A case of chronic asymptomatic hypercalcemia in an individual with insulin resistance syndrome

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European Journal of Medical Case Reports
Volume 5(6):187–190
https://doi.org/10.24911/ejmcr/173-1614468533

ABSTRACT

Background: Calcium, the major inorganic component in bone, plays an important role in insulin secretion and insulin resistance. Insulin resistance is essential in the pathophysiology of non-alcoholic steatohepatitis (NASH), polycystic ovarian syndrome (PCOS), and Type 2 diabetes mellitus (DM).

Case Presentation: We present a case of chronic asymptomatic hypercalcemia in an individual with NASH, PCOS, and DM. She was noted to have a serum calcium of 12.8 mg/dl and a homeostatic model assessment of insulin resistance (HOMA-IR) of 4.7 in the last 2 years. Almost all other causes of hypercalcemia were ruled out. The patient was treated conservatively and advised to avoid factors that can aggravate hypercalcemia.

Conclusion: The insulin effect on calcium homeostasis is impaired in conditions of insulin resistance. There is increasing evidence of the association between hypercalcemia and insulin resistance. However, it remains a diagnosis of exclusion.

Keywords: Liver disease, hypercalcemia, non-alcoholic steatohepatitis, insulin resistance, diabetes mellitus.

Received: 27 February 2021 **Accepted:** 25 May 2021 **Type of Article:** CASE REPORT **Specialty:** Nephrology

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Background

Calcium is the major inorganic component in bone and is vital for contraction and relaxation of muscles. Serum calcium is closely regulated by parathyroid hormone (PTH), estrogen, testosterone, vitamin D, phosphate, and magnesium. When the serum calcium level drops, parathyroid gland increases the secretion of PTH which in turn has effects on kidneys and bones. In the kidney, PTH blocks reabsorption of phosphate, increases calcium reabsorption, and calcitriol formation which in turn acts on the small intestine to increase dietary calcium absorption. In the bone, PTH causes osteoclast resorption which leads to the release of calcium. Normal calcium level ranges from 8.4 to 10.6 mg/dl but varies by lab and age. Hypercalcemia is the condition in which the serum calcium level is above normal.

There are several studies demonstrating a relationship between serum calcium and insulin resistance [1]. Higher serum calcium levels appear to precede peripheral insulin resistance [1]. Insulin resistance is one of the leading causes of non-alcoholic steatohepatitis (NASH) and contributes to the pathophysiology of polycystic ovarian syndrome (PCOS) and Type 2 diabetes mellitus (DM). Calcium homeostasis plays an important role in insulin secretion and insulin resistance. Calcium influx through voltage-gated calcium channels is necessary for insulin secretion from the pancreatic β cells. Changes in calcium or insulin concentration can result in altering this pathway. Here we report the case of an individual with unexplained, chronic and asymptomatic hypercalcemia.

Case Presentation

A 52-year old Caucasian female is seen at a nephrology follow-up visit for treatment of diabetic nephropathy [Chronic Kidney Disease (CKD) Stage 3]. She has a history of type 2 DM for 14 years, essential hypertension, obesity, hyperlipidemia, bronchial asthma, and PCOS. Review of her medical records shows asymptomatic intermittent elevated calcium level over the last 2 years. She was noted to have serum calcium of 10.7 mg/dl during her last visit with a prior highest calcium level of 12.8 mg/dl over the last 2 years. Her ionized calcium was 5.6 mg/dl (normal levels 4.8-5.6 mg/dl) and her homeostatic model assessment of insulin resistance (HOMA-IR) levels were 4.7 (February 2019), 3.7 (April 2019) and 2.8 (May 2019). Her albumin and total protein levels were normal. Figure 1 shows the serum calcium and PTH levels over the last 2 years. She has no previous history or family history of hypercalcemia. She is a non-smoker and does not

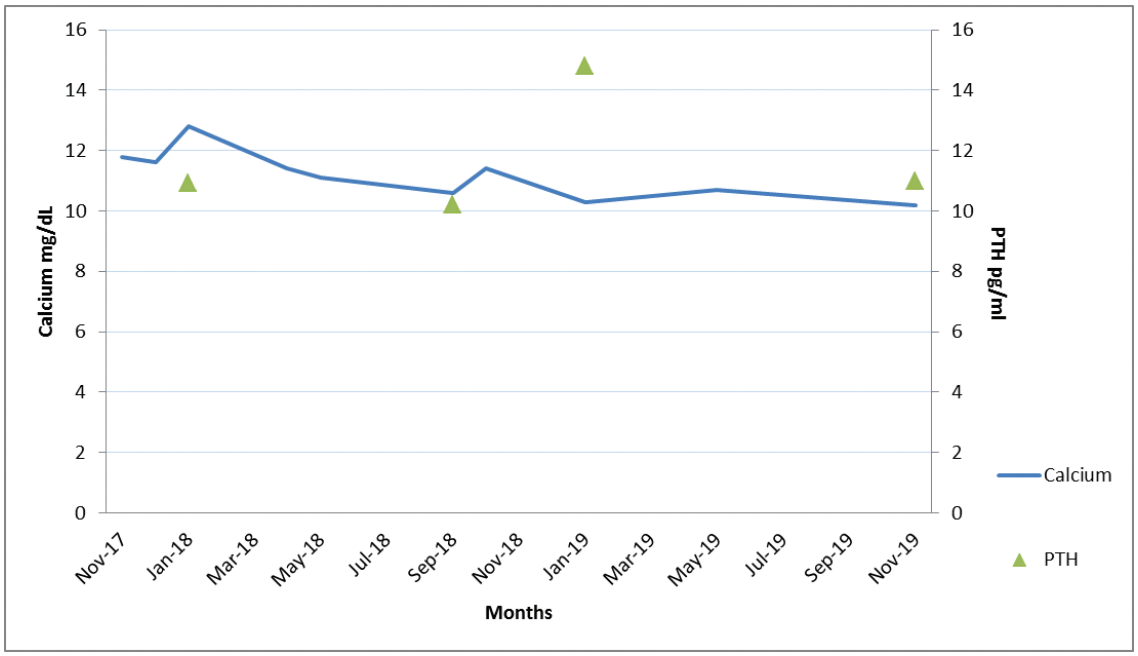

Figure 1. *Serum calcium and PTH levels during the last 2 years.*

Table 1. *Laboratory results from her clinic visits.*

Test	Results				Normal range
	January, 2018	May, 2018	January, 2019	May, 2019	
HbA1C	7.4	7.1	7.1	7.3	4.0-6.0
Calcium	10.8	11.1	10.3	10.7	8.4-10.6 mg/dl[a]
Albumin	4.8	4.8	4.6	4.6	3.2-5.5 g/dl
Total protein	7.3	7.6	7.7	7.0	6.0-8.3 g/dl
HOMA-IR	-	-	4.7 (February, 2019)	2.8	
Ionized calcium	-	-	-	5.6	4.8-5.6 mg/dl
PTH	10.91	-	14.78	-	15-59 pg/ml
Total 25 OH vitamin D	27	-	27	-	30-100 ng/ml
1,25 OH vitamin D	-	-	14 (September, 2018)	-	18-72 pg/ml
24-hour urine calcium	329	-	-	-	35-250 mg/24 hour
Creatinine	1.12	1.11	1.45	1.12	0.4-1.3 mg/dl
eGFR	56.1	56.6	40.8	55.6	90-120 ml/min/1.73m^2
PTH-RP	-	-	-	19	14-27 pg/ml
TSH	1.29	1.33	1.33	-	0.35-5.50 mIU/ml

[a]Not adjusted for age.
Note: Some laboratory tests were not done on all visits.

use alcohol or any illicit drugs. She is post-menopausal and has never been pregnant. Physical examination was unremarkable except for obesity (BMI = 38.1). Her medications include albuterol, bupropion, aspirin, insulin, metformin, allopurinol, empagliflozin, statin, spironolactone, pioglitazone, and fexofenadine.

She underwent a systematic investigation for hypercalcemia. Patient denied any current vitamin D or calcium supplements. Her lab results are listed in Table 1. Angiotensin-converting enzyme (ACE) levels were not checked. A skeletal survey showed no lesions, CT of the abdomen and pelvis showed no evidence of a tumor and CT of the chest showed no abnormalities. An electrocardiogram was normal. A renal biopsy showed diabetic nephropathy with moderate interstitial fibrosis and tubular atrophy. Bone marrow biopsy ruled out plasma cell disorders or lymphomas. She had a fibroscan performed that revealed advanced fibrosis/cirrhosis. She had a subsequent liver biopsy that showed inflammation from fatty liver (NASH) with stage 3 fibrosis. The patient was treated conservatively and advised to avoid factors that can aggravate hypercalcemia.

Discussion

We describe a case of hypercalcemia associated with NASH, PCOS and Type 2 DM related to severe insulin resistance. It has been hypothesized that an increased PTH level leads to increased intracellular free calcium and decreased insulin stimulated tissue uptake of glucose which in turn can cause insulin resistance [2]. However, hyperparathyroidism induced hypercalcemia was ruled out due to low PTH levels in the patient. The 25 hydroxy vitamin D and 1,25 hydroxy vitamin D levels measured by liquid chromatography/tandem mass spectrometry were also appropriately low. In granulomatous diseases, there is an increased production of 1,25 hydroxy vitamin D leading to hypercalcemia. There is no history of TB, silicosis, histoplasmosis, Wegener's granulomatosis or Crohn's disease. Thyroid hormone increases bone resorption which results in mild hypercalcemia. Her thyroid parameters were all normal. She also did not have a history of hypercalcemia in her family and her high 24-hour urine calcium ruled out familial hypocalciuric hypercalcemia. Tumors stimulate osteoclastic bone resorption which results in hypercalcemia. Two major mechanisms by which malignancy causes hypercalcemia are excessive production of parathyroid hormone-related protein (PTHrP) by the tumor and osteolytic metastatic disease. Normal PTHrP measured by immunoassay, negative history and imaging performed ruled out tumors and bone metastasis in this patient. Although immobilization is a cause of hypercalcemia, our patient was never bedridden or hospitalized. The patient did not have a history of vitamin A or D supplements, antacids, milk, thiazide, antiestrogen therapy or theophylline intake. Normal calcium levels can vary with age. A calcium level more than 10 mg/dl in a woman over 50 years is abnormal.

Insulin secretion is a calcium dependent process. Any alteration in calcium concentration can affect the release of insulin from the beta cells. Influx of calcium into the beta cell causes insulin secretion which is amplified by glucose metabolism. Calcium influx increases in states of high glucose. High intracellular calcium reduces insulin receptor activity by inhibiting dephosphorylation of insulin receptor and glycogen synthase [3]. Resnick et al. [4] showed that the higher intracellular calcium was associated with increased insulin resistance. An increase in extracellular calcium may also correlate with an increase in serum calcium. A previous study showed that an increased serum calcium lead to the increased influx of calcium from the serum to the arterial vessels which increased cytosolic calcium resulting in muscle contraction and elevation in blood pressure [5]. The insulin effect on calcium homeostasis is impaired in conditions of insulin resistance.

Chronic liver disease (CLD) has been described as a cause of hypercalcemia with or without malignancy, but it is a diagnosis of exclusion. Gerhardt et al. [6] described 16 individuals with liver disease who had hypercalcemia, 11 of which had no evidence of tumor. However, 56% of them were taking vitamin D supplements and many of them had CKD [6]. Kuchay et al. [7] described two cases of CLD who developed hypercalcemia which normalized upon treatment with saline diuresis, calcitonin and improvement of liver function. These patients were not on any supplements [7]. NASH is one of the most common forms of CLD.

NASH and PCOS are closely associated with insulin resistance. Chitturi et al. [8] reported that 98% of patients with NASH had insulin resistance in his study. In a study of 271 PCOS patients and 260 controls, the prevalence of insulin resistance was 64% in the PCOS group [9]. A meta-analysis of 17 studies showed that PCOS was significantly associated with high risk of NASH and was interrelated to insulin resistance [10].

CKD can also contribute to insulin resistance. Inflammation, oxidative stress, elevations in aldosterone, angiotensin II, uremic toxins, and metabolic acidosis have been implicated [11]. Individuals with higher insulin levels and HOMA-IR have a more rapid GFR loss [12].

Several studies suggest a HOMA-IR value [calculated by using the formula; Fasting insulin (mIU/l)*fasting glucose (mg/dl)/405] of more than 2 is associated with insulin resistance. Her latest HOMA-IR level was 2.8. Wu et al. [1] in a study of 8,653 participants, showed a 1-directional relationship from elevated serum calcium to peripheral insulin resistance. Another study of 1,182 subjects in the Newfoundland population showed that patients in the high calcium group had the highest glucose and insulin resistance compared to the low calcium group [13]. A study of 16,592 Korean individuals demonstrated that, 60% of those diagnosed with NASH were in the highest calcium quartile [14]. In a study of 271 men and 209 women with Type 2 DM, a positive correlation between serum calcium and HOMA-IR ($r = 0.2$, $p = 0.002$) in men was observed [15]. DM is a condition in which calcium homeostasis is impaired. In the Insulin Resistance Atherosclerosis Study, a high serum calcium was associated with an increased risk of developing Type 2 DM [16].

Conclusion

We present a case of chronic hypercalcemia in an individual with NASH, PCOS, and Type 2 DM. This disease association is becoming more common in literature and clinical practice. There is increasing evidence of the association between hypercalcemia and insulin resistance. However, it remains a diagnosis of exclusion.

What is new?

There is increasing evidence of the association between hypercalcemia and insulin resistance. However, it remains a diagnosis of exclusion. The authors present a case of chronic hypercalcemia in an individual with NASH, PCOS and Type 2 DM.

Abbreviations

ACE	Angiotensin-converting enzyme
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
DM	Diabetes Mellitus
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
NASH	Non-alcoholic steatohepatitis
PCOS	Polycystic ovarian syndrome
PTH	Parathyroid hormone

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this case report.

Funding

None.

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 52 years old
2	**Final diagnosis**	Hypercalcemia
3	**Symptoms**	Asymptomatic
4	**Medications**	Conservative treatment
5	**Clinical procedure**	None
6	**Specialty**	Nephrology, Endocrinology