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Case Report

An Overlooked Medication-Induced Celiac Flare Complicating Treatment of Osteoporosis

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ABSTRACT

Background/Objective: Celiac disease, an immune reaction to gluten causing nutrient malabsorption, and long-term glucocorticoid therapy adversely affect bone metabolism and increase fracture risk.
Case Report: A patient with long-standing celiac disease on a strict gluten-free diet and long-term glucocorticoid therapy status post kidney transplant for Sjögren syndrome–induced interstitial nephritis presented for management of osteoporosis. Initial evaluation was notable for secondary hyperparathyroidism, which resolved after switching to a gluten-free calcium citrate supplement. Given normal serum total alkaline phosphatase (ALP) and parathyroid hormone (PTH), she began treatment of osteoporosis with abaloparatide. Two months later, she reported abrupt onset of diarrhea with significant weight loss. Biochemical investigation revealed a threefold increase in serum ALP level. As a precaution, abaloparatide was suspended, yet symptoms persisted with elevated ALP and PTH levels. Endoscopy revealed a celiac flare. The clinic-based pharmacist found that her pharmacy had inadvertently dispensed prednisone tablets containing wheat starch. A switch to a gluten-free formulation led to rapid resolution of the diarrhea with weight regain. Serum ALP and PTH levels normalized, and abaloparatide was resumed without biochemical abnormalities.
Discussion: An unintended switch to a gluten-containing prednisone formulation resulted in uncontrolled celiac disease causing calcium malabsorption, secondary hyperparathyroidism, elevated ALP levels, and an interruption in osteoporosis therapy. Common supplements and drugs can be a hidden source of gluten. Collaboration with a clinic-based pharmacist enhances the detection and prevention of medication-induced adverse reactions.
Conclusion: This case highlights the importance of a careful review of gluten-containing medications and supplements in patients with celiac disease.

Introduction

Celiac disease is an enteropathy caused by an autoimmune reaction to gluten, resulting in inflammation and damage of the small intestine mucosa, which ultimately leads to nutrient malabsorption.[1] The spectrum of disease presentation can range from severe gastrointestinal complaints, such as diarrhea and weight loss, to more subclinical disease identified on history or laboratory abnormalities. Currently, lifelong avoidance of gluten-containing products, such as wheat, barley, and rye, is the main treatment.[1] One of the most common complications of celiac disease is reduced bone mass resulting in a higher risk of fracture. Aside from immunologic mechanisms increasing bone turnover, a main factor contributing to the adverse bone effects is malabsorption of minerals, such as calcium.[2] These deficiencies lead to poor bone mineralization and secondary hyperparathyroidism, which increases bone turnover with net bone loss.

Glucocorticoid therapy can also cause loss of bone mass and increase the risk of fracture mainly through its toxic effects on osteoblasts and osteocytes involved in bone formation.[3,4] There is also evidence of increased osteoclast activity and reduced calcium absorption.[3,4] Anabolic drug therapies, such as teriparatide (recombinant human parathyroid hormone [PTH] [1-34]) and abaloparatide (analog to PTH-related peptide), rapidly increase bone

Abbreviations: ALP, alkaline phosphatase; PTH, parathyroid hormone.

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formation early in the course of therapy and subsequently increase resorption.[5] Randomized controlled trials have shown that these forms of anabolic therapy are superior to oral bisphosphonate therapy in increasing spine bone mineral density and reducing vertebral fracture risk in glucocorticoid-induced osteoporosis.[6,7] However, teriparatide and abaloparatide are contraindicated in those with underlying hyperparathyroidism or other metabolic bone disorders associated with high alkaline phosphatase (ALP) levels .[5] In this report, we describe a case of treatment of osteoporosis with abaloparatide, which was complicated by an unexpected flare of celiac disease.

Case Report

A 65-year-old woman with long-standing celiac disease, Sjögren syndrome–induced interstitial nephritis status post kidney transplant requiring prednisone 15 mg every other day, and chronic kidney disease stage 3a (estimated glomerular filtration rate, 54-59 mL/min/1.73 m^2), presented for evaluation and management of osteoporosis in June 2020. This patient had maintained a strict gluten-free diet for over 15 years and had no gastrointestinal complaints for many years on initial presentation. She had been on risedronate for the treatment of osteoporosis for several months in 2020; however, owing to recurrent dental extractions, risedronate was discontinued in the spring of 2020. She reported taking 1200 mg of elemental calcium as calcium carbonate and 2000 IU of vitamin D3 supplementation daily.

Initial biochemical evaluation in June 2020 revealed an elevated serum PTH level of 82.2 pg/mL (reference range, 18.4-80.1 pg/mL) with a low-normal albumin-corrected serum calcium level of 8.52 mg/dL (reference range, 8.5-10.5 mg/dL), estimated glomerular filtration rate of 59 mL/min/1.73 m^2, 25-hydroxyvitamin D level of 40 ng/mL, total ALP level of 69 U/L (reference range, 30-117 U/L), and an undetectable 24-hour urine calcium excretion of <5 mg (reference range, 100-250 mg). The patient switched to 1200 mg of elemental calcium as a gluten-free calcium citrate supplement, and a subsequent serum PTH level decreased to 58 pg/mL in September 2020 (Table).

With resolution of her secondary hyperparathyroidism and a normal ALP level, she began abaloparatide 80 mcg daily for treatment of osteoporosis in October 2020. In December 2020, she developed severe diarrhea, weakness, and fatigue, followed by an unintentional approximately 9-kg loss in body weight by February 2021. Biochemical testing in December 2020 revealed normal liver function test results but notable for a newly elevated serum ALP level of 217 U/L with a predominant bone fraction of 70% (Table). This level was a threefold increase from the levels in June 2020. Additional testing revealed an elevated fasting morning serum C-telopeptide level, a bone resorption marker, of 1616 pg/mL (reference range, 40-465 pg/mL). Abaloparatide can cause transient mild elevations in serum total ALP levels[8] and increases bone resorption markers such as C-telopeptide.[9] However, the overall presentation of severe diarrhea and rapid weight loss raised concern for more pronounced elevations in ALP level related to calcium malabsorption related to secondary hyperparathyroidism.[10] Nevertheless as a precaution, abaloparatide was suspended in early February 2021. In March 2021, diarrheal symptoms persisted and serum ALP levels remained elevated at 170 U/L, and the bone-specific ALP level was 34.5 mcg/L (reference range, 7.0-22.4 mcg/L). Concurrently, the PTH level was significantly elevated at 200 pg/mL with a normal serum calcium level (Table). In mid-March 2021, the patient underwent an endoscopy, which revealed a severe flare of celiac disease. This result greatly puzzled the patient and her care team as she had maintained a strict gluten-free diet with gluten-free supplements. Over the ensuing weeks, a pharmacist embedded in the endocrinology clinic conducted a comprehensive investigation of the patient's medications and discovered her prednisone tablets had been changed by her pharmacy to a new formulation in mid-November 2020, not long before the onset of the diarrhea. The new formulation contained "wheat starch" according to the manufacturer. With the assistance of the clinical pharmacist, the patient's pharmacy replaced the prednisone tablets with a clearly labeled gluten-free formulation by April 2021. The clinical pharmacist also ensured that her pharmacy records had proper safety alerts.

After the switch to the gluten-free prednisone, she noted a rapid resolution of the diarrhea within a couple of weeks with gradual weight regain over the ensuing months. In June 2021, serum levels of ALP and PTH normalized (Table). With these new laboratory results, the intention was to reinitiate abaloparatide treatment; however, there was a delay due to a prolonged hospitalization for COVID-19 illness in October 2021. Abaloparatide treatment resumed in January 2022. Subsequent biochemical testing on abaloparatide revealed no ALP or PTH abnormalities in June 2022 (Table).

Highlights

- Uncontrolled celiac disease can cause calcium malabsorption, leading to secondary hyperparathyroidism and increased bone loss
- Medications, both prescription and over-the-counter, can be a hidden source of gluten in patients experiencing a flare of celiac disease
- Collaboration between pharmacists and the main health care provider can greatly enhance the quality of care for patients with celiac disease, especially those who are on polypharmacy

Clinical Relevance

This case highlights how a celiac flare can alter bone-specific laboratory testing, how medications and supplements can be a hidden source of gluten, and how collaboration between clinical pharmacists and the main health care provider enhances the quality of care for patients with celiac disease, especially those who are on polypharmacy.

Discussion

This case describes how traces of wheat starch in prescription prednisone tablets caused a severe flare of celiac disease, which, in turn, led to calcium malabsorption with secondary hyperparathyroidism despite daily gluten-free calcium and vitamin D supplementation. This event also led to a prolonged interruption of osteoporosis treatment with abaloparatide. As a result of collaboration with a clinic-based pharmacist, the investigation of this patient's polypharmacy was conducted efficiently, resulting in the identification of the offending medication and effective communication with both the patient and pharmacy.

Untreated celiac disease results in damage and loss of the duodenal intestinal villi,[1] which is important in calcium absorption even when the circulating levels of 25-hydroxyvitamin D are maintained in an optimal range as in our patient. The malabsorption of calcium stimulates PTH synthesis and secretion, resulting in a secondary hyperparathyroidism. PTH increases bone turnover to promote calcium release from bone.[10] Consequently, serum calcium concentration is maintained in the low-normal range at the expense of increased bone resorption and loss of bone mineral.[10] The use of

Table
Timeline With Laboratory Data

Timeline	Albumin-adjusted calcium 8.5-10.5 mg/dL	PTH 18.4-80.1 pg/mL	ALP 30-117 U/L	25(OH)D ng/mL	eGFR mL/min/1.73 m^2
June 2020	8.7	82.2	69	40	59
June 2020 → Switched to gluten-free calcium citrate supplement					
September 2020	8.9	58	…	…	54
October 2020 → Started abaloparatide					
November 2020 → Gluten-containing prednisone dispensed with the onset of diarrhea					
December 2020 to January 2021	10.1	…	203 217	37	49
February 2021 → Stopped abaloparatide					
March 2021	9.5	200	170	46	…
April 2021 → Gluten-containing prednisone switched to gluten-free formulation					
May 2021 → Resolution of diarrhea and weight regain					
June 2021	9.1	42.5	96	46	46
October 2021 → COVID-19 hospitalization					
January 2022 → Resumed abaloparatide					
June 2022	9.2	43	94	36	54

Abbreviations: ALP = alkaline phosphatase; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; 25(OH)D = 25-hydroxyvitamin D.

abaloparatide is contraindicated in those with underlying secondary hyperparathyroidism[5] and, thus, was discontinued in our patient.

Starch is a common excipient in medications and dietary supplements. Although the most common type of starch excipient used in drugs is derived from corn, wheat-derived starches, which contain gluten, are also used. In the United States, the Food and Drug Administration released a draft guidance document in December 2017 recommending elimination of gluten-containing excipients in drug products.[11] However, there is no law mandating that drugs be "gluten-free" or that drug manufacturers disclose the source of excipients in any public record or database. Therefore, there are still many prescriptions and over-the-counter medications, vitamins, and dietary supplements that contain traces of wheat starch but do not provide adequate product labeling.[12] Moreover, because excipients and processes of manufacturing can evolve over time and may be performed overseas with suboptimal oversight, there is a risk of a specific product that may have been "gluten-free" to change its excipients to contain traces of wheat starch.

Although there are databases online to identify gluten-containing and gluten-free manufacturers in the United States, many health care providers lack the necessary knowledge to access these databases compared with pharmacists.[13] Our case also highlights the importance of a clinic-based pharmacist who can provide adequate support to physicians and other health care providers caring for patients with celiac disease. Further efforts are needed to integrate electronic medical records for providers and pharmacies to prospectively identify gluten-containing medications and improve community pharmacist knowledge of celiac disease.[12,13]

In summary, when caring for patients with celiac disease, in addition to counseling on diet and food labeling, it is important to educate on drug and supplement labeling. A multidisciplinary team that includes a pharmacist would help better manage such patients and prevent relapses due to potential gluten-containing therapies.

Disclosure

The authors have no conflicts of interest to disclose.

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Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

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