Skeletal health in adult growth hormone deficiency

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It has been several decades since the seminal experimental studies of Harris and Heaney suggested that growth hormone (GH) has a relevant role in skeletal health [1]. Early clinical studies primarily explored the role of GH replacement in linear bone growth, using GH of human cadaveric origin [2]. At that time, GH was available in scarce quantities which were rationed for the treatment of GH-deficient children and adolescents. With the availability of recombinant human GH in practically unlimited quantities, it became possible to study the effects of GH replacement in adults in the past 2 decades. Several studies have shed light on the phenotype of GH-deficient adults and the effects of GH replacement, but have provided relatively limited information regarding the vertebral fracture risk in patients receiving GH replacement.

In the present issue of the Journal, Mazziotti et al. have reported the findings of a prospective study of 40 GH-deficient hypopituitary adults who were followed over a 6-year period [3]. They found that 30 % of their patients developed morphometric vertebral fractures during observation. In this study, patients with unreplaced GH deficiency had a significantly higher risk of developing vertebral fractures, even after adjusting for differences in age between GH replaced and unreplaced subgroups. These data affirm and extend previous observations on the effects of GH on the adult skeleton. Indeed, several retrospective studies have reported an increased risk of fracture (vertebral or all sites combined) among GH-deficient adults in comparison with either the

general population or hypopituitary patients without GH deficiency [4–6].

What are the possible factors that might account for the increased fracture risk in hypopituitarism? In addition to GH deficiency, these patients may often have other hormone deficiencies, which may influence bone health, either directly (hypogonadism) or indirectly as a consequence of excess replacement therapies (hypoadrenalism and hypothyroidism) [7]. Several lines of evidence, including in vitro, experimental and clinical studies, support the direct relevance of the GH and insulin-like growth factor 1 (IGF-1) axis in skeletal physiology [7]. Lack of GH leads to decreased bone turnover and decreased bone mineral density (BMD) in patients with GH deficiency of adult onset [7]. Whether GH deficiency of childhood onset is similarly associated with decreased BMD in adult life is controversial [8]. In these patients, the validity of dual-energy X-ray absorptiometry (DXA) in assessing BMD can be compromised as a consequence of their smaller bone size, prompting the use of quantitative computed tomography (QCT) in order to yield unbiased estimates of bone density in this population (patients with childhood onset GHD) [8]. Nevertheless, adults with childhood onset GH deficiency also appear to be at increased fracture risk [8].

Based on these considerations, GH replacement would be anticipated to be beneficial for bone health. Indeed, available data suggest that GH replacement in adults exceeding 12–18 months in duration raises BMD [9]. Whether the fracture risk decreases in response to GH replacement has been more difficult to establish definitively, owing to the lack of randomized control clinical trials with fracture endpoints. The present, prospective study provides important data showing a lower risk of vertebral fracture among patients who received GH replacement, and extends the findings of previous retrospective investigations [3]. In the

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current study, the presence of vertebral fracture at study entry (prevalent fracture) increased the risk of incident vertebral fracture. In contrast, baseline lumbar spine BMD did not appear to predict the development of morphometric vertebral fractures, suggesting that critical aspects of bone quality that are crucial to skeletal strength are not captured by densitometric data.

The current prospective study by Mazziotti et al. has led to important, novel insights into the effects of GH replacement on the adult skeleton [3]. Their data affirm the skeletal benefits of GH replacement and support the use of this therapy in GH-deficient adults. However, several questions remain unanswered. Ultimately, a randomized clinical trial is needed in order to unequivocally establish the salutary effects of GH replacement on fracture prevention and quantify the magnitude of the protection from fracture in the central and appendicular skeleton. Such a clinical trial may be feasible and ethical only in countries where adult GH replacement is not currently available. Whether GH replacement decreases the risk of fracture in women as well as in men also needs to be clarified. Indeed, women do not appear to show the same improvement in BMD in response to GH replacement in many studies [9]. This finding has been attributed to GH under-replacement in women receiving oral sex steroids, since oral estrogen blunts the effect of GH on hepatic IGF-1 synthesis [9]. However, it appears that this hypothesis may not be sufficient as an explanation for the apparent gender-dimorphic effect of GH replacement on BMD, since such a gender-dimorphic effect has been observed even in studies where adequate GH replacement was documented in both women and men, based on the systemic IGF-1 levels during GH replacement [10]. Other issues that require further study include the interaction between GH replacement and additional pituitary hormone replacement therapies. Furthermore, whether GH replacement may have an additive beneficial effect on fracture risk when administered together or sequentially to other anabolic or antiresorptive therapies will need to be examined.

Like other well-conducted studies, the current article by Mazziotti et al. has not only improved our knowledge but also led us to formulate more provocative questions. It is anticipated that future investigations will further our understanding of the putative protective effects of GH replacement on the adult skeleton.

Compliance with ethical standards

Conflicts of interest The author has received institution-directed research support from Ipsen, Pfizer, and Novo Nordisk.

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