Case Report

Hypocalciuric Hypercalcemia due to Impaired Renal Tubular Calcium Excretion in a Type 2 Diabetic Patient

Sihao Yang,1,2 Yan Ren,1 Xi Li,1 Haoming Tian,1 Zhenmei An,1 and Tao Chen1

1Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, Chengdu, China
2Department of Chinese Traditional Medicine, The Second People’s Hospital of Yibin, Yibin, China

Correspondence should be addressed to Zhenmei An; 848948343@qq.com and Tao Chen; dr.chentao@qq.com

Received 17 November 2016; Accepted 9 January 2017; Published 11 April 2017

Academic Editor: Wayne V. Moore

Copyright © 2017 Sihao Yang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The case we presented here was a 73-year-old gentleman, who was admitted to endocrinology department due to recurrent fatigue for 1 year. He had medical histories of type 2 diabetes for 18 years and developed CKD 4 years ago. He also suffered from dilated cardiomyopathy, and coronary heart disease, moderate sleep apnea syndrome, primary hypothyroidism, and gout. His treatment regimen was complicated which included Caltrate D and compound \( \alpha \)-keto acid (1200mg calcium/d). Laboratory examination revealed that his serum calcium level elevated, 24-hour urine calcium output decreased, PTH level was suppressed, and 25-hydroxyvitamin D was in normal low range. No other specific abnormalities were found in serum bone turnover markers, ultrasonography, computed tomography, and bone scintigraphy. The diagnosis was suggested to be hypocalciuric hypercalcemia but was different from familial or acquired hypocalciuric hypercalcemia which were featured by elevated PTH level. The patient was asked to restrict calcium intake and to take diuretics; then his serum calcium level gradually lowered. In brief, patients with CKD could present with hypocalciuric hypercalcemia due to impaired renal calcium excretion. In this case, calcium restriction should be applied for treatment.

1. Introduction

Hypercalcemia related to PTH, malignancy diseases (PTHrP or destruction), and vitamin D metabolites usually could be easily diagnosed according to clinical setting [1]. However, in other cases, especially in cases with PTH independent hypercalcemia, the etiology is often difficult to identify. A published review summarized the rare causes of hypercalcemia and showed the potential mechanisms including calcitriol overdosage, occult milk-alkali syndrome, some medications (e.g., omeprazole, theophylline toxicity, and growth hormone), and other diversity causes [2]. Other recent studies showed that sarcoidosis [3], granulomatosis/granuloma [4, 5], diabetic ketoacidosis [6], and methylmethacrylate for cosmetic purposes [7] could also be causes for PTH independent hypercalcemia. However, hypercalcemia due to impaired renal calcium excretion was rarely reported. Here, we presented a case of hypocalciuria hypercalcemia with suppressed PTH levels. The mechanism could be impaired renal tubular calcium regulation.

2. Case Report

The patient was a 73-year-old man who was admitted in September 21, 2015, due to recurrent fatigue for 1 year. He was diagnosed as type 2 diabetes 18 years ago, developed chronic kidney disease 4 years ago, and began to take compound \( \alpha \)-keto acid (2520mg three times a day, approximately containing 600mg calcium/d). Laboratory examination revealed that his serum calcium level elevated, 24-hour urine calcium output decreased, PTH level was suppressed, and 25-hydroxyvitamin D was in normal low range. No other specific abnormalities were found in serum bone turnover markers, ultrasonography, computed tomography, and bone scintigraphy. The diagnosis was suggested to be hypocalciuric hypercalcemia but was different from familial or acquired hypocalciuric hypercalcemia which were featured by elevated PTH level. The patient was asked to restrict calcium intake and to take diuretics; then his serum calcium level gradually lowered. In brief, patients with CKD could present with hypocalciuric hypercalcemia due to impaired renal calcium excretion. In this case, calcium restriction should be applied for treatment.
# Table 1: The changes of the patient’s serum and urine calcium levels and their related biochemical indexes in recent 7 years.

| Events          | Calcium 600 mg/d | Added compound α-keto acid (600 mg calcium/d) | Initially suspected hypercalcemia during review | Diagnosed as hypercalcemia; ceased calcium, Alphacalcidol | This admission; ceased compound α-keto acid | Compound α-keto acid (150 mg calcium/d) |
|-----------------|------------------|-----------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------|------------------------------------------|
| Serum BUN       | 7.15             | 17.62                                         | 9.2–12.1                                        | 11.66                                           | 11.78                                     | 13.36–20.65                             | 15.8                                     | 22.4                                     | 25.6–33.7                                |
| Serum creatinine| 95.6             | 181.5                                         | 128.4–140.2                                     | 128.3                                           | 164.3                                     | 142.0–183.0                             | 212.0                                    | 134.0                                    | 137.0–182.0                             |
| eGFR            | N/A              | N/A                                           | N/A                                             | N/A                                             | N/A                                      | N/A                                      | 7.43                                     | N/A                                      | N/A                                      |
| PH value        | N/A              | N/A                                           | N/A                                             | N/A                                             | N/A                                      | N/A                                      | N/A                                      | N/A                                      | N/A                                      |
| Serum calcium   | 2.34             | 2.28                                          | 2.16–2.65                                       | 2.67                                            | **3.41**                                  | **2.24–2.93**                           | **3.24**                                 | **2.02**                                 | 2.20–2.59                                |
| Serum phosphate | 0.95             | 0.99                                          | 0.65–1.65                                       | 1.33                                            | 1.29                                     | 1.3–1.4                                  | 0.94                                     | 1.06                                     | 1.07–1.41                                |
| Urine calcium<sup>a</sup> | 5.01 | N/A                                           | 1.63<sup>b</sup>                                | N/A                                             | 2.51                                     | N/A                                      | 2.21                                     | 0.29                                     | 0.19–0.34                                |
| Urine volume (L) | 1.50             | N/A                                           | 2.4                                             | N/A                                             | 1.50                                     | N/A                                      | 1.21                                     | 0.6                                      | 1.4–2.0                                  |
| PTH             | 5.48             | 18.05                                         | 3.58–5.19                                       | **0.76**                                        | **0.82**                                  | 0.79–0.82                                | 0.79                                     | 11.44                                    | 8.12                                     |
| 25(OH)D         | 40.61            | 26.56                                         | 36.3–372                                        | 71.08                                           | 44.62                                     | N/A                                      | 50.11                                    | 27.16                                    |                                         |
| 1,25(OH)<sub>2</sub>D<sup>a</sup> | 30.47 | 165.65                                        | 30.93                                           | N/A                                             | N/A                                      | N/A                                      | N/A                                      | N/A                                      | N/A                                      |
| bALP            | 8.67             | 12.94                                         | N/A                                             | N/A                                             | 12.02                                     | N/A                                      | 14.23                                    | N/A                                      | N/A                                      |
| CTX             | U/A              | 0.10                                          | N/A                                             | 0.117                                           | N/A                                      | 0.154                                    | N/A                                      | N/A                                      | N/A                                      |

Reference value: 1,25(OH)<sub>2</sub>D 39–193 pmol/L; 25(OH)D 477–144 pmol/L; 24-hour urine calcium 2.5–7.5 mmol/24 hours; bALP 11.4–24.6 μg/L; CTX 0.3–0.584 ng/mL; eGFR 56–122 mL/min/1.73 m<sup>2</sup>; PTH 16–69 pmol/L; serum BUN 3.82–8.86 mmol/L; serum creatinine 53.0–140.0 μmol/L; serum calcium 2.1–2.7 mmol/L; serum phosphate 0.81–1.45 mmol/L.<sup>a</sup>Measurement of 1,25(OH)<sub>2</sub>D was unavailable since the end of 2013.<sup>b</sup>24-hour urine calcium was 1.63 mmol when serum calcium was at the level of 2.2 mmol/L.
Table 1

| Procedure                  | Results                        |
|----------------------------|--------------------------------|
| Serum calcitonin           | 25pg/ml (normal 3.9–12.8 pg/ml) |
| 25-hydroxyvitamin D        | Normal                        |
| 24-hour urine calcium       | Normal                        |
| Urine creatinine           | Normal                        |
| Calcium-stimulated parathyroid hormone (CSF) | Normal |

**3. Discussion**

Hypocalciuric hypercalcemia as familial pattern was well-known [1]. In recent two decades, acquired hypocalciuric hypercalcemia was reported and was supposed to be resulting from autoantibody against calcium-sensing receptor (CSRP) [8, 9]. A typical feature of acquired hypocalciuric hypercalcemia was to have slightly elevated PTH level, which is due to increased set point of parathyroid cell for serum calcium. While, in this case, PTH was suppressed when serum calcium increased. PTH elevated when serum calcium decreased, indicating normal function of CSRP in this patient's parathyroid gland. Thus, we deduced that his hypercalcemia was caused by impaired calcium excretion from urine.

In normal person, about 59% of total serum calcium is filtered into crude urine. Then, 90% of those were reabsorbed by proximal tubules, henry loop, and early distal tubules and nearly 10% reabsorbed by early collecting ducts and late distal tubular. The latter portion is relatively few but more important in calcium hemostasis because it is highly dependent on the blood calcium ion concentration. A slightly elevation of serum calcium level, under the regulation of PTH, will result in strikingly increasing calcium excretion from urine [8, 10].

In this case, the patient's serum PTH level changed corresponding to alteration of serum calcium level but failed to maintain serum calcium to the normal range. Thus, we proposed that the patient's hypocalciuric hypercalcemia resulted from impaired response of late distal tubular and early collecting ducts to the changed PTH level. We searched Medline (PubMed, update to May 2, 2016) using Mesh term “Hypocalciuric Hypercalcemia” but failed to retrieve any similar reports. We were unable to perform renal biopsy because of the patient's refusal. So, we could not, regrettably, demonstrate the exact mechanism of how the patient's renal tubular failed to respond to changed serum calcium level. The differential diagnosis of hypercalcemia without clear etiology is often very difficult; therefore, the case we presented here might provide some valuable information for future clinical practice.

**4. Conclusion**

PTH independent hypocalcaemia could be caused by decreased urine calcium excretion in patients with complicated clinical conditions. Calcium restriction and carefully monitoring were the key points in treatment.

**Competing Interests**

The authors declare that they have no competing interests.

**Authors’ Contributions**

Sihao Yang and Yan Ren contributed equally to this paper.

**References**

[1] F. Bringhurst, M. Demay, and H. Kronenberg, “Hormones and disorders of mineral metabolism,” in Williams Textbook of Endocrinology, S. Melmed, K. Polonsky, P. Larsen, and H. Kronenberg, Eds., pp. 1260–1277, Elsevier Saunders, Philadelphia, Pa, USA, 12th edition, 2011.

[2] T. P. Jacobs and J. P. Bilezikian, “Clinical review: rare causes of hypercalcemia,” Journal of Clinical Endocrinology and Metabolism, vol. 90, no. 11, pp. 6316–6322, 2005.

[3] R. Lupica, M. Buemi, A. Campenni et al., “Unexpected hypercalcemia in a diabetic patient with kidney disease,” World Journal of Nephrology, vol. 4, no. 3, pp. 438–443, 2015.

[4] P. Hardy, P. H. Morinère, B. Tribout et al., “Liver granulomatosis is not an exceptional cause of hypercalcemia with hyperparathyroidism in dialysis patients,” Journal of Nephrology, vol. 12, no. 6, pp. 398–403, 1999.

[5] S. M. Hindi, Y. Wang, K. D. Jones et al., “A case of hypercalcaemia and overexpression of CYP27B1 in skeletal muscle lesions in a patient with HIV infection after cosmetic injections with polymethylmethacrylate (PMMA) for wasing,” Calcified Tissue International, vol. 97, no. 6, pp. 634–639, 2015.

[6] T. Makaya, S. Chatterjee, P. Arundel, C. Bevan, and N. P. Wright, “Severe hypercalcemia in diabetic ketoacidosis: a case report,” Diabetes Care, vol. 36, no. 4, article no. e44, 2013.

[7] D. V. Rados and T. W. Furlanetto, “An unexpected cause of severe and refractory PTH-independent hypercalcemia: case report and literature review,” Archives of endocrinology and metabolism, vol. 59, no. 3, pp. 277–280, 2015.

[8] J. C. Pallais, O. Kifor, Y.-B. Chen, D. Slovik, and E. M. Brown, “Acquired hypocalciuric hypercalcemia due to autoantibodies against the calcium-sensing receptor,” New England Journal of Medicine, vol. 351, no. 4, pp. 362–369, 2004.

[9] N. Makita, J. Sato, K. Manaka et al., “An acquired hypocalciuric hypercalcemia autoantibody induces allosteric transition among active human Ca-sensing receptor conformations,” Proceedings of the National Academy of Sciences of the United States of America, vol. 104, no. 13, pp. 5443–5448, 2007.
[10] A. Guyton and J. Hall, "Renal regulation of potassium, calcium, phosphate, and magnesium; Integration of renal mechanisms for control of blood volume and extracellular fluid volume," in Guyton and Hall Textbook of Medical Physiology, pp. 371-373, Elsevier Saunders, Philadelphia, Pa, USA, 12th edition, 2006.