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Chapter 5

Glucocorticoids are not always deleterious for bone

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Abstract

A 25 year old man with the rare sclerosing bone disorder van Buchem disease presented with progressively worsening headaches eventually becoming persistent and associated with papilloedema. Increased intracranial pressure was diagnosed and the patient had a ventriculo-peritoneal drain inserted as well as simultaneously receiving treatment with prednisone. Before starting treatment, there was biochemical evidence for increased bone turnover and for steady increases in BMD at spine and total hip, despite the patient having reached his peak height of 197 cm at the age of 19 years. Treatment with prednisone resulted in biochemical and histological suppression of bone formation as well as of bone resorption, and in arrest of further bone accumulation.

Our data suggest that glucocorticoids (GC) may represent an attractive alternative to the high risk surgical approaches used in the management of patients with progressive sclerosing bone disorders. Our findings also suggest that whereas sclerostin may not be required for the action of GC on bone formation, it may well be important for the action of GC on bone resorption. The exact mechanism by which sclerostin may be involved in the regulation of bone resorption is as yet to be explored.
Introduction

Van Buchem disease is a rare bone sclerosing disorder described for the first time in 1955.(1) It belongs to the group of craniotubular hyperostoses and is characterized by progressive generalized osteosclerosis, particularly of the mandible and the skull, due to excessive bone formation.(2) It is caused by a 52kb deletion 35kb downstream the SOST gene which encodes sclerostin on chromosome 17q12-21.(3,4) This protein is produced in the skeleton exclusively by the osteocytes and inhibits bone formation by antagonizing the Wnt signaling pathway.(5) Clinical manifestations of the disease are due to entrapment of cranial nerves often associated with facial palsy, and loss of hearing and smell.(2) Van Buchem disease is thought to have milder clinical manifestations than sclerosteosis, a craniotubular hyperostosis with similar phenotype due to inactivating mutations of the SOST gene.(6,7) Management of the complications of both these sclerosing dysplasias is surgical, aiming at removal of the excess of bone, a technically difficult and sometimes dangerous procedure.(8,9,10) No medical treatment is available for either sclerosing diseases. Glucocorticoids are known inhibitors of bone formation(11,12) and we hypothesized that administration of these agents to patients with complications due to bone overgrowth may arrest its further progress.

We present here sequential observations of a patient with van Buchem disease with life-threatening increased intracranial pressure who was successfully treated with prednisone.

Case Report

The patient first came under our care at the age of 10 years with an established diagnosis of van Buchem disease. The disease was clinically and radiologically diagnosed in infancy and later genetically confirmed by the finding of a 52kb homozygous deletion 35 kb downstream the SOST gene on chromosome 17q12-q21 [the patient was briefly described (patient 15) by Staeling-Hampton et al(3)]. The parents are consanguinous and were both confirmed to be heterozygotes for the disease. There were 3 phenotypically normal sisters in whom no genetic testing has been so far undertaken.
As described in this disorder, clinical manifestations started early in childhood. The patient had a facial palsy at the age of 3 years and developed progressive deafness requiring the use of a hearing aid by the age of 10 years, followed by bilateral Bone Anchored Hearing Aids. He has been otherwise well with normal growth development along the 95th centile reaching a final height of 197 cm by the age 19 years. He completed his secondary education and is employed as office assistant manager. He married at the age of 20 years and he is father to 3 healthy children.

He demonstrated the typical clinical and radiological features of van Buchem disease, with enlarged head and mandible and no syndactyly or other digit malformations. During the 15-year duration of follow-up there were no other clinical signs or symptoms and blood pressure was normal. Haematological and biochemical parameters, including these of mineral metabolism demonstrated no abnormalities over the years. Skeletal radiographs showed thickening of the calvarium, base of the skull and long bones and sclerosis of the vertebrae (Figure 1). Bone Mineral Density (BMD) of the spine and hip were markedly increased at presentation (Z-score +6.2) and continued to increase in parallel with that of his healthy peers without, however, attaining a peak (highest z-score being 7.7). Biochemical markers of bone turnover were always increased compared to normal values for age, but followed a normal pattern of change with a further increase during the growth spurt and a progressive decline thereafter, although never reaching the normal range (Figure 2).

At the age of 23 years the patient complained of progressive headaches, eventually becoming persistent, associated with dizziness and by worse signs of increased intracranial pressure, in the form of papilloedema. The diagnosis was confirmed radiologically and a ventricular-peritoneal drain was implanted and he was concomitantly started on prednisone 30 mg/d which was reduced to 10 mg /d within one month. In the following 2 years he received different doses of prednisone, as depicted in Figure 3. These interventions were followed by rapid improvement of his symptoms which was sustained during the follow-up period.
Figure 1: Radiographs of the skull, showing thickening of the calvarium and the base of the skull, and of the hand illustrating the absence of syndactyly or other malformations.

Figure 2. Sequential measurement of serum Alkaline Phosphate (AP) in U/l, urinary hydroxyproline to creatinine ratio (OHP/Cr) in μmol/mmol and height (cm) in a patient with van Buchem disease over a 10-year period. Interrupted lines indicate the upper limit of the normal range.
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Methods

The biochemical markers of bone turnover P1NP and β-CTX were measured in serum at regular intervals using the E-170 system (Roche BV, Woerden, Holland). BMD was measured by DXA (Hologic QDR 4500, Waltham, MA, USA). An iliac crest biopsy was obtained after in vivo labeling with two courses of tetracycline separated by 12 days. Bone histomorphometry was performed on undecalcified histological bone sections by Dr Pascale Chavassieux, INSERM Unit 831, University of Lyon, Faculty of Medicine R Laennec, France). Immunohistochemical staining for sclerostin was performed in our laboratory using a previously described technique.(13)

Results

Biochemical markers of bone turnover
The changes in serum P1NP and β-CTX before and during prednisone treatment are depicted in Figure 3. Before treatment, values of both markers of bone turnover were elevated and decreased to within the normal reference adult range within 4 weeks of starting treatment with prednisone. The effect of prednisone on bone turnover was dependent on the dose administered and attempts to reduce the dose below 5 mg/d were associated with increases in serum markers of bone turnover. It was notable that during treatment there was a close relationship between serum β-CTX and P1NP values, with the two markers demonstrating parallel changes during adjustments of the dose of prednisone, suggesting a tight coupling of bone resorption and bone formation. There was a highly significant correlation between the two markers throughout the 2-year period of follow up (R2=0.765).

BMD
The changes in BMD measured at the spine and at the hip for the 6 years preceding the start of prednisone treatment and for 2 years thereafter are shown in Table 1. Despite high baseline values, BMD continued to increase steadily during adulthood by about 4% per two years, demonstrating no further increase after two years of treatment with prednisone.
Bone histology

On an iliac crest biopsy, taken two years after the start of prednisone treatment, there was sclerosis and no evidence of active bone remodeling. Cancellous bone volume was clearly increased and bone trabeculae were thick and well connected. The extent of eroded surfaces was very low (0.4%; normal 3.1±1.1%) and Howship’s lacunae were devoid of osteoclasts. In addition, no osteoid seams were seen and there was no tetracycline uptake upon examination under fluorescent light. As expected and previously described,(14) osteocytes did not stain for sclerostin.

Figure 3. Biochemical markers of bone formation and resorption before and during treatment with prednisone. P1NP: diamonds and solid line; β-CTX: closed circles and interrupted line.


**Discussion**

This case illustrates the beneficial effect of prednisone treatment on bone metabolism in a patient with van Buchem disease and life-threatening increased intracranial pressure. Treatment resulted in a histologically documented dramatic decrease in bone formation. Following therapy there was also no further increase in BMD at the spine and the hip. Although clinical manifestations of increased intracranial pressure improved significantly, this cannot be solely attributed to treatment with prednisone, as the patient had a ventriculo-peritoneal drain simultaneously implanted at the time of starting prednisone.

Before prednisone treatment, the patient had an increased rate of bone turnover, as assessed biochemically, associated with a continuous increase in BMD of the spine and at the hip. The biochemical markers of bone formation P1NP and osteocalcin have been previously reported to be elevated in 6 patients with van Buchem disease compared to their levels in disease carriers, being above the upper limit of the normal range in 3 of them.\(^{15}\) Urinary NTX levels were higher in 4 patients with the disease compared to carriers. Bone density measured in the phalanges by radiographic absorptiometry was elevated in all these patients.\(^{15}\) There are however to date no longitudinal data reported in patients with van Buchem disease. In our patient,
at least up to the age of 23 years, both biochemical markers of resorption and formation were increased. The clinical progression of the disease, which was due to bone overgrowth, as also evidenced by the steady increase in BMD, prompted us to use glucocorticoids in an attempt to arrest the process of bone accumulation.

The beneficial use of glucocorticoids has been previously reported in a patient with craniotubular hyperostosis due to an unidentified genetic defect. (16) In this patient, prednisone given for three courses of 10 weeks each, reduced serum osteocalcin but had no effect on urinary deoxypyridinoline and there were no reported changes in BMD. In a few cases with progressive diaphyseal dysplasia, a craniotubular hyperostotic disorder distinct from van Buchem disease, which is due to mutations of the gene encoding TGFβ, prednisone treatment during childhood and adolescence led to clinical(17,18) and in one case radiological improvement.(19)

Glucocorticoids have a deleterious effect on the skeleton, increasing bone fragility by systemic and local actions.(11) Their main action on bone metabolism is to decrease bone formation by inhibiting of the proliferation and differentiation of osteoblasts and increasing their rate of apoptosis.(12,20) Glucocorticoids have also been reported to increase bone resorption, particularly during the early phase of treatment, by stimulating osteoclastic activity and survival through an effect on the RANKL/OPG signaling pathway.(21-23) Consistent with these findings, studies in animals(24) and in humans(25-33) have shown that administration of glucocorticoids significantly reduce biochemical markers of bone formation, but have no effect or even increase those of bone resorption. Remarkably, administration of prednisone to our patient did not only decrease bone formation, but also bone resorption within 4 weeks of starting of treatment. Serum P1NP and β-CTX decreased and increased concurrently during alterations of prednisone dose, suggesting a tight coupling of bone resorption and formation during treatment. This was further supported by the strong correlation between the two biochemical markers of bone turnover before and during prednisone treatment.

The reason for this unique response of bone resorption to prednisone is not apparently clear but may well be related to the genetic defect of our patient with van Buchem disease. Recent studies have indicated that at least some of the negative effects of glucocorticoids on osteoblast function are due to inhibition of the canonical Wnt
signaling pathway through stimulation of the Wnt antagonists Dkk1, Sfr1 and sclerostin and activation of GSK3β.\(^{(34-36)}\) In addition, it has been reported that in osteoblasts Wnt signalling decreases bone resorption by downregulating the expression of RANKL and upregulating that of OPG,\(^{(37-40)}\) an action that can be reversed by glucocorticoids.\(^{(21-23)}\) It may thus be that sclerostin is not required for the action of glucocorticoids on bone formation, as suggested by the clear reduction of bone formation in our patient in the absence of sclerostin. In contrast, sclerostin may well be important for the action of glucocorticoids on bone resorption. We propose that in the absence of sclerostin glucocorticoids may lose their ability to stimulate RANKL and decrease OPG by a mechanism that is as yet to be explored. In support of this hypothesis are the data in above mentioned patient with craniotubular hyperostosis treated with prednisone.\(^{(16)}\) This patient was phenotypically very similar to ours and had increased bone turnover before treatment, although genetic analysis excluded abnormalities in the SOST gene. In this patient, prednisone treatment was associated with a significant decrease in serum osteocalcin but with no parallel change in urinary DPD excretion, a response compatible with that reported in other human studies. It may be therefore that sclerostin besides its critical role in the regulation of bone formation is also involved in the regulation of bone resorption as has also been reported for Dkk1, another inhibitor of the Wnt signaling pathway.\(^{(41)}\)

The long-term follow-up of this patient with life-threatening complications as a result of excess bone formation, illustrates the beneficial effect of prednisone treatment on bone metabolism and suggests that using glucocorticoids may represent an attractive medical alternative to the currently used technically difficult and complication associated surgical treatments of such patients. The results suggest further that sclerostin may be involved in the regulation of bone resorption by a mechanism that needs to be further explored.

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References


13. van Bezooijen RL, Roelen BA, Visser A, Wee-Pals L, de WE, Karperien M, Hamersma H,


Bornefalk E, Dahlen I, Michaelsson K, Ljunggren, Ljunghall S. Age-dependent effect of oral


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