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Research Article

Long-term clinical and bone mineral density changes of adult patients with sclerostin deficiency due to van Buchem disease: a follow-up study

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Abstract

Van Buchem disease (VBD) is an inherited rare sclerosing bone disorder, due to defective synthesis of sclerostin, a negative regulator of bone formation. Our earlier cross-sectional studies of patients with VBD and the closely related sclerosteosis suggested that the accrual of bone mass does not continue after puberty but longitudinal studies of patients with sclerostin deficiency are not available. The aim, therefore, of the present study was the long-term assessment of adult patients with VBD. Fifteen previously evaluated patients with genetically confirmed VBD were invited to participate in the study and 11 (4 women) consented. Mean follow-up time was 8.9 ± 1.1 yr and median age at follow-up was 47 yr (range 20-60). Seven patients developed permanent facial paresis, 9 had progressing hearing loss, and 2 developed had increased intracranial pressure requiring cranial surgery. Dental problems were common, and 3 patients developed osteoarthritis during follow-up. None experienced a cardiovascular event. BMD did not change at the LS or the left FN; Z-scores were 10.2 ± 1.3 SD vs 9.4 ± 2.3 SD, p=.62, and 8.9 ± 2.2 SD vs 7.7 ± 2.2 SD, p=.15, respectively. The variability of the clinical expression and progression of the disease, despite the stabilization of BMD but with progressive cranial nerve compression, requires continuous monitoring of these patients for whom no disease-specific therapy is currently available.

Keywords: sclerostin, van Buchem disease, high bone mass, skeletal dysplasia, rare bone disorder, Wnt pathway

Van Buchem disease (VBD) is a rare genetic disorder. It causes dense bones and high bone mass. The disease is caused by a decreased sclerostin, a protein that inhibits bone formation. In VBD bones continue to grow thicker till adulthood and we think that it stops becoming thicker afterwards. A total of 11 patients with VBD were followed over 9 yr. We found that their bones do not become thicker but the thick skull bone can give complaints like hearing loss or facial nerve problems. Since patients can still develop complaints despite reaching adulthood we advocate that patients are monitored on regular intervals.

Introduction

Van Buchem disease (VBD), or "hyperostosis corticalis generalisata familiaris", is a very rare, autosomal recessive bone sclerosing disorder characterized by bone overgrowth and very high bone mass.[1,2] It is caused by deletion of an element essential for the transcription of the SOST gene, which encodes sclerostin, a protein produced in the skeleton by the osteocytes which inhibits bone formation by antagonizing the Wnt signaling pathway in osteoblasts.[3–7] Clinical manifestations result from the increased bone mass and include enlargement of the forehead, overgrowth of the mandible, entrapment of cranial nerves, and rarely increased intracranial pressure.[2,8] In most cases it appears that the activity of the disease is attenuated with aging. Importantly, similar observations have been made in patients with the closely related disorder sclerosteosis in which sclerostin deficiency is caused by loss-of-function mutations of the SOST gene.[8] We have previously suggested that in both diseases bone mass stabilizes in adulthood,[2,9,10] raising questions about the long-term effects of sclerostin deficiency on bone metabolism. The evidence, however, leading to these suggestions has been obtained in cross-sectional studies because longitudinal observations are not available. This information is crucial for understanding the long-term effects of having little or no sclerostin, particularly in patients with sclerostin deficiency. It also provides valuable insights into the possible long-term impacts of sclerostin inhibitors, which are currently used to treat patients with osteoporosis and a high risk of fractures as in the future these agents might be given repeatedly. To address these questions we assessed long-term clinical and bone mass changes in a previously reported cohort of adult patients with VBD.[2]

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Materials and methods

Subjects

Patients with VBD included in our previously reported study[2] were invited to participate in the present study. The diagnosis of VBD had been genetically confirmed by the finding of a 52-kB homozygous deletion 35 kB downstream of the SOST gene on chromosome 17q12-a21 in all patients.

Study procedures

A detailed medical history was obtained from all patients, with special attention to new complaints since baseline assessment in 2010 and to symptoms, signs, or reports of cardiovascular events. Physical examination included measurement of blood pressure, neurological examination, and hearing evaluation with Rinne and Weber hearing tests; speech and whistling were examined, and electrocardiograms were performed in all patients.

Serum biochemistry

Non-fasting blood samples were obtained from all patients and measured for biochemical parameters of bone metabolism and biochemical markers of glucose and lipid metabolism. Serum creatinine was measured by semiautomated techniques. Alkaline phosphatase (ALP) was measured by a fully automated P800 modulator system (Roche BV, Woerden, the Netherlands), P1NP and beta-crosslabs by the E-170 system (Roche BV) and 25-OHD by the Liaison 25-OH Vitamin D TOTAL assay (DiaSorin S.A./N.V., Brussels, Belgium). Highly sensitive serum CRP was measured using Tina-quant C-Reactive Protein assay (Roche BV). Triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, remnant cholesterol, and the CHOL-HDLc ratio were measured by commercially available enzymatic assays (Roche Diagnostics, Woerden, the Netherlands). Plasma glucose was measured by an assay from Instruchemie, Delfzijl, the Netherlands. LDL-cholesterol was calculated by the Friedewald equation[11] and glomerular filtration rate was estimated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.[12]

BMD

BMD was measured at the spine and the hip by DXA with a mobile DXA scanner (Lunar Prodigy; GE Healthcare, Hoevelaken, the Netherlands; as also used in the previous study). NHANES III reference values compatible with reference values for the Dutch population were used to calculate Z-scores. Reports and films from relevant radiological examinations were obtained from hospital records to evaluate comorbidities like fractures.

The study was approved by the Ethics Committee of the Leiden University Medical Center and written informed consent was obtained from all participants.

Statistical analysis

All statistical analyses were performed using the SPSS 25.0 software (SPSS, Inc, Chicago, IL, United States). Results are presented as mean ± SD unless otherwise specified.

Results

Subjects

Eleven of the original 15 patients were included in the follow-up analyses (Figure 1). One elderly patient died during the follow-up period and 3 patients declined participation. Of the 11 included patients, 4 were females and 7 were males. The median age at follow-up was 45.6 yr (range 20-60 yr) and the mean follow-up period was 8.9 ± 1.1 yr. Demographic characteristics are shown in Table 1.

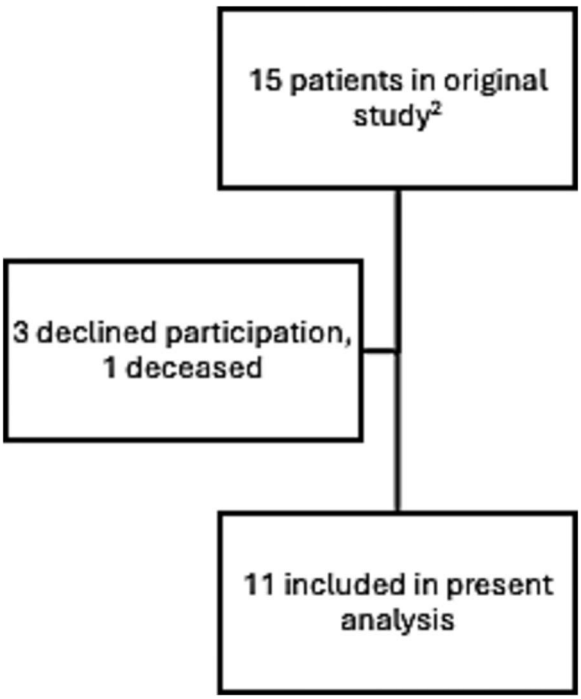

Figure 1. Flowchart patient inclusion.

Table 1. Baseline and follow-up characteristics.

	Baseline	Follow-up
Male/female	7/4	7/4
Age (yr)	36.6 ± 13.0	45.6 ± 12.5
Height (cm)	178.0 ± 7.7	179.2 ± 16.5
Weight (kg)	93.3 ± 15.6	89.1 ± 25.1
Creatinine (umol/L)	86.6 ± 38.5	80.5 ± 18.5
25-OHD (nmol/L)	53.3 ± 17.4	61.4 ± 21.4
P1NP (ng/mL)	88.8 ± 77.5	87.5 ± 46
Alkaline phosphatase (U/L)	79.3 ± 37.0	105.0 ± 25.7
β-CTX (ng/mL)	NA	0.5 ± 0.2
Glucose	NA	5.9 ± 1.5
High-sensitive CRP	NA	0.4 ± 0.2
Total cholesterol	NA	6.1 ± 0.14
HDL	NA	1.3 ± 0.4
LDL-c (Friedewald)	NA	3.5 ± 1.6
Triglycerides	NA	2.8 ± 2.1
Left FN BMD g/cm^2	2.2 ± 0.3	2.0 ± 0.4
Left FN Z score (SD)	8.9 ± 2.2	7.7 ± 2.2
LS BMD g/cm^2	2.4 ± 0.2	2.3 ± 0.3
LS Z score (SD)	10.2 ± 1.5	10.0 ± 1.5

Abbreviations: β-CTX, beta crosslaps; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL-c, low-density lipoprotein.

Clinical features

Baseline data were previously reported.[2] In summary, all patients had experienced in the past one or more episodes of facial palsy; the mean age at first occurrence was 4.8 ± 4.5 yr, and 3 patients experienced multiple recurrences during follow up. Nine patients had visible frontal bossing, of whom 5 also had an enlarged mandible. During follow-up nine patients

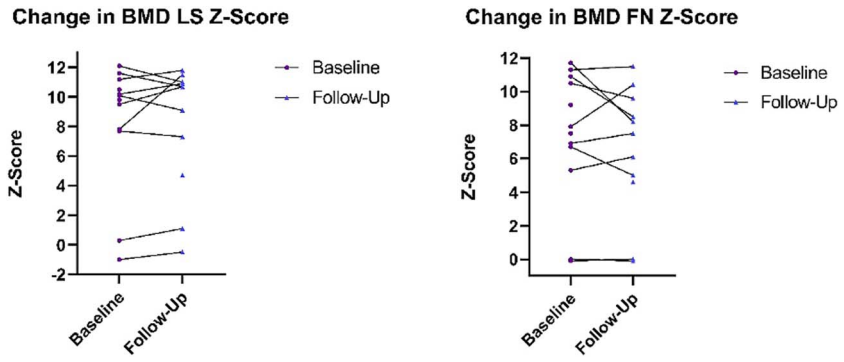

Figure 2. BMD, bone mass density.

reported hearing loss, which was mild in 3 of them. Three of these patients were using hearing aids and 1 patient used them in the past but stopped wearing them. In addition, 2 patients had raised intracranial pressure during follow-up and one of them received a ventriculoperitoneal shunt; this patient also suffered from cervical stenosis and experienced 6 recurrent episodes of facial palsy in the past. In retrospect, complaints of increased intracranial pressure were already present during the first study in 1 patient who experienced a remarkable disease course during follow-up requiring recurrent decompressive craniotomies and bilateral cranioplasty due to cranial hyperostosis. Decompressive craniotomy surgery was further complicated by postoperative aphasia, abducens palsy, and left cortical edema/bleeding. Cognitive complaints improved postoperatively.[13] This patient also underwent decompressive surgery of the orbita on both sides due to proptosis of the eyes with progressive visual field deterioration during follow-up.

During follow-up permanent abnormal function of the facial nerve was documented in 7 patients (64%) while in the remaining 4 there had been no deterioration or new episodes of facial nerve abnormalities compared to baseline. There was no progression in hearing loss. Visual problems were reported by 2 patients. Importantly, 4 patients reported regular headaches, in 2 of them, described above, raised intracranial pressure was documented. Two patients were diagnosed with benign paroxysmal positional vertigo and 1 reported long-standing tinnitus. Five patients required extraction of one or more molars by an oral maxillofacial surgeon, 1 patient received a denture, and another patient had 2 dental implants and orthognathic surgery of the mandible during follow-up. In addition, 3 patients developed osteoarthritis (OA) (2 gonarthrosis and 1 cervical spondylosis leading to neck osteoarthritis) but did not require surgical intervention. Other musculoskeletal problems were reported by 7 patients and included cervical radiculopathy and shoulder complaints. There have been no reports of fractures, heart disease, vascular disease, or diabetes during the follow-up period. One patient developed tongue cancer which was treated with curative surgical resection and radiotherapy.

Physical examination revealed no heart or lung abnormalities, and blood pressure and ECGs were normal in all patients.

BMD

At follow-up, BMD was measured in 9 patients, because 2 patients declined the invitation but agreed to provide all other information (Figure 2). Whole group BMD, at both the FN and at the LS, did not change during follow-up; FN-BMD was 2.16 ± 0.31 g/cm^2 at baseline and 2.02 ± 0.36 g/cm^2 at follow-up and LS-BMD was 2.39 ± 0.22 and 2.36 ± 0.25 g/cm^2, respectively. Mean Z-score of FN-BMD was 8.9 ± 2.2 at baseline, compared to 8.6 ± 2.1 at follow-up while Z-score of LS-BMD was 10.2 ± 1.3 at baseline and 9.4 ± 2.3 at follow-up. One patient increased in BMD during follow up, this was our youngest participant that at baseline had not reached peak bone mass at time of the first measurement.

In 2 women, however, significant decreases in BMD were documented. These were aged 58 and 47 yr and had their menopause during the follow-up period. In the first, FN-BMD decreased by 16.1% and LS-BMD by 7.0% while in the second the respective decreases were 10.4% and 8.8%.

Laboratory investigations

During the follow-up period there were no changes in measured biochemical parameters of bone metabolism except for serum ALP activity that increased from 79.3 ± 37.0 U/L to 105.0 ± 25.7 U/L (Table 1); levels of liver enzymes in serum were normal. Values, however, of serum ALP and P1NP showed large inter-individual variations.

Serum lipids and plasma glucose levels were normal in all patients and plasma HbA1c was not increased in any patient. Total cholesterol levels and cholesterol spectrum were also normal (Table 1). No patient had levels of highly sensitive CRP above the reference range (<5.00 mg/L) and all had normal renal function.

Discussion

In this first longitudinal study of adult patients with sclerostin deficiency, we show that during a follow-up period of 9 yr there was no further increase in the very high BMD values of a previously reported cohort of Dutch patients with VBD.[2] This finding confirms our hypothesis from cross-sectional data that in patients with sclerostin deficiency the profound increases in BMD occur early in life but do not progress during adulthood.[2,8–10] There is, thus, an amplification of the increase in bone accrual by bone modeling that occurs during normal growth which is not continued in adulthood. This pattern, consistent with changes in healthy subjects, is further supported by the observed stabilization of circulating P1NP values with aging. The absence, therefore, of sclerostin does not act as a constant stimulus of increased bone formation in adults. This is probably due to the presence of an increased pool of osteoblasts in the young to meet the needs for skeletal growth that decreases after skeletal maturity when bone formation occurs mainly as part of bone remodeling

and osteoblast numbers and activity are far less than those required for bone modeling. Moreover, in 2 women in the present study significant bone loss was observed during the menopause and in an earlier study we demonstrated a significant effect of exogenous glucocorticoids on bone metabolism in a patient with VBD.[14] It appears, therefore, that in adult VBD patients skeletal responses to hormonal signals are similar to those observed in the general population, despite the absence of sclerostin.

The question is whether the lack of sclerostin is solely responsible for these effects or whether other factors are contributory. Studies in animal models and humans with sclerosteosis and VBD have indicated that sclerostin deficiency is associated with an increased production of other inhibitors of the Wnt-signaling pathway of which Dickkopf-1 (Dkk1) is the most extensively studied.[15–19] Dkk1 is a Wnt antagonist that blocks the signaling cascade by binding to LRP5/6, a process facilitated by its coreceptor, Kremen, and inhibits bone formation by acting at different stages of osteoblast development.[20,21] However, these documented increases in Dkk1 do not compensate for the profound increase in bone mass in patients with sclerostin deficiency. We have previously shown that there is a significant inverse relationship between age and serum Dkk1 levels in patients and carriers of sclerosteosis and VBD and young patients had the highest Dkk1 values.[15] Thus, those with the highest increases in BMD had the highest Dkk1 values which were, however, insufficient to protect against the excessive bone formation characteristic of both disorders. Clearly, therefore, it is highly unlikely that increased Dkk1 secretion is solely responsible for the stabilization of BMD in adults with sclerostin deficiency. Whether other inhibitors, which act collectively in adults, are involved is unlikely but remains to be investigated in humans.

All clinical studies reported so far, including the present, indicate that the consequences of the disease in individual patients vary greatly despite very similar biochemical and densitometric characteristics. Long-term consequences range from detection of only past episodes of facial palsy to progressive, life-threatening intracranial complications. Unfortunately, the lack of further increases in bone mass with aging is not associated with stability of the clinical expression of the disease in all patients, particularly those with the most severe phenotype. In such patients, complications may progress due to persistent craniofacial bone overgrowth requiring repeated interventions to decrease raised intracranial pressure, as also shown here. The reason for the differences in clinical expression is not apparent. Moreover, in some patients other complications that may be related to sclerostin deficiency appeared or progressed during follow-up. Sclerostin is produced in the skeleton by osteocytes but is also expressed by other terminally differentiated cells embedded in mineralized matrices such as cementocytes in teeth and mineralized hypertrophic chondrocytes.[19] Not systematically assessed during our first study but remarkably present during this long-term follow-up was the increased need for dental care. We have previously shown that sclerostin expression was absent or largely decreased in teeth and the mandible of patients with VBD,[22] a finding that might contribute to the hyperostosis of the maxilla and mandible which makes tooth extraction more difficult to perform and may also cause crowding of the teeth. In addition, abnormal function of the facial nerve that was present in most of the patients weakens facial muscles and thus drooling of saliva and difficulties with mastication, which, in turn, may facilitate dental complications such as caries. Advice for intensive oral hygiene is, therefore, mandatory.

Importantly, during the period of observation there were no clinical or electrocardiographic signs of cardiovascular complications. These results are reassuring because, despite the small size of our study and the still rather young age of the patients, since the patients were lifelong exposed to very low or no sclerostin levels accounting for ~500 person-yr of observation.

A limitation of our study is the small number of participants. Although we included nearly half of known alive adult patients with VBD, their number makes the interpretation of the results at the group level difficult due to the large variability of individual presentations. Furthermore we only report on "self reported" OA development as structured photographs were not performed. This might underestimate the true incidence of OA. Despite these limitations, studies of humans with sclerostin deficiency are important, not just for the interpretation of responses to sclerostin lowering therapy for osteoporosis but foremost for the management of sufferers from these rare disorders. While this study showed that in adulthood BMD stabilizes it also signaled the appearance of an increased risk of other conditions such as osteoarthritis and dental problems that are potentially associated with sclerostin deficiency. Moreover, it demonstrated the possibility of the development and the progress of potentially life-threatening increase in intracranial pressure. Two patients in the present study had this complication and we recently saw a young boy with VBD with longstanding headaches and nausea which resolved after placing a ventriculoperitoneal shunt (not included in this study).

The results of this study, illustrating the wide variability of the clinical expression of the disease, emphasize the necessity of a personalized approach to the management of patients with VBD. Continuous monitoring, especially at a younger age for signs of increased intracranial pressure that occurs not only in patients with sclerosteosis but also in those with VBD, as shown here, is essential. In addition, specific attention to dental care and musculoskeletal complaints is necessary. There is currently no disease-specific treatment and only surgical interventions to treat complications are available. Glucocorticoids that can retard the pathological increase in bone accrual in the young are the only non-surgical treatment option.[14,23] A few years ago, we stressed the need for a joined effort of the pharmaceutical industry and the academic community to seek ways to treat the disease.[8] Unfortunately, an initial therapeutic attempt with sclerostin replacement therapy of a mouse model with sclerostin deficiency[24] was not followed by any other studies. Efficacious therapy for these individuals who have greatly contributed to our knowledge of the role of sclerostin in bone metabolism is still awaited.

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Author contributions

Conception, design of the study, interpretation of data, drafting the manuscript: NMA-D, SEP. Data Analysis: TMA, NMA-D. Acquisition of the data: NMA-D, MS, EMW, AvL. Reviewing and final approval of the manuscript: all authors. NMA-D is fully accountable for all aspects of the work. Natasha M. Appelman-Dijkstra (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation,

Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing), Telli Merve Avci (Formal analysis, Project administration), Manuela Schoeb (Data curation, Writing—review & editing), Elizabeth M. Winter (Data curation, Writing—review & editing), Antoon H. van Lierop (Conceptualization, Data curation, Writing—review & editing), and Socrates E. Papapoulos (Conceptualization, Methodology, Visualization, Writing—original draft, Writing—review & editing).

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Conflicts of interest

N.M.A.-D. received a grant from UCB for this study and received speaking/consulting fees from Amgen/UCB, E.M.W. received speaking/consulting fees from Amgen/UCB, S.E.P. received speaking/consulting fees from Amgen, Entera Bio, Qualix Dot, Radius Health, and UCB.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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