Bone mineral status and metabolism in patients with Williams-Beuren syndrome

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Introduction: Williams-Beuren Syndrome (WBS) is a genetic multisystemic disorder caused by a hemizygous microdeletion on chromosome 7 (prevalence 1:10000 to 1:15000 live births). WBS is characterized by cardiovascular disease, distinctive facies and personality, mild intellectual disability, connective tissue abnormalities, growth retardation and endocrine dysfunction. Among the multiple endocrine abnormalities, bone mineral status and metabolism have not been deeply investigated although hypercalcemia has been already reported in 5-50% WBS patients.

The aim of this study was to evaluate bone quality and metabolism in a cohort of children, adolescents, and young adults with WBS in comparison with a control group

Patients and Methods: his study was carried out on 31 children (15 females, 16 males; mean age 9.6±2.74 years) and 10 young adults (6 females, 4 males; mean age 21.4±5.11 years) with WBS (41 patients, 20 females and 21 males; mean age 12.5±6.11 years), and compared with two age-, sex-, and body-size-matched healthy control groups of 205 patients, recruited from December 2012 until February 2015, at Anna Meyer Children's University Hospital in Florence, Italy. WBS diagnosis was made according to clinical and confirmed by the fluorescent in situ hybridation or array CGH. IN WBS and controls we evaluated ionised and total calcium, phosphate, parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, osteocalcin, bone alkaline phosphatase levels, and urinary deoxypyridinoline concentrations. We also calculated the phalangeal amplitude-dependent speed of sound (AD-SoS) and the bone transmission time (BTT) z-scores.

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Table 1. Baseline characteristics of Williams-Beuren syndrome (WBS) patients and controls

	WBS	Controls	P
Subjects, number	41	205	-
Male:female ratio	20:21	105:100	-
Age, yrs			
Children	9.6 ± 2.74	9.7 ± 2.93	0.861
Adults	22.4 ± 5.11	22.3 ± 5.42	0.957
Height, SDS		-	
Children	-0.7 ± 0.60	-0.1 ± 0.81	< 0.001
Adults	-0.8 ± 0.53	-0.1 ± 0.74	0.006
BMI, SDS			
Children	-0.3 ± 0.74	0.1 ± 0.62	0.001
Adults	-0.2 ± 0.62	0.2 ± 0.81	0.146
History of fracture, %	12.2	10.2	0.505
Ad-SOS, z-score	-1.4 ± 1.39	0.3 ± 1.25	< 0.001
Children	-1.2 ± 1.40	0.0 ± 0.81	< 0.001
Adults	-1.9 ± 1.27	-0.1 ± 0.89	< 0.001
BTT, z-score	-0.8 ± 1.15	0.3 ± 1.02	< 0.001
Children	-0.8 ± 1.17	0.3 ± 0.98	< 0.001
Adults	-0.9 ± 1.14	0.2 ± 0.74	< 0.001
Calcium intake, mg/day	760 ± 239	805 ± 250	0.290
Children	778 ± 252	845 ± 300	0.246
Adults	746 ± 223	789 ± 201	0.546
Vitamin D intake	163 ± 43	178 ± 47	0.059
Children	176 ± 46	194 ± 51	0.070
Adults	153 ± 40	171 ± 44	0.236
Total calcium, mmol/L	2.4 ± 0.06	2.2 ± 0.16	< 0.001
Ionised calcium, mmol/L	1.3 ± 0.14	1.1 ± 0.13	< 0.001
Phosphorus, mmol/L	1.2 ± 0.25	1.3 ± 0.22	0.010
PTH, pg/mL	51.7 ± 17.74	25.2 ± 11.07	< 0.001
BSAP, U/L	100.9 ± 29.83	103.2 ± 33.51	0.683
Osteocalcin, ng/mL	66.9 ± 28.76	91.0 ± 23.62	< 0.001
Urinary deoxypiridinoline, nM/mM creatinine	21.4 ± 10.18	40.2 ± 15.61	< 0.001
25(OH)D, ng/mL	23.7 ± 7.28	31.8 ± 13.24	< 0.001
1,25(OH)2D, pg/mL	83.2 ± 17.64	45.3 ± 22.12	< 0.001

BMI: body mass index; 25(OH)D: 25-hydroxyvitamin D; 1,25(OH)2D: 1,25-dihydroxyvitamin D; PTH: parathyroid hormone

Results: WBS patients showed a significantly reduced AD-SoS z-score ($p<0.0001$) and BTT z-score ($p<0.0001$) than controls. This finding persisted when we divided the sample into paediatric or adult patients. WBS also had significantly higher ionised ($p<0.001$) and total calcium ($p<0.0001$) levels as well as higher PTH levels ($p<0.0001$) compared with controls. However, WBS children and adolescents had significantly lower serum osteocalcin levels ($p<0.001$) and urinary deoxypyridinoline concentrations ($p<0.0001$) than controls. Spearman's (rank) correlation test showed that AD-SoS z-score values were significantly inversely correlated with age ($p < 0.005$). Both BSAP and osteocalcin levels also showed a significant correlation with total calcium values ($p < 0.005$). PTH correlated significantly with ionised calcium ($p < 0.05$) and osteocalcin ($p < 0.005$).

Figure 1b

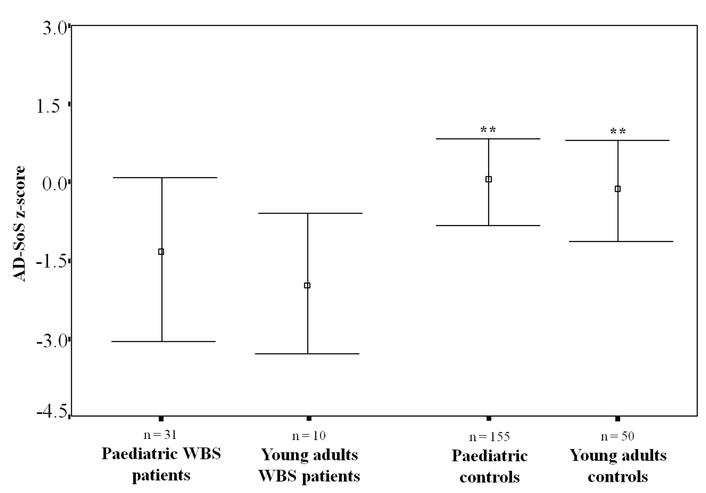
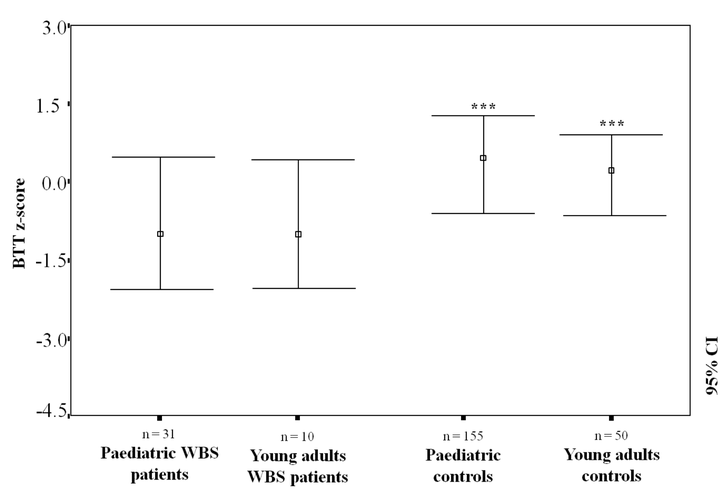


Figure 2b



Conclusions: WBS subjects exhibit a significant reduction in bone mineral status and impaired bone metabolism; we may hypothesize a deregulation of calcium-PTH metabolism. As a matter of fact, calcium homeostasis is likely altered in patients with WBS due to infancy hypercalcaemia, hypercalciuria, or medullary nephrocalcinosis. Impairment of bone metabolism in WBS patients is poorly understood though an increased renal sensitivity to PTH in normocalcemic WBS patients or a reduced 1,25-dihydroxyvitamin D3 degradation have been proposed. Furthermore, the deficiency of Williams syndrome transcription factor (WSTF), a nuclear protein, may play a role in the aetiology of hypercalcaemia in WBS because of abnormal chromatin remodelling activity. Haploinsufficiency of the general transcription factor II-I gene (GTF2I, *601679) may also have an effect on the impaired calcium metabolism.

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