THEMATICAL REVIEW

The physiology of growth hormone (GH) in adults: translational journey to GH replacement therapy

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Abstract

The fact that growth hormone (GH) plays an important role in health after the cessation of growth requiring replacement therapy in adult life has only been recognised in the last three decades. This has only been made possible by recombinant technology providing GH supplies required to undertake investigations in the physiology of GH action and the benefits of replacement therapy in patients identified by rigorously validated diagnostic tests for GH deficiency (GHD). Human studies have revealed important regulatory roles in substrate metabolism, sodium homeostasis, body composition, and physical function. GH-induced anabolism is achieved by stimulating amino acid incorporation into protein while reducing oxidative loss simultaneously enhancing lipid utilisation by stimulating fatty acid oxidation and reducing lipid storage. Sodium and fluid retention are enhanced by activating the renin–angiotensin system and distal renal tubular reabsorption. GH stimulates the aerobic and anaerobic energy systems that underpin muscle and cardiovascular function. These pleiotropic actions explain the clinical picture of increased adiposity, reduced lean mass, and impaired physical and psychological function in the GHD adult, all of which are reversed when GH is replaced. Women require a greater replacement dose of GH than men. This is because androgens enhance while oestrogens attenuate GH action. The oestrogen effect is route-dependent, occurring with oral delivery blunting the liver-mediated actions of GH by directly inhibiting GH receptor signalling, global experience spanning over 30 years has attested to the safety, efficacy, and benefits of replacement therapy for adults with GHD.

Hormone replacement therapy is a tenet of endocrinology. The recognition that growth hormone (GH) is biologically important beyond promoting growth in childhood has only been accepted recently despite its isolation over 70 years ago. In addition to growth, accumulating evidence had emerged in the last decades supporting the regulatory roles of GH in lipid, protein and glucose metabolism, sodium homeostasis, and body composition. A putative role in adult health can only be established from human studies. Even fundamental questions such as how GH deficiency (GHD) is diagnosed or how deficiency affects health require evaluation in humans. The translational challenge is unique not only because of the dependence on human evidence but also because of the spectrum of evidence required to justify replacement therapy.
The cloning of the GH gene along with the subsequent development of recombinant technology offered abundant supplies of GH necessary for critical evaluation in adult life. The first controlled human studies reporting benefits were undertaken in the late 1980s followed by numerous studies worldwide investigating effects on metabolic, physical, and psychological health (Jorgensen et al. 1989, Salomon et al. 1989). GH was first reimbursed nationally for the treatment of adults with GHD in Sweden in 2000, in the United Kingdom in 2004, and in Australia in 2017.

This invited narrative review on adult GHD provides an Australian contribution to and perspective of human physiology, diagnosis, regulatory interactions, efficacy, safety, and cost-effectiveness of GH replacement therapy covering the translational journey of replacement therapy.

**Physiology**

GH is the most abundant hormone in the adult pituitary gland. Several early pharmacodynamic studies in humans supported a metabolic role based on consistent and distinct effects on lipids, carbohydrates, and proteins. Following the cloning of the GH receptor, it became evident that the receptor was widely distributed indicating that GH acts on organs, tissues, and body systems beyond effects on growth and metabolism (Ballesteros et al. 2000). Table 1 shows the widespread actions on the tissues and organs of various systems including the renal, cardiovascular, musculoskeletal, haematological, and central nervous system. Coverage of these pleotropic effects is beyond the scope of this review which will focus mainly on substrate and energy metabolism, sodium homeostasis, and physical function.

![Table 1](https://i.imgur.com/3.png)

<table>
<thead>
<tr>
<th>Tissue or organ</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>Heart</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>Lung</td>
<td>Respiratory function</td>
</tr>
<tr>
<td>Muscle</td>
<td>Mass, strength, and power</td>
</tr>
<tr>
<td>Kidney</td>
<td>GFR, ECW, and vascular volume</td>
</tr>
<tr>
<td>Bone</td>
<td>Growth and turnover</td>
</tr>
<tr>
<td>Liver</td>
<td>Growth factors and substrate metabolism</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipid utilisation</td>
</tr>
<tr>
<td>Skin</td>
<td>Exocrine function and hair growth</td>
</tr>
<tr>
<td>Brain</td>
<td>Neurogenesis</td>
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</tbody>
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ECW, extracellular water; GFR, glomerular filtration rate.

**Substrate metabolism**

GH is a major regulator of substrate and energy metabolism (Møller & Jørgensen 2009). Insights as to how GH regulates the metabolism of protein, carbohydrate, and lipids have come from the application of steady-state tracer methodology which allows the metabolic fate of the substrate of interest to be tracked. In the case of protein metabolism, isotopic leucine has been frequently used to track the loss of and synthesis of proteins. Amino acids released from protein breakdown are either reutilised in protein synthesis or irreversibly lost via oxidation (Horber & Haymond 1990). GH acutely stimulates whole-body protein turnover, enhancing synthesis more than protein breakdown (Horber & Haymond 1990, Burt et al. 2008b). This change in equilibrium results in a reduction in irreversible oxidative loss of protein from the body, which in turn results in a gain of lean body mass (Burt et al. 2008a). Conversely, a lack of GH increases the oxidative loss of protein resulting in diminished lean mass.

GH enhances energy and fat metabolism. GH stimulates resting energy expenditure in a dose-dependent manner, reducing the number of calories available for storage in fat depots (Stenlof et al. 1995, Burt et al. 2008a). Several mechanisms contribute to increased energy expenditure including the energy required for protein synthesis itself, increased conversion of thyroxine to tri-iodothyronine and stimulation of uncoupling protein expression (Pedersen et al. 1999). GH stimulates lipolysis in adipose tissue, an effect mediated by the enzyme hormone-sensitive lipase. GH also stimulates the expression of triglyceride hydrolases while repressing the expression of genes promoting triglyceride storage (Zhao et al. 2011). Moreover, GH inhibits lipoprotein lipase, the major enzyme responsible for the breakdown of triglycerides into free fatty acids prior to uptake by adipose tissue (Richelsen et al. 2000). As such, GH reduces uptake and enhances the output of free fatty acid in adipose tissue. Studies using indirect calorimetry demonstrate that GH also stimulates lipid oxidation (Stenlof et al. 1995, Gibney et al. 2005). These multiple effects on protein, energy, and fat metabolism translate to a reduction in body fat and an increase in the functional and structural elements of the fat-free mass (Burt et al. 2006).

**Sodium homeostasis**

Early accounts of the biological effects of GH derived from pituitary extracts reported fluid retention and weight gain (Beck et al. 1958, Ikkos et al. 1958). Balance
studies observed that GH-induced fluid retention was accompanied by a marked reduction in the renal excretion of sodium. The possibility of contaminants in pituitary extracts causing fluid retention could not be excluded (Baumann et al. 1972). With the availability of recombinant human GH (hGH), we revisited the issue of fluid retention and the mechanism involved. These studies revealed that activation of the renin-angiotensin system was a mechanism involved in the antinatriuretic action of GH (Ho & Weissberger 1990, Hoffman et al. 1996). GH administration for 5–7 consecutive days increased plasma renin activity by 3-fold and aldosterone concentration by 7-fold, a change accompanied by a 75% reduction of daily sodium excretion and a 50% reduction in urine output (Ho & Weissberger 1990) but no change in ANP or arginine vasopressin levels (Hoffman et al. 1996). GH treatment does not significantly affect lithium clearance, a maker of proximal renal tubular sodium absorption suggesting that the sodium and water retaining effects occur in the distal tubule (Johannsson et al. 2002). There is also evidence from animal and human studies that GH acts directly on epithelial sodium channels in the distal nephron (Kamenicky et al. 2008, Kamenicky et al. 2014). These observations indicate that the fluid-retaining effects of GH on the kidney are mediated directly and indirectly. The regulation of sodium and fluid homeostasis remains an intriguing dose-dependent property of GH, manifesting frequently as oedema and myalgia in patients commencing GH therapy.

**Physical function**

The stimulation of protein anabolism by GH has led to the widespread expectation that it increases physical function. Physical function is a generic term covering strength and power. Muscle power, a measure of work performed per unit time, is assessed in different ways that vary in duration. The energy required to support muscle work can be drawn from the oxidative metabolism of substrates or from pre-formed stores (Wells et al. 2009). The performance capacity of muscle is influenced by the availability of energy or energy type at the time of assessment which in turn sustains aerobic or anaerobic capacity (Chikani & Ho 2014).

**Strength**

Muscle strength has been intensively studied in adults with GHD. Most studies have reported a significant reduction of muscle strength in adults with GHD. The reduction in strength is in proportion to the reduction in muscle mass rather than from reduced contractile function (Widdowson & Gibney 2010, Chikani & Ho 2014).

**Aerobic capacity**

Aerobic exercise capacity is a measure of physical endurance – the ability to sustain work for prolonged periods with energy provided principally from the oxidation of carbohydrates or lipids in the mitochondria. Several studies have confirmed that aerobic capacity, measured as VO₂ max, is impaired in GHD (Cuneo et al. 1991, Nass et al. 1995, Gullestad et al. 1998). The underlying mechanisms are multifactorial. Oxygen delivery to exercising muscles depends on cardiac function, lung capacity, and oxygen-carrying capacity of blood. Cardiac function is impaired (Merola et al. 1993), lung capacity is diminished (Merola et al. 1996), and red cell mass is reduced (Christ et al. 1997) in adults with GHD, which collectively contribute to the reduction in endurance capacity.

**Anaerobic capacity**

Anaerobic exercise capacity is defined as the total amount of work expanded during a maximal exhausting exercise of a short duration, which is underpinned by anaerobic ATP supply (Green 1995). For sports that involve short-term high-intensity physical activity such as sprinting, the main energy source is stored ATP. All physical activities including those of daily living also depend on anaerobic energy upon initiation for the first few seconds before aerobic metabolism becomes the predominant energy source (Cahill et al. 1997). Studies in our laboratory reported for the first time that anaerobic capacity is impaired in adults with GHD (Chikani et al. 2015), while also confirming that aerobic capacity is also impaired in the same patients. The functional significance of these two measures of physical performance capacity was assessed by stair-climb testing, 7-day pedometry testing, and a QoL questionnaire. We found that anaerobic and not aerobic capacity to be an independent predictor of stair-climb performance and of QoL. Aerobic capacity significantly influenced pedometry performance but not stair-climbing ability (Chikani et al. 2016). The results suggest that subnormal anaerobic capacity is a likely factor determining certain aspects of daily living that affected QoL in patients with GHD.
The phenotype of adult GHD

As may be predicted from the metabolic actions of GH, the individual with GHD is overweight manifesting central obesity and a lack of musculature. In a cross-sectional comparison, we observed that GH-deficient subjects have increased fat mass, reduced lean mass, and reduced bone mineral content. The contraction of the lean mass is due to a proportionate reduction of extracellular water and body cell mass (Hoffman et al. 1995). The complexion is pale with thin skin, scarcity of body hairs, and obscure venous vasculature. Investigations may reveal mild normochromic normocytic anaemia, metabolic syndrome, and a fatty liver. A clinical history may divulge impaired physical and psychological health such as weakness, fatigue, low mood, demotivation, disinterest, and passivity. These problems collectively diminish the quality of life (QoL) by causing depression, loss of vitality, fatigue, and lack of strength. These, in turn, reduce metabolic health, working capacity, productivity, and life satisfaction (Cuneo et al. 1992, Kaiser & Ho 2016, Melmed 2019).

Diagnosis

The clinical GHD phenotype is recognisable but not distinct because features are shared with the aging process, an unhealthy lifestyle, or with depression. For these reasons, GHD requires confirmation by a diagnostic test. Several validated tests are now available for diagnosing GHD. However, at the time of global interest in investigating the consequences and benefits of GH therapy, the question of how GHD is best diagnosed was unclear. A number of approaches had been developed to assess GH status at the time: the peak GH response to a provocative test, integrated GH levels over a 24-h period, or by measuring blood concentrations of GH-responsive proteins such as insulin-like growth factor-1 (IGF1).

Our laboratory undertook a systematic comparison of these approaches using the insulin tolerance test (ITT) as a provocative test (Hoffman et al. 1994). We observed a clear separation of peak GH concentrations to the ITT but not of integrated 24 h GH and IGF1 values between normal subjects and patients with severe hypopituitarism (Fig. 1). The diagnostic accuracy has since been replicated in several studies such that the ITT is regarded as the gold standard diagnostic test by several professional societies worldwide (Ho & Participants 2007, Molitch et al. 2011).

The risks associated with hypoglycaemia during an ITT have been a concern as well as the requirement for intensive clinical monitoring. These concerns have led to the search for alternative provocative tests. To date, the following other tests have been validated: GHRH plus arginine test, the glucagon test, and the macimorelin test. Unfortunately, GH-releasing hormone (GHRH) is...
no longer manufactured. The unavailability of GHRH has brought glucagon greater attention as a simple diagnostic test for GHD when the ITT is not desirable. The glucagon stimulation test (GST) is simple, safe, and well tolerated although some patients develop nausea, headaches, and mild hyperglycaemia (Gomez et al. 2002, Hamrahian et al. 2016). The GST is affected by obesity and recent evaluation has recommended a lower cut-off of <1 μg/L for BMI over 30 kg/m². Recently macimorelin, an oral GH secretagogue has been validated as a diagnostic test that has received approval from the Food and Drug Administration (FDA) (Hamrahian et al. 2016).

In summary, dynamic testing of the peak GH response to a stimulatory test is regarded as the gold standard for detecting GHD in adults, and of the available tests, the ITT is regarded as the reference standard.

### Management

#### Hormone interactions

Significant interactions of clinical importance occur between the GH axis and the other pituitary axes for the patient with GHD. The most relevant are the thyroid, adrenal and gonadal axes (Table 2). Our laboratory has had a major interest in characterising the interactions between sex steroids and the GH system and their clinical significance. Androgens and oestrogens modify the actions of GH in distinct and diametrically opposite ways (Meinhardt & Ho 2006) through receptor-mediated and metabolic pathways.

#### Androgens

Testosterone augments the effects of GH on substrate and energy metabolism. In men with hypopituitarism, testosterone amplifies the GH-induced increase in IGF1 concentration; however, testosterone alone does not increase blood IGF1 concentration (Gibney et al. 2005). GH and testosterone enhance protein anabolism with combined therapy having a greater effect than each hormone alone. The observation indicates that the effect of testosterone on protein metabolism occurs independently of IGF1. The stimulation of resting energy expenditure and lipid oxidation by GH is also enhanced by testosterone which exerts similar metabolic effects that are in turn amplified by GH (Gibney et al. 2005, Meinhardt & Ho 2006, Birzniece et al. 2011). GH itself increases androgen receptor gene expression in the muscle of hypogonadal men (Hayes et al. 2001). Collectively, androgens increase tissue responsiveness to GH and these effects are reflected in the observation that androgen-sufficient men require a lower replacement dose of GH than women (Gotherstrom et al. 2001).

#### Oestrogens

In contrast to testosterone, oestrogens antagonise GH action, the physiological and therapeutic ramifications of which are relevant in the management of the hypopituitary woman.

### GH signalling

Work from our laboratory showed that the mechanism of oestrogen inhibition occurs at the level of GHR signalling. GH binding results in receptor dimerisation triggering the activation of the JAK-STAT pathway and the transcription of GH-responsive genes (Brooks & Waters 2010). These include the suppression of cytokine signalling (SOCS) proteins which terminate GH signalling, constituting an intracellular short-loop system regulating GH action. SOCS2 was identified as a major inhibitor of GH action on account of the observation that transgenic mice lacking SOCS2 show an overgrowth phenotype (Metcalf et al. 2000). In vitro studies from our laboratory showed that the inhibition by oestrogens of GH stimulation of the JAK-STAT pathway was mediated by SOCS2 (Leung et al. 2003). This action of oestrogens extends beyond the GHR affecting the action of a range of cytokine receptors. The regulatory interactions at the level of GHR expression and signalling offer the basis

<table>
<thead>
<tr>
<th>System</th>
<th>Interactions</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Thyroid</td>
<td>GH enhances T4 conversion to T3</td>
<td>T4 falls during GH therapy</td>
</tr>
<tr>
<td>Adrenal</td>
<td>GH stimulates the conversion of active cortisol to inactive cortisone</td>
<td>Risk of hypoadrenalism</td>
</tr>
<tr>
<td>Gonadal</td>
<td>Oestrogens impair GH action; androgens enhance GH action</td>
<td>Women require more GH; men require less GH</td>
</tr>
</tbody>
</table>

Table 2 GH interactions with hormones of the thyroid, adrenal, and gonadal axes.
for some of the physiological interplay between oestrogen and the GH system relevant to the therapeutic use of oestrogen in GHD and hypopituitarism (Leung et al. 2004).

**Route dependency**

Oestrogen compounds are available in different formulations that can be taken orally or via a non-oral route (Birzniece & Ho 2017, Birzniece & Ho 2021). Oestrogens impair the action of GH when taken orally (O’Sullivan et al. 1998, Wolthers et al. 2001). This phenomenon arises from a first-pass hepatic effect of oestrogens which attenuate the responsiveness to GH reducing blood levels of IGF1, the main mediator of the anabolic actions of GH. This is a pharmacological consequence of liver exposure to high concentrations of oestrogens absorbed from the gut and which does not occur when oestrogens are delivered by a non-oral route (Kelly et al. 1993, O’Sullivan et al. 1998, Birzniece & Ho 2021).

Blood IGF1 levels, whole-body fatty acid oxidation, and protein synthesis during GH therapy are significantly lower during oral compared with transdermal oestrogen therapy in hypopituitary women (Figs. 2 and 3) (Wolthers et al. 2001). The GH-regulated endocrine and metabolic function of the liver are, therefore, highly susceptible to the inhibitory effects of oestrogen (Leung et al. 2004, Birzniece & Ho 2017). Only small replacement doses are required to treat oestrogen deficiency in contrast to the supraphysiological doses required to suppress the pituitary–gonadal axis for contraception.

However, several studies have reported that the majority of hypogonadal women with pituitary disease and hormone deficiencies are not only treated with oral oestrogens but are prescribed oral contraceptives (Mah et al. 2005, Isotton et al. 2011). Oral contraceptives are more potent than oestrogen compounds used in oestrogen replacement regimens (Mashchak et al. 1982) and as such inhibit GH action to a greater degree. On average, patients taking oral contraceptive pills require a 55–70% greater GH dose, while those taking oestrogen replacement doses require 20–30% higher GH dose than those replaced by a transdermal route (Birzniece & Ho 2012). Selective estrogen receptor modulators (SERMs), such as raloxifene, are used instead of oestrogens, for example, to treat osteoporosis or to avoid withdrawal bleeding. However, raloxifene offers no advantage over oestrogen to GH-deficient women during GH replacement therapy since SERMs have oestrogen-like effects on liver function (Birzniece et al. 2012). Treatment of oestrogen deficiency with a tablet cannot be advocated in women with hypopituitarism. This route is unphysiological and wasteful of GH particularly if contraceptive formulations are prescribed (Birzniece & Ho 2012).

**GH replacement therapy**

Knowledge transfer required to implement GH replacement therapy globally was spearheaded by the GH Research Society which convened an inaugural international consensus workshop. The Workshop developed rigorous guidelines for the selection, evaluation, diagnosis, treatment, and monitoring of adult patients with GHD (Growth Hormone Research Society Workshop 1998). The participants comprised major stakeholders including representatives from the FDA and European Medicines Agency (EMA). This inaugural Workshop in 1997 was held in Port Stephens outside Sydney. The Workshop recommendations were adopted by regulatory agencies including the FDA, EMA, and the Therapeutics Goods Authority (TGA) of Australia. The recommendations were updated in 2007 following a Workshop in Sydney in a position statement from the GH Research Society, the European Endocrine Society, the Japan Endocrine Society, and the European Society for Paediatric Endocrinology and the Lawson Wilkins Society (Ho 2007).
Efficacy

The physiologic actions of GH highlighted earlier provide a strong rationale for replacing GH in adults with GHD, the outcomes of which have been extensively investigated.

Body composition

The most consistent and striking benefits of GH replacement are on body composition which occurs without a significant change in body weight. GH replacement reduces fat mass by 3 kg on average and increases lean body mass by a similar amount (Maison et al. 2004). There is a greater reduction in visceral than in s.c. adipose tissue. Changes in body composition predominantly occur during the first 12 months of GH replacement and plateau thereafter (Gotherstrom et al. 2009). There is an expansion of extracellular water from the anti-natriuretic actions of GH (Birzniece et al. 2014). Bone remodelling is activated by GH evident from increases in markers of both bone resorption and formation accompanied by a biphasic time-dependent change with an initial decline in BMD (bone mineral density) in the first 6–12 months followed by an increase, and plateauing after 3 years (Gotherstrom et al. 2007). A prospective observational cohort study reported that fracture risk was lower in hypopituitary patients prescribed GH replacement compared to an untreated cohort (Mo et al. 2015).

Physical function

Most studies report that GH replacement improves aerobic capacity and exercise performance in adults with GHD (Woodhouse et al. 2006). Most randomised controlled trials of up to 6 months duration have not observed a gain in muscle strength (Widdowson & Gibney 2010). However, long-term open-label studies report that muscle strength is increased by GH replacement (Gotherstrom et al. 2009) suggesting that improvement in muscle strength only manifests during long-term treatment.

The anaerobic energy system provides energy for the initiation of physical activity and intensive activities of a brief duration. As mentioned earlier, anaerobic energy capacity is significantly reduced in patients with GHD (Chikani et al. 2015). GH replacement acutely stimulated the expression of genes that govern anaerobic energy production (Sjogren et al. 2007) and longer-term therapy increases anaerobic capacity (Chikani et al. 2016). The improvement in anaerobic capacity is significantly linked to a parallel improvement in measures of QoL in the domains of energy and vitality (Chikani et al. 2016). It is likely that energy systems required to drive physical activity and function affect QoL.

Quality of life

Patients with GHD have, on average, reduced QoL, as measured by both generic- and disease-specific questionnaires (Woodhouse et al. 2006). However, there is substantial heterogeneity in the impact of GHD on the QoL. For example, impairment is more evident in patients with adult-onset compared to childhood-onset GHD (Attanasio et al. 1997). Given the multiplicity of GH’s actions, there are likely to be several mechanisms contributing to impaired QoL including GH-dependent physical dysfunction and cognitive effects. Although
there is variability in results, most randomised controlled trials have reported that GH replacement improves the QoL (Hazem et al. 2012). Improvements in QoL are more commonly reported when disease-specific questionnaires are used to assess the response to GH replacement.

Safety of GH

The commonest adverse effect of GH replacement is fluid retention, which arises because of the anti-natriuretic action of GH (Hoffman et al. 1996). This adverse effect is dose-dependent and can be mitigated by a reduction in GH dose. Because of increased adiposity among patients with GHD and because GH increases insulin resistance, there has been concern about the risk of developing metabolic syndrome or diabetes during GH therapy. A meta-analysis of 13 studies reported an average increase of 0.22 mmol/L in fasting glucose during GH replacement therapy (Maison et al. 2004). The risk of developing metabolic syndrome is not increased in patients with a BMI below 30 kg/m² (Attanasio et al. 2011). These data suggest that the risk of diabetes secondary to GH-induced insulin resistance is low.

An important consideration is whether GH replacement increases the risk of pituitary tumour recurrence or development of other cancers. However, there is no evidence that GH replacement increases the risk of recurrence of pituitary adenomas or craniopharyngiomas (Boguszewski et al. 2022). Some observational studies have reported a reduction in cancer risk (Widdowson & Gibney 2008, Stochholm et al. 2014, Olsson et al. 2017). The possibility of a selection bias favouring such an outcome cannot be ruled out. Finally, a recent large post-marketing observational study involving over 18,000 patients followed for up to 18 years has reported neutral effects on glucose and lipid metabolism and no increased risk of de-novo cancers providing reassuring evidence of the safety of GH replacement therapy (Johannsson et al. 2022).

Cost-effectiveness

GH treatment is expensive costing an average of AUD 6000–10000 annually depending on dosage, making it unaffordable for many unless there is reimbursement. Sweden was the first country to approve reimbursed GH treatment nationally for adults with GHD. In Australia, the TGA, the therapeutic regulatory agency of Australia, approved GH as an indication for adults with GHD in 2000. However, reimbursement was only obtained in 2017 after two unsuccessful applications from the industry. The successful application was unusual in that it was lodged by a professional organisation (the Endocrine Society of Australia and the Australian Paediatric Endocrine Group) as a public interest submission providing information meeting the rigorous threshold assessment for cost-effectiveness (Lipworth et al. 2018).

Future directions

Long-acting analogues have been developed to improve adherence and compliance. These formulations are based on linking GH to a larger moiety to increase its biological half-life without interfering with its action (Christiansen et al. 2016). Depot, pegylated, pro-drug, and fusion protein formulations have been developed and undergone clinical trials. At the time of writing of this review, only one long-acting formulation (Somapacitam, Novo Nordisk) has been approved for clinical use in GHD adults by the FDA and by the TGA in Australia (Johannsson et al. 2020). It is anticipated that more analogues will become available in the clinic and may gain a greater foothold as GH therapy. Notwithstanding this pharmacological development, more data are required to gauge the long-term safety of GH replacement therapy which has a relatively short therapeutic history in adults compared to other replacement therapies for hormone deficiencies.

Conclusion

GH exerts pleiotropic actions regulating substrate metabolic, body composition, physical, and psychological functions in adult life. GHD impairs health. Over 30 years of research have contributed to the increasing weight of evidence that GH replacement therapy is beneficial and cost-effective for an adult with GHD. While significant safety issues have not been identified, long-term surveillance data are required to consolidate its safety profile.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.
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