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Muscle and skeletal health in children and adolescents with GH deficiency

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In addition to promoting linear growth, GH plays a key role in the regulation of bone and muscle development and metabolism. Although GH deficiency is frequently listed among the causes of secondary osteoporosis in children, its impact on bone and muscle health and on fracture risk is still not completely established. Current data suggest that childhood-onset GH deficiency can affect bone and muscle mass and strength, with GH replacement therapy exerting beneficial effects. Moreover, GH withdrawal at final height can result in reduced peak bone and muscle mass, potentially leading to increased fracture risk in adulthood.
Thus, the muscle-bone unit in GH deficient subjects should be monitored during childhood and adolescence in order to prevent

Abbreviations: AMI, axial moment of inertia; AO-GHD, adult-onset GHD; BMC, bone mineral content; BMD, bone mineral density; CO-GHD, childhood-onset GHD; CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; GH, growth hormone; GHD, GH deficiency; GHR, GH receptor; GHRT, GH replacement therapy; IGF-1, insulin-like growth factor-1; IGF-2, insulin-like growth factor-2; IGFBPs, IGF binding proteins; LV, left ventricle; MPHD, multiple pituitary hormone deficiency; MRI, magnetic resonance imaging; OPG, osteoprotegerine; pQTC, peripheral quantitative computed tomography; QMT, quantitative muscle testing; QUS, quantitative ultrasound; RANKL, receptor activator of nuclear factor-kB ligand; rh, recombinant human; SD, standard deviation; SSI, stress–strain index; STAT, signal transducer and activator of transcription.

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osteoporosis and increased fracture risk and GH replacement should be tailored to ensure an optimal bone and muscle health.

Introduction

The primary effect of Growth Hormone (GH) in childhood is to promote linear growth; however, it also influences body composition, cardiovascular metabolism and bone and muscle development and function [1]. GH enhances muscle and bone mass accrual during childhood and its anabolic effects continue for several years after the attainment of adult height, promoting the achievement of an optimal peak bone mass [2]. Even though GH deficiency (GHD) is frequently listed among the causes of secondary osteoporosis in children [3], data on the outcomes of recombinant human (rh) GH treatment in terms of bone and muscle status and fracture risk in children are scanty and contrasting.

This review focuses on the effects of GHD and GH replacement therapy (GHRT) on bone and muscle health in children and adolescents.

The role of the GH/IGF-1 axis on bone

The relationship between the GH/insulin-like growth factor-1 (IGF-1) axis and bone is still partially unraveled, as it involves a complex interaction with multiple autocrine or paracrine hormones and proteins, including IGFs and IGF binding proteins (IGFBPs), nutritional status, mechanical stimuli, and cytokines [4,5].

The binding of GH to the cell surface GH receptor (GHR) initiates signaling cascades, with the signal transducer and activator of transcription (STAT)-5b pathway being critical in regulating IGF-1 transcription. IGF-1 is mainly produced by the liver (75%) and secondarily by other tissues, like fat, muscle and bone and circulates in a ternary complex with IGFBPs and the acid labile subunit (ALS). IGF-1 may act as an endocrine, autocrine or paracrine hormone, through its tyrosine kinase receptor (IGF-1R). Both GHR and IGF-1R are expressed on the surface of chondrocytes and all osteogenic cells [6].

Bone modeling

Bone modeling consists of endochondral and appositional growth, which allow long bones lengthening and thickness increase, respectively [7]. GH stimulates endochondral ossification by acting on the chondrocytes at the level of the growth plate, which consists of a thin layer of cartilage present in most of the skeletal bones, except flat bones.

The growth plate is divided into three zones: resting, proliferative, and hypertrophic zone. These zones reflect the processes of chondrocyte progenitors proliferation and differentiation into mature chondrocytes, which secrete cartilage extracellular matrix, thus generating new cartilage. Then, chondrocytes undergo apoptosis, allowing resident osteoblasts and osteoclasts to remodel and calcify cartilage into a bone tissue [5,8].

Initially, somatomedin hypothesis suggested that the effects of GH on the growth plate are mediated by IGF-1 produced by the liver [9,10]. Subsequently, the detection of extrahepatic expression of IGF-1 and insulin-like growth factor-2 (IGF-2) suggested that GH promotes linear growth by stimulating local production of such growth factors [11]. Several studies have demonstrated that GH, IGF-1 and IGF-2 have independent and differential functions on bone, so that they exert additive and synergistic effects[11–13]. Indeed, in vivo and in vitro data support the so-called “dual effector hypothesis” which suggests a differential site of GH and IGF-1 action; the former has a prevalent effect in the resting zone where it promotes proliferation and differentiation of chondrocyte precursors, while the latter acts in the proliferative zone, where it induces chondrocytes proliferation and hypertrophy [10,14]. IGF-2, a peptide highly homologous to IGF-1 acting via the IGF-1R with autocrine and paracrine actions, is also expressed by proliferating chondrocytes and is thought to mediate pro-mitotic action of GH in the proliferative zone [5].