THEMATIC 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.

Key Words

- growth hormone deficiency
- hypopituitarism
- adult
- replacement therapy

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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.

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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 pleiotropic effects is beyond the scope of this review which will focus mainly on substrate and energy metabolism, sodium homeostasis, and physical function.

Table 1 The pleotropic actions of GH on the metabolic and structural function of tissues and organs across body systems.

Tissue or organ	Action
Heart	Cardiac output
Lung	Respiratory function
Muscle	Mass, strength, and power
Kidney	GFR, ECW, and vascular volume
Bone	Growth and turnover
Liver	Growth factors and substrate metabolism
Fat	Lipid utilisation
Skin	Exocrine function and hair growth
Brain	Neurogenesis

ECW, extracellular water; GFR, glomerular filtration rate.

Substrate metabolism

GH is a major regulator of substrate and energy metabolism (Moller & Jorgensen 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.* 2008*b*). 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.* 2008*a*). 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.* 2008*a*). 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

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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 VO_2 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.

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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

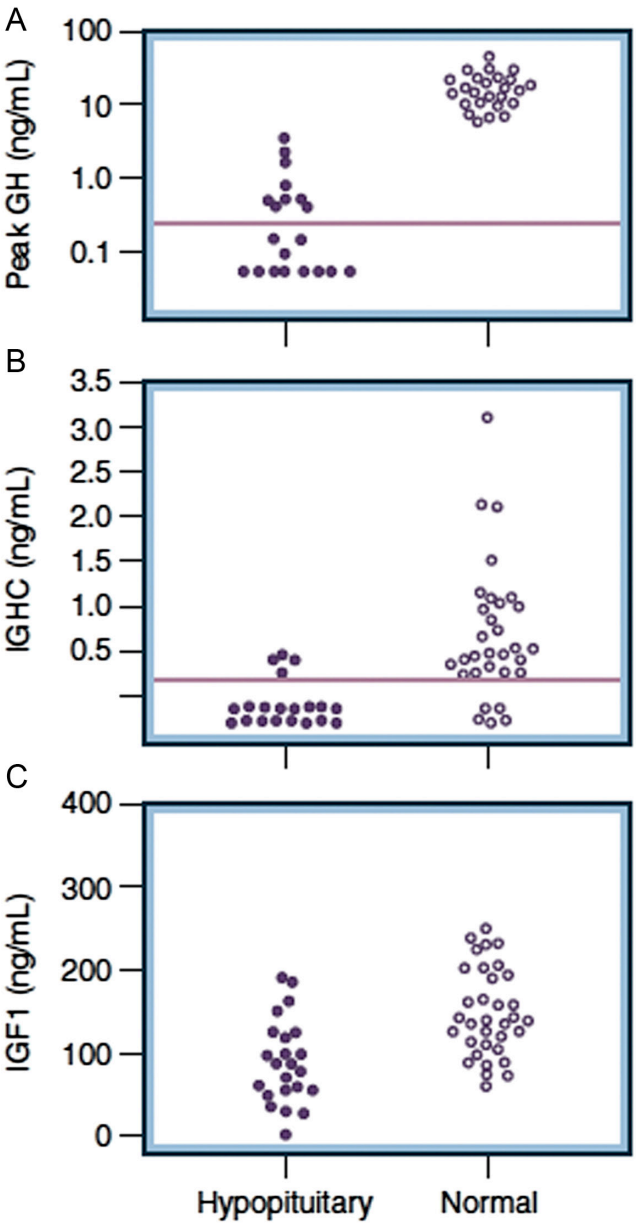

Figure 1
Comparison of peak growth hormone (GH) concentration obtained during an insulin-tolerance test (A), integrated GH concentration (IGHC) obtained from blood samples withdrawn every 20 min over 24 h (B), and insulin-like growth factor 1 (IGF1) (C) in patients with organic hypopituitarism (closed circles) and sex-matched normal subjects (open circles). Horizontal lines represent the limit of reading (s). Reproduced, with permission, from Hoffman DM, O'Sullivan AJ, Baxter RC & Ho KK, Diagnosis of growth-hormone deficiency in adults, *The Lancet*, volume 343, pages 1064–1068. Copyright 1994, The Lancet.

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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/m^2. 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 2 GH interactions with hormones of the thyroid, adrenal, and gonadal axes.

System	Interactions	Consequence
Thyroid	GH enhances T4 conversion to T3	T4 falls during GH therapy
Adrenal	GH stimulates the conversion of active cortisol to inactive cortisone	Risk of hypoadrenalism
Gonadal	Oestrogens impair GH action; androgens enhance GH action	Women require more GH; men require less GH

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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).

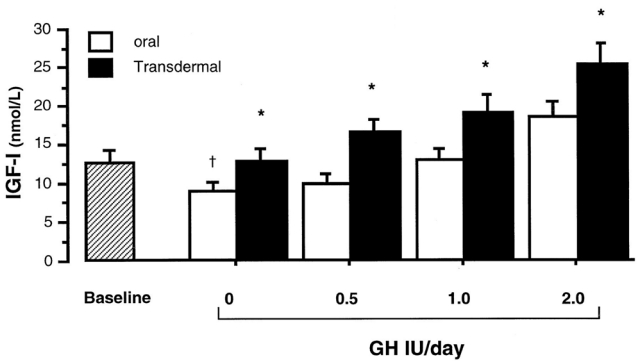

Figure 2
Serum IGF1 concentrations (nmol/L, mean 6 SE.) before and during incremental dosages of GH (0.5, 1.0, and 2.0 IU/day) during oral and transdermal oestrogen therapy in hypopituitary women. *$P = 0.05$ by ANOVA, oral vs transdermal. Reproduced, with permission, from Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M & Ho KK, Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women, *American Journal of Physiology. Endocrinology and Metabolism*, volume 281, pages E1191–E1196. Copyright 2001, the American Physiological Society.

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).

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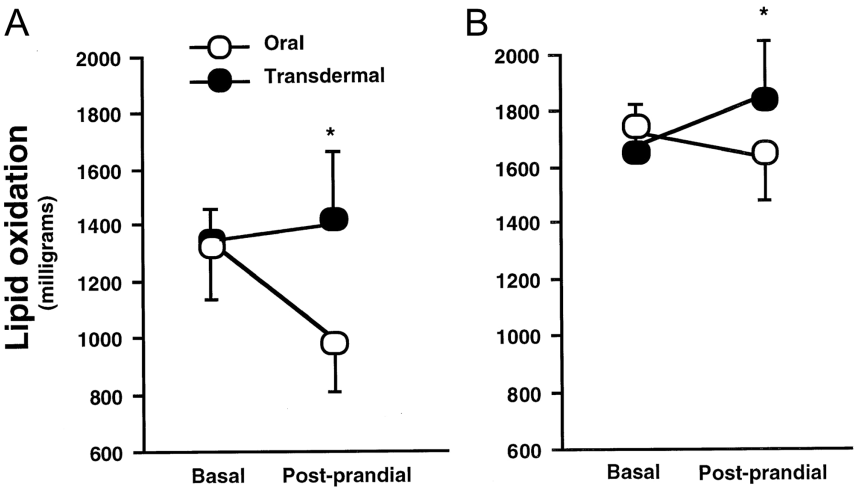

Figure 3
Lipid oxidation (mg over 30 min, mean 6 S.E.) during fasting and 1 h after a standardised mixed meal (postprandial). Lipid oxidation is shown before (A) and after (B) GH replacement therapy (2 IU/day) during oral and transdermal oestrogen administration. *P = 0.05, oral vs transdermal. Reproduced, with permission, from Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M & Ho KK, Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women, *American Journal of Physiology. Endocrinology and Metabolism*, volume 281, pages E1191–E1196. Copyright 2001, the American Physiological Society.

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

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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/m^2 (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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References

Attanasio AF, Jung H, Mo D, Chanson P, Bouillon R, Ho KK, Lamberts SW, Clemmons DR & HypoCCS International Advisory Board 2011 Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. *Journal of Clinical Endocrinology and Metabolism* **96** 2255–2261. (https://doi.org/10.1210/jc.2011-0448)

Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson BA & Strasburger CJ 1997 Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult growth hormone deficiency study group. *Journal of Clinical Endocrinology and Metabolism* **82** 82–88. (https://doi.org/10.1210/jcem.82.1.3643)

Ballesteros M, Leung KC, Ross RJ, Iismaa TP & Ho KK 2000 Distribution and abundance of messenger ribonucleic acid for growth hormone receptor isoforms in human tissues. *Journal of Clinical Endocrinology and Metabolism* **85** 2865–2871. (https://doi.org/10.1210/jcem.85.8.6711)

Baumann G, Rayfield EJ, Rose LI, Williams GH & Dingman JF 1972 "Trace" contamination of corticotropin and human growth hormone with vasopressin--clinical significance. *Journal of Clinical Endocrinology and Metabolism* **34** 801–804. (https://doi.org/10.1210/jcem-34-5-801)

Beck JC, McGarry EE, Dyrenfurth I & Venning EH 1958 The metabolic effects of human and monkey growth hormone in man. *Annals of Internal Medicine* **49** 1090–1105. (https://doi.org/10.7326/0003-4819-49-5-1090)

Birzniece V & Ho KK 2012 Growth and development: patching up a better pill for GH-deficient women. *Nature Reviews. Endocrinology* **8** 197–198. (https://doi.org/10.1038/nrendo.2012.9)

Birzniece V & Ho KKY 2017 Sex steroids and the GH axis: implications for the management of hypopituitarism. *Best Practice and Research. Clinical Endocrinology and Metabolism* **31** 59–69. (https://doi.org/10.1016/j.beem.2017.03.003)

Birzniece V & Ho KKY 2021 Mechanisms in endocrinology: paracrine and endocrine control of the growth hormone axis by estrogen. *European Journal of Endocrinology* **184** R269–R278. (https://doi.org/10.1530/EJE-21-0155)

Birzniece V, Khaw CH, Nelson A, Meinhardt U & Ho KK 2014 A critical evaluation of bioimpedance spectroscopy analysis in estimating body composition during GH treatment: comparison with bromide dilution and dual X-ray absorptiometry. *European Journal of Endocrinology* **172** 1–9. (https://doi.org/10.1530/EJE-14-0660)

Birzniece V, Meinhardt UJ, Gibney J, Johannsson G, Armstrong N, Baxter RC & Ho KK 2012 Differential effects of raloxifene and estrogen on body composition in growth hormone-replaced hypopituitary women. *Journal of Clinical Endocrinology and Metabolism* **97** 1005–1012. (https://doi.org/10.1210/jc.2011-2837)

Birzniece V, Meinhardt UJ, Umpleby MA, Handelsman DJ & Ho KK 2011 Interaction between testosterone and growth hormone on whole-body protein anabolism occurs in the liver. *Journal of Clinical Endocrinology and Metabolism* **96** 1060–1067. (https://doi.org/10.1210/jc.2010-2521)

Boguszewski MCS, Boguszewski CL, Chemaitilly W, Cohen LE, Gebauer J, Higham C, Hoffman AR, Polak M, Yuen KCJ, Alos N, *et al.* 2022 Safety of growth hormone replacement in survivors of cancer and intracranial and pituitary tumours: a consensus statement. *European Journal of Endocrinology* **P52** 35. (https://doi.org/10.1530/EJE-21-1186)

Brooks AJ & Waters MJ 2010 The growth hormone receptor: mechanism of activation and clinical implications. *Nature Reviews. Endocrinology* **6** 515–525. (https://doi.org/10.1038/nrendo.2010.123)

Burt MG, Gibney J & Ho KK 2006 Characterization of the metabolic phenotypes of Cushing's syndrome and growth hormone deficiency: a study of body composition and energy metabolism. *Clinical Endocrinology* **64** 436–443. (https://doi.org/10.1111/j.1365-2265.2006.02488.x)

Burt MG, Gibney J, Hoffman DM, Umpleby AM & Ho KK 2008*a* Relationship between GH-induced metabolic changes and changes in body composition: a dose and time course study in GH-deficient adults. *Growth Hormone and IGF Research* **18** 55–64. (https://doi.org/10.1016/j.ghir.2007.07.005)

Burt MG, Johannsson G, Umpleby AM, Chisholm DJ & Ho KK 2008*b* Impact of growth hormone and dehydroepiandrosterone on protein metabolism in glucocorticoid-treated patients. *Journal of Clinical Endocrinology and Metabolism* **93** 688–695. (https://doi.org/10.1210/jc.2007-2333)

Cahill BR, Misner JE & Boileau RA 1997 The clinical importance of the anaerobic energy system and its assessment in human performance. *American Journal of Sports Medicine* **25** 863–872. (https://doi.org/10.1177/036354659702500623)

Chikani V, Cuneo RC, Hickman I & Ho KK 2015 Impairment of anaerobic capacity in adults with growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* **100** 1811–1818. (https://doi.org/10.1210/jc.2015-1006)

Chikani V, Cuneo RC, Hickman I & Ho KK 2016 Growth hormone (GH) enhances anaerobic capacity: impact on physical function and quality of life in adults with GH deficiency. *Clinical Endocrinology* **85** 660–668. (https://doi.org/10.1111/cen.13147)

Chikani V & Ho KK 2014 Action of GH on skeletal muscle function: molecular and metabolic mechanisms. *Journal of Molecular Endocrinology* **52** R107–R123. (https://doi.org/10.1530/JME-13-0208)

Christ ER, Cummings MH, Westwood NB, Sawyer BM, Pearson TC, Sonksen PH & Russell-Jones DL 1997 The importance of growth hormone in the regulation of erythropoiesis, red cell mass, and plasma volume in adults with growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* **82** 2985–2990. (https://doi.org/10.1210/jcem.82.9.4199)

Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BM, Boguszewski MC, Casanueva FF, Chanson P, Chatelain P, Choong CS, Clemmons DR, *et al.* 2016 Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. *European Journal of Endocrinology* **174** C1–C8. (https://doi.org/10.1530/EJE-16-0111)

Cuneo RC, Salomon F, McGauley GA & Sonksen PH 1992 The growth hormone deficiency syndrome in adults. *Clinical Endocrinology* **37** 387–397. (https://doi.org/10.1111/j.1365-2265.1992.tb02347.x)

Cuneo RC, Salomon F, Wiles CM, Hesp R & Sonksen PH 1991 Growth hormone treatment of growth hormone deficient adults.II. Effects on exercise performance. *Journal of Applied Physiology* **70** 695–700. (https://doi.org/10.1152/jappl.1991.70.2.695)

Gibney J, Wolthers T, Johannsson G, Umpleby AM & Ho KK 2005 Growth hormone and testosterone interact positively to enhance protein and energy metabolism in hypopituitary men. *American Journal of Physiology. Endocrinology and Metabolism* **289** E266–E271. (https://doi.org/10.1152/ajpendo.00483.2004)

Gomez JM, Espadero RM, Escobar-Jimenez F, Hawkins F, Pico A, Herrera-Pombo JL, Vilardell E, Duran A, Mesa J, Faure E, *et al.* 2002 Growth hormone release after glucagon as a reliable test of growth hormone assessment in adults. *Clinical Endocrinology* **56** 329–334. (https://doi.org/10.1046/j.1365-2265.2002.01472.x)

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Gotherstrom G, Bengtsson BA, Bosaeus I, Johannsson G & Svensson J 2007 Ten-year GH replacement increases bone mineral density in hypopituitary patients with adult onset GH deficiency. *European Journal of Endocrinology* **156** 55–64. (https://doi.org/10.1530/eje.1.02317)

Gotherstrom G, Elbornsson M, Stibrant-Sunnerhagen K, Bengtsson BA, Johannsson G & Svensson J 2009 Ten years of growth hormone (GH) replacement normalizes muscle strength in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* **94** 809–816. (https://doi.org/10.1210/jc.2008-1538)

Gotherstrom G, Svensson J, Koranyi J, Alpsten M, Bosaes I, Bengtsson B-A & Johannsson G 2001 A prospective study of 5 years of GH replacement therapy in GH- deficient adults: sustained effects on body composition, bone mass and metabolic indices. *Journal of Clinical Endocrinology and Metabolism* **86** 4657–4665. (https://doi.org/10.1210/jcem.86.10.7887)

Green S 1995 Measurement of anaerobic work capacities in humans. *Sports Medicine* **19** 32–42. (https://doi.org/10.2165/00007256-199519010-00003)

Growth Hormone Research Society Workshop 1998 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *Journal of Clinical Endocrinology Metabolism* **83** 379–381. (https://doi.org/10.1210/jcem.83.2.4611)

Gullestad L, Birkeland K, Bjonerheim R, Djoseland O, Trygstad O & Simonsen S 1998 Exercise capacity and hormonal response in adults with childhood onset growth hormone deficiency during long-term somatropin treatment. *Growth Hormone and IGF Research* **8** 377–384. (https://doi.org/10.1016/s1096-6374(98)80307-9)

Hamrahian AH, Yuen KC, Gordon MB, Pulaski-Liebert KJ, Bena J & Biller BM 2016 Revised GH and cortisol cut-points for the glucagon stimulation test in the evaluation of GH and hypothalamic-pituitary-adrenal axes in adults: results from a prospective randomized multicenter study. *Pituitary* **19** 332–341. (https://doi.org/10.1007/s11102-016-0712-7)

Hayes VY, Urban RJ, Jiang J, Marcell TJ, Helgeson K & Mauras N 2001 Recombinant human growth hormone and recombinant human insulin-like growth factor I diminish the catabolic effects of hypogonadism in man: metabolic and molecular effects. *Journal of Clinical Endocrinology and Metabolism* **86** 2211–2219. (https://doi.org/10.1210/jcem.86.5.7517)

Hazem A, Elamin MB, Bancos I, Malaga G, Prutsky G, Domecq JP, Elraiyah TA, Abu Elnour NO, Prevost Y, Almandoz JP, *et al.* 2012 Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis. *European Journal of Endocrinology* **166** 13–20. (https://doi.org/10.1530/EJE-11-0558)

Ho KK & 2007 GH Deficiency Consensus Workshop Participants 2007 Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *European Journal of Endocrinology* **157** 695–700. (https://doi.org/10.1530/EJE-07-0631)

Ho KY & Weissberger AJ 1990 The antinatriuretic action of biosynthetic human growth hormone in man involves activation of the renin-angiotensin system. *Metabolism: Clinical and Experimental* **39** 133–137. (https://doi.org/10.1016/0026-0495(90)90065-k)

Hoffman DM, Crampton L, Sernia C, Nguyen TV & Ho KK 1996 Short term growth hormone (GH) treatment of GH deficient adults increases body sodium and extracellular water but not blood pressure. *Journal of Clinical Endocrinology and Metabolism* **81** 1123–1128. (https://doi.org/10.1210/jcem.81.3.8772586)

Hoffman DM, O'Sullivan AJ, Baxter RC & Ho KK 1994 Diagnosis of growth-hormone deficiency in adults. *Lancet* **343** 1064–1068. (https://doi.org/10.1016/s0140-6736(94)90181-3)

Hoffman DM, O'Sullivan AJ, Freund J & Ho KK 1995 Adults with growth hormone deficiency have abnormal body composition but normal energy metabolism. *Journal of Clinical Endocrinology and Metabolism* **80** 72–77. (https://doi.org/10.1210/jcem.80.1.7829643)

Horber FF & Haymond MW 1990 Human growth hormone prevents the protein catabolic side effects of prednisone in humans. *Journal of Clinical Investigation* **86** 265–272. (https://doi.org/10.1172/JCI114694)

Ikkos D, Luft R & Gemzell CA 1958 The effect of human growth hormone in man. *Lancet* **1** 720–721. (https://doi.org/10.1016/s0140-6736(58)91141-3)

Isotton AL, Wender MC, Casagrande A, Rollin G & Czepielewski MA 2011 Effects of oral and transdermal estrogen on IGF-1, IGFBP-3, IGFBP-1, serum lipids and glucose in patients with hypopituitarism during growth hormone treatment: a randomized study. *European Journal of Endocrinology* **166** 207–213. (https://doi.org/10.1530/EJE-11-0560)

Johannsson G, Gordon MB, Hojby Rasmussen M, Hakonsson IH, Karges W, Svaerke C, Tahara S, Takano K & Biller BMK 2020 Once-weekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized Phase 3 trial. *Journal of Clinical Endocrinology and Metabolism* **105** e1358–e1376. (https://doi.org/10.1210/clinem/dgaa049)

Johannsson G, Sverrisdottir YB, Ellegard L, Lundberg PA & Herlitz H 2002 GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. *Journal of Clinical Endocrinology and Metabolism* **87** 1743–1749. (https://doi.org/10.1210/jcem.87.4.8394)

Johannsson G, Touraine P, Feldt-Rasmussen U, Pico A, Vila G, Mattsson AF, Carlsson M, Korbonits M, Van Beek AP, Wajnrajch MP, *et al.* 2022 Long-term safety of growth hormone in adults with growth hormone deficiency: overview of 15 809 GH-treated patients. *Journal of Clinical Endocrinology and Metabolism* **107** 1906–1919. (https://doi.org/10.1210/clinem/dgac199)

Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE & Christiansen JS 1989 Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* **1** 1221–1225. (https://doi.org/10.1016/s0140-6736(89)92328-3)

Kaiser U & Ho KKY 2016 Pituitary physiology and diagnostic evaluation. In *Williams Textbook of Endocrinology*, 13th ed. Eds S Melmed, KS Polonsky, PR Larsen & HM Kronenberg. Amsterdam, Netherlands: Elsevier. (https://doi.org/10.1016/C2013-0-15980-6)

Kamenicky P, Mazziotti G, Lombes M, Giustina A & Chanson P 2014 Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. *Endocrine Reviews* **35** 234–281. (https://doi.org/10.1210/er.2013-1071)

Kamenicky P, Viengchareun S, Blanchard A, Meduri G, Zizzari P, Imbert-Teboul M, Doucet A, Chanson P & Lombes M 2008 Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. *Endocrinology* **149** 3294–3305. (https://doi.org/10.1210/en.2008-0143)

Kelly JJ, Rajkovic IA, O'Sullivan AJ, Sernia C & Ho KK 1993 Effects of different oral oestrogen formulations on insulin-like growth factor-I, growth hormone and growth hormone binding protein in post-menopausal women. *Clinical Endocrinology* **39** 561–567. (https://doi.org/10.1111/j.1365-2265.1993.tb02410.x)

Leung KC, Doyle N, Ballesteros M, Sjogren K, Watts CK, Low TH, Leong GM, Ross RJ & Ho KK 2003 Estrogen inhibits GH signaling by suppressing GH-induced JAK2 phosphorylation, an effect mediated by SOCS-2. *PNAS* **100** 1016–1021. (https://doi.org/10.1073/pnas.0337600100)

Leung KC, Johannsson G, Leong GM & Ho KK 2004 Estrogen regulation of growth hormone action. *Endocrine Reviews* **25** 693–721. (https://doi.org/10.1210/er.2003-0035)

Lipworth W, Ambler G, Burt MG, Fairchild J, Inder WJ, Werther G & Ho K 2018 A will and a way to fund medicines for rare diseases: the story of human growth hormone replacement for adults with growth hormone deficiency. *Internal Medicine Journal* **48** 999–1002. (https://doi.org/10.1111/imj.13943)

Mah PM, Webster J, Jonsson P, Feldt-Rasmussen U, Koltowska-Haggstrom M & Ross RJ 2005 Estrogen replacement in women of fertile years with

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hypopituitarism. *Journal of Clinical Endocrinology and Metabolism* **90** 5964–5969. (https://doi.org/10.1210/jc.2005-1207)

Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P & Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials 2004 Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. *Journal of Clinical Endocrinology and Metabolism* **89** 2192–2199. (https://doi.org/10.1210/jc.2003-030840)

Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF & Mishell DR Jr 1982 Comparison of pharmacodynamic properties of various estrogen formulations. *American Journal of Obstetrics and Gynecology* **144** 511–518. (https://doi.org/10.1016/0002-9378(82)90218-6)

Meinhardt UJ & Ho KK 2006 Modulation of growth hormone action by sex steroids. *Clinical Endocrinology* **65** 413–422. (https://doi.org/10.1111/j.1365-2265.2006.02676.x)

Melmed S 2019 Pathogenesis and diagnosis of growth hormone deficiency in adults. *New England Journal of Medicine* **380** 2551–2562. (https://doi.org/10.1056/NEJMra1817346)

Merola B, Cittadini A, Colao A, Longobardi S, Fazio S, Sabatini D, Sacca L & Lombardi G 1993 Cardiac structural and functional abnormalities in adult patients with growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* **77** 1658–1661. (https://doi.org/10.1210/jcem.77.6.8263155)

Merola B, Longobardi S, Sofia M, Pivonello R, Micco A, Di Rella F, Esposito V, Colao A & Lombardi G 1996 Lung volumes and respiratory muscle strength in adult patients with childhood- or adult-onset growth hormone deficiency: effect of 12 months' growth hormone replacement therapy. *European Journal of Endocrinology* **135** 553–558. (https://doi.org/10.1530/eje.0.1350553)

Metcalf D, Greenhalgh CJ, Viney E, Willson TA, Starr R, Nicola NA, Hilton DJ & Alexander WS 2000 Gigantism in mice lacking suppressor of cytokine signalling-2. *Nature* **405** 1069–1073. (https://doi.org/10.1038/35016611)

Mo D, Fleseriu M, Qi R, Jia N, Child CJ, Bouillon R & Hardin DS 2015 Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: a prospective observational cohort study. *Lancet. Diabetes and Endocrinology* **3** 331–338. (https://doi.org/10.1016/S2213-8587(15)00098-4)

Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML & Endocrine Society 2011 Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* **96** 1587–1609. (https://doi.org/10.1210/jc.2011-0179)

Moller N & Jorgensen JO 2009 Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocrine Reviews* **30** 152–177. (https://doi.org/10.1210/er.2008-0027)

Nass R, Huber RM, Klauss V, Muller OA, Schopohl J & Strasburger CJ 1995 Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood. *Journal of Clinical Endocrinology and Metabolism* **80** 552–557. (https://doi.org/10.1210/jcem.80.2.7852519)

Olsson DS, Trimpou P, Hallen T, Bryngelsson IL, Andersson E, Skoglund T, Bengtsson BÅ, Johannsson G & Nilsson AG 2017 Life expectancy in patients with pituitary adenoma receiving growth hormone replacement. *European Journal of Endocrinology* **176** 67–75. (https://doi.org/10.1530/EJE-16-0450)

O'Sullivan AJ, Crampton LJ, Freund J & Ho KKY 1998 Route of estrogen replacement confers divergent effects on energy metabolism and body composition in postmenopausal women. *Journal of Clinical Investigation* **102** 1035–1040. (https://doi.org/10.1172/JCI2773)

Pedersen SB, Kristensen K, Fisker S, Jorgensen JO, Christiansen JS & Richelsen B 1999 Regulation of uncoupling protein-2 and -3 by growth hormone in skeletal muscle and adipose tissue in growth hormone-deficient adults. *Journal of Clinical Endocrinology and Metabolism* **84** 4073–4078. (https://doi.org/10.1210/jcem.84.11.6109)

Richelsen B, Pedersen SB, Kristensen K, Borglum JD, Norrelund H, Christiansen JS & Jorgensen JO 2000 Regulation of lipoprotein lipase and hormone-sensitive lipase activity and gene expression in adipose and muscle tissue by growth hormone treatment during weight loss in obese patients. *Metabolism: Clinical and Experimental* **49** 906–911. (https://doi.org/10.1053/meta.2000.6738)

Salomon F, Cuneo RC, Hesp R & Sonksen PH 1989 The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *New England Journal of Medicine* **321** 1797–1803. (https://doi.org/10.1056/NEJM198912283212605)

Sjögren K, Leung KC, Kaplan W, Gardiner-Garden M, Gibney J & Ho KK 2007 Growth hormone regulation of metabolic gene expression in muscle: a microarray study in hypopituitary men. *American Journal of Physiology: Endocrinology and Metabolism* **293** E364–E371. (https://doi.org/10.1152/ajpendo.00054.2007)

Stenlof K, Sjostrom L, Lonn L, Bosaeus I, Kvist H, Tolli J, Lindstedt G & Bengtsson BA 1995 Effects of recombinant human growth hormone on basal metabolic rate in adults with pituitary deficiency. *Metabolism: Clinical and Experimental* **44** 67–74. (https://doi.org/10.1016/0026-0495(95)90291-0)

Stochholm K, Berglund A, Juul S, Gravholt CH & Christiansen JS 2014 Socioeconomic factors do not but GH treatment does affect mortality in adult-onset growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* **99** 4141–4148. (https://doi.org/10.1210/jc.2014-1814)

Wells GD, Selvadurai H & Tein I 2009 Bioenergetic provision of energy for muscular activity. *Paediatric Respiratory Reviews* **10** 83–90. (https://doi.org/10.1016/j.prrv.2009.04.005)

Widdowson WM & Gibney J 2008 The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *Journal of Clinical Endocrinology and Metabolism* **93** 4413–4417. (https://doi.org/10.1210/jc.2008-1239)

Widdowson WM & Gibney J 2010 The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis. *Clinical Endocrinology* **72** 787–792. (https://doi.org/10.1111/j.1365-2265.2009.03716.x)

Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M & Ho KK 2001 Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women. *American Journal of Physiology. Endocrinology and Metabolism* **281** E1191–E1196. (https://doi.org/10.1152/ajpendo.2001.281.6.E1191)

Woodhouse LJ, Mukherjee A, Shalet SM & Ezzat S 2006 The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. *Endocrine Reviews* **27** 287–317. (https://doi.org/10.1210/er.2004-0022)

Zhao JT, Cowley MJ, Lee P, Birzniece V, Kaplan W & Ho KK 2011 Identification of novel GH-regulated pathway of lipid metabolism in adipose tissue: a gene expression study in hypopituitary men. *Journal of Clinical Endocrinology and Metabolism* **96** E1188–E1196. (https://doi.org/10.1210/jc.2010-2679)

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