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Immobilization hypercalcaemia with severe bone mineral loss and hypogonadism

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Summary

Moderate hypercalcaemia occurred in a 17-year-old male who was immobilized with abdominal and right hip sepsis for 9 months after a motor vehicle accident.

The hypercalcaemia was due to bone resorption, with a urine hydroxyproline:creatinine ratio of 0.203 (normal <0.017) and a urine calcium loss of 22.9 mmol/24 hr, associated with impaired renal function. There was radiological evidence of severe bone demineralization in the pelvis over 42 weeks.

Radiocalcium absorption, using ^{45}Ca , was decreased (0.17, normal range 0.35-1.30), renal tubular maximum for calcium reabsorption was decreased (1.61 mmol/l glomerular filtrate, normal range 1.8-2.2), the serum parathyroid hormone concentration was in the low normal range (3.2, 3.6 u/l, normal range 2-6) and the plasma 1,25-dihydroxy-vitamin D concentration was decreased despite a normal 25-hydroxy-vitamin D concentration, indicating suppression of the parathyroid, 1,25-dihydroxy-vitamin D axis. The patient was found to be hypogonadal at 41 weeks after admission and testosterone therapy was begun, with associated improvement in mobilization and a reduction of the hypercalcaemia.

KEY WORDS: hypercalciuria, immobilization, bone resorption, osteopenia, acute renal failure.

Introduction

Albright *et al.* (1941) were the first to describe a syndrome of hypercalcaemia, hypercalciuria and renal failure in immobilized patients. In the majority

of cases the hypercalcaemia has been mild (Hulley *et al.*, 1971; Laurence *et al.*, 1973; Claus-Walker *et al.*, 1975a; Claus-Walker *et al.*, 1975b; Bergman *et al.*, 1977; Naftchi *et al.*, 1980; Stewart *et al.*, 1982) although severe hypercalcaemia has been documented (Henke, Thompson and Kaufer, 1975). The case to be described was studied in detail to increase understanding of the aetiology of the condition and effects of various treatment options.

Case report

A 17-year-old male received severe head, abdominal and limb injuries in a motor vehicle accident. A right hip injury became septic and intra-abdominal sepsis impaired his nutrient intake necessitating parenteral and enteral nutrition. He was immobilized either in traction or a hip spica for 30 weeks and also suffered a severe weight loss, falling to 50% of his ideal weight.

Plasma ionized calcium was calculated from total calcium, albumin and globulin concentrations (Hodgkinson and Knowles, 1976) to overcome the problem of the effects of hypoalbuminaemia on plasma total calcium concentration.

Hypercalcaemia was first evident on multiple biochemical analysis 4 weeks after admission when he was recovering from acute renal failure. Subsequently he was normocalcaemic for a few days and then became hypercalcaemic for 35 weeks (Fig. 1). Calcium was not given with the parenteral nutrition and the hypercalcaemia did not decrease when parenteral nutrition was stopped temporarily in the 16th to 19th weeks. After persistent hypercalcaemia for 30 weeks, further investigations were performed. Serum parathyroid hormone (PTH) concentrations

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FIG. 1. Sequential plasma biochemical changes during immobilization hypercalcaemia. Normal ranges shown in shaded areas.

were low normal (3.2, 3.6 u/l) (normal range 2-6) measured by a C-terminal assay (CIS, Belgium). Urine calcium excretion was markedly increased at 22.9 mmol/24 hr (normal range 2.5-7.5), phosphate excretion was normal at 26 mmol/24 hr (normal range 13-55) and creatinine clearance was decreased at 54 ml/min. The plasma creatinine concentration was normal (0.10 mmol/l) indicating a severe decrease in muscle mass. The calcium:creatinine and

hydroxyproline:creatinine molar ratios obtained on fasting urine samples were increased at 3.0 (normal range 0.06-0.45) and 0.203 (normal range for men 0.003-0.015 (Hodgkinson and Thompson, 1982)). Renal tubular maximum for calcium reabsorption (Nordin, Horsman and Aaron, 1976) was decreased at 1.6 mmol/l of glomerular filtrate (normal range 1.8-2.2) and tubular maximum for phosphate (Nordin *et al.*, 1976) was normal at 0.85 mmol/l glomeru-

FIG. 2. Radiographs of lesser trochanter area of left femur before (left) and after (right) 42 weeks of immobilization showing loss of bone density and coarsening of trabecular pattern.

lar filtrate (normal range 0.7–1.3). The hourly fractional rate of calcium absorption (Marshall, 1976) using ^{45}Ca , was decreased at 0.17 (normal range 0.35–1.30). The 25-hydroxy-vitamin D concentration was 21 nmol/l (normal range 40–160). A random plasma cortisol concentration was 540 nmol/l excluding hypofunction of the adrenal cortex, and the effective thyroxine ratio was 1.06 (normal range 0.94–1.18).

There was no evidence of renal calcification on radiography but a marked loss of bone density, with development of coarse trabecular markings in the spine, pelvis and femurs, was seen over a 42-week period (Fig. 2).

The hypercalcaemia was treated initially with increased fluid intake, oral phosphate tablets 500 mg twice daily, and salmon calcitonin 100 units subcutaneously, twice daily with no response. The plasma 1,25-dihydroxy-vitamin D after 41 weeks was 23 pmol/l (normal range 50–150) and at this time the serum 25-hydroxy-vitamin D concentration had increased to 50 nmol/l. This was attributed to maintenance quantities of vitamin D (200 u/l) given in his enteral feed (Osmolite, Abbott Laboratories) which had begun seven weeks before the plasma calculated ionized calcium reached a peak of 1.67 mmol/l (normal range 1.06–1.17). The normalized androgen ratio (Gilliland, Smeaton and Rowland, 1978) was then found to be decreased at 0.85 (normal range 1.03–1.47) with total serum androgens 1.9 $\mu\text{g/l}$ (normal range 4–11) and a normal luteinizing hormone concentration of 2 u/l (normal range 0–15). Follicle stimulating hormone (8 u/l, normal range 5–20) and prolactin (4 $\mu\text{g/l}$, normal range 0–12)

concentrations were also normal. Testosterone 100 mg intramuscularly every 2 weeks was given from week 41 and he became able to stand for short periods soon after. At 43 weeks he could walk between parallel bars and the hypercalcaemia had improved markedly. The fasting urinary calcium:creatinine ratio decreased to normal (0.38) at 47 weeks with the hydroxyproline:creatinine ratio still being increased at 0.098.

Discussion

The hypercalcaemia initially occurred in this patient during the recovery phase from acute renal failure and this has been well described (Llach, Felsenfeld and Haussler, 1981). Its recurrence at 80 days, however, can be attributed to prolonged bed rest. Prolonged immobilization, such as occurs after spinal cord injury, poliomyelitis or extensive trauma, is regularly associated with bone demineralization and hypercalciuria (Stewart *et al.*, 1982) and this increases the risk of renal stone formation and impaired renal function. Approximately 30% of bone mineral is lost from the calcaneus over 5–6 months (Hulley *et al.*, 1971) and trabeculae that have been lost completely probably cannot be restored (Editorial, 1980a). Increased bone resorption, indicated by increased urinary calcium and hydroxyproline excretion occurs after 4 weeks' immobilization, reaches a maximum at approximately sixteen weeks and may continue for 12 months (Bergman *et al.*, 1977; Naftchi *et al.*, 1980; Lerman, Canterbury and Reiss, 1977). Hypercalcaemia is, however, rare in immobilized patients and probably only occurs when increased bone turnover (as in young subjects or

Paget's disease) is associated with impaired renal function as in the case above (Henke *et al.*, 1975). There are only a few reports of hypercalcaemia occurring in immobilized Paget's disease patients (Nathan *et al.*, 1982).

The pathogenesis of the bone resorption associated with immobilization is uncertain. Previous investigators have reported increased (Henke *et al.*, 1975; Lerman *et al.*, 1977), normal (Claus-Walker *et al.*, 1975b) or decreased (Laurence *et al.*, 1973; Stewart *et al.*, 1982) serum PTH concentration. The data in this patient follow a model of primary resorptive hypercalcaemia and hypercalciuria. Suppression of the PTH 1,25-dihydroxy-vitamin D axis is clearly demonstrated by the decreased renal tubular maximum for calcium absorption associated with a serum PTH in the low normal range (the concentration of PTH with this assay does not suppress below the normal range in hypoparathyroid states). A primary disorder of bone turnover of uncertain aetiology following a loss of mechanical stresses seems to be responsible for the changes—similar changes accompany the weightlessness of space travel (Editorial, 1980a).

In the case described here, hypogonadism was discovered after 41 weeks and probably contributed to the increased bone resorption. Oestrogen lack is a commonly accepted cause of post-menopausal bone loss and testosterone has been shown to decrease bone resorption in males with osteoporosis (Nordin *et al.*, 1981).

The most effective treatment is to mobilize the patient as this reduces both the bone resorptive process and the secondary hypercalciuria and hypercalcaemia. Oral phosphate therapy (1,327 mg/24 hr) prevented hypercalciuria in five male volunteers immobilized for 24–34 weeks but showed only slight protection against negative calcium balance, as faecal calcium tended to increase (Hulley *et al.*, 1971). Calcitonin (Chiroff and Jowsey, 1970) and diphosphonates (Editorial, 1980b) may protect bone mass, by decreasing resorption, and at the same time decrease hypercalcaemia while sex steroids may do the same in females who are deficient (Horsman *et al.*, 1977). Anabolic steroids have been reported to decrease bone resorption in immobilized patients (Heaney, 1962) and in the patient described here an improvement in hypercalcaemia was noted after beginning testosterone therapy but mobilization occurred at the same time. Corticosteroids decrease bone resorption *in vitro* (Claus-Walker *et al.*, 1975a) but were not used in this case because of the presence of infection. Saline diuresis, although it may decrease the plasma calcium by increasing renal calcium excretion, cannot be expected to decrease the bone mineral loss. There is no benefit to be gained by lowering the dietary calcium (Stewart *et al.*, 1982; Heaney, 1962) as calcium absorption is markedly

decreased in these patients. Vitamin D supplements however may exacerbate bone resorption and hence are undesirable (Nordin *et al.*, 1980). In the case described here there was worsening of hypercalcaemia after a nutritional formula, containing maintenance amounts of vitamin D, was administered.

Further studies of the resorptive process are required if excessive bone loss in these patients is to be prevented but nutritional and sex steroid deficiencies should be identified and corrected when present.

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