Can atorvastatin calcium cause asymptomatic hypercalcemia?

Atorvastatin kalsiyum semptomsuz hiperkalsemiye neden olabilir mi?

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Summary– The use of statins may have unnatural effects. A 54-year-old woman was admitted to the hospital with an incidental finding of hypercalcemia (10.8 mg/dL). There was no disease other than hyperlipidemia, and the patient had been on a course of atorvastatin calcium 10 mg for 1.5 years. A workup investigation to diagnose the cause of hypercalcemia was completed. The investigation did not reveal any pathological diseases that may have caused the hypercalcemia. The hypercalcemia resolved after atorvastatin-calcium was stopped, and the patient developed hypercalcemia shortly after the initiation of the atorvastatin calcium. Here, we report a clinical case of recurrent hypercalcemia possibly induced by atorvastatin calcium administration.

Özet– Statinlerin kullanımı sırasında bazı beklenmeyen yan etkiler olabilir. Elli dört yaşındaki kadın hasta rastlantısal olarak saptanan hiperkalsemi (10.8 mg/dL) ile kliniğimize başvurdu. Hastanın hikayesinde hiperlipidemi sebebiyle 1.5 yıl önce atorvastatin kalsiyum 10 mg başlandığı ve başka ek bir hastalığın olmadığı öğrenildi. Hiperkalseminin nedenini teşhis etmek için ileri inceleme yapıldı. İncelemelerin sonucunda hiperkalsemiye neden olabilecek herhangi bir patolojik hastalık ortaya konulamadı. Hastanın hiperlipidemisi için aldığı atorvastatin kalsiyum kesildiğinde hiperkalsemisi düzeldi, tekrar ilaç başlandığında ise kısa bir süre içerisinde hastanın hiperkalsemisi tekrarladı. Bu olgu, atorvastatin tedavisinin tekrarlayan hiperkalsemiye neden olabileceğini göstermek amacıyla sunuldu.

Patients with asymptomatic or mildly symptomatic hypercalcemia (calcium <12 mg/dL) do not require immediate treatment.[1] Clearly, mild asymptomatic hypercalcemia may be easily overlooked, and the diagnosis of hypercalcemia is most often made in asymptomatic patients during routine checkups. The specific cause of hypercalcemia should be thoroughly investigated. On the other hand, the safety and tolerability of statins support their use as a first-line treatment for hypercholesterolemia, but as with all medication, statins have potential side effects. We herein report a case of hypercalcemia related to atorvastatin treatment,a relatively rare condition.

CASE REPORT

A 52-year-old female patient was referred for hypercalcemia. The patient presented in excellent clinical condition and did not report any symptoms related to hypercalcemia, although she had a chronic hyperlipidemia for which she had been taking atorvastatin calcium 10 mg daily for the previous 1.5 years, this being her only medication. She did not smoke cigarettes, take multivitamins or consume alcohol.

Abbreviations:

CHD	*Cardiovascular disease*
CT	*Computed tomography*
DPD	*Deoxpyridinoline*
DST	*Dexamethasone suppression test*
HR	*Hazard ratio*
OVX	*Ovariectomies*

The patient had normal thyroid, renal, and hepatic functions. Initial laboratory evaluation showed hypocalcemia at 10.8 mg/dL (Figure 1; normal: 8.5-10.2), iPTH as 27 pg/mL (normal: 15-65) normal albumin 4.6 g/L, phosphorus level 3, 9 mg/dL (normal: 2.5-4.8), 24 h urinary calcium excretion was found to be 248 mg/day (normal: 100-300). Her complete blood

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count was normal, and her serum albumin, alkaline phosphatase, erythrocyte sedimentation rate concentrations were within normal limits. Further blood tests demonstrated alkaline phosphatase level of 64 U/L (normal: 35-104), and 25-hydroxy vitamin D level of 38 ng/mL (normal: 20-30), slightly elevated from normal limits. On additional testing, as her hypocalcaemia was mild and with no symptoms, she did not require immediate measures to correct this.

A workup investigation to exclude other causes of hypercalcemia was done. A computed tomography (CT) of thorax, neck, abdomen and bone scan did not reveal any malignancy. Although, serum phosphorus was normal, and iPTH was not increased, thus ruling out hyperparathyroidism, evaluation of the parathyroid glands was performed using ultrasound and MIBI scan, both of which were normal. Other attempts were then made to rule out other potential causes of high calcium levels. The differential diagnosis of hypercalcemia includes calcium supplements, hypervitaminosis D, milk-alkali syndrome, granulomatous diseases, medications, inflammatory and rheumatic diseases, and other endocrine disorders.

Tuberculin tests and a thorax CT were normal, ruling out a granulomatous process (tuberculosis or sarcoidosis). Erythrocyte sedimentation rate and antinuclear antibody levels were normal, ruling out inflammatory and rheumatic diseases. There were no signs or symptoms suggestive of Cushing's disease, adrenal insufficiency, acromegaly, or pheochromocytoma. Normal prolactin levels and insulin-like growth factor-I in the age-and gender-matched normal range, respectively excluding the diagnosis of prolactinoma and acromegaly in our patient. The basal cortisol level was 18 mcg/dL, so we could rule out adrenal insufficiency. The overnight dexamethasone suppression test (DST) was done. After a 1 mg dose DST, the plasma cortisol level was 0.8 µg/dL. Hence, we could rule out Cushing's syndrome. A 24-h total urinary metanephrines and fractionated catecholamines were within normal range. The patient had no evidence of leukemia and lymphoma and a normal complete blood count. Serum and urine protein electrophoresis did not show a paraprotein. She had no history of taking vitamin A, vitamin D, calcium supplements and thiazide medication and no recent history of immobilization.

A dual energy X-ray absorptiometry scan was performed, which revealed mild osteopenia at the lumbar T score −1.8. Assessment of bone metabolism using markers of bone turnover could yield useful information and guide management decisions in our case. Urinary post-menopausal free deoxypyridinoline/creatinine ratio 16.2 nM/mM was significantly increased, whereas serum osteocalcin was under the normal limit (15.2 ng/mL; normal: 22-55 years-15-46 ng/mL) while taking atorvastatin calcium therapy.

Due to the possibility of atorvastatin calcium-induced hypercalcemia, this medication was stopped immediately (Figure 1). Therapeutic lifestyle changes and diet were recommended for her hyperlipidemia. The hypercalcemia was corrected by stopping atorvastatin calcium medication. Calcium levels returned to normal (Figure 1; 10.1 mg/dL, normal: 8.5-10.2 mg/dL). In order to establish a cause-and-effect relationship between atorvastatin calcium and hypercalcemia, the patient started taking the atorvastatin calcium again. Hypercalcemia recurred after exposure to atorvastatin calcium medication (Figure 1). Then, atorvastatin calcium was discontinued again. 10 days later she was discharged, and a 4-week review, indicated that her calcium levels remained normal, with no recurrence of hypercalcemia (Figure 1). 25-hydroxy vitamin D level was 22 ng/mL (normal: 20-30), within normal limits. The patient did not have a strong family history of cardiovascular disease (CHD), but had other risk factors for CHD. Her low-density lipoprotein-cholesterol was under 130 mg/dL, and she did not require a statin medication. When the atorvastatin was stopped, urinary post-menopausal free deoxypyridinoline/creatinine ratio 8.3 nM/mM was significantly decreased, while serum osteocalcin was within normal limits. (18.6 ng/mL; Nl: 22-55 years; 15-46 ng/mL).

DISCUSSION

Our patient presented with asymptomatic hypercalcemia. An extensive workup was performed to diagnosis its cause. Investigations excluded all known causes of hypercalcemia. Our report demonstrated alterations in calcium metabolism, while taking atorvastatin calcium include increased calcium in the blood. We believe that this patient developed hypercalcemia due to long-term treatment with atorvastatin calcium, to which she was exposed because of her hyperlipidemia. Serum calcium increased from the normal range during the 1.5 years of atorvastatin calcium adminis-

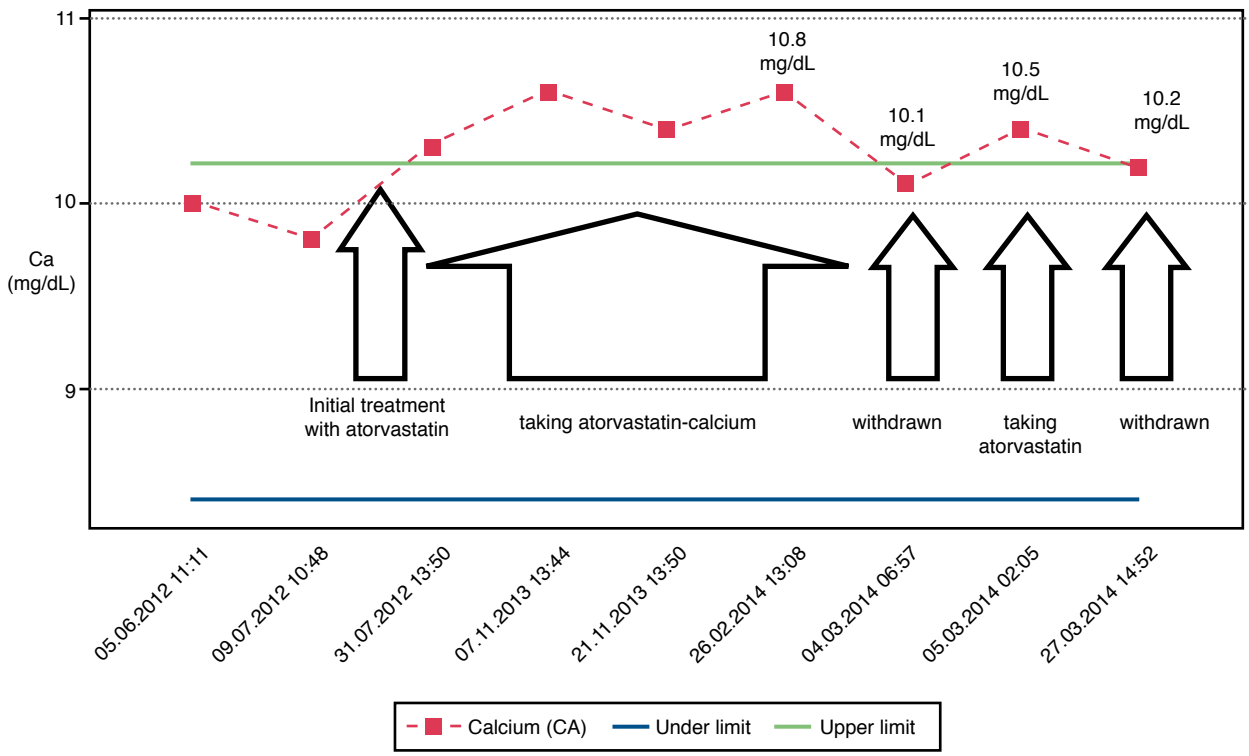

Figure 1. Changes in calcium concentration in the patient while taking atorvastatin-calcium and when the offending agent was withdrawn.

tration and may have continued to rise above normal from exposure to years of atorvastatin calcium.

Although the relationship between atorvastatin and hypercalcemia is uncertain, there are at least several mechanisms thought to be contributing to hypercalcemia in this setting.

Thus, it might be plausible to consider that hypercalcemia is due to drug interaction. Serum calcium levels returned to normal after 2 days when the offering agent was withdrawn (Figure 1). Moreover, hypercalcemia has a rapid onset, which characteristically occurs within 1 day after starting therapy (Figure 1), and serum calcium levels return to normal again when the offering agent is withdrawn (Figure 1). In general, the following four criteria are used to prove a causal relationship between the drug and symptom: The symptom should develop after drug administration, all known underlying causes of hypercalcemia should be excluded, hypercalcemia should improve after cessation of the drug, and the symptom should be recurrent after exposure.[2] In this respect, hypercalcemia meets all four criteria in our patient. The temporary relationship of the onset of hypercalcemia and administration of atorvastatin calcium strongly suggests a causal role for the drug.

Another cause of elevated calcium levels might be the influence of statins on bone metabolism, in terms of increased bone resorption. Biochemical bone resorption markers can determine the rate of bone loss. During osteoclastic bone resorption, pyridionoline cross-links are released into circulation that are degraded and excreted through the kidneys in urine. Therefore, urinary deoxpyridinoline (DPD) levels are derived almost exclusively from bone osteoclastic degradation.[3] According to Vesper et al. study, reference values of DPD/mmol of creatinine ratio are age, gender, ethnicity, geographic effect, race and method dependent.[4]

There was a study on DPD/mmol of creatinine ratio reference interval specified by the menopause state in a healthy population in Turkey. In this report, to assess the severity of the osteoporosis, subjects were divided into three groups according to menopausal state, low losers (normal pre-menopausal), high losers (normal post-menopausal), and very high losers (os-

teoporotic post-menopausal), depending upon urinary DPD/urinary creatinine ranges means of 8.23, 9.76, and more than 20 nmol of DPD/mmol of creatinine, respectively.[5]

A biochemical bone resorption assessment was done, while the patient was taking atorvastatin calcium, in conjunction with a bone mineral density measurement, which identified the patient as having high bone turnover and a sustained high rate of bone loss. Handal et al.[6] reported that atorvastatin calcium appeared to decrease bone strength. Research by Maritz et al.,[7] also using ovariectomies (OVX) rat model, demonstrated significant reductions in femoral BMD in rats treated with atorvastatin. In the literature, using the OVX rat model, Kawane et al.[8] demonstrated that atorvastatin could significantly increase the concentration levels of serum calcium in OVX rats. These findings are consistent with our case. However, our patient had optimal vitamin D levels, there was an increase in free deoxypyridinoline/creatinine ratio (16.2 nM/mM) with she had osteopenia while taking atorvastatin medication and free deoxypyridinoline\ creatinine ratio (8.3 nM/mM) was normalized when the atorvastatin was stopped.

On the other hand, the difference of osteocalcin levels during and after the treatment may also be related to the atorvastatin, and the probable reason for hypercalcemia. The serum levels of osteocalcin have been found to be a specific biochemical parameter of bone formation. In healthy subjects, osteoblastic bone cells respond to the influx of calcium by composing a matrix upon which calcium precipitates. In the process of creating this matrix, 50-70% of the involved osteoblasts die. The greater the influx of calcium, the greater the rate of osteoblast apoptosis. An increased osteoblast apoptosis rate leads to a decrease in age-related osteoblast replicative capacity. Due to the eventual resulting lack of osteoblast activity, microfractures cannot be repaired.[9] These findings are consistent with our case; there was a decrease in serum osteocalcin (15.2 ng/mL; normal: 22-55 years-15-46 ng/mL) while taking atorvastatin medication, and serum osteocalcin was normalized when the atorvastatin was withdrawn.

The dietary reference intakes for vitamin D and calcium report, issued in 2011 by the Institute of Medicine, proposes ≥20 ng/mL as the definition of sufficiency based solely on requirements to prevent osteoporosis.[10] Although it has been hypothesized that serum 25-hydroxy vitamin D concentrations of ≥30-32 ng/mL are optimal in healthy populations,[11] and most patients with vitamin D toxicity have levels <150 ng/mL,[12] some literature has shown that the toxicity of 25-hydroxy vitamin D level begins in lower doses.

An Australian study found an increased fracture risk not only with low 25-hydroxy vitamin D levels (<15 ng mL; hazard ratio [HR] = 4.5]), but also when serum 25-hydroxy vitamin D levels were >30 ng mL (HR of 3.5);[13] however, this U-shaped relationship between fractures and vitamin D status is unclear. Pooling the results of studies on vitamin D and calcium absorption revealed a significant increase in the fraction of calcium absorbed as 25-hydroxy vitamin D levels were increased from 20 to 30 ng/mL (50 to 75 nmol/L), suggesting that the minimum level of vitamin D necessary to maintain optimal calcium absorption should be >30 ng/mL rather than >20.[14-16] On the other hand, another cause of hypercalcemia might include atorvastatin-increased 25-hydroxy vitamin D concentrations. In the literature, some studies reported that atorvastatin therapy increased circulating 25-hydroxy vitamin D levels.[17-20] Elevated 25-hydroxy vitamin D concentrations may induce bone loss, which may cause hypercalcemia. HMG-CoA enzyme reductase is key to the synthesis of cholesterol, whereas ultraviolet radiation causes the formation of 25-hydroxy vitamin D. Inhibition of the enzyme by atorvastatin may increase levels of 7-dehydrocholesterol and increase the synthesis of 25-hydroxycholecalciferol, thereby increasing vitamin D levels.[20] Hypercalcemia may also be an idiosyncratic reaction of the atorvastatin calcium medication and is usually unpredictable until the drug is given.

This case illustrates that atorvastatin calcium-induced hypercalcemia, although rare, should be considered in patients in whom other causes have been excluded, thus presenting resolution of symptoms after medication withdrawal, supported the possibility of drug-induced hypercalcemia. Serum calcium should also be monitored periodically during atorvastatin calcium treatment. When it is decided that atorvastatin calcium should be withdrawn, calcium concentrations may return to the appropriate level within the 1st day after administration stops. The pathophysiology of atorvastatin calcium induced by hypercal-

cemia remains unclear. Future studies evaluating the effect of atorvastatin on calcium metabolism will help clarify these relations.

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Anahtar sözcükler: Atorvastatin; hiperkalsemi; deoksipiridin.