D status and mild renal insufficiency. An association between PTH and aortic stenosis can also be noted in mild and

classical primary hyperparathyroidism.[3,4] Overall, this possibly indicates that there is an association between PTH and aortic stenosis.

During our literature search, another published case report was noted with similar findings.[6] Their patient was slightly younger and had hypertension, hyperlipidemia, and hypothyroidism as comorbidities. Similar to our patient, this patient had mild aortic stenosis at baseline with a mean gradient of 19 mm Hg. After initiating teriparatide, there was rapid progression to moderate aortic stenosis with mean gradients of 30 and 36 mm Hg at 4 and 7 months, respectively. There were no clinical trials that were performed to investigate the association of teriparatide with aortic stenosis in human beings. However, a recent in vitro study conducted by Vadana et al[8] proved that chronic exposure of human valvular endothelial cells to PTH led to endothelial cell dysfunction, which, in turn, triggered valvular interstitial cells to an osteogenic phenotype. Animal studies demonstrate mixed data. A study by Hsu et al[9] showed that PTH neither accelerated nor attenuated aortic valve calcification.

The exact mechanism of how teriparatide potentially accelerates aortic stenosis remains unknown but can be theorized as follows: the calcification of the aortic valve appears to be both active and passive. The active process starts with chronic inflammation, lipid deposition due to underlying comorbidities such as hypertension and hyperlipidemia. During this process, osteoblast-like cells are recruited from precursor vascular smooth muscle cells as well as macrophages. These cells in theory could be influenced by bone turnover signals such as PTH or, in this case, teriparatide.[5,10] Furthermore, studies have demonstrated a process similar to bone formation in the aortic valve due to the expression bone formation proteins such as osteopontin and osteocalcin in the aortic valve.[10,11] The passive component is hypothesized due to excessive availability of calcium in the blood caused by increased bone turnover from a high PTH level, resulting in deposition of calcium in the valve at the site of inflammation.[5]

Conclusion

The potential for teriparatide to accelerate the process of aortic stenosis deserves further investigation, especially in geriatric patients with preexisting aortic stenosis because severe forms of aortic stenosis can cause significant morbidity and mortality. If aortic stenosis is more prevalent in patients with hyperparathyroidism and it has the potential to progress faster, a case can be made that teriparatide, which is similar in properties, could also contribute to an accelerated progression of aortic stenosis. Until we obtain more data in this field, we recommend that in patients with preexisting aortic stenosis being treated with teriparatide, coordination of care with cardiology and echocardiographic monitoring while on treatment should be considered.

Disclosure

The authors have no conflicts of interest to disclose.

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