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 hypercalcaemia 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 hybridization 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.

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 levels (p < 0.005). PTH correlated significantly with ionised calcium (p < 0.05) and osteocalcin (p < 0.05).

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, hypercalcuria, 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. Haplosufficiency of the general transcription factor II-I gene (GTF2I, *601679) may also have an effect on the impaired calcium metabolism.