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REVIEW ARTICLE

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Somatotropic-Testicular Axis: A crosstalk between GH/IGF-I and gonadal hormones during development, transition, and adult age

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Abstract

Background: The hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-somatotropic (HPS) axes are strongly interconnected. Interactions between these axes are complex and poorly understood. These interactions are characterized by redundancies in reciprocal influences at each level of regulation and the combination of endocrine and paracrine effects that change during development.

Objectives: To comprehensively review the crosstalk between the HPG and HPS axes and related pathological and clinical aspects during various life stages of male subjects.

Materials and methods: A thorough search of publications available in PubMed was performed using proper keywords.

Results: Molecular studies confirmed the expressions of growth hormone (GH) and insulin-like growth factor-I (IGF-I) receptors on the HPG axis and reproductive organs, indicating a possible interaction between HPS and HPG axes at various levels. Insulin growth factors participate in sexual differentiation during fetal development, indicating that normal HPS axis activity is required for proper testicular development. IGF-I contributes to correct testicular position during minipuberty, determines linear growth during childhood, and promotes puberty onset and pace through gonadotropin-releasing hormone activation. IGF-I levels are high during transition age, even when linear growth is almost complete, suggesting its role in reproductive tract maturation. Patients with GH deficiency (GHD) and insensitivity (GHI) exhibit delayed puberty and impaired genital development; replacement therapy in such patients induces proper pubertal development. In adults, few studies have suggested that lower IGF-I levels are associated with impaired sperm parameters.

Discussion and conclusion: The role of GH-IGF-I in testicular development remains largely unexplored. However, it is important to evaluate gonadic development in children with GHD. Additionally, HPS axis function should be evaluated in children with urogenital malformation or gonadal development alterations. Correct diagnosis and prompt therapeutic intervention are needed for healthy puberty, attainment of complete gonadal development during transition age, and fertility potential in adulthood.

KEYWORDS
growth hormone, IGF-I, testicle, growth hormone deficiency, puberty, transition age

1 | INTRODUCTION

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) receptors are present in gonads[1] and can modulate the activity of sex hormones.[2] The hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-somatotropic (HPS) axes are more strongly interconnected than that generally perceived, working to fine-tune each other's activities. During puberty, GH secretion proportionally increases with sex hormone secretion,[3-5] whereas in late adulthood, both total testosterone and GH secretions mutually decrease over time.[6]

Interactions between the two axes have not been entirely elucidated. The redundancy of reciprocal influences at each level of regulation, which changes during different developmental stages, and the combination of endocrine and paracrine effects make the crosstalk particularly complex. Although studies using animal models provide some insights, studies based on the in vivo effects of GH and IGF-I on gonadal development, steroidogenesis, and fertility report controversial findings.

In this review, we discuss physiological mechanisms of the crosstalk between HPG and HPS axes and their clinical presentation and implications in function of various stages during development from infancy through puberty, transition age and, finally, adult life stages of male subjects.

A computerized literature search was performed using the following keywords: "adolescence," "fertility," "GH," "ghrelin," "IGF-I," "Leydig cell," "puberty," "Sertoli cell," "spermatogenesis," "steroidogenesis," "testis," "testosterone," and "transition age." Keywords were properly combined with Boolean operators to optimize the search.

2 | PHYSIOLOGY OF CROSSTALK: THE CHICKEN AND THE EGG

The interaction between HPS and HPG axes is observed at various stages and is likely to be mutual. GH and IGF-I receptors are found in

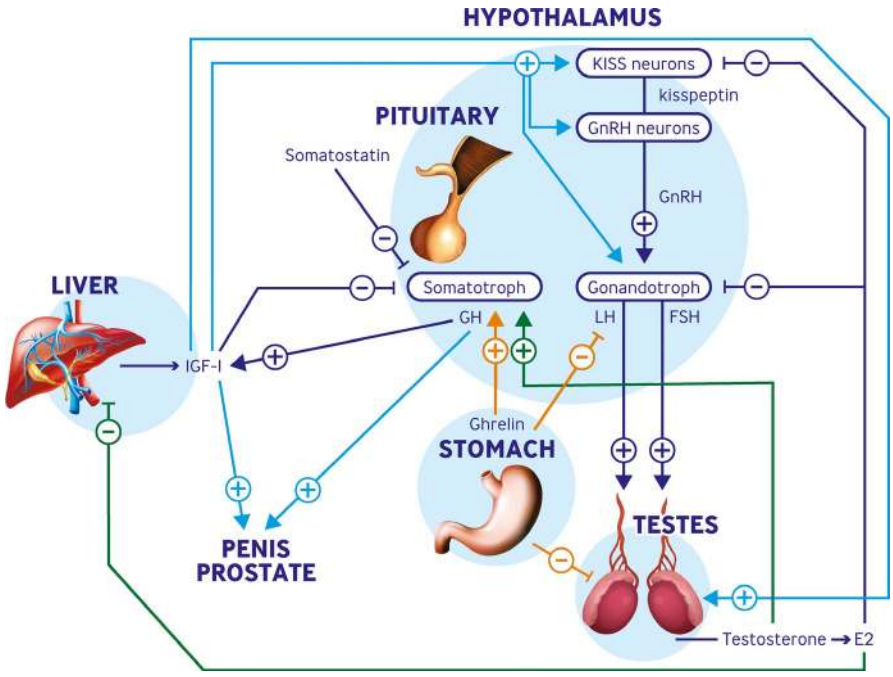

FIGURE 1 Schematic representation of the crosstalk between growth and gonadal hormones. *Effects of growth on gonadal hormones* (arrows in light blue): Pituitary somatotroph cells produce GH that stimulate liver to produce IGF-I. Somatostatin is the main negative regulator of GH secretion. IGF-I acts at many levels: (1) on hypothalamus activating GnRH neurons and kisspeptin neurons for puberty development, (2) on the pituitary gland activating gonadotroph cells, (3) on the testicles (for details, see Figure 2), and (4) on penis ad prostate probably influencing growth and development; GH can also directly act on prostate and penis. *Effects of gonadal on growth hormones* (arrows in green): FSH and LH released from gonadotroph pituitary cells directly stimulate the testicle (for details, see Figure 2); testosterone released from the testes and E2 trough aromatization are important facilitators of GH release from pituitary somatotroph cells; E2 is able to inhibit liver production of IGF-I. *Effects of ghrelin* (arrows in orange): Ghrelin is able to stimulate GH release from somatotroph cells and inhibits LH release from gonadotroph cells; moreover, ghrelin can act directly on the testes inhibiting both steroidogenesis and spermatogenesis (for details, see Figure 2)

the reproductive tract, on gonadotropin-releasing hormone (GnRH) neurons, and in pituitary gonadotroph cells.[7-10] On the other hand, sex steroids act on the HPS axis for both neuroendocrine regulation of GHRH secretion and modulation of peripheral responsiveness to GH. Because these reciprocal influences change during development, which axis acts first and which axis is dominant remain unclear. Acquiring knowledge on this issue has clinical implications, especially in terms of treatment. A summary of this complex crosstalk is presented in Figure 1.

2.1 | How GH and IGF-I influence the HPG axis

GH and IGF-I have a central effect on hypothalamic GnRH neurons, kisspeptin neurons, and gonadotropin-secreting cells in the pituitary gland. Injection of IGF-I into rats, either centrally in the cerebrospinal fluid or peripherally, results in activation of the kisspeptin neurons in the anteroventral periventricular nucleus.[11] Moreover, IGF-I seems to facilitate LH secretion from pituitary cells both in rats and in bovines.[12-14]

In mouse models, knockout (KO) of GH receptors (*GHR*) or *IGF-I* or *IGF-I* receptor (IGF-IR) genes impairs sexual development and delays the onset of puberty.[9,15,16] This phenotype overlaps with that observed in Kisspeptin1R KO mice,[17] suggesting that IGF-IR signaling is vital for GnRH neuron maturation and synaptogenesis needed for pubertal onset.[18] Although inhibition of systemic GH/IGF-I hormone levels does not prevent animals from achieving reproductive competence, a significant slowing down of gonadal development is observed, as detailed below.[19,20] These findings suggest the existence of paracrine or alternative signals that keep receptor signaling active, although at a lower level.

The testis produces GH and IGF-I both in Leydig cells (LCs) and in Sertoli cells (SCs) (Figure 2). In the human testis, immunostaining for IGF-I is mainly observed in SCs and to a lesser extent in LCs. *GHR* and *IGF-IR* are expressed both by LCs and SCs as well as germ cells (primary spermatocytes, secondary spermatocytes and early spermatids).[21] Testicular GH, and more importantly, locally produced IGF-I generate many paracrine and autocrine signals involved in both spermatogenesis and steroidogenesis. This ultrashort paracrine loop appears to be controlled by FSH and LH, which stimulate IGF-I.[22,23]

The effect of IGF-I on steroidogenesis has been widely demonstrated. Administration of IGF-I alone in dwarf mice with growth hormone deficiency (GHD) has a mild effect on basal steroidogenesis, but it increases the number of hCG receptors on LCs, thereby indicating that IGF-I may potentiate gonadotropin-induced steroidogenesis.[24] IGF-I also stimulates proliferation of LC progenitors and their differentiation.[25] Similarly, GH enhances steroidogenic acute regulatory protein (StAR) and increases *3β-HSD* gene expression[26-28] in LCs.

As stated above, IGF-I may act as an autocrine factor for the regulation of spermatogenesis. Further, *GHR*-KO mice show reduced fertility, which supports this conclusion. However, spermatogenesis is not abolished, probably because of a GH-independent production of IGF-I within the seminal tubules.[29] In addition, IGF-I treatment increases sperm motility in the same mouse model.[30]

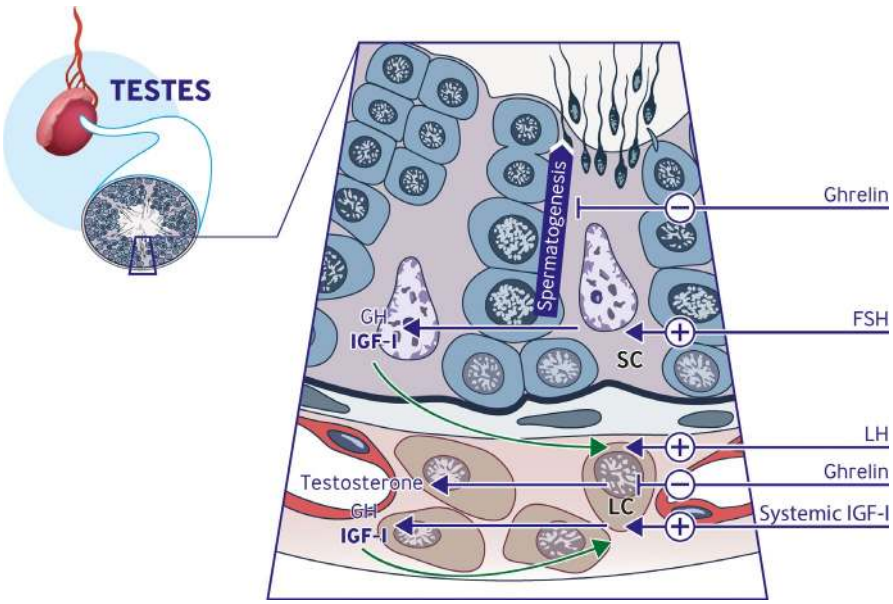

FIGURE 2 Schematic representation of the crosstalk between growth and gonadal hormones in the testis. Both Leydig (LC) and Sertoli cells (SC) are able to produce GH and—even more—IGF-I, under the control of FSH and LH. Ghrelin has an inhibitory function on growth hormone release from LC and SC and also on spermatogenesis. Locally produced IGF-I is able to generate many paracrine and autocrine signals involved in both spermatogenesis and steroidogenesis (arrows in green). Effects on steroidogenesis: IGF-I is also able to stimulate the proliferation of LC progenitors and their differentiation; GH enhances steroidogenic acute regulatory protein (StAR) and increases 3β-HSD gene expression in LC. IGF-I action on spermatogenesis is not yet fully confirmed and is not shown in the figure

2.2 | How sex hormones can shape the HPS axis

The influence of sex steroids on the somatotropic axis can be described by two major activities: central neuroendocrine regulation of GH secretion and peripheral modulation of GH responsiveness.

Testosterone and estradiol (E2) are important facilitators of GH secretion. Testosterone replacement therapy increases GH release by the pituitary gland in hypogonadal patients[3,31] by increasing the amplitude of GH secretion bursts during puberty.[32] This effect observed in these patients is due to testosterone and its aromatization to E2. Moreover, the role of estrogens is supported by impaired GH and IGF-I secretion[33] in males with congenital aromatase deficiency.

Animal models have shown sex-related differences in sex hormone-driven somatotropic secretion. Male mice have more regular GH secretory pulses of high amplitude, whereas females show irregular secretory peaks of lower amplitude but higher interpulse GH levels.[34,35] This sex-related effect seems to be mediated by somatostatin, the primary negative regulator of GH secretion, which exhibits a similar sex-specific secretion pattern.[36-39] Studies in rats indicate that signal transduction may also contribute to the dimorphic effects of GH on growth. The rhythmic GH release typical in males is more efficient in activating the STAT5b signaling cascade, which when switched off in male STAT5b-KO rats, determines female-like growth despite the persistence of a male-like GH secretion pattern.[40]

Additionally, GH secretion in humans is sexually dimorphic: larger nocturnal pulses and relatively smaller daily pulses are observed in males than in females who display more continuous secretion and frequent irregular pulses.[41] Sexual dimorphism in GH secretion likely contributes to differences in body growth: sex hormone levels during prepuberty are extremely low, and the HPS axis mediates skeletal growth without distinct differences between boys and girls. During puberty, sex hormones accelerate truncal growth more than appendicular growth until growth plate closure and cessation of growth. This process is principally mediated by E2, which explains why boys are taller than girls and display a longer growth period.[42]

Furthermore, the two sex hormones appear to influence the HPS axis also in adulthood. Testosterone positively modulates ghrelin, a hormone that stimulates GH release, in inducing higher GH bursts.[43] Moreover, recent findings suggest that E2 is an important regulator of GH secretion in adult males.[44] Pituitary receptors ERα and ERβ can synergistically act with the pituitary-specific transcription factor Pit1 to activate pituitary *Gh* gene transcription through high-affinity binding.[45]

Sex hormones also play a major role in regulating peripheral responsiveness to GH, which is also gender related. In prepubertal age, both GH and IGF-I levels are comparable between boys and girls.[46,47] Evidences from studies on adults show that GH circulating levels are lower in males than in females, which can be explained, at least in part, by higher GH clearance in males than in females owing to androgenic effects.[46] IGF-I levels instead are higher in adult males[48] than in females, also in GHD condition.[49] This observation is mainly owing to the effect of E2 for lowering liver sensitivity to GH on the release of IGF-I. This is possibly the reason why males with GHD likely respond better to lower doses of rhGH with greater increases in IGF-I and bone mass than females.[50,51] Similarly, normal[49] or even acromegalic[52] females tend to show lower IGF-I/GH ratios than their male counterparts.

The underlying mechanism of lower GH sensitivity in females is the estrogenic upregulation of cytokine signaling-2 suppressors and/or phospholipase C (PKC) activation in the liver,[53,54] both concurring to reduce Janus kinase 2 (JAK-2) phosphorylation and thus downregulate GH signal transduction.[55] The final result is an E2-dependent inhibition of IGF-I secretion from hepatocytes.

2.3 | How the extratesticular effects of GH and IGF-I impact the reproductive system

Apart from the above effects on testicular function, the HPS axis plays a role in the development of other reproductive organs. GH appears to be involved in penile growth in children because some studies have reported GHD- and GH-resistant subjects with reduced penis size, which was partially improved with GH therapy.[56-58]

Further, GH may have a beneficial role in erectile function, facilitating smooth muscle relaxation and reducing venous leakage, possibly through a stimulating effect on cyclic guanosine monophosphate (cGMP) generation in human cavernous smooth muscle.[58] This biological mechanism was suggested through an in vivo human study that demonstrated that ED is associated with low levels of GH as well as NO and cGMP in cavernosal blood[59,60.]

Finally, an in vitro model of mouse organ cell cultures showed that anti-rGH antibody blocked Wolffian duct differentiation, specifically in the presence of fetal cells, and GH therapy reversed this condition. This observation indicates a possible role of GH/IGF-I in the fetal development of Wolffian duct-derived structures, such as the prostate and seminal vesicles,[61] through an endocrine, a paracrine, or an autocrine mechanism that has not yet been defined.

The HPS axis has a more clearly defined role in adult prostatic disease: through its actions in promoting cell growth and survival,[62,63] it appears to increase prostatic volume (PV), raising the risk of benign prostatic hyperplasia (BPH). GHD patients, in fact, show a reduced PV,[64,65] while the opposite is true in acromegalic patients[65,66] compared with healthy age-matched controls. In particular, in acromegaly, PV mostly correlates with duration of disease, rather than patients' age.[65] Indeed, BPH is reported in approximately half the acromegalic subjects[65,67] and the prevalence of parenchymal alterations (ie, cysts, calcifications and nodules) is also increased.[65,66,68] Slight increase in PSA levels and International Prostate Symptom Scores (IPSS) are also reported in these patients, although prostatic symptoms are often absent.[67,69] Moreover, as results from a large population study, prostatic cancer (PCa) incidence is increased both in healthy individuals with IGF-I levels in the upper reference range[70,71] and in acromegalic patients.[72] However, a recent meta-analysis of 23 studies in acromegaly reveals some potential sources of bias in the association between acromegaly and PCa: for example, cancer incidence was more

pronounced in smaller and single-center studies (selection bias) and the enlarged PV in acromegaly may lead to more frequent US examination (diagnostic workup bias).[73]

In GHD patients, replacement therapy restores prostate size to normal, with no increase in prostate abnormalities or PSA levels; an even greater increase in PV is observed in hypogonadal patients also receiving concurrent testosterone replacement therapy.[64] On the other side, effective pharmacological treatment of acromegaly for 1-2 years via somatostatin analogs results in a reduction of PV in young subjects (<50 years old), but not in older ones, despite a rise in testosterone levels.[66,74]

2.4 | The additional control level: ghrelin

Ghrelin, which is among the primary activators of the HPS axis, is a peptide produced by the stomach that increases food intake and decreases energy consumption. Upon binding of its receptor, the GH receptor-secretagogues (GHS-R) ghrelin potently stimulate GH release. Ghrelin is found in the human testis in both interstitial LCs and also SCs, even if in lower amounts. GHS-R is detectable in germ cells, mainly pachytene spermatocytes, and in somatic SCs and LCs.[75] Ghrelin has been proposed to link the neuroendocrine system and somatic growth with metabolism and reproduction.[76]

Ghrelin acts centrally, inhibiting LH production, and peripherally, reducing testosterone synthesis (Figure 1). In addition, ghrelin exerts a negative effect on germ cell development and LC proliferation[77] (Figure 2) through the inhibition of the gene encoding stem cell factor (SCF), a c-Kit ligand,[78,79] with implications on extragonadal effects of GH, such as cardiovascular function.[80,81] Thus, the hormone may act as an inhibitor of spermatogenesis and steroidogenesis. Evolutionarily, this action could depend on the need to inhibit reproductive function under conditions of fasting, underweight, and inadequate calorie uptake: ghrelin, indeed, is found at high levels under all these conditions.[76] Likewise, leptin, an adipose tissue-derived anorexigenic hormone, acts on the reproductive tract, and its receptors are indeed expressed in the gonads.[82-84] Leptin mainly acts as a permissive factor in the hypothalamus, where a minimum level is required for normal HPG axis activity; however, at higher levels, it inhibits LC steroidogenesis.[85]

In summary, fertility appears to be strictly linked to metabolic balance through leptin and ghrelin, and its full potential is achieved only in favorable nutritional environment after the completion of the transition age.

3 | GROWING UP: FROM SEXUAL DIFFERENTIATION TO TRANSITION AGE

3.1 | Fetal development and infancy

The interaction between the HPS and HPG axes starts in the first weeks of gestation, during which IGF-I and insulin-like family of growth factors play important roles in gonadal development and sexual differentiation.[86] XY mice KO for *Igf1r* and *Insr* show reduced expression of *Sry* and lack of activation of some genes crucial for testicular differentiation, such as *Sox9*, *Fgf9*, and *Ptgds*. SCs and LCs fail to develop as a result.[87] A second study by the same group showed that selective *Igf1r-Insr* inactivation in SC impairs their proliferation during late fetal and early neonatal development, resulting in smaller testes and lower sperm output later in life.[88] However, mutant mice are fertile, demonstrating that the absence of IGF-I signaling restricted to SC does not have a severe effect on spermatogenesis. Lower testes volume is likely to be related to reduced SC number. Notably, FSH amplifies IGF-I-mediated PI3K/AKT protein kinase signaling in SCs, highlighting the importance of this signal for SC proliferation.[89]

Shortly after birth, GnRH activation stimulates gonadotropin secretion as well as testosterone, inhibin B, and anti-Müllerian hormone (AMH) production in boys. This process, called minipuberty, occurs approximately between months 1 and 6 of postnatal life: a rise in testosterone levels is considered responsible for greater linear growth observed in males than in females.[90] This effect is synchronous with that of the activation of the HPS axis; IGF-I also increases shortly after birth and continues to escalate linearly until puberty.[91]

A recent study attributes a permissive role to IGF-I during minipuberty, along with LC and SC function, in consolidating testicular position in the scrotum to a low-enough location from which the testes are unlikely to ascend to high scrotal or suprascrotal position during childhood.[92] IGF-I levels during minipuberty strictly correlate with testicular distance to the pubic bone (TDP) and thus with a lower testicular location in a linear mixed-effect model.[92] After minipuberty, IGF-I levels slowly and linearly increase throughout infancy as a function of insulin levels and nutritional status.[91] After the first year of life until late childhood, a deceleration of height velocity growth is observed, which is reversed only when puberty starts.

3.2 | Puberty and transition age

The GnRH pulse generator is activated at pubertal onset to trigger the hormonal cascade necessary for sexual maturation. This activation is strictly related to body mass and nutritional state; thus, anabolic hormones such as insulin and IGF-I contribute to GnRH pulsatiliy.[9] At the same time, the amplitude of GH secretion bursts increases, along with the overall daily output of pituitary GH.[32] Both are needed for linear and pubertal development.

Mechanisms underlying HPS axis activation during puberty are not entirely clear but likely involve augmented hypothalamic release of GHRH mediated by testosterone surge[93]; kisspeptin neurons that activate pituitary somatotroph cells and increase their sensitivity to GHRH stimulation[80] are also likely to be involved.

Transition age is defined as the phase between the end of puberty and young adulthood. The beginning of transition corresponds to the

achievement of Tanner stage V, while the end of transition corresponds to the achievement of peak bone mass.[94] Transition age is therefore a crucial period as of the maturation of HPG and HPS axes[95] and their mutual influence is especially relevant during this period.

IGF-I progressively increases in Tanner stages from I to III, concomitantly with the increase in testicular volume and then decreases during Tanner stages IV and V.[47] These observations are confirmed by analysis of both bioavailable IGF-I and free IGF-I levels,[96,97] thus excluding confounding factors. As recently highlighted in a short review by Juul and Skakkebaek, IGF-I levels usually peak 2 years after pubertal spurt, but the levels remain elevated for few years afterward, suggesting that GH and IGF-I are important for longitudinal growth but likely play a role in full maturation of the reproductive system.[98]

As a matter of fact, HPS axis activation is needed for proper pubertal onset and maturation. For example, higher levels of serum IGF-I at 8 years of age are associated with early menarche in normal girls, even after adjustment for BMI, height, and prepubertal state.[99] Moreover, girls with central precocious puberty have markedly elevated IGF-I levels compared with prepubertal peers, and their IGF-I levels gradually return to prepubertal levels after linear growth ceases or following GnRH agonist therapy.[100] An interesting retrospective study conducted on prepubertal boys with constitutional delays in growth and puberty (CDGP)[101] suggests a correlation between the degree of HPS axis activation and pubertal initiation. Lowest IGF-I levels were found in patients with hypogonadotropic hypogonadism, whereas highest IGF-I levels were found in patients with an early puberty. Taken together, these studies suggest an important role of the HPS axis in the physiological activation of the HPG axis (Table 1).

Conversely, HPS axis impairment during childhood and puberty can affect genital development. Conditions such as micropenis,[102,103] hypospadias, and cryptorchidism[104] frequently occur in patients with isolated GHD. Patients with Laron syndrome, GH insensitivity (GHI) due to a mutation in GH-receptor[105] or *STAT5b*[106] genes, offer an ideal model to study this crosstalk. All affected patients have delayed pubertal onset and a prolonged pace.[107,108] Interestingly, treatment with recombinant human IGF-I (rhIGF-I) stimulates testicular and penile growth in these boys.[109,110] Similarly, delayed puberty was observed in a 15-year-old boy born short for gestational age who harbored a mutation in the *IGF-1* gene[111] and in patients with mutations in genes encoding for other components of the HPS axis, such as *IGF-2*,[112] *IGF-1R*,[113] and *ALS*[114] (Table 2). Several studies on rhGH therapy in boys with GHD have reported faster progression of pubertal maturation[115] compared with those with untreated GHD. Boys with GHD more frequently exhibited delayed puberty.[116-120] In treated patients, age at onset of spontaneous puberty positively correlated with the commencement of GH therapy, as observed in 319 boys with idiopathic and non-congenital GHD.[121]

A retrospective study examined 37 prepubertal children (boys and girls) with congenital isolated growth hormone deficiency[122] who were treated with rhGH. The authors observed delayed pubertal onset to be more evident in boys with age at first ejaculation occurring 3.5-4 years later than in the reference population.[123] The authors once more suggested a positive correlation between age at initiation of treatment and age at pubertal onset. Stretched penile length at the end of puberty was shorter than that of the reference population average, although it significantly increased following rhGH therapy.[56-58] Testicular volume was normal at the end of therapy, positively correlating with treatment duration and negatively with age at initiation of treatment. Age at first ejaculation was significantly higher than that in normal boys, and rhGH therapy induced a greater increase in testicular volume in patients who started therapy before 10 years of age; these observations emphasize that rhGH promotes pubertal development, even if it does not normalize it. These studies appear to confirm that better responses on puberty and sexual differentiation result when replacement therapy is promptly started at an early age. However, no clear evidence emerges on the correlation with treatment duration or dosage. One study observed a negative correlation between GH dose and pubertal onset but no correlation with treatment duration.[124] In addition, a more recent study that evaluated pubertal onset in 111 GHD children aged 3-16 years after 48 months of rhGH administration at different doses (25, 50, and 100 μg/kg/day) did not find any significant differences, even if the wide age range of inclusion and lack of control group may bias the findings[125] (Table 1).

It remains controversial whether sex steroid priming during pubertal development improves the specificity of GH stimulation test for GHD diagnosis, thus reducing false-positive results. However, adjusted data on cut-off values post-priming are missing, and therefore, no clear consensus exists regarding the use of sex steroids outside of delayed puberty.[126]

Apart from children with GHD, rhGH is also used in children affected by idiopathic short stature (ISS). Data on the onset and pace of puberty and/or genital development after therapy in this setting are conflicting (Table 1). Some studies showed that treated children, as opposed to control patients, have an earlier pubertal onset and/or pace of puberty[127,128] and faster progression of bone age. Kawai et al[128] in a small population treated with 24 μg/kg/day of rhGH and Kamp et al in a larger (26 boys) population[127] randomized to receive 70 μg/kg/day of rhGH for 2-4 years before puberty or no treatment, observed that a prepubertal exposure to rhGH can accelerate pubertal development.

Nevertheless, a number of larger studies found no effects.[129-132] A controlled study of 91 boys with ISS randomized to receive rhGH or no therapy reported no differences in the timing of pubertal onset, age at which maximum mean testicular volume was reached, or duration of puberty in the treated population. However, at the end of puberty, significantly larger testicular volume was observed in GH-treated boys than in controls, but smaller testicular volume was observed in GH-treated boys than the expected value when compared to that of the national reference population.[130] Other studies observed no difference in age at pubertal onset, pace of pubertal progression,[131] or duration of puberty in GH-treated boys compared with untreated subjects, even across different dosages[132]

Finally, results of a large multicentric study[129] showed that different replacement regimens do not seem to influence pubertal

TABLE 1 Summary of interventional studies on the effects of rhGH/rhIGF-I treatment in males during infancy and puberty, listed by pathology: congenital isolated growth hormone deficiency (cI-GHD), growth hormone deficiency (GHD), idiopathic short stature (ISS), growth hormone insensitivity (GHI). For articles including both male and female study populations, the data reported in the table refer only to the male population.

	Study	n	Age (ys)	Population	Treatment dose	Times a wk	Treatment duration (ys)	Pubertal onset	Puberty duration	Final TV	Penile length
cI-GHD	Smuel et al 2015[122]	RT	M: 21 F: 16	7.5 ± 4.8 (m)	Prepubertal children with cI-GHD	hGH: 35 μg/kg/d	NA	9.4 ± 4.1 (m)	Delayed age at first ejaculation vs population reference values	NA	↓vs population reference values	↓vs population reference values
GHD	Levy and Husmann 1996[58]	RT	M: 8 F: -	7.5 (M)	GHD with micropenis	Unclear	Unclear	Unclear	NA	NA	NA	↑ vs baseline
	Tatò et al 1996[120]	RCT	M: 15 F:-	10.7 ± 1.7 (m)	Group 1: GHD (n = 8) Group 2: MPD (n = 7)	Group 1: rhGH 23 μg/kg/d Group 2: rhGH 0.7 IU/kg/d + hCG 200 IU (3/wk) + hMG 500 IU (2/d)	6	Group 1: 5.3 ± 0.4 Group 2: 8.0 ± 0.4	↔ between treatment groups	↓Group 2 *vs* Group 1	↔ between treatment groups	↔ between treatment groups
	Rogol et al 2013[125]	RCT Multi	M: 75 F: 36	7.7 ± 2.8 (m)	Prepubertal children	Group 1: rhGH 25 μg/kg/d Group 2: rhGH 50 μg/kg/d Group 3: rhGH 100μg/kg/d	7	3.5 ± 1.1 (m)	↔ between treatment groups	NA	↔ between treatment groups	NA
ISS	Kawai et al 1997[128]	RT	M: 27 F: -	11 (m)	ISS	Group 1: rhGH or pGH 24 μg/kg/d Group 2: None	5-6	4.2 (m)	1,8 yr earlier in Group 1 vs Group 2	↓ Group 1 *vs* Group 1 (2yr)	NA	NA
	Rekers-Mombarg et al 1999[132]	Mixed RT and P	M: 49 F: 35	11.5 (m)	ISS (15 SGA)	Group 1: rhGH 28-43 μg/kg/d Group 2: None	6	5.6 (m)	↔ between treatment groups	↔ between treatment groups	NA	NA
	Leschek et al 2001[131]	RPCT DB	M: 49 F: -	12.5 ± 0.3 (m)	Prepubertal or early pubertal boys	Group 1: hGH 74 μg/kg Group 2 placebo	3	Group 1: 4.6 ± 0.3 Group 2 4.2 ± 0.3	↔ vs placebo	↔ vs placebo	↔ vs placebo	NA

(Continues)

TABLE 1 (Continued)

		Study	n	Age (ys)	Population	Treatment dose	Times a wk	Treatment duration (ys)	Pubertal onset	Puberty duration	Final TV	Penile length
	Kamp et al 2002[127]	RCT	M:26 F:9	7.9 ± 1.8 (m)	Prepubertal children with ISS	hGH 0.5-2.5 mg/m^2 Group 1: 0.5 mg/m^2 + w.o.+1mg/m^2 + w.o + 1 mg/m^{2a} Group 2: None	7	2-4 (until 1 yr after pubertal onset)	1.7 yr earlier in Group 1 vs Group 2	NA	NA	NA
	Crowe et al 2006[129]	INT Rnd Multi	M:158 F:81	10.2 ± 2.3 (m)	Prepubertal children with ISS (33 with SGA)	Group 1: hGH 0.24 mg/kg/wk Group 2: hGH 0.240.37 mg/kg/wk (after 1 yr) Group 3: hGH 0.37 mg/kg/wk	6	2	↔ between treatment groups	↔ between treatment groups	↔ between treatment groups	NA
	Albin et al 2011[130]	RCT	M:91 F: 33	10-15 (R)	Short children	Group 1: rhGH 33 μg/kg/d Group 2: rhGH 67 μg/kg/d Group 3: none	7 (?)	5.8 ± 1.1 (m)	↔ between treatment groups	↔ between treatment groups	Group 1, 2: ↑ vs control group	NA
GHI	Laron et al 1998[110]	INT	M: 6 F: -	6.1 ± 4.8 (m)	6 prepubertal boys with GHI	rhIGF-I: 150 μg/kg/d	7	1-5 (R)	NA	NA	↑ vs baseline (n = 2 experiencing puberty)	↑ vs baseline (n = 2 experiencing puberty)

Abbreviations:: (m), mean; (M), median; (R), range; (ys), years; CR, case report; Cs, crossover study; INT, interventional study; MPD, multiple pituitary deficiency; Multi, multicentric trial; NA, not available; P, prospective trial; RCT, randomized control trial; Reg, registry trial; Rnd, randomized trial; RPCT DB, randomized placebo control trial double-blinded; RT, retrospective trial; SGA, short for transitional age.

[a]For Kamp et al 2002: Dosage increase consisted of 3 months of therapy for each dosage followed by 3 months of wash-out.

TABLE 2 Case reports of mutation in genes associated with GH insensitivity presenting with impaired genital development and puberty

	n	Mutation	Age at diagnosis (ys)	Growth (height SDS)	Clinical presentation	Genital characteristics
Castilla-Cortazar et al 2017[103]	M: 1	*IGF1R* (hom) & *IGFALS* (het)	14.8	−14	VLBW (born at 26 wks of gestation) Respiratory difficulties at birth	Micropenis Hypospadias Tanner stage I
Kofoed et al 2003[106]	F: 1	*STAT5b* (hom)	16.5	−7.5	VLBW (born at 33 wks of gestation) Facial dysmorphism Respiratory difficulties at birth Failure to thrive Lymphoid interstitial pneumonia Severe hemorrhagic varicella, Recurrent herpes zoster Pneumocystis carinii pneumonia	Delayed puberty Tanner stage III
Walenkamp et al 2005[111]	M: 1	*IGF1* (hom)	55 yr	−8.6	VLBW (born at 32 wks of gestation) Failure to thrive Microcephaly Deaf-mutism Motor unrest IQ < 40 Arterial hypertension Bilateral cataract Severe osteoporosis	Small penis Delayed puberty (pubarche and gonadarche at 20 yrs of age)
Begemann et al 2015[112]	M: 2 F: 2	*IGF2* (het)[a]	7.1 (m)	R: −1.6, −4	(V)LBW SRS-like facial dysmorphism Feeding difficulties during infancy Ulnar ray defects High-pitched voice Intellectual disability	Delayed puberty Hypospadias Cryptorchidism
Gannagé-Yared et al 2013[113]	F: 1	*IGF1R* (hom)	13.5 yr	−4.4	LBW (born at 41 wks of gestation) Facial dysmorphism Mild intellectual disability Cardiac malformations High-pitched voice Acanthosis nigricans Hypertriglyceridemia	Delayed puberty
Domené et al 2004[114]	M: 1	*ALS* (hom)	14.6 yr	−2.1	Micrognathia Truncal obesity	Delayed puberty

Abbreviations:: (V) LBW, (very) low birthweight; F, female; het, heterozygosis; hom, homozygosis; IQ, intelligent quotient; M, male; m, mean; R, range; SRS, Silver-Russell syndrome; ys, years.

[a]IGF-2 is a maternally imprinted gene.

development. In 158 prepubertal boys, randomized to receive 34 or 74 μg/kg/day, no differences were found in age at onset, duration, or testicular volume during pubertal development between the two groups (Table 1).

Despite transition age being a crucial period for the full maturation of the reproductive system, few data are available for this specific age range. One report of four males aged 17-25 years treated with rhGH for ISS[133] showed reduced testicular volume, hypergonadotropic hypogonadism, and impaired spermatogenesis. These findings were not replicated in other studies, thus allowing to exclude a detrimental effect of rhGH therapy on male gonadal function. A large study involving 111 boys treated with rhGH for GHD or ISS[134] for at least 4 years and in which treatment began at least 1 year before pubertal onset showed normal testicular size and normal serum testosterone levels. Similar results have been reported in another study on eight young males aged 16-18 years previously treated with rhGH for ISS or CDGP[135] evidenced by normal testicular volume and endocrine function as well as mostly "normal" semen parameters at follow-up.

In conclusion, published data are very heterogeneous. Some studies were conducted in children with known congenital or acquired GHD and others in ISS children without GHD. Additionally, some boys were treated during infancy, whereas others were treated just before or during puberty. Combining all data, it can be concluded that a minimum HPS axis basal activity is needed to achieve most HPG effects on sexual maturation, but once this is achieved, additional doses of exogenous GH do not provide any additional benefit. Another limitation of the available studies is that the criteria for idiopathic GHD diagnosis varied with respect to the provocative test(s) and serum GH cut-off(s) used or with respect to sex steroid priming. An alternative hypothesis is that GH has a narrow time- and dose-dependent window for effects on puberty. Time dependency

is suggested by the correlation between the age at which therapy starts and the age of pubertal onset in patients with GHD.[127] Dose dependency is supported by positive results of some studies not definitively refuted by Crowe et al.[129] In this regard, recent guidelines[136] define therapeutic dosages in a range of 22-35 mcg/kg/day for GHD and 34-67 mcg/kg/day for ISS. However, these ranges are established considering linear growth as the main outcome and not gonadal development. In several studies examined so far, higher doses were used instead because the aim was to observe possible effects on gonadal development. Standardization of dosages in this context would help to obtain more homogeneous results.

Finally, most studies did not employ proper control groups of untreated children, examined broad age ranges (ie, enrolled both prepubertal and pubertal children), and most importantly, were not adequately powered to clarify the role of rhGH therapy in pubertal pathophysiology.

4 | THE GROWN-UP: CROSSTALK IN THE YOUNG ADULT

Crosstalk between HPS and HPG axes is essential for sexual maturation during growth, but evidence in adult life is fragmentary and inconclusive. Sample sizes are often very low. Most studies included less than 10 patients,[137-142] and larger studies were retrospective and observational.[143,144] Few available prospective interventional studies were often under-powered and used very different protocols. Some trials focused on patients with GHD[139,144-146] (post-surgical, adult GHD, childhood-onset GHD, and panhypopituitarism) and others on infertile males[137,138,147-149] (oligoasthenoteratozoospermia, azoospermia, and idiopathic infertility) as well as on hypogonadal patients.[140,142] Most studies addressed GHD and only few addressed GH excess. A report on reproductive function in acromegalic males showed lower androgen concentration and sperm parameters that improved after pharmacological or surgical control of the disease.[150] This observation is consistent with that of animal studies.[151]

GH replacement studies used different durations and dosages that do not permit the determination of whether non-significant results could be owing to insufficient treatment duration or insufficient dose regimen.

Furthermore, GH therapy was often associated with gonadotropin treatment,[137-140] masking the effects ascribed to one or the other replacement. Finally, outcomes of interest were not homogeneous. Some studies evaluated only sperm parameters, whereas others evaluated IGF-I levels in the seminal fluid or only hormonal profiles. Only few investigations on adult populations considered testicular volumes.[140,142,143,145,146]

4.1 | Endocrine function

Both LCs and SCs can produce local GH and IGF-I involved in paracrine and autocrine effects.

A recent study conducted using gas chromatography/mass spectrometry revealed that if GHD is associated with hypogonadotropic hypogonadism, it has an additional lowering effect on testosterone, DHT, and E2 levels compared with isolated hypogonadotropic hypogonadism. This finding suggests a synergistic effect of GH on basal LC function.[143] From these assumptions, one would expect that GH therapy would increase testosterone levels. However, the literature in this regard is not univocal.

With regard to GH therapy, the only studies that showed an increase in testosterone levels included azoospermic[140] or hypogonadal patients[139] who were also receiving gonadotropin therapy. Other studies on GHD patients showed no change in total testosterone levels after GH therapy.[144,148] However, Carani et al, observed that even if total testosterone levels did not change after treatment, CG-stimulated testosterone levels increased after GH therapy compared with baseline.[145] However, non-GHD patients with oligozoospermia displayed no change in testosterone levels after GH therapy.[138,148] Interestingly, in an experimental study on healthy volunteers receiving alternating rhGH and Pegvisomant therapy,[141] Andreassen et al reported stable testosterone levels. For completeness, one study with a very small sample size found a reduction of total testosterone levels after GH therapy in patients with isolated GHD.[152]

As previously reported, E2 rather than testosterone plays a major role in regulating the HPS axis in males, increasing pulsatile GH secretion,[44] while inhibiting liver IGF-I response at a peripheral level.[153] In healthy volunteers, GH and IGF-I were positively correlated with serum E2.[141] In contrast, a placebo-controlled study reported an increase in E2 levels after GH therapy, but no changes were found in GnRH-stimulated gonadotropins, basal or hCG-stimulated androgens, or inhibin B levels.[146] The authors hypothesized that E2 levels are probably linked to an increase in aromatase activity (both testicular and peripheral). Conversely, males with congenital aromatase deficiency have reduced GH and IGF-I levels.[33] The central role of E2 in HPS regulation and *vice versa* is evident even for biological actions, which are traditionally attributed to testosterone in males. In a recent review, starting from the evidence that E2 circulates at higher levels in males than in post-menopausal females, the authors concluded that E2 has a central role in HPG axis regulation and reproductive function in males.[42]

None of the previously cited study reported a change in gonadotropin levels.[144-146,148] Andreassen et al indicated that AMH levels dropped after GH treatment in healthy controls, suggesting a maturation effect on SCs probably owing to intratesticular sex steroid syntheses and/or local estrogen increase.[141]

Thus, GH might reduce SHBG concentration by a direct action on liver receptors. Both males with acromegaly[152,154,155] and those with obesity with continuous GH infusion[156] showed low SHBG levels. In contrast, other studies observed no changes in SHBG concentrations after GH therapy.[141,145,146]

Only few studies described the HPG function in acromegaly: commonly, HPG axis dysfunction is described in both male and female acromegalic patients.[65,157,158] Although the underlying

pathophysiology has not been evaluated in detail, possible mechanisms include gonadotropin deficiency, hyperprolactinemia (in mixed GH/prolactin pituitary adenomas), and tumor mass effect (in macroadenomas). They are therefore mostly indirect mechanism rather than related to GH excess itself. Males typically show a hypogonadotropic hypogonadal picture with reduced FSH, testosterone, and DHT levels compared with age-matched controls.[150,159] A decrease in sexual desire together with an impairment of erectile function are frequent findings in patients with active acromegaly.[160-162] Disease control via somatostatin analogs (or clomiphene) is effective in increasing testosterone and DHT levels in these patients in the short term (6 months), while LH and FSH levels only increase in patients achieving disease control.[150]

4.2 | Reproductive function

The effect of GH and IGF-I on spermatogenesis is even more intriguing and under-explored than that on endocrine function. IGF-I is secreted by SCs, but IGF-IR is found on SCs themselves,[163] secondary spermatocytes, spermatids, and spermatozoa.[164,165] Moreover, IGF-I stimulates sperm maturation and influences sperm motility.[166]

Abnormal sperm parameters seem to correlate with lower serum IGF-I levels but not to seminal plasma IGF-I levels,[167] implying a more endocrine rather than paracrine function. Shimonovitz et al, reported that azoospermic patients are more likely to have a low GH response after clonidine administration compared with oligozoospermic and normozoospermic males.[168] However, other authors reported normal GH and IGF-I levels both in basal condition and after clonidine administration in azoospermic patients affected by either primary or secondary hypogonadism.[169]

A series of prospective intervention studies explored the impact of GH therapy on seminal parameters in infertile males. Some studies confirmed a beneficial effect in patients with fertility problems. Hypogonadotropic hypogonadal patients who failed to respond adequately to conventional treatment showed increased testosterone secretion and improved sperm production and fertility outcomes after GH cotreatment with gonadotropins.[142] Infertile males or patients with idiopathic severe oligoasthenoteratozoospermia also displayed an improvement in sperm concentrations,[149] and asthenozoospermic patients showed an increase in sperm motility.[148] Unfortunately, these latter studies had a very low sample size.

In contrast, other studies found no influence of GH replacement in males with hypogonadotropic hypogonadism cotreated with GH and gonadotropins,[138] in males with idiopathic oligozoospermia,[147] or in normogonadotropic patients with severe oligoasthenoteratozoospermia.[145] Moreover, in a small group of hypogonadotropic hypogonadal azoospermic patients, 6 months of GH replacement therapy after previous 6 months of gonadotropin treatment, while increasing testicular volume and testosterone levels, failed to induce the appearance of spermatozoa.[140] Finally, a number of studies showed an increase in seminal volume, suggesting a synergistic effect with testosterone but without improvement in other sperm parameters.[140,145,148]

The only two published studies on semen quality in acromegalic patients report discordant data. In 35 patients with active disease seminal volume, sperm count, total motility (and forward progression), normal morphology, and vitality were all significantly lower than in controls; 6 months of treatment with somatostatin analogs were able to ameliorate sperm number (and total motility in those achieving disease control). Post-treatment IGF-I levels were also found to inversely correlate with total motility, implying a noxious effect of GH/IGF-I excess on spermatogenesis.[150] More recently, a study on 10 acromegalic men revealed no differences in semen parameters with healthy controls, despite severely reduced serum testosterone and calculated free testosterone levels.[170] In contrast, hypogonadotropic hypogonadal patients without GH excess had reduced motile spermatozoa, possibly supporting a positive effect of GH/IGF-I on sperm motility.

5 | CONCLUSIONS

The evidence reviewed herein supports the existence of a crosstalk between the HPG and HPS axes. Molecular studies confirmed the expressions of both GH and IGF-I receptors at each level of the HPG axis and on reproductive organs. IGF-I signaling may be necessary for GnRH neuron maturation and timely pubertal onset, acting directly and indirectly through kisspeptin neurons and LH-secreting cells. Moreover, a paracrine network of locally produced GH and IGF-I by LC and SC functions within the testis to produce measurable effects on steroidogenesis and probably with less clear results on spermatogenesis.

In turn, sex hormones regulate HPS activity. First, GH secretion and receptor sensitivity exhibit a clear sex-related pattern. Second, both testosterone and E2 seem to control GH secretion, with E2 apparently being the dominant regulatory hormone at the central level, where it exerts a stimulatory effect, and at the peripheral level, where it inhibits IGF-I production.

The complexity of the interaction is further increased by the emerging role of ghrelin, which is an orexigenic hormone and one of the main drivers of HPS axis activation, but it also inhibits LH secretion, spermatogenesis, and steroidogenesis. Fertility and gonadal maturity strictly depend on metabolic balance and reach their full potential only after the completion of the transition age.

The actual in vivo effects of the somatotropic axis on the reproductive system and sexual organs are not entirely clear, but available literature suggests that physiological levels of activity of the HPS axis are required for proper testicular development from the early stages of fetal development throughout childhood. Insulin growth factors play an essential role in sexual differentiation. Moreover, during minipuberty, IGF-I seems to be decisive for the consolidation

of the correct testicular position and contributes to linear growth during childhood.

IGF-I actively contributes to GnRH activation, puberty onset, and pubertal pace. Patients with GHD and GHI show delayed puberty and often impaired genital development. In these patients, prompt replacement therapy with rhGH/rhIGF-I may contribute to timely pubertal onset, correct pubertal development, and achievement of higher testicular volumes and penile lengths compared with controls. IGF-I levels during transition age remain high, even when linear growth is almost completed, suggesting a role in the maturation of the reproductive tract. Lower IGF-I levels in adult males seem to correlate with worse sperm parameters, but no solid evidence is available regarding whether therapy can improve semen characteristics and fertility outcomes in both GHD and idiopathic infertility. Long-term follow-up of GHD patients and studies on infertile males are definitely needed.

The role of GH-IGF-I interactions in sexual maturation and development during puberty and even more during transition age has not received sufficient attention and requires further investigation.

Nevertheless, evaluation of gonadal development in children with GHD is always important to initiate prompt therapy aimed at accurate gonadal maturation. Furthermore, investigation of the function of the HPS axis in children with alterations of the urogenital tract and gonadal development (micropenis, cryptorchidism, and hypospadias) may prove important for therapeutic intervention.

In conclusion, correct diagnosis and prompt therapy are needed for healthier puberty, attainment of complete gonadal development during the transition age, and fertility in adulthood.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the publication of this article.

AUTHORS' CONTRIBUTIONS

All the authors contributed to the conception and design of the review. MT, FC, BC, and GK contributed to revising of literature and acquisition of data. MT, FC, and B.C wrote the first draft, and designed tables and figures. M.T and DG performed a first revision and synthesis of the manuscript. CP and ES were involved in a second critical revision of data. AMI, CK, and DG performed the last critical revision for important intellectual content and final approval of the version to be published. All authors are accountable for the accuracy and integrity of the work; they all reviewed and approved the final manuscript.

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