Hypocalcemia following Treatment for Hyperthyroidism

Claire L. Meek,[1*] Felicity Kaplan,[2] R. Scott Pereira,[3] and Adie Viljoen[1]

[1] Departments of Chemical Pathology, [2] Endocrinology, and [3] Immunology, Lister Hospital, Stevenage, UK.

* Address correspondence to this author at: Department of Chemical Pathology, Lister Hospital, Corey's Mill Lane, Stevenage SG1 4AB, UK. E-mail claire.meek@nhs.net.

CASE

A 17-year-old female was referred to the endocrinology clinic after blood test results suggestive of hyperthyroidism. She had mild symptoms of thyrotoxicosis, including menstrual disturbance with intermittent palpitations and tremor. On examination, the patient was normotensive, tachycardic (100 beats/min), and of slim build with poor dentition. She had a small diffuse goiter without retrosternal extension or bruit. There was conjunctival injection but no evidence of lid lag or proptosis. Auscultation of the precordium revealed murmurs in systole and diastole consistent with mixed aortic valve disease.

The only child of healthy nonconsanguineous parents, the patient had previously been well. Her medical history included mild learning difficulties, a bicuspid aortic valve, recurrent urinary tract infections, and severe constipation as a child that required a colostomy, which was later reversed. Apart from an osmotic laxative, she received no other regular medication. A recent echocardiogram had demonstrated a bicuspid aortic valve with good flow and minor regurgitation.

Biochemically, the patient had an undetectable serum concentration of thyroid-stimulating hormone (TSH) (<0.03 mIU/L; reference interval, 0.3–5.6 mIU/L) and an increased concentration of free thyroid hormone (fT4) [43 pmol/L (3.3 ng/dL); reference interval, 7.5–21.1 pmol/L]. Her baseline serum concentrations of total calcium [2.27 mmol/L (9.08 mg/dL)] and phosphate [1.26 mmol/L (3.9 mg/dL)] were both within their reference intervals (2.20–2.60 mmol/L and 0.75–1.36 mmol/L, respectively).Theserum albumin concentration was 41 g/L (reference interval, 35–50 g/L), and the magnesium concentration was 0.71 mmol/L (reference interval, 0.74–1.00 mmol/L). The results of her other biochemical tests were unremarkable. An immunologic analysis demonstrated increased thyroid peroxidase antibodies (582 IU/L; reference interval, 0–60 IU/L) and increased TSH receptor antibodies (6.9 U/L; reference interval, 0–1.5 U/L), confirming Graves disease. Thyroid imaging revealed a diffusely enlarged thyroid gland, with no visible parathyroid tissue apparent on ultrasound and MRI evaluations.

After daily treatment with 30 mg carbimazole and 25 mg atenolol, the fT4 concentration in the patient decreased as expected (fT4, 19.2 pmol/L; TSH, 0.03 mIU/L). Concomitantly, the patient developed asymptomatic hypocalcemia [calcium, 1.72 mmol/L (6.88 mg/dL)]. The total 25-hydroxyvitamin D concentration was 38 nmol/L (reference interval, 15–100 nmol/L), and her serum magnesium concentration was 0.87 mmol/L (reference interval, 0.74–1.00 mmol/L). Both were within their respective reference intervals. The serum phosphate concentration was 1.28 mmol/L (reference

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interval, 0.9 –1.35 mmol/L), and the albumin concentration was 48 g/L (reference interval, 35–50 g/L). The parathyroid hormone (PTH) concentration was also within the reference interval [4.8 pmol/L (4.8 ng/L); reference interval, 1.6 –9.3 pmol/L] and thus inappropriately normal given the degree of hypocalcemia. A diagnosis of hypoparathyroidism was made, and the patient was treated with 0.5 _g alfacalcidol daily. The calcium concentration briefly normalized (Table 1).

After this improvement, the patient stopped complying with her carbimazole and alfacalcidol treatment regimen, and the results of thyroid function tests returned to near pretreatment concentrations [fT4, 58.4 pmol/L (4.5 ng/dL); TSH,<0.03 mIU/L; calcium, 2.34 mmol/L (9.36 ng/dL); Table 1]. With improved patient compliance, the fT4 results improved, approaching euthyroidism. The patient eventually achieved a normocalcemic state [fT4, 13.5 pmol/L (1.0 ng/dL); calcium, 2.35 mmol/L (9.4 mg/dL)]. More recently, compliance has been a concern with recurrent increased fT4 concentrations (Table 1).

The patient gave full written consent for the use of her clinical information and laboratory tests for the purposes of submission of a case report to the medical literature. She has very mild learning difficulties but was able to understand, process, and retain the information given.

Table 1. Chronological changes in the serum concentrations of total calcium and fT4 as treatment progressed.[a]

Analyte	Reference interval	Months after presentation					
		0	5	6	12	22	36
TSH, mIU/L	0.3–5.6	**<0.03**	**0.03**	**0.03**	**<0.03**	**<0.03**	**<0.03**
fT4, pmol/L	10–21	**43.0**	19.2	11.8	**58.4**	13.5	**54.1**
Total calcium, mmol/L (mg/dL)	2.2–2.6 (8.8–10.4)	2.27 (9.08)	**1.72 (6.88)**	2.21 (8.84)	2.34 (9.36)	2.35 (9.40)	2.44 (9.76)
Phosphate, mmol/L	0.9–1.35	1.26	1.28	1.20	NA	1.25	0.83
Albumin, g/L	35–50	41	48	**53**	NA	NA	43

[a] At presentation of thyrotoxicosis, treatment with carbimazole caused fT4 to improve, with a significant reduction in calcium. Concomitant treatment with alfacalcidol caused calcium concentrations to normalize. Treatment noncompliance 12 months after presentation caused a thyrotoxicosis relapse, which was treated to achieve euthyroidism and normocalcemia. The most recent results demonstrate recurrent thyrotoxicosis, which may also be related to noncompliance. Values in boldface are outside the reference interval. NA, data not available.

Questions to Consider
• What effect does thyrotoxicosis have on serum calcium?
• What other endocrine disorders affect serum calcium?
• What genetic diseases can affect serum calcium?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the June 2011 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol57/issue6 and follow the link to the Clinical Case Study and Commentaries.

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