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● *Original Contribution*

BONE QUANTITATIVE ULTRASOUND IN CONGENITAL AND ACQUIRED CHILDHOOD MULTIPLE PITUITARY FAILURE

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Abstract—The aim of the present study is to investigate bone status by phalangeal quantitative ultrasound (QUS) in a cohort of hypopituitaric pediatric subjects, and to relate measurement outcome to their clinical, laboratory, and therapeutical features. Forty-three hypopituitaric children were submitted to bone measurement by QUS with DBM sonic bone profiler 1200 (IGEA, Carpi, Modena, Italy). This method measures bone transmission time (BTT) and amplitude-dependent speed of sound (AD-SoS) of an ultrasound beam crossing the first four phalanges of the hand and provides respective standard deviation scores (SDS). These two parameters provide information on bone mineral density and structure. Clinical, laboratory and therapeutical features were considered to look for correlations. Overall BTT and AD-SoS SDS were significantly reduced (-0.87 ± 1.52, $p = 0.001$, and -0.97 ± 1.56, $p = 0.001$) as well as respective height- or bone age-corrected SDS. Bone condition proved significantly worse in subjects with higher number of hormonal deficiencies ($p = 0.001$ for both parameters) and in those with acquired hypopituitarism ($p = 0.020$ for BTT and $p = 0.010$ for AD-SoS) than in those with congenital forms. In participants under growth hormone (GH) treatment, regression analysis revealed that QUS measurement outcome was significantly associated with age at GH therapy start ($p = 0.001$), time interval before therapy initiation ($p = 0.011$), treatment duration ($p = 0.007$) and administered dosage ($p = 0.036$). Our data show that childhood hypopituitarism is associated with bone morbidity, detectable at QUS measurement independently of potential confounders as stature and bone age. Skeletal impairment is related to acquired hypopituitarism, number of hormonal deficiencies and duration of disease before replacement therapies, whereas GH treatment duration and doses are associated with a better skeletal condition. Phalangeal QUS measurements of BTT and AD-SoS promise as a reliable method for obtaining quantitative measurements of bone disease in individuals with hypopituitarism but more studies are needed for verification. (E-mail: mussa_alessandro@yahoo.it) **© 2010 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Bone density, Bone quality, Quantitative ultrasound, Hypopituitarism, Children.**

INTRODUCTION

Isolated growth hormone (GH) deficiency is a well known cause of bone impairment. Actually, GH is one of the major regulators of bone homeostasis and growth, enhancing bone formation both directly and indirectly, by inducing an increased synthesis of insulin-like growth factor I (IGF-I) (Bex and Bouillon 2003). In adults, GH deficiency is responsible for an almost doubled fracture risk (Wüster et al. 2001) and replacement therapy is able to normalize mineral density and turnover in a dose-dependent manner (Drake et al. 2001; Rota et al. 2008). Multiple pituitary failure as well is associated with bone loss (Drake et al. 2001; Okinaga et al. 2002; Wüster et al. 2001). Although GH deficiency plays a key role in bone impairment, other pituitary hormones deficiencies, respective substitutive therapies and other factors may contribute to this phenomenon, affecting not only mineral density but also bone organic compartment and microarchitecture (Colao et al. 1999; Okinaga et al. 2002; Nilsson 2000; Rota et al. 2008): excessive glucocorticoids replacement therapy, untreated hypogonadism and delayed puberty, thyroid hormone deficiencies and excess, diabetes insipidus (Pivonello et al. 1998) and cytotoxic drugs are all known to negatively affect bone metabolism.

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To date, despite several investigations of bone condition in children with isolated GH deficiency (Baroncelli et al. 1998; Baroncelli and Saggese 2005; Saggese et al. 1996; Schweizer et al. 2003; Vignolo et al. 2007) and in adults with childhood onset pituitary failure (Drake et al. 2001; Colao et al. 1999), a systematic evaluation of bone condition in childhood combined multiple pituitary failure is still lacking. Moreover, bone status has been mostly explored by radiologic methods. Actually, a definitive technique for bone assessment in pediatrics is still a largely debated issue (Baroncelli 2008). A recent interest towards quantitative ultrasound (QUS) methods has been registered, as they offer a novel approach to bone evaluation by mechanically soliciting skeletal tissue. QUS explores bone both quantitatively and qualitatively, by indices encompassing bone mineral density, connectivity and skeletal microarchitecture (Baroncelli 2008) and providing, thus, a ''bone quality'' measurement employed as an overall indicator of bone strength. Given the many actions that pituitary hormones exert on skeletal tissue by regulating bone growth, maturation, mineral density and architecture, bone measurement in hypopituitaric children is clearly a critical appraisal. Thus, QUS could potentially offer a comprehensive evaluation of bone tissue encompassing all these aspects. Moreover, reducing ionizing radiation exposure, QUS could represent an interesting option to assess short and long-term bone modifications in patients requiring frequent evaluations. Growing amounts of data have been collected in the latest years and QUS techniques appear promising in a scenario characterized by a growing demand for assessing the effects of chronic pathologies on bone health. The aim of the present study is to investigate bone status by phalangeal QUS in a cohort of congenital and acquired hypopituitaric pediatric subjects and to relate measurement outcome to their clinical, laboratory and therapeutic features.

MATERIALS AND METHODS

Subjects

Forty-three subjects (27 females and 16 males) with congenital ($n = 20$) or acquired ($n = 23$) hypopituitarism, diagnosed and followed up at the Department of Pediatric Endocrinology and Diabetology of the University of Torino from January 1998 to December 2008, were submitted to QUS evaluation, at mean age of 13.1 ± 4.9 years (range 4.4–20.1). The study was approved by the local ethics committee. Parents' informed consent was obtained. Exclusion criteria were: (1) suboptimal nutrition, defined as a dietary restriction with a caloric intake less than 70% of recommended values for the age; (2) deformities or previous fractures of the phalanges; (3) presence of pathologies affecting bone metabolism; (4) age below 3 years; and (5) severe mental retardation or conditions affecting a reliable QUS measurement. All participants had multiple hypopituitarism with anterior and posterior hormone deficiencies diagnosed according to standard methods (Dattani 2001; Growth Hormone Research Society 2000; Richmond and Rogol 2008; Rosenbloom and Conno 2007) through the following evaluations: (1) auxologic parameters (height, weight, height velocity, pubertal stage according to Tanner; (2) bone age according to Tanner-Whitehouse method, version 2; (3) free T4, TSH, IGF-I, morning cortisol and ACTH, prolactin blood dosage; (4) two GH stimulation tests (Dattani 2001; Growth Hormone Research Society 2000) or one in those subjects with defined central nervous system pathology, history of irradiation, or previously known multiple pituitary deficiency ($n = 21$), as commonly considered sufficient (Rosenbloom and Conno 2007; Growth Hormone Research Society 2000). Standard tests included basal GH after 12 h fasting, peak blood GH after the administration of a stimulus, according to standardized methods (Dattani 2001); (5) in subjects with no sign of pubertal development at 13 (females) or 14 years (males), LH, FSH, estradiol (in females) and testosterone (in males) blood levels, as well as standard GnRH secretion test (Dattani 2001) were performed; and (6) for posterior pituitary function, fluid balance, blood and urine sodium level, urinary gravity and osmolality and, in case of alteration, dehydration test. At the diagnosis, all subjects underwent brain MRI for an etiological characterization of the hypopituitarism. Causes of pituitary failure and participant's characteristics are detailed in Table 1. Mean age at the diagnosis was 6.8 ± 4.1 years. Chemotherapy was administered to six subjects (five suffering from Langerhans cell histiocytosis and one from germinoma) and radiotherapy to five (all affected by craniopharingioma). Subjects with ACTH, TSH, ADH deficiency were treated with respective substitutive therapy within 15 days after the diagnosis, by orally administering cortone acetate (12 mg/m^2/day), orally l-Tyroxine (2–5 mg/kg/day, according to age-related recommendations), oral or intranasal desmopressine (60–200 mcg/day). In peripubertal subjects with gonadotropin deficiency, transdermal substitutive estrogen (0.025 mg twice weekly) in 12 years-old female and ester of testosterone intramuscular (100 mg monthly) in 13 years-old males were started. All participants had GH deficiency. Substitutive treatment with recombinant human GH (0.11–0.29 mg/kg/week subcutaneously) was administered in 32 subjects and was started 1.3 ± 1.7 years after the diagnosis of GH deficiency according to the etiology of hypopituitarism; age at GH deficiency diagnosis and at treatment start and years of GH treatment were recorded. Twenty-three of the treated subjects were on GH therapy at the time of QUS evaluation.