Serum Insulin-Like Growth Factor I Levels in Growth Hormone-Deficient Adults: Influence of Sex Steroids

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Abstract

Measurement of serum insulin-like growth factor I (IGF-I) concentrations remains the single most important tool in the evaluation of growth hormone (GH) replacement in GH-deficient adults, and the therapeutic goal is to maintain the level within the age-adjusted normal range. In healthy adults, IGF-I levels do not differ between males and females, whereas spontaneous GH secretion is approximately twofold higher in females. Untreated GH-deficient women exhibit lower IGF-I levels compared with men, and the increase in serum IGF-I during GH replacement is also significantly less. Put together, these data suggest resistance to GH in women, which in healthy individuals is compensated for by increased GH secretion. Administration of oral oestrogen in healthy post-menopausal women suppresses hepatic IGF-I production and increases pituitary GH release, and oral oestrogen replacement in women with GH deficiency lowers IGF-I concentrations and increases the amount of GH necessary to obtain IGF-I target levels during treatment. These data clearly suggest that hepatic suppression of IGF-I production by oestrogen subserves the gender difference in GH sensitivity, but it is also likely that sex steroids may interact with the GH/IGF axis at further levels. There is also circumstantial evidence to indicate that testosterone stimulates IGF-I production, and it is speculated that a certain threshold level of androgens is essential to ensure hepatic IGF-I production. Whether these data should translate into earlier discontinuation of oestrogen replacement therapy in adult women with hypopituitarism merits consideration.

Introduction

Measurement of total serum insulin-like growth factor I (IGF-I) concentrations has stood the test of time as a cornerstone in the management of patients with growth hormone (GH) deficiency. It is of particular relevance in the follow-up of GH-deficient adult patients during GH replacement as no single hard clinical end-point is available for this treatment modality. The therapeutic goal is to maintain serum IGF-I levels within the age-adjusted normal range [1]. In addition, serum IGF-I measurements are frequently used in the diagnosis of the disease, even though it is recognized that normal IGF-I levels do not
exclude adult GH deficiency (GHD), and that the diagnosis is ultimately based on a subnormal response to GH stimulation tests within an appropriate clinical context [2].

It has been observed for several years that a gender difference exists between serum IGF-I levels in GH-deficient adults, both in the untreated state and during GH replacement. Female patients exhibit lower IGF-I levels prior to treatment, and the increase in IGF-I during GH replacement is also reduced [2–4]. This is of potential clinical significance, and it is therefore pertinent to review our understanding of the underlying mechanisms and to speculate about the practical implications.

In this paper, we focus on the effects of sex steroids on serum IGF-I levels in GH-deficient adults with a particular emphasis on the impact of concomitant oestrogen replacement therapy in women.

Gender Differences in Spontaneous GH Secretion and IGF-I Levels in Healthy Adults

Spontaneous 24-hour GH secretion is significantly increased in women compared with men, which to a large extent is corroborated by increased GH pulse amplitude without a difference in pulse frequency [5, 6]. The underlying mechanisms are not fully clarified, but regression models suggest that abdominal adiposity rather than gender per se is an important and negative determinant. In spite of this robust difference in GH levels, serum IGF-I levels do not differ to any substantial degree between adult females and males in cross-sectional studies [3, 7]. Still, it has been reported that serum IGF-I levels in individual women may change during the menstrual cycle, with a moderate elevation in the early follicular period in association with increased GH secretion [8].

Impact of Oestrogen Replacement on GH Secretion and IGF-I Levels in Healthy Postmenopausal Women

The observation of higher GH levels in females led to the suggestion of a direct effect of oestrogen on the GH/IGF axis, which was subsequently tested by Weissberger et al. [9]. Otherwise healthy postmenopausal women were studied before and after 2 months’ replacement with either oral or transdermal oestrogen. Both routes of administration were tested to account for the possibility that oral oestrogen might exert a non-physiological first-pass effect on hepatic IGF-I production. The study revealed that oral oestrogen induced a 30% reduction in serum IGF-I concentrations and a threefold increase in mean 24-hour GH levels, whereas transdermal oestrogen was accompanied by a more modest increase in serum IGF-I levels without detectable alterations in GH secretion [9]. It was subsequently reported that the effects of oral oestrogen on serum IGF-I concentrations and GH secretion could be reproduced by three different oral oestrogen formulations [10]. Based on data from rodent studies indicating that oestrogen inhibits hepatic IGF-I mRNA expression, these human studies are compatible with the hypothesis that high portal levels of oestrogen directly suppress hepatic IGF-I production and secretion, which results in increased pituitary GH release due to reduced feedback inhibition from IGF-I. It is, however, more difficult to explain why transdermal oestrogen slightly increases IGF-I levels in the absence of significant changes in GH release.

Gender Differences in Serum IGF-I Levels in Adult GH-Deficient Patients

Women with untreated GHD have lower IGF-I levels compared with their male counterparts (fig. 1) [2–4]. Fisker et al. also recorded lower IGF-I levels in women receiving oestrogen replacement compared with women considered eugonadal without replacement [3]. Moreover, the lowest IGF-I levels were encountered in women receiving hydrocortisone replacement on the basis of adrenocorticotropic hormone deficiency (fig. 2) [3]. In simple regression analysis, IGF-I correlated positively with testosterone concentrations in female patients, and testosterone levels were completely suppressed in female patients treated with hydrocortisone [3].

During GH replacement therapy with a fixed dose, the relative and absolute increments in IGF-I are lower in females [4]. The female participants in these trials were heterogeneous in terms of gonadal function and oestrogen replacement, which complicates interpretation of the underlying mechanisms. In a subsequent study in 38 hypopituitary women with documented GH deficiency and hypogonadism, we evaluated the impact of oestrogen discontinuation during continued GH replacement on serum IGF-I concentrations. At baseline, all patients had IGF-I levels within the normal range, but these levels increased significantly by 20% following oestrogen discontinuation for 2 months (unpublished data). Cook et al. [11] have shown that the GH replacement dose required to obtain
normal IGF-I levels was increased by more than 50% in women on concomitant oral oestrogen replacement, compared with women not receiving sex steroids. The GH dose requirement in the latter group did not differ from that of age-matched male patients.

### Discussion

The observation that IGF-I levels in healthy mid-life adults are gender independent despite significantly higher GH secretion in females is indicative of compensated GH resistance in females. A direct inhibitory effect of oestrogen on hepatic IGF-I production is an obvious underlying mechanism. Along this line, one could speculate that a closed-loop feedback system operates in eugonadal women, in whom the suppressive effect of endogenous oestrogen on hepatic IGF-I production is balanced by increased GH secretion. Administration of oral oestrogen introduces an open-loop feedback system, during which a constant and unphysiologic suppression of hepatic IGF-I production and release is only partly compensated for by increased pituitary GH secretion. The hypothesis is further supported by the findings in GH-deficient women of reduced basal and GH-stimulated IGF-I levels. Moreover, in the same patients, the resistance to GH administration is removed by discontinuation or omission of oestrogen replacement.

This hypothesis, however, does not explain either the apparent ability of transdermal oestrogen to increase IGF-I levels in healthy post-menopausal women in the absence of detectable changes in GH secretion, or the observation that both GH secretion and IGF-I levels increase in the early follicular phase in normal young women. It is likely that endogenous oestrogen also exerts extra-hepatic effects on the GH/IGF axis.

The hypothesis that androgens may affect IGF-I generation is less well substantiated, although there is circumstantial evidence to suggest a positive association between circulating levels of testosterone and IGF-I. Testosterone administration in males has been shown to increase serum IGF-I concentrations [12], and endogenous testosterone levels correlate with IGF-I in hypopituitary women with unsubstituted GHD [3]. Moreover, extremely low IGF-I levels are recorded in hypopituitary women receiving hydrocortisone replacement [3]. The latter observation obviously does not imply a causal relationship between IGF-I and testosterone, but could relate to an effect of glucocorticoids or simply reflect profound hypopituitarism. It is, however, noteworthy that hypopituitary women receiving oestrogen and hydrocortisone display almost completely suppressed androgen levels, and it is tempting to speculate that a certain threshold of androgens is necessary and plays a permissive role for IGF-I stimulation by GH and other factors.

From a clinical point of view, it is important to recognize the gender difference in GH sensitivity and responsiveness when treating hypopituitary patients. Female patients, as a group, require a higher GH dose to normalize IGF-I levels. This applies to young eugonadal patients as well as to patients receiving oral oestrogen. The obser-
vation that omission of oestrogen replacement significantly reduces the GH dosage [11] merits some consideration in light of the recent concern about untoward effects of oestrogen treatment on cardiovascular disease and cancer risk. Although epidemiological data in healthy women cannot always be extrapolated to simulate the clinical complexity of hypopituitarism, one could argue that early discontinuation of oestrogen replacement in GH-treated hypopituitary women would reduce GH dose requirements (and cost) and at the same time lower their risk of developing cardiovascular disease and certain cancers. It is recommended that the potentially ambivalent effects of oestrogen replacement are considered by the physician in the counselling of elderly women with hypopituitarism.

References