CASE REPORT

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Osteoporosis reversibility in a patient with celiac disease and primary autoimmune hypothyroidism on gluten free diet – A case report

Reverzibilnost koštanih promena kod bolesnice sa celijakijom i autoimunskim hipotireoidizmom

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Abstract

Introduction. Secondary osteoporosis occurs in many diseases. Celiac disease-induced osteoporosis is the consequence of secondary hyperparathyroidism. Biochemical bone markers show predominance of bone resorption, thus making the bisphosphonates the first line therapy option. Intestinal mucosal changes are reversible on gluten-free diet. Osteoporosis reversibility is also possible, provided postmenopausal osteoporosis risk factors independent from celiac disease are not present. **Case report.** We presented a postmenopausal woman with at least a 10-year history of celiac disease prior to diagnosis, which had overt secondary hyperparathyroidism with insufficient status of vitamin D and a significant bone mass reduction. At the time of diagnosis of celiac disease the patient was receiving 250 μg of levothyroxine daily without achieving optimal substitution. Three years after the initiation of gluten-free diet the patient was without any signs and symptoms of the disease. All laboratory findings were within normal range. It was decided to treat the underlying disease and to supplement calcium and vitamin D without the initiation of bisphosponate therapy. **Conclusion.** Osteoporosis regression justified this therapeutic approach. The presence of primary autoimmune hypothyroidism makes this case specific, since the inability for optimal substitution therapy with a high daily dose of levothyroxine provoked the suspicion of celiac disease.

Key words:
celiac disease; hypothyroidism; diet, gluten-free; treatment outcome.

Apstrakt

Uvod. Sekundarna osteoporoza može se javiti u brojnim oboljenjima. Osteoporoza u glutenskoj enteropatiji posledica je sekundarnog hiperparatireoidizma. Koštani biohemijski markeri pokazuju dominaciju koštane resorpcije, što upućuje na bisfosfonate kao terapijsku opciju. Promene na crevnoj sluzokoži postaju reverzibilne konzumiranjem hrane bez glutena. **Prikaz bolesnika.** Prikazana je žena u postmenopauzi kod koje je verovatno najmanje 10 godina bila prisutna glutenska eneteropatija pre nego što je postavljena dijagnoza jasnog sekundarnog hiperparatireoidizma, sa nedovoljnim statusom vitmina D i izraženom redukcijom koštane mase. U vreme dijagnoze, bolesnica je dobijala 250 μg levotiroksina dnevno, bez postizanja optimalne supstitucije. Zauzet je stav da se kod bolesnice preduzme samo lečenje osnovne bolesti, uz adekvatnu suplementaciju kalcijumom i vitaminom D, bez uvođenja bisfosfonatne terapije. Tri godine posle uvođenja dijete bez glutena, bolesnica je bez tegoba, sa normalnim laboratorijskim nalazima. **Zaključak.** Regresija osteoporoze u stabilnu osteopeniju pokazala je opravdanost primenjenog terapijskog stava. Specifičnost ovog slučaja je i istovremeno prisustvo primarnog autoimunskog hipotireoidizma i činjenica da je nemogućnost postizanja optimalne supstitucije visokom dnevnom dozom levotiroksina bila jedan od razloga da se sprovede dijagnostika u pravcu glutenske enteropatije.

Ključne reči:
celijakija; hipotireoidizam; dijeta bez glutena; lečenje, ishod.

Introduction

Celiac disease is a multisystem disorder on the grounds of inadequate immune response to even minimal quantities of gluten from food [1]. Impaired immune response leads to chronic inflammation of small intestine mucosa with lymphocytic infiltration of the epithelium and *lamina propria*, villi atrophy and cryptal hyperplasia resulting in malabsorption syndrome. This is genetically determined in individuals with HLA class II DQ2/DQ8 alleles [2]. It can

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occur at any age and it can be accompanied with other autoimmune diseases.

The characteristics of osteoporosis are the reduction of bone mineral density (BMD), impairment of bone microstructure and increased fracture risk. It is most common in postmenopausal women as primary multifactorial disease, although many diseases and disorders, such as celiac sprue, can cause secondary osteoporosis. Regardless of what caused the osteoporosis its significance is in increased risk for fractures (vertebral, radial, hip fractures). Gold standard for the diagnosis is dual-energy x-ray absorptiometry (DXA) on the hip and lumbar spine. The result is T- or Z- score i.e. the difference between the acctually measured BMD and the expected standard, expressed in standard deviation (SD). These results are interpreted in assembly with other risk factors in order to estimate the individual risk for fractures and decide upon the treatment.

Recommendations to obtain DXA in each patient with celiac disease are justified by the fact that 20–75% of individuals with newly diagnosed celiac disease already have reduction of BMD (osteopenia and osteoporosis) [3]. Osteoporosis in women under 50 years of age, especially in the childbearing age, should always initiate further diagnostics in order to find the cause of secondary osteoporosis, with celiac disease being one of the most common [4–6].

Celiac disease and osteoporosis are linked through malabsorption syndrome and secondary hyperparathyroidism. Receptor activator of nuclear factor kappa-B ligand (RANKL) osteoclastogenesis and bone resorption are stimulated by inflammatory cytokines which appear as the consequence of impaired immune response to gluten. About 20% of celiac disease patients have osteoprotegerine autoantibodies, with predomination of bone resorption over bone formation [7]. Thus, the relative fracture risk in celiac disease patients is increased – 1.4 for all fractures, 2.1 for hip fractures [8].

Proximal small intestine villi atrophy reverses on gluten free diet and serologic markers of this disease (endomysial and/or tissue transglutaminase antibodies) become undetectable [9]. Furthermore, malabsorption syndrome consequences gradually improve, so bone remodeling becomes normal with the increase of BMD, making osteoporosis reversible, too [10]. The question to be answered is how osteoporosis on the grounds of celiac disease should be treated.

Case report

We presented a 58-year-old female with a 12-year history of primary autoimmune hypothyroidism admitted to the Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center of Novi Sad, Serbia, in June 2008. The patient's levotyroxine daily dose had been successively increased to up to 250 μg due to inability to achieve adequate substitution. The patient presented with swelling of face and lower extremities, muscle weakness in lower extremities and chronic fatigue. Her laboratory analysis showed anemia. The medical history revealed she had been anemic for 10–15 years. In the course of her childhood and adolescence she had had chronic diarrhea, but for the last several years her stool had been normal. Clinical findings revealed undernourishment (body mass index 16.98 kg/m^2), pale skin and mucosa, doughy swellings of face and lower extremities. Malabsorption syndrome was suspected. The initial laboratory findings are shown in Table 1. Endoscopic procedure with proximal small intestine mucosal biopsy was done. Histology showed loss of intestinal villi, reduction of intestinal glands with extensive lymphocytes, neutrophiles and plasma cells infiltration. The diagnosis of celiac disease was made. Since this was a postmenopausal woman, we did DXA. It showed osteoporosis with T-score -2.7 (SD) and -3.4 (SD) on lumbar spine and hip, respectively (Figure 1). Osteocalcine level was in normal range (29.3 ng/mL), while

Table 1

Laboratory parameters before and during the treatment of celiac disease

Parameter	Baseline	6 months	18 months	3 years	Normal range
RBC ($\times 10^{12}$/L)	3.08	4.35	3.76	3.82	3.9–6.0
Hgb (g/L)	91.7	127	118	124	120–160
Hct (%)	27.1	37	35.2	35.9	37–50
Fe (μmol/L)	3.7	11.4	14.8	21	10.7–32.2
Mg (mmol/L)	0.64	0.73	0.71	0.76	0.73–1.06
Ca (mmol/L)	2.03	2.38	2.52	2.54	2.20–2.70
P (mmol/L)	0.93	1.47	1.19	1.06	0.81–1.45
Albumin (g/L)	38.9	46.5	52.4	48.3	35–52
Vitamin D (nmol/L)	36.3	55	69	51	30–100
PTH (pg/mL)	83.1	84.2	40.9	47.9	15–65
β-Crosslaps (pg/mL)	1197	1273	162	160	162–436
Osteokalcin (ng/mL)	29.3	154.3	31	24.1	12–41
Alkaline phosphatase (U/L)	150	145	51	40	30–115
FreeT4 (pmol/L)	9.3	14.1	18.6	19.9	9.1–19.1
FreeT3 (pmol/L)	1.8	4.2	4.1	3.9	2.6–5.7
TSH (mIU/L)	45.18	0.27	1.67	2.27	0.35–4.94
AntiTPO antibodies (IU/mL)	> 1,000	/	> 1,000	> 1,000	< 5.6
Anti-transglutaminase antibodies	positive	/	negative	negative	negative

RBC – red blood cells; Hgb – hemoglobin; Hct – hematocriti; PTH – parathyroid hormone; TSH – thyroid-stimulating hormone; anti-TPO antibodies – anti-thyroid peroidase antibodies.

β-cross laps level was elevated (1197 pg/mL), implying the dominance of bone resorption over formation. The level of 25-hydroxy-vitamin D (25OHD) was 36.3 nmol/L. The patient was an active smoker and that was the only positive independent fracture risk factor.

The patient started with gluten-free diet, with supplementation of 3,000 IU of cholecalciferol daily and 250 μg of levothyroxine. Three months later thyroid-stimulating hormone (TSH) level was 0.001 mIU/L and the dose was reduced to 150 μg daily. Control laboratory analyses and DXA were done after 6 months of gluten-free diet and vitamin D supplementation. TSH values were in the lower part of normal range with normal levels of free T3 and free T4. Circulatory levels of albumine, magnesium, calcium and phosphorus were also normal. Level of 25OHD was 55 nmol/L-still below desirable value of 75 nmol/L with parathyroid hormone (PTH) still slightly elevated (84.2 pg/mL). Osteocalcine was rising (154.3 ng/mL), crosslaps remained elevated (1273 pg/mL). Iron-deficiency anemia was corrected. DXA showed positive trend of T score value (Figure 1). Iron-deficiency improvement of clinical finding was noted, too. The patient was suggested to maintain gluten-free diet, with a combined preparation of 1,000 mg of calcium and 800 IU of cholecalciferol. Levothyroxine was further reduced to 100 μg daily.

Next control exams were done after one year and after 18 months of gluten-free diet. The patient was feeling well and had no signs and symptoms of the disease. The disappearance of anti-tissue-transglutaminase antibodies was noted. Thyroid function tests, albumin, calcium, phosphorus and magnesium were normal. Level of 25OHD increased further to 69 nmol/L, PTH level was normal (40.9 pg/mL), as well as osteocalcine and crosslaps. DXA on the spine and the hip showed a significant improvement of T- score, implying opsteopenia (Figure 1). The patient was advised to stay on gluten-free diet with calcium and cholecalcipherole supplementation. Levothyroxine was reduced to 87.5 μg daily.

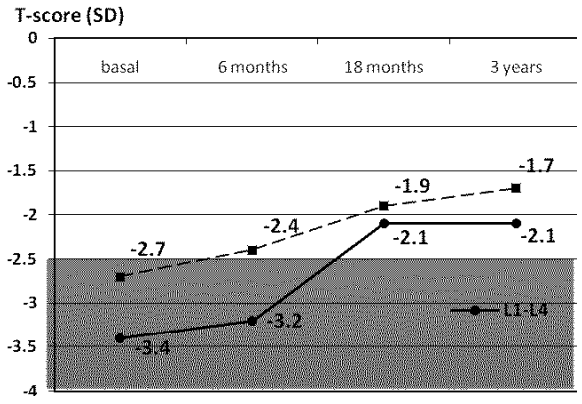

Fig. 1 – Lumbar (dashed line) and hip full line dual-energy x-ray absorptimetry before and during the treatment of celiac disease.

SD – standard deviation.

Three years after the initiation of gluten-free diet the patient was without any signs and symptoms of the disease. All laboratory findings were within normal range. DXA showed T-score -1.7 and 2.1 SD on the lumbar spine and the hip, respectively (Figure 1). During the follow-up period the patient did not have any fractures.

Discussion

Although genetically determined, celiac disease is often diagnosed in adulthood, most commonly between the fourth and sixth decade. Usually, those are the latent forms of the disease, while classical forms with diarrheal syndrome, abdominal pain, weight loss and rash are more often seen in children. Not surprisingly, the study on 1,612 celiac patients done in the USA showed that the duration of the disease prior to the diagnosis was 11 years and 15% of patients did not present with diarrhoea [11]. Anaemia, undernourishment and muscle weakness as manifestations of malabsorption dominate in the absence of typical clinical picture [12].

The presented patient was diagnosed with celiac disease at the age of 58. Immediate cause for the expanded diagnostics was the inability to achieve optimal hypothyroidism substitution, as well as a long history of iron-deficiency anaemia, oedema on lower extremities, undernourishment and muscle weakness. Symptoms of nutrient deficit dominated in the absence of diarrhoea and abdominal pain. According to anamnesis, we could assume it took ten years to make the diagnosis of celiac disease.

Celiac disease is frequently associated with other autoimmune disorders, most often with autoimmune hypothyroidism [13]. Considering the site of levothyroxine intestinal absorption, there is the need for unusually high levothyroxine daily dose with inability to reach optimal TSH feedback. This problem during treatment of primary hypothyroidism should provoke suspicion of malabsorption syndrome and celiac disease [14]. At the time of the diagnosis of celiac disease our patient was receiving 250 μg of levothyroxine daily without achieving optimal substitution. After the initiation of gluten-free diet levothyroxine dose declined to 87.5 μg with TSH in the reference range. Titre of anti-thyroidperoxidase (TPO) antibodies which remains high during the observation period proves the hypothyroidism to be autoimmune. Clinical presentation of celiac disease may be modified by joined autoimmune disorders. This was the case with our patient who had had the history of diarrhoea in adolescence but normal stools later on and presented with lower extremities swelling, chronic fatigue, depression all of which could be contributed to hypothyroidism.

Approximately 2–5% of patients with autoimmune thyroid disorder have celiac disease [15]. Up to 43% of patients with autoimmune thyroid disorder have typical markers of celiac disease in the sense of increased density of T-cell receptors carrying intraepitel lymphocytes with signs of mucosal T-cell activation [13]. This justifies screening for celiac disease in individuals with autoimmune thyroid disorder, especially if optimal substitution with levothyroxine is difficult to achieve as in our patient. Screening for autoimmune thyroid disorder in celiac disease should also be done, especially if clinical presentation is not fully improved by gluten-free diet [16].

The gold standard for the diagnosis of celiac disease is histological picture of proximal small intestine villi atrophy

that is fully reversible in the course of gluten-free diet. Antiendomysial and anti-transglutaminase (anti-t-TG) antibodies are serological markers of the disease. These markers become undetectable when the patient is put on the gluten-free diet, hence they can be used for monitoring of the effect of therapy and patient compliance [9]. Celiac disease diagnosis in our patient was made according to cotemporary standards. In the presence of signs and symptoms of malabsorption syndrome and positive anti-tissue-transglutaminase antibodies, diagnosis was confirmed with proximal small intestine mucosal biopsy. Decline of anti-tTG antibodies titre and later their negativisation showed patient adherence to dietary advice and consequent correction of immune response in the absence of gluten. Since all clinical and laboratory parameters suggested restitution, control mucosal biopsy was not done according to the current recommendations [17].

Small intestine mucosal atrophy in celiac disease leads to malabsorption of many nutrients: proteins, calcium, magnesium, vitamin K, iron, vitamin D, etc. Malabsorption of calcium and vitamin D results in hypocalcaemia, an secondary, regulative, hyperparathyroidism with increase of markers of bone resorption and remodelling (high turnover) [18]. Circulatory levels of 25OHD are usually in the reference range, over 30 but below 75 nmol/L. This level is not sufficiently high to maintain PTH and calcium within normal range [19]. This is the key mechanism for the reduction of BMD (osteoporosis and osteopenia) in celiac disease. Rarely, there is the apparent vitamin D deficit (below 30 nmol/L) which results in impairment of bone mineralisation and osteomalacia. In such a case, DXA method cannot differentiate osteoporosis and osteomalacia. Optimal vitamin D and calcium supplementation is important since in the milieu of gluten-free diet since it corrects hyperparathyroidism and suppresses bone resorption resulting in the increase of BMD. The significance of vitamin D status for muscular function and thus prevention of falls and fractures in terms of the reduction of BMD is a well-known fact.

At the time of the diagnosis of celiac disease our patient had a typical laboratory finding for regulatory hyperparathyroidism: hypocalcaemia, hypophosphatemia, low 25OHD and elevated PTH and bone resorption parameters. Regulatory hyperparathyroidism, a key factor for the occurrence of osteoporosis, vanished during the therapy for celiac disease. Vitamin D status was significantly improved after cholecalciferol substitution (calculated on the basis of the status of vitamin D and target values) and gluten-free diet were initiated. We achieved normal values of calcium, phosphorus, PTH and β-cross laps. Individualisation of daily dose and adequate intestinal absorption during gluten-free diet are preconditions for optimal substitution of vitamin D [20].

A common reduction in BMD in celiac disease patients justifies screening for osteoporosis. The degree of BMD reduction is particularly pronounced if celiac disease appears during skeletal growth and development and it is proportional to duration of untreated disease, *i.e.* to the duration of exposure to gluten [21]. Decision to screen for osteoporosis also depends on the presence of other risk factors for osteoporosis and fractures.

We diagnosed osteoporosis in the presented patient by DXA. We had both celiac disease dependent and independent reasons to carry out diagnostics of osteoporosis. Firstly, although it is impossible to be certain, we assumed our patient had a long history of celiac disease. Secondly, she reached menopause at the age of 46, had a low BMI and was an active smoker. Accelerated metabolic activity estimated by biochemical markers was considered as indicator of increased fracture risk independent of BMD [22]. DXA showed osteoporosis – T-score on lumbar spine and hip -2.7 SD and -3.4 SD respectively. According to the European guidance for the diagnosis and management of osteoporosis in postmenopausal women our patient was a candidate for initiation of medicamentous therapy with bisphosphonates [23].

However, gluten-free diet leads to correction of bone metabolism and vitamin D status, improvement of calcium absorption and increase of BMD within a year [24]. So, the question to be answered is how to treat osteoporosis in celiac disease and what does the treatment option depend on. The current recommendations state that during the first year osteoporosis should be treated only by treating celiac disease itself (gluten-free diet, supplementation of vitamin D and calcium) and by the correction of other independent risk factors and that achieved effect in that period is of prognostic value for at least the next three years [25]. If BMD remains low after a year, risk for fractures should be calculated [(the Fructure Risk Assessment Tool (FRAX) questionnaire)] and osteoporosis should be treated as in individuals who do not have celiac disease [26]. Medicamentous therapy of osteoporosis is initiated parallel with the start of celiac disease therapy if T-score is below -1.5 SD in the presence of other risk factors or previous small trauma fracture or if T-score is below -3.0 SD independently of the presence of other risk factors. Medicamentous therapy of osteoporosis implies bisphosphonates [27], selective estrogen receptor modulators, calcitonine, bone anabolic (teriparatide), strontium ranelate with adequate supplementation of vitamin D and calcium [28].

The presented patient was younger than 60 years, did not have small trauma fractures or family history of fractures, was undernourished and had accelerated bone metabolism because of celiac disease. On the basis of these facts, we decided upon a less aggressive treatment of osteoporosis, i.e. to treat it merely by treating celiac disease. Even more, bisphosphonates were contraindicated because of lesions of intestinal mucosa, hypocalcaemia and insufficient levels of vitamin D. The FRAX questionnaire was not used since there is still no its modification for Serbian population.

The patient was put on gluten-free diet and this resulted in significant corrections in any fields of this complex case in a few months. All signs and symptoms of the disease disappeared and weight gain was noticed. All parameters of calcium homeostasis and bone remodelling returned to normal. Brief elevation of biochemical bone markers coincided with short period of iatrogenous thyrotoxicosis before levothyroxine dose was reduced [29]. Disappearance of anti-tTG antibodies from circulation showed positive evolution of the disease together with good patient compliance to the given therapy.

Considering these results, DXA was done 6 months after the initiation of the therapy and it showed only positive

trend of BMD. After 18 months there was a significant improvement of osteoporosis, i.e. we found only osteopenia that was stable even after 36 months. In the meantime the patient had neither fall, nor small trauma fracture. This outcome justified our decision to treat osteoporosis merely by treating the underlying condition with supplementation of calcium and vitamin D. At the same time, osteoporosis reversibility showed that our postmenopausal patient had only secondary osteoporosis on the grounds of celiac disease.

Conclusion

Since celiac disease may be the cause of secondary osteoporosis with increased fracture risk, screening for osteoporosis should be performed in each patient with celiac disease. Proximal small intestinal mucosal changes in celiac disease patients are reversible on gluten-free diet, so the mechanism that leads to osteoporosis is reversible, too. Gluten-free diet and vitamin D supplementation make osteoporosis reversible.

The decision upon medicamentous treatment of osteoporosis in celiac disease depends on the degree of osteoporosis and on the presence of other independent fracture risk factors in postmenopausal women. Celiac disease is often accompanied by other autoimmune diseases, most commonly primary hypothyroidism. This complicates and modifies clinical manifestations of both diseases, making optimal substitution of hypothyroidism very difficult.

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