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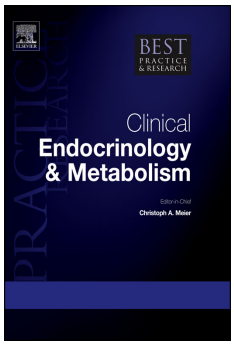

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Sex steroids and the GH axis: implications for the management of hypopituitarism

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Abstract

Growth hormone (GH) regulates somatic growth, substrate metabolism and body composition. Sex hormones exert profound effect on the secretion and action of GH. Estrogens stimulate the secretion of GH, but inhibit the action of GH on the liver, an effect that occurs when administered orally. Estrogens suppress GH receptor signaling by stimulating the expression proteins that inhibit cytokine receptor signaling. This effect of estrogens is avoided when physiological doses of estrogens are administered via a non-oral route. Estrogen-like compounds, such as selective estrogen receptor modulators, possess dual properties of inhibiting the secretion as well as the action of GH. In contrast, androgens stimulate GH secretion, driving IGF-1 production. In the periphery, androgens enhance the action of GH. The differential effects of estrogens and androgens influence the dose of GH replacement in patients with hypopituitarism on concomitant treatment with sex steroids. Where possible, a non-oral route of estrogen replacement is recommended for optimising cost-benefit of GH replacement in women with GH deficiency. Adequate androgen replacement in conjunction with GH replacement is required to achieve the full anabolic effect in men with hypopituitarism.

Keywords: estrogen, tamoxifen, testosterone, GH action, anabolism, liver

1. Introduction

Growth hormone (GH) regulates substrate metabolism, body composition, physical performance and general wellbeing in adult life. The importance of the physiological action of GH is exemplified by the consequences of GH deficiency (GHD), characterized by a reduction in lean body mass and an increase in fat mass [1]. These body composition

abnormalities, including reduced muscle mass, are reversed by GH replacement therapy [2-6]. Muscle strength [7-9] improves with GH replacement [10, 11].

In addition to reduced muscle strength, aerobic exercise capacity, measured as VO_2max, is impaired in adults who are GH-deficient by about 20% [7]. A meta-analysis of 11 randomized placebo controlled studies has reported that GH replacement improves VO_2max in people who are GH deficient [12]. The improvements occur through several mechanisms, which include effects on cardiorespiratory function, red cell and blood volume. Recent evidence indicates that GH enhances anaerobic exercise capacity by promoting anaerobic metabolism. In patients with GHD, anaerobic exercise capacity is reduced [13]. A study in recreational athletes revealed that GH stimulates sprint capacity, a performance measure dependent on the anaerobic energy system [14]. Therefore, many aspects of metabolism, body composition, physical function and wellbeing are affected in patients with GHD and improved by GH replacement.

During GH replacement, many factors influence the response to, and effectiveness of, treatment. The response to GH therapy is influenced by the actions of several hormones. Sex steroids require special consideration, as they are one of the most influential regulators of GH secretion and peripheral action. Here, we will discuss how sex steroids interact with the GH/IGF-1 system and the clinical implications for GHD patient management.

2. Estrogens and GH

GH is secreted in a pulsatile manner, stimulated by GH-releasing hormone and inhibited by somatostatin (SST). Many factors regulate GH secretion. These include GH releasing peptide (GHRP; ghrelin), glucose, free fatty acids, amino acids (arginine), sex steroids, thyroid hormones, corticotropin-releasing hormone, adrenergic system, neurotransmitters,

neuropeptide Y, leptin, IGF-1, and GH itself [15]. Sex steroids not only influence GH secretion directly, but also modulate many factors that regulate GH secretion [16-18].

2.1. Sexual Dimorphism

Strong evidence indicates that sex steroids modulate GH secretion in men and women. Regulation of gender-dimorphic GH secretion patterns is largely SST-dependent [19]. Women have higher baseline and mean GH levels than men [20, 21]. This differential pattern of GH secretion result in gender-dimorphic expression of several hepatic genes involved in glucose and lipid metabolism, energy and protein processing, including the cytochrome p450 gene [22].

2.2. GH Secretion Regulation by Estrogens

During the female menstrual cycle, a peri-ovulatory increase occurs in GH secretion. Estrogen regulation of GH secretion occurs at the pituitary [23, 24] and hypothalamus [25, 26]. High levels of estrogen receptors ERα are expressed in the hypothalamus and the pituitary. Recent evidence has also revealed expression of ERβ in the somatotroph, with both receptor subtypes involved in the regulation of GH gene expression [27, 28]. Furthermore, estrogen reduces SST receptor expression, which in turn results in enhancing GH secretion [29-31]. Estrogen also enhances ghrelin-induced increase in GH secretion [18, 32]. Therefore, estrogens play a major role in the regulation of GH secretion.

2.2. Paracrine Regulation

Strong evidence has shown that local estrogens, derived from aromatization of testosterone, stimulates GH secretion in humans. In human pituitaries, more than 80% of the somatotropes co-express aromatase [33]. Aromatase knockout (ArKO) mice or human aromatase gene mutation present unique models in understanding the role of estrogen in the regulation of

somatotroph function. In ArKO mice, pituitaries are hypoplastic and GH secretion is reduced [34]. In men with aromatase deficiency, the GH response to stimulation is substantially blunted and is not restored by systemic estradiol replacement [35]. This observation indicates that locally produced rather than circulating estrogen stimulates the secretion of GH. There is strong evidence that local rather than systemic estrogens drive GH secretion in women. We reported that blockade of estrogen action by tamoxifen reduced GH secretion in postmenopausal women [36, 37]. As the menopause is an estrogen-deficient state and tamoxifen did not change circulating estrogen levels, this finding provides compelling evidence that estrogen regulates GH secretion via a paracrine mechanism. Therefore, local estrogens derived from aromatization of androgens drives GH secretion in both men and women.

2.3. Endocrine Effect

The effect of estrogen on GH secretion is dependent on the route of administration. Administration of estrogen by the oral route stimulates GH secretion, whereas administration by the transdermal route does not [38]. When administered orally, estrogen reduces hepatic IGF-1 production as a result of first-pass effect, whereas this does not occur when administered transdermally [38]. The fall in IGF-1 after oral estrogen therapy reduces negative feedback on GH secretion. Therefore, oral estrogen administration indirectly stimulates GH secretion by restraining the central feedback inhibition of IGF-1 (Figure 1A). Oral estrogen delivery but not transdermal delivery also attenuates whole body fat oxidation and protein anabolism in women with hypopituitarism during GH therapy [39]. Furthermore, oral estrogen increases the concentration of IGFBP-1 [40], reducing the bioactivity of an already reduced concentration of IGF-1, leading to a further loss of an anabolic effect. Collectively, estrogen exerts mechanistically distinct and site-specific effects on the GH system: a paracrine action in central stimulation of GH secretion and an endocrine action in inhibiting hepatic GH action, resulting in secondary activation of GH secretion.

2.4. Effect on the GH Receptor

Strong evidence indicates that estrogens inhibit the function of the GH receptor. The JAK-STAT pathway is a major effector of GHR signaling, necessary for the transcriptional regulation of IGF-1. Estrogen inhibits GH activation of the JAK/STAT pathway. The inhibition is dose-dependent and suppresses GH-induced JAK2 phosphorylation and downstream transcriptional activity [41]. The termination of GHR signaling is controlled by the suppressors of cytokine signaling (SOCS) proteins and by protein tyrosine phosphatases. Estrogen does not affect phosphatase activity but stimulates hepatic expression of SOCS-2, which in turn inhibits JAK2 activation [41]. Therefore, estrogen suppresses GH receptor signaling by stimulating SOCS-2 expression, which in turn inhibits JAK2 phosphorylation, explaining the inhibitory effect of GH action on the liver.

Estrogens affect the expression and function of GHRs in a tissue specific manner. Gonadotropic and somatotropic axes exert overlapping roles in regulating bone growth in men and women [42]. Contrary to the hepatic effect, estradiol stimulates GH signaling by reducing SOCS-2 expression in osteoblasts [43]. Estrogen amplifies GH-induced STAT-5 phosphorylation in osteoblasts, increasing GH-induced bone-sialoprotein, osteopontin and IGF-2 mRNA expression [43]. GH co-treatment with estrogen synergistically induce osteoblast proliferation [44]. Therefore, estrogen potentiates the effect of GH on bone formation at least partly through the reduction of SOCS-2 negative feedback, which stimulates GH-responsive gene expression in bone.

In summary, local estrogen derived from aromatization stimulates GH secretion in men and women. Estrogen exerts tissue-specific effect on GH signaling, inhibiting hepatic GH action resulting in a reduction of IGF-1 production. In bone, estrogen potentiates GH signaling

promoting bone formation.

3. Estrogen compounds and GH

Therapeutic compounds that modulate estrogen action or its availability affect the GH-IGF-1 system. Estrogen compounds fall into two important therapeutic classes: selective estrogen receptor modulators (SERMs) and aromatase inhibitors.

3.1. SERMs

SERMs are synthetic estrogen compounds that exert agonist or antagonistic action in a tissue-specific manner. They have emerged as therapeutic agents for infertility, osteoporosis and breast cancer. Examples of SERMs in therapeutic use are clomiphene, tamoxifen and raloxifene. Tamoxifen exerts central estrogen receptor antagonistic but peripheral agonistic effect on the liver [45, 46]. As discussed above, estrogen drives GH secretion, a paracrine action that is unmasked by tamoxifen which blocks estrogen action and reduces GH secretion. Acting as estrogen agonist on the liver, tamoxifen reduces hepatic IGF-1 production via a first-pass effect [36, 37]. Despite the fall in feedback inhibition by IGF-1, GH secretion is not enhanced but rather reduced by tamoxifen, a manifestation of its powerful estrogen receptor antagonistic effect centrally [36]. SERMs, therefore, exert a double negative effect on the GH-IGF-1 axis, inhibiting GH secretion centrally and GH action peripherally in the liver, collectively inducing a state of GH deficiency (Figure 1B).

3.2. Aromatase Inhibitors

Aromatase inhibitors are used increasingly for breast cancer therapy. Exemestrane, anastrozole and letrozole are aromatase inhibitors approved for clinical use. Inhibition of aromatase activity predictably reduce GH secretion [47]. Central effect of aromatase inhibitors is expected to be similar to that of tamoxifen, as these drugs reduce local estrogen

availability. Because aromatase is not expressed in the adult liver [48, 49], aromatase inhibitors do not affect the hepatic action of GH. Therefore, its pharmacodynamics effect on the GH system is purely central but less than that of SERMs, which exert dual central and peripheral effects.

Estrogens, SERMs and aromatase inhibitors, therefore, all affect GH secretion and IGF-1, in different ways and degrees. These effects are presented in Table 1.

3.3. Gender Differences

The effect of SERMs and aromatase inhibitors on the GH axis is different between men and women [37]. This is because, in men, SERMs concurrently stimulate the pituitary-gonadal axis, increasing testosterone production, which mitigates suppression of the GH system. Like the GH system, estrogen regulates gonadotrophin secretion via a paracrine mechanism. Unlike the GH system, local estrogen derived from aromatization inhibits gonadotrophin secretion [50]. We reported that central estrogen blockade with SERMs enhanced LH secretion, consequently increasing testosterone levels [37, 51]. The higher testosterone levels in turn result in secondary stimulation of GH secretion. As this mitigating effect does not occur in women, the inhibitory effect of SERMs on GH secretion is greater in women than in men [37]. For a similar reason, the suppression of fat oxidation by tamoxifen is also greater in women but not in men [52].

In summary, both SERMs and aromatase inhibitors suppress GH secretion. The effect of SERMs on the GH system is mitigated by concurrent stimulation of the gonadal system in men. This results in suppression of the GH system and of fat metabolism that are gender-dependent with effects that are greater in women than in men.

4. Testosterone and GH

4.1 GH Secretion

Testosterone exerts anabolic effect in part by stimulating the GH-IGF-1 system [53-57]. In men with hypogonadism, testosterone replacement stimulates GH secretion that drives IGF-1 production [58]. Importantly, non-aromatizable androgens do not stimulate GH secretion [59], whereas aromatase inhibitor or central estrogen antagonism attenuates the stimulation of GH secretion by testosterone [47, 58]. These findings provide unequivocal evidence that local estrogens play a pivotal role in the regulation of GH secretion in men. Therefore, testosterone in men requires conversion to estradiol to stimulate GH secretion.

4.2. GH action

With regard to mechanisms mediating testosterone-modulation of GH action, there is evidence that testosterone modifies GHRs in the liver and in extrahepatic tissues. Testosterone increases the expression of GHR mRNA in the liver and in growth plates of castrated rabbits [60]. A similar effect occurs in the growth plates of hypophysectomized rats [61]. Testosterone, therefore, modulates the peripheral action of GH on the growth plate and liver by enhancing GHR expression.

Human studies show that testosterone augments the biological effects of GH. In children with hypopituitarism, stimulation of growth by GH is augmented by co-treatment with testosterone [62]. In men with hypopituitarism, testosterone augments the stimulation of fat oxidation and protein synthesis [57, 63], and muscle IGF-1 gene expression [64, 65] induced by GH. GH itself increases androgen receptor gene expression in muscle of hypogonadal men [66]. These observations provide strong evidence that androgens increase tissue responsiveness to GH, in part by enhancing GHR abundance.

4.3 Protein Metabolism

Human studies from our laboratory show strong interactions between testosterone and GH in regulating whole body protein anabolism. In hypopituitary men, GH and testosterone independently stimulate protein synthesis, with the effect being additive when co-treated [57].

Testosterone replacement induced a protein anabolic effect only in the presence of GH [67]. Both hormones are required to optimize protein anabolism and the interaction occurs in the liver. In men with hypogonadism with sufficient GH, oral administration of a low dose of testosterone that exposes only the liver to testosterone enhanced whole body protein anabolism [67]. This effect is equivalent to that of systemic testosterone administration by the transdermal route. This interesting finding indicates that the liver rather than peripheral tissues is the site where GH and testosterone positively interact in enhancing whole body protein anabolism. We replicated this finding in post-menopausal women in whom administration of low-dose oral testosterone also stimulated whole-body protein anabolism [68]. We also observed that oral testosterone administration increased circulating IGF-1 levels [67, 68]. These observations indicate that the liver is the primary site where testosterone and GH interact in regulating whole body protein anabolism.

4.4 Physical effects

The anabolic effects of GH on physical performance are potentiated by androgens. In a study of recreational athletes, combined administration of GH and testosterone increased the functional component of muscle mass, the body cell mass [14]. Testosterone also augmented other aspects of GH action, such as collagen tissue synthesis. GH increases collagen synthesis in skeletal muscle and tendon [69], and the stimulatory effect of GH on circulating markers of collagen synthesis is potentiated by testosterone [70]. GH administration stimulated sprint capacity when administered alone, and the effect was potentiated when combined with testosterone [14]. These findings indicate that both GH and testosterone interact in enhancing anabolism and muscle function.

In summary, testosterone stimulates GH secretion through aromatization to estradiol and directly enhances GHR function. The liver is a primary site where testosterone and GH

interact to regulate protein metabolism. Both GH and testosterone are required to exert full anabolic effects.

5. Clinical practice implications

The regulatory interactions of the GH system by sex steroids have practical and clinically relevant information for women and men with hypopituitarism. The information should guide clinical practice in the therapeutic use of sex steroids and related compounds in women with hypopituitarism who are GH deficient.

5.1 Women

Women with hypopituitarism of reproductive age usually receive estrogen replacement therapy until they reach menopausal years, usually around the age of 50 years. In clinical practice, such women are rarely replaced with estrogens beyond the age of 50 years. Although rare, some women with hypopituitarism may not be able to tolerate estrogen therapy and may be considered for treatment with SERMs if osteoporosis co-exists.

5.1.1. Estrogen replacement

Because estrogen antagonizes the metabolic actions of GH on the liver, estrogen should be replaced by a non-oral route of administration in women with hypopituitarism. For women with hypopituitarism with GH deficiency and not replaced with GH, oral estrogen administration will worsen the GH deficient state. For those taking GH replacement, oral estrogen replacement reduces the therapeutic benefit of GH.

Unfortunately, parenteral estrogen replacement is not widely practised. In a single centre survey, among GH deficient women receiving concurrent estrogen therapy, only 19% received estrogen via a transdermal route [71]. IGF-1 levels were lower in those taking ethinyl estradiol despite this group receiving a much higher dose of GH. The study also estimated that oral estrogen therapy substantially increases the annual cost of GH therapy

[71]. From the Pfizer KIMS database, among 315 women with hypopituitarism taking estrogens, 86% were prescribed oral formulations, with one-third using oral contraceptive steroids [72]. On average, those taking oral contraceptives required 55–70% more GH, and those taking oral formulations 20–30% more than those using transdermal patches [71, 72]. The GH sensitivity index, expressed as a change in IGF-1 over GH dose, is least for ethinyl estradiol, followed by estradiol valerate, and highest with transdermal estrogen replacement [73]. Therefore, the route and type of estrogen therapy determine the cost and benefits of GH replacement in GH deficient women.

5.1.2. Effects of SERMs

SERMs may be used in the management of women with hypopituitarism who are intolerant of estrogen therapy, eg. from menorrhagia or irregular bleeding.

The effects of SERM on the GH and gonadal axes are dependent on the dose and the type. In studies comparing tamoxifen and raloxifene, we observed tamoxifen to be more potent in suppressing the GH axis in the doses used. A dose of 20 mg tamoxifen significantly reduced circulating IGF-1 concentration, an effect greater than that from a 120 mg dose of raloxifene [37]. Therefore, tamoxifen in the doses used is more potent than raloxifene in inhibiting the GH axis.

The effects of raloxifene on IGF-1, substrate metabolism and body composition in hypopituitary during GH therapy have been compared with 17ß-estradiol. During GH therapy, the increase in IGF-1 is reduced equally by raloxifene or 17ß-estradiol; however, raloxifene mitigates the beneficial effects of GH on fat mass, lean body mass and bone mineral density to a greater degree than 17ß-estradiol [74, 75]. As raloxifene but not estradiol increase the principle IGF-1 binding protein IGFBP-3, a fall in IGF-1 bioactivity may explain reduced anabolism observed with raloxifene treatment [74]. However, the raloxifene effects on

bioactive IGF-1 are similar to that of estrogen, highlighting that other mechanisms to IGF-1 mediation are involved [76]. Therefore, raloxifene offers no advantage over oral estrogen to GH-deficient women during GH replacement and may well be detrimental.

GH plays a major role in the regulation of hepatic lipid metabolism, as revealed by a prevalence of fatty liver of up to 77% of patients with GH deficiency [77]. As GH stimulates hepatic triglyceride export and fatty acid oxidation, the inhibitory effect on hepatic GH action by SERMS may lead to suppress hepatic lipid metabolism resulting in liver steatosis development [52, 74, 78, 79]. Fatty liver development is a risk of tamoxfen therapy in women with breast cancer [80]. In contrast to SERMs, fatty liver is not an adverse effect of aromatase inhibitors as they do not affect hepatic GH action.

This inhibitory effect of SERMs on hepatic GH action has been exploited recently as a treatment option for acromegaly. Tamoxifen treatment up to 40 mg daily reduced circulating IGF-1 levels in 80% and normalized IGF-1 in almost 50% patients with acromegaly [81]. Although tamoxifen should be used with caution in patients with GH deficiency as GH replacement dose adjustments may be required, in acromegaly, tamoxifen might prove to be an effective adjuvant therapy.

In summary, the prevalence of oral estrogen use in women with hypopituitarism is very high. The treatment of estrogen deficiency by oral formulations in women with hypopituitarism cannot be recommended, as it substantially reduces GH effectiveness, increasing GH replacement cost. When contraceptive instead of replacement doses of estrogen are prescribed, the waste of GH is even greater. SERMs in therapeutic doses induce similar if not greater antagonism of GH action and their use in women with hypopituitarism is to be avoided.

5.2. Men

Testosterone and GH exert similar effects on body composition and physical function; they also act together in augmenting each other's effects. In men with hypopituitarism, concomitant GH and testosterone replacement is needed to achieve optimal effects on protein anabolism, body composition and muscle function. The adverse effects of GH and testosterone, however, are more frequent when co-administered [14, 82]. This is important information when initiating GH and testosterone replacement, in minimizing side-effects such as edema, myalgia and arthralgia. For this reason, stepwise introduction of GH and testosterone replacements along with gradual dose adjustments is advised.

6. Summary and conclusion

In summary, sex steroids regulate the secretion and action of GH through a mix of paracrine and endocrine mechanisms. In both men and women, local estrogens derived from the aromatization of androgens stimulate GH secretion. Estrogens and androgens exert distinct and opposite endocrine-mediated effects on hepatic IGF-1 production, protein and lipid metabolism. Drugs that inhibit central local estrogen production or action reduce GH secretion, whereas oral estrogen formulations and estrogen agonists antagonize GH action on the liver. Androgens enhance the secretion and action of GH.

In conclusion, sex steroids substantially influence substrate metabolism and body composition through paracrine and endocrine modulation of the GH-IGF axis. Drugs that mimic or block estrogen action or estrogen availability are widely used as therapeutic substances, and have the potential of impairing metabolic health. The therapeutic benefit of GH in women with hypopituitarism is unaffected when estrogens are replaced by a non-oral route. Testosterone maximizes the metabolic and anabolic benefits of GH.

Practice Points.

- In women with hypopituitarism, contraceptive formulations of estrogens are to be avoided and estrogen should be replaced by a non-oral route of administration.
- SERMs offer no metabolic advantage over estrogens in women with hypopituitarism.
- In men with hypopituitarism, androgens can be replaced by an oral or non-oral route of administration.
- In patients with hypopituitarism replaced with sex steroids, women require a larger replacement dose of GH than men.

Research agenda

- The metabolic consequences of SERMs in men and women should be investigated.
- Regular auditing of appropriate prescriptive use of estrogens in women with hypopituitarism should be undertaken.

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Table 1. Effects of sex steroids and estrogen compounds on GH secretion and circulating IGF-1 levels

	Effect on GH	Effect on IGF-1
Oral estrogen	↑	↓↓
SERMs	↓	↓↓
Aromatase inhibitors	↓	↓
Testosterone	↑	↑

Figure legends

Figure 1: A: Estrogen administered via oral route acts on the liver to reduce IGF-1 production through first pass hepatic effect. The reduction in IGF-1 lessens negative feedback to the hypothalamus and pituitary gland and GH secretion is stimulated. B: Tamoxifen treatment also reduces IGF-1 levels, however due to central estrogen receptor antagonism by tamoxifen, GH secretion is attenuated. Studies indicate an important role of locally produced estrogen from testosterone through aromatization in the neuroregulation of GH secretion. (Adopted from [36]).

Figure 1