Bone xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Sclerostin deficiency in humans

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ARTICLE INFO

Article history:
Received 12 June 2016
Revised 9 September 2016
Accepted 10 October 2016
Available online xxxx

Keywords:
Sclerostin
Sclerosteosis
Van Buchem disease
Bone formation
Bone resorption

ABSTRACT

Sclerosteosis and van Buchem disease are two rare bone sclerosing dysplasias caused by genetic defects in the synthesis of sclerostin. In this article we review the demographic, clinical, biochemical, radiological, and histological characteristics of patients with sclerosteosis and van Buchem disease that led to a better understanding of the role of sclerostin in bone metabolism in humans and we discuss the relevance of these findings for the development of new therapeutics for the treatment of patients with osteoporosis.

1. Introduction

Sclerosteosis and van Buchem disease are two very rare bone sclerosing dysplasias belonging to the group of craniotubular hyperostoses. They were first described in the 1950s by Truswell and van Buchem et al. as "osteopetrosis with syndactyly", and "hyperostosis corticalis generalisata familiaris", respectively [1,2], and are characterized by endosteal hyperostosis and generalized osteosclerosis. The two disorders have very similar phenotypes caused by genetic deficiency of sclerostin. Osteocyte-produced sclerostin decreases bone formation by antagonizing the canonical Wnt signalling pathway in cells of the osteoblast lineage at the bone surface, an action facilitated by LRP4 [3]. In addition, sclerostin acts on neighbouring osteocytes and increases RANKL expression and the RANKL/OPG ratio increasing, thus, osteoclastic bone resorption [4,5]. Although osteocytes are the predominant source of sclerostin, the protein is also expressed by other terminally differentiated cells within mineralized matrices, such as cementocytes [6] and hypertrophic chondrocytes [7]. A detailed description of the control of the synthesis and mechanism of action of sclerostin is provided elsewhere [8,9].

We review here the clinical, biochemical, radiological, and histological characteristics of patients with sclerosteosis and van Buchem disease that led to a better understanding of the role of sclerostin in bone metabolism in humans and we discuss the relevance of these findings for the development of new therapeutics for the treatment of patients with osteoporosis. For this, we reviewed the medical records of 66 South African patients with sclerosteosis and 15 Dutch patients with van Buchem disease and we performed a literature search of nine electronic databases (PubMed, Embase, Web of Science, Cohrane, Science Direct, CINAHL, Academic Search Premier, Wiley, HighWire) using the terms sclerosteosis and van Buchem disease, or combinations of the two, to identify additional cases. A total of 241 unique references were found and checked; we excluded abstracts of meetings.

2. Sclerosteosis

We identified 96 cases of sclerosteosis born between 1896 and 2011 (Table 1). Sixty-six of these patients were members of the Afrikaner community of South Africa, descendants of Dutch settlers in this country in the 17th century; the remaining 30 patients were from the USA ($n = 9$), Brazil ($n = 7$), Germany ($n = 2$), Morocco ($n = 1$), Turkey ($n = 3$), Saudi Arabia ($n = 1$), Egypt ($n = 2$), Senegal ($n = 1$), India ($n = 1$), Japan ($n = 1$, and China ($n = 2$) [10–24]. The disorder is inherited as an autosomal recessive trait and is caused by loss-of-function mutations in the *SOST* gene on chromosome 17q12-q21, which encodes sclerostin. Eleven different mutations have been so far reported in patients with sclerosteosis [13,14,16–18,20,22,24–26]. Recently, patients with sclerosteosis phenotypes due to loss-of-function mutations of LRP4 were described [27–29]. In such patients the lack of a functional co-receptor (LRP4) impairs the action of sclerostin leading to upregulation of the Wnt pathway and to a phenotype similar to that of patients with sclerostin deficiency. Serum sclerostin levels are, however, increased rather than decreased and this condition is, therefore, not further discussed in this article.

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http://dx.doi.org/10.1016/j.bone.2016.10.010
8756-3282/

Table 1
Studies of patients with sclerosteosis.

Origin	Number of patients	SOST gene mutation	Mutation type
South Africa	66	c.69C > T	Nonsense [26]
USA	9	c.376C > T	Nonsense [25]
Brazil	7	c.373G > A	Nonsense [13,25]
Germany	2	IVS1 + 1G > C	Spice site [14]
Morocco	1	c.79C > T	Nonsense [16]
Turkey	2	c.449T > C	Missense [17]
	1	c.371G > A	Nonsense [18]
Egypt	2	c.87-88insC	Frame shift [20]
Senegal	1	IVS1 + 3A > T	Splice site [25]
India	1	c.296_297insC	Frame shift [22]
China	2	c.444_445TC > AA	Premature stop codon [24]
Japan	1	No genetic confirmation [23]	
Saudi Arabia	1	No genetic confirmation [19]	

2.1. Clinical features

In the majority of patients with sclerosteosis the first manifestation of the disorder is *syndactyly*. It was present in 66% of patients (56/85) and usually involved the 2nd and 3rd finger, although other fingers and toes could also be affected [16,20,22]. The severity of syndactyly ranged from soft tissue webbing to complete bony union of phalanges [10,18]. In patients without syndactyly minor deformities of digits such as radial deviation of the phalanges or nail dysplasias were often observed. Otherwise, prenatal skeletal development is normal and weight, length and facial proportions of affected individuals are within normal limits at birth.

Postnatally, longitudinal growth is increased and patients with sclerosteosis are already *taller* than their peers at school age. Closure of the growth plates occurs normally and growth is arrested after puberty when patients are often exceptionally tall. The median height of 28 male adult patients was 190 cm (range 170–209 cm), and 179 cm of 23 adult female patients (range 151–194 cm). Interestingly, the height of patients from Brazil, China and India has been reported normal. In 19 South African patients and 26 related heterozygous gene carriers, the Z-score of height of the patients was significantly higher than that of carriers (+0.84 and −0.48 SD, respectively) [30]. Canonical Wnt signalling promotes differentiation and maturation of chondrocytes and sclerostin is expressed by terminally differentiated chondrocytes [7]. Sclerostin may, therefore, inhibit Wnt signalling in chondrocytes in the growth plate similarly to its action on osteoblasts in bone. In sclerosteosis, lack of sclerostin may lead to increased differentiation towards hypertrophic chondrocytes resulting in a larger hypertrophic zone in the growth plate and, therefore, more new bone accrual and more longitudinal growth [30].

The clinical signs and symptoms of the disease are largely due to the increased growth of cranial bones caused by sclerostin deficiency (Fig. 1). To obtain a better insight in the clinical features of sclerosteosis (and van Buchem disease) we combined information reported in the literature with data from clinical records of studied patients. In the calculation, however, of the prevalence of complications we included only cases in which absence or presence of each complication was specifically mentioned.

2.2. Facial deformities

Severe facial distortion due to excessive growth of the mandible and enlargement and bossing of the forehead starts in childhood and progresses in adulthood. Bossing of the forehead was present in 90% of patients (71/79) and the average head circumference of 20 adult patients was 61.1 cm (Z-score +2.9). Mandibular overgrowth was present in 91% of patients (72/79); eight patients required corrective surgery and in one of them 2 kg of bone was removed from the mandible. In another patient, growth of the mandible progressed after corrective surgery at the age of 52 years requiring another operation 7 years later, after which the mandibular size remained stable. Other, less frequent facial deformities include proptosis, due to bone overgrowth in the orbitae, hypertelorism and midfacial hypoplasia [31].

2.3. Entrapment of cranial nerves

Complications result from thickening of the skull base and dome causing cranial nerve entrapment syndromes, of which *facial palsy* is very common and the first presenting sign. In total 93% of patients (77/83) experienced at least one attack of facial palsy at a median age of 3 years; this occurred within the first 3 months of life in a few patients ($n = 6$) but could also develop in early adulthood ($n = 3$, ages 19 to 21 years). During childhood patients may experience transient bilateral attacks of facial nerve palsy up to the age of 20 years, following which no more episodes generally occur. However, permanent paralysis of the facial muscles occurs frequently, and is accompanied by synkinesis, asymmetry, contractures and crocodile tears [15,32]. Facial palsies are caused by the narrowing of the neural foramina and fallopian canal, whereby the labyrinthine segment is most severely affected [15]. The impairment of the facial nerve is the result of direct compression by the thickened bone, venous occlusion leading to oedematous swelling with subsequent impingement of the facial nerve, or nerve ischemia resulting from the occlusion of the stylomastoid artery [15].

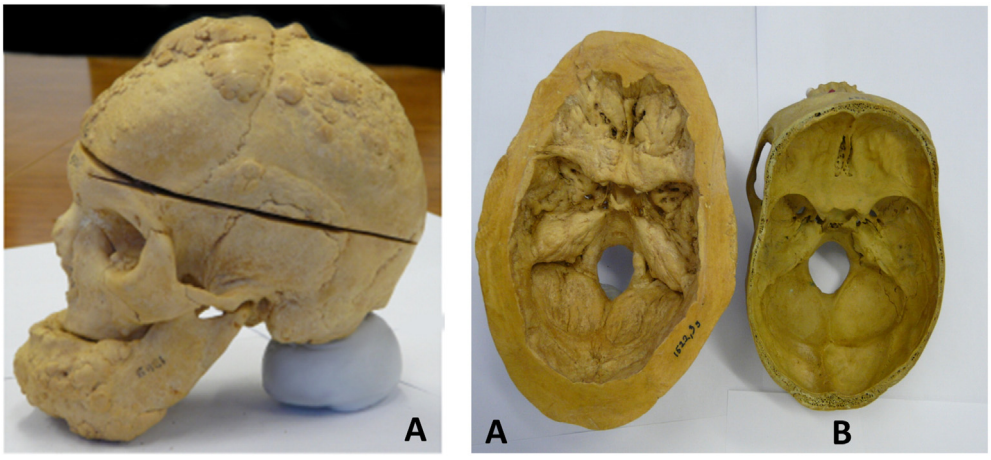

Fig. 1. Photos of the skull of a patient with sclerosteosis (A) and an individual without bone disease (B).
From the collection of the University of Pretoria, South Africa.

Please cite this article as: A.H. van Lierop, et al., Sclerostin deficiency in humans, Bone (2016), http://dx.doi.org/10.1016/j.bone.2016.10.010