Action of GH on skeletal muscle function: molecular and metabolic mechanisms

Viral Chikani and **Ken K Y Ho**

Department of Diabetes and Endocrinology, Centres for Health Research, Princess Alexandra Hospital; The Translational Research Institute and the University of Queensland, 37 Kent Street, Wooloongabba, Brisbane, Queensland 4102, Australia

Correspondence should be addressed to K K Y Ho
Email
k.ho@uq.edu.au

Abstract

Skeletal muscle is a target tissue of GH. Based on its anabolic properties, it is widely accepted that GH enhances muscle performance in sports and muscle function in the elderly. This paper critically reviews information on the effects of GH on muscle function covering structure, protein metabolism, the role of IGF1 mediation, bioenergetics and performance drawn from molecular, cellular and physiological studies on animals and humans. GH increases muscle strength by enhancing muscle mass without affecting contractile force or fibre composition type. GH stimulates whole-body protein accretion with protein synthesis occurring in muscular and extra-muscular sites. The energy required to power muscle function is derived from a continuum of anaerobic and aerobic sources. Molecular and functional studies provide evidence that GH stimulates the anaerobic and suppresses the aerobic energy system, in turn affecting power-based functional measures in a time-dependent manner. GH exerts complex multi-system effects on skeletal muscle function in part mediated by the IGF system.

Key Words
- growth hormone
- muscle
- strength
- power
- metabolism

Journal of Molecular Endocrinology
(2014) **52**, R107–R123

Journal of Molecular Endocrinology

Introduction

Skeletal muscles are specialised contractile tissues that control posture and physical activity while having an important role in energy metabolism. Their function is dependent on the composition and strength of fibre types that require energy to drive and sustain contractile work.

Muscle function is regulated by many factors including genes, nutrition, lifestyle and hormones. Many hormones including growth hormone (GH), thyroid hormones, testosterone and glucocorticoids exert major effects on skeletal muscle growth and function. The stimulation of muscle protein anabolism and growth by GH has led to widespread expectation that it increases muscle strength and power. GH is considered to be one of the most widely abused performance-enhancing agents in sports (Barroso *et al*. 2008, Holt & Sonksen 2008). Outside the sporting arena, GH is marketed as an antiageing therapy for frailty and disability secondary to loss of muscle mass. Despite its unequivocal protein accreting properties, evidence supporting a beneficial effect on muscle function is limited (Birzniece *et al*. 2011).

Muscle function is assessed in many ways, most commonly as strength and power (Abernethy *et al*. 1995). These endpoints reflect overlapping but distinct aspects of muscle function. Strength is dependent on muscle size, types and quality of contractile proteins. 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

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

from pre-formed stores or generated from the metabolism of substrates (Wells *et al*. 2009). Energy metabolism can be anaerobic or aerobic. Muscle power is influenced by the availability of energy or energy type at the time of assessment. The recognition of mitochondrial myopathies as a class of functional muscle disorders arising from defects in mitochondrial respiratory chain enzymes highlights bioenergetics as an important mechanism influencing skeletal muscle function dependent on oxidative phosphorylation (Schaefer *et al*. 2001). The intersection between muscle structure, function and the muscle energy system has been a neglected area of active research. However, recent advances in GH research have highlighted that the bioenergetics of muscle is an important player determining aspects of muscle function.

This paper reviews the effects of GH on muscle structure and composition, and on protein and energy metabolism. By drawing together animal and human studies and relating the information on function to structure and bioenergetics, this review will give a new perspective on the regulation of skeletal muscle function by GH.

GH effects on protein metabolism

Protein turnover is defined as the continuing breakdown and synthesis of proteins, with recycling of amino acids. At a steady state, the rate of protein breakdown equals the rate of protein synthesis, and there is no net gain or loss of proteins. Amino acids released from protein breakdown are either reutilised in protein synthesis or irreversibly lost via oxidation. Over the last two decades, isotope tracer methods such as leucine turnover technique have made it possible to accurately measure these components of whole-body protein metabolism by tracking the metabolic fate of a labelled amino acid (Wagenmakers 1999).

Lean body mass (LBM) and muscle mass are reduced in adults with GH deficiency (GHD), suggesting that there is an underlying perturbation of protein metabolism (Woodhouse *et al*. 2006). Hoffman *et al*. (1998) compared protein metabolism in ten GHD patients with healthy controls using labelled leucine and found that the rate of protein synthesis and breakdown were significantly reduced in GHD subjects. These results corroborate previous findings of Beshyah *et al*. (1993) and suggest that the whole-body protein turnover is reduced in adults with GHD.

GH replacement in adults with GHD improves protein balance by partitioning amino acids away from oxidative towards synthetic pathways (Russell-Jones *et al*. 1993, 1998, Lucidi *et al*. 2000, Mauras *et al*. 2000, Shi *et al*. 2003). Russell-Jones *et al*. (1993) observed an increase in protein synthesis and a reduction in protein oxidation without any change in protein breakdown after 2 months of GH in GHD subjects. The same findings were obtained by Shi *et al*. (2003) following 2 weeks, and by Binnerts *et al*. (1992) after 1 month of GH therapy in adults with GHD. These anabolic effects of GH are also observed in healthy adults supplemented with GH. In healthy subjects, Copeland & Nair (1994) observed an acute reduction in whole-body protein oxidation following GH administration. Similar effects were reported by healthy volunteers during fasted and fed states, following 7 days of GH treatment (Horber & Haymond 1990).

Long-term studies on adults with GHD have observed attenuation in anabolic effects after prolonged therapy (Beshyah *et al*. 1993, Shi *et al*. 2003). Binnerts *et al*. (1992) observed that GH-induced reduction in protein oxidation was diminished after 6 months of GH therapy. In another study, the reduction of protein oxidation seen at 2 weeks of GH therapy had returned to baseline at 12 weeks, indicating a waning GH effect with time (Burt *et al*. 2008). Studies have shown that the reduction in protein oxidation is a predictor of a later increase in LBM, which occurs over the first few months (Beshyah *et al*. 1993, Burt *et al*. 2008). Thus, GH causes a time-dependent change in whole-body protein metabolism. In the early weeks, GH reduces the rate of protein oxidation, leading to an accrual of protein mass. However, as the increase in LBM begins to plateau, this is with a gradual return in the rate of protein oxidation to baseline, protein balance reaches a new steady state. The metabolic mechanisms accounting for this adaptation are unknown.

Whole-body protein turnover studies do not provide information regarding the site of protein synthesis although it is widely assumed that this is muscle. To address the direct effects of GH on skeletal muscle protein turnover, investigators have measured the arterio-venous difference of labelled and unlabelled amino acids across the forearm or leg (Wagenmakers 1999). Using this technique, Fryburg *et al*. (1991) and Fryburg & Barrett (1993) reported that GH induced an increase in protein synthesis without affecting the rate of protein breakdown in forearm muscles. However, Copeland & Nair (1994) found no significant stimulation of protein synthesis in the leg during GH infusion, despite observing a concomitant stimulation of whole-body protein synthesis. The latter findings were corroborated by Yarasheski *et al*. (1993) who also failed to observe any effect on protein synthesis of quadriceps muscle following GH therapy. These observations suggest that a greater proportion of

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

whole-body protein anabolism occurs in tissues and organs than in skeletal muscle. This could explain why the improvement by GH in muscle strength in GHD is slow, and the paucity of evidence supporting a beneficial effect in GH-replete subjects.

According to the somatomedin hypothesis, the anabolic action of GH is mediated by circulating insulin-like growth factor 1 (IGF1), which is mainly derived from the liver (Daughaday *et al*. 1972, Le Roith *et al*. 2001). However, it is recognised that IGF1 produced locally in tissues under GH stimulation mediate some of the growth-promoting actions of GH (Le Roith *et al*. 2001, Adams 2002). The extent to which circulating and local IGF1 contribute to tissue growth has been the subject of great interest in the field and remains controversial. Human studies employing recombinant IGF1 provide the strongest evidence that circulating IGF1 is anabolic. IGF1 enhances protein anabolism by reducing the rate of proteolysis, an action similar to that of insulin (Fukagawa *et al*. 1985, Tessari *et al*. 1986, Jacob *et al*. 1989). When IGF1 is infused in rats, it leads to a reduction in protein breakdown without any change in protein synthesis (Jacob *et al*. 1989). Thus, the protein anabolic effects of systemic IGF1 are similar to insulin and different from GH, which regulates the metabolic fate of amino acids from oxidative to synthesis pathways. These observations indicate that the effects of GH on amino acid fluxes are mediated by mechanisms in addition to those mediated by IGF1.

In summary, GH regulates protein anabolism via IGF1-dependent endocrine and paracrine mechanisms as well as IGF1 independent pathways. The net effect of GH on whole-body protein metabolism is the metabolic partitioning of amino acids towards synthesis and away from irreversible oxidative loss but with tissue effects that differ between muscle and extra-muscular tissues.

GH regulation of functional muscle proteins and muscle fibre type distribution

Skeletal muscle is composed of fibres that are made up of different proteins with distinct properties. Actin and myosin are functional proteins that are responsible for the contractile function of muscle, whereas tropomyosin and troponin are structural proteins that keep the contractile proteins in proper alignment and give muscle fibres elasticity and extensibility. Myosin protein consists of two heavy chain and four light chains. Muscle fibres are classified by myosin heavy chain (MHC) isoforms mainly into two types (Dubowitz & Pearse 1960). Type I fibres, also known as slow twitch fibres, contain an abundance of mitochondria and rely on aerobic or oxidative pathways for energy production. These fibres determine the endurance capacity of muscle. In contrast, type II fibres, also known as fast twitch fibres, generate energy from anaerobic or glycolytic pathways due to their low mitochondrial content. These fibres have high contractile force, but easy fatigability. They subserve high intensity activities such as sprinting and weight lifting.

MHC isoforms are distinguished by various methods including myofibrillar adenosine triphosphatase staining (Brooke & Kaiser 1970), immunohistochemistry with specific MHC isoform antibodies (Bottinelli *et al*. 1991) and electrophoretic isoform separation (Danieli Betto *et al*. 1986). Several factors determine fibre type distribution in skeletal muscle. These include age, exercise, functional usage, neural input and hormones (Staron & Johnson 1993). For example, ageing is associated with a reduction in type II fibres (Porter *et al*. 1995), whereas thyroid hormone excess leads to a reduction in type I fibres (Larsson *et al*. 1994). The effects of GH on contractile muscle proteins have been investigated in rodents and humans by studying the consequences of GHD and GH treatment.

Animal studies

Yamaguchi *et al*. (1996) reported a significant increase in type I fibres and decrease in type II fibres in rodents after hypophysectomy. These findings were supported by Roy *et al*. (1996), who observed a significant increase in fibres expressing MHC type I in hypophysectomised rats. A study investigating the long-term effects of hypophysectomy in rats reported a complete loss of type II fibres after 33 months (Shorey *et al*. 1993). In contrast to these findings, Ayling *et al*. (1989) reported 50% reduction in type I fibres after hypophysectomy. Loughna & Bates (1994) also observed a significant reduction of type I and an increase in type II MHC mRNA expression in hypophysectomised rats. In these studies, GH replacement almost completely reversed the changes observed after hypophysectomy (Ayling *et al*. 1989, Loughna & Bates 1994). However, some studies have reported no change in the composition of type I or type II fibres after GH replacement in hypophysectomised rats (Everitt *et al*. 1996, Roy *et al*. 1996). The reasons for these discrepancies are unclear. Possible explanations include the variable duration of GHD, which ranged between 21 and 50 days, and the duration of GH therapy, which ranged from 7 days to 33 months. Most studies did not account for the effects

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

of other pituitary hormone deficiencies on muscle fibre types, in particular thyroid hormone. When investigating the effects of GH in normal rats, Florini & Ewton (1989) observed no significant change in the number of type I or type II fibres after 6 months. These results in normal rats have been confirmed by other groups (Ullman & Oldfors 1989, Bigard *et al*. 1994, Aroniadou-Anderjaska *et al*. 1996).

Human studies

There are few human studies investigating the GH regulation of muscle fibre composition, and most of these entail small numbers. Most studies on adult subjects with GHD have reported no significant difference in fibre-type distribution from matched normal subjects (Whitehead *et al*. 1989, Cuneo *et al*. 1992, Bottinelli *et al*. 1997). A time-dependent relationship between the duration of GHD and fibre-type composition is unlikely from a comparison of findings between patients with childhood-onset and adult-onset GHD (Whitehead *et al*. 1989, Cuneo *et al*. 1992, Bottinelli *et al*. 1997). Daugaard *et al*. (1999) found no relationship between IGF1 levels and MHC composition, suggesting that the severity of GHD does not influence MHC composition. Studies of GH replacement up to 6 months have reported no significant change in muscle fibre composition in adults with GHD (Whitehead *et al*. 1989, Cuneo *et al*. 1992, Daugaard *et al*. 1999). One of these studies reported an increase in muscle size and improvement in endurance capacity, but observed no change in the number of type I or II fibres (Cuneo *et al*. 1992). It is unclear from this study whether the relationship between the improvement in endurance and in type I fibre size is associative or causal. This study did not test muscle function reflective of type II fibre type that subserve high intensity contractile activity. There is insufficient evidence to support a role of GH in the regulation of type I or II fibres in human skeletal muscle, and more studies with larger numbers are required to determine whether GH regulates skeletal muscle fibre composition.

Bioenergetics in skeletal muscle

The contractile function of skeletal muscle relies on a constant supply of chemical energy. During muscle contraction, chemical energy is converted to mechanical energy that leads to movement.

Figure 1 illustrates the metabolic processes involved in energy production in a muscle cell and the concept of energy continuum during physical activity. In humans, chemical energy is available in the form of ATP, which is generated by two energy systems: anaerobic and aerobic (Bonora *et al*. 2012). The anaerobic energy system relies on preformed ATP as phosphocreatine (PCr) stores or ATP production from anaerobic glycolysis, i.e. breakdown of glucose in the absence of oxygen. The aerobic energy system generates ATP from oxidation of metabolic fuels such as carbohydrates, lipids and proteins. In the cytoplasm, glycolysis leads to the production of pyruvate. In the absence of oxygen, pyruvate is reduced to lactate, which is released into the circulation and converted to glucose in the liver. In tissues with adequate oxygen supply, pyruvate and fatty acid (FA) are converted to acetyl CoA in the mitochondria. Acetyl CoA undergoes oxidation via the tricarboxylic acid (TCA) cycle and the mitochondrial respiratory chain, producing ATP. The amount of preformed ATP present in the muscle cells is only sufficient to sustain physical activity for the first 5–10 s; thereafter, anaerobic glycolysis provides energy for further 30–40 s, when aerobic metabolism begins to take over and provides energy for prolonged sustained activity (Baker *et al*. 2010).

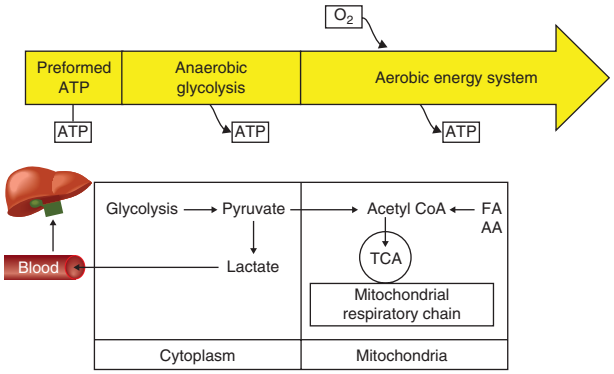

Figure 1
Anaerobic and aerobic energy systems. AA, amino acid; FA, fatty acid; TCA, tricarboxylic acid cycle; O_2, oxygen.

Thus, muscle function is dependent on the availability of metabolic fuels and its capacity to synthesise ATP. The energy synthesis from substrate utilisation in exercising muscle is regulated by nutritional, genetic and hormonal factors as well as physical training. GH stimulates lipolysis during resting condition (Moller *et al*. 1992, Gravholt *et al*. 1999, Hansen *et al*. 2002) as well as exercise (Healy *et al*. 2003, 2006), leading to an increase in plasma FA levels. GH also increases plasma glucose concentration by various mechanisms including augmentation of glycogenolysis

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

(Ghanaat & Tayek 2005) and gluconeogenesis (Moller *et al.* 1991). Thus, GH may enhance muscle function by increasing availability of FA and pyruvate as metabolic fuels for energy production.

It is known that GH stimulates whole-body lipid oxidation and reduces carbohydrate utilisation in healthy adults (Moller *et al.* 1990, 1992, Krag *et al.* 2007) and in adults with GHD (Jorgensen *et al.* 1993, Wolthers *et al.* 2001, Gibney *et al.* 2005). Given that LBM accounts for the majority of substrate metabolism in the body, and muscle comprises almost 50% of total LBM, it is widely assumed that an increase in whole-body lipid oxidation is a reflection of its action on skeletal muscle. This traditional thinking was challenged by studies on rodents as well as humans, suggesting GH action is rather tissue-specific. Tollet-Egnell *et al.* (2004) reported that GH inhibits the expression of genes involved in lipid oxidation in skeletal muscle of rats. Evidence from a study of metabolic gene expression in skeletal muscle of adults with GHD suggests that GH downregulates genes governing lipid metabolism (FA transport and β-oxidation) as well as, TCA cycle activity and mitochondrial respiration (Fig. 2; Sjogren *et al.* 2007). For example, the expression of oxoglutarate dehydrogenase and succinate dehydrogenase complex B in the TCA cycle and ATP synthase and NADH (reduced nicotinamide adenine dinucleotide) dehydrogenase in the mitochondrial respiratory chain were reduced by up to 40%. Assuming that these transcriptional changes reflect effects on protein expression, these findings suggest that GH inhibits oxidative metabolism of substrates and may

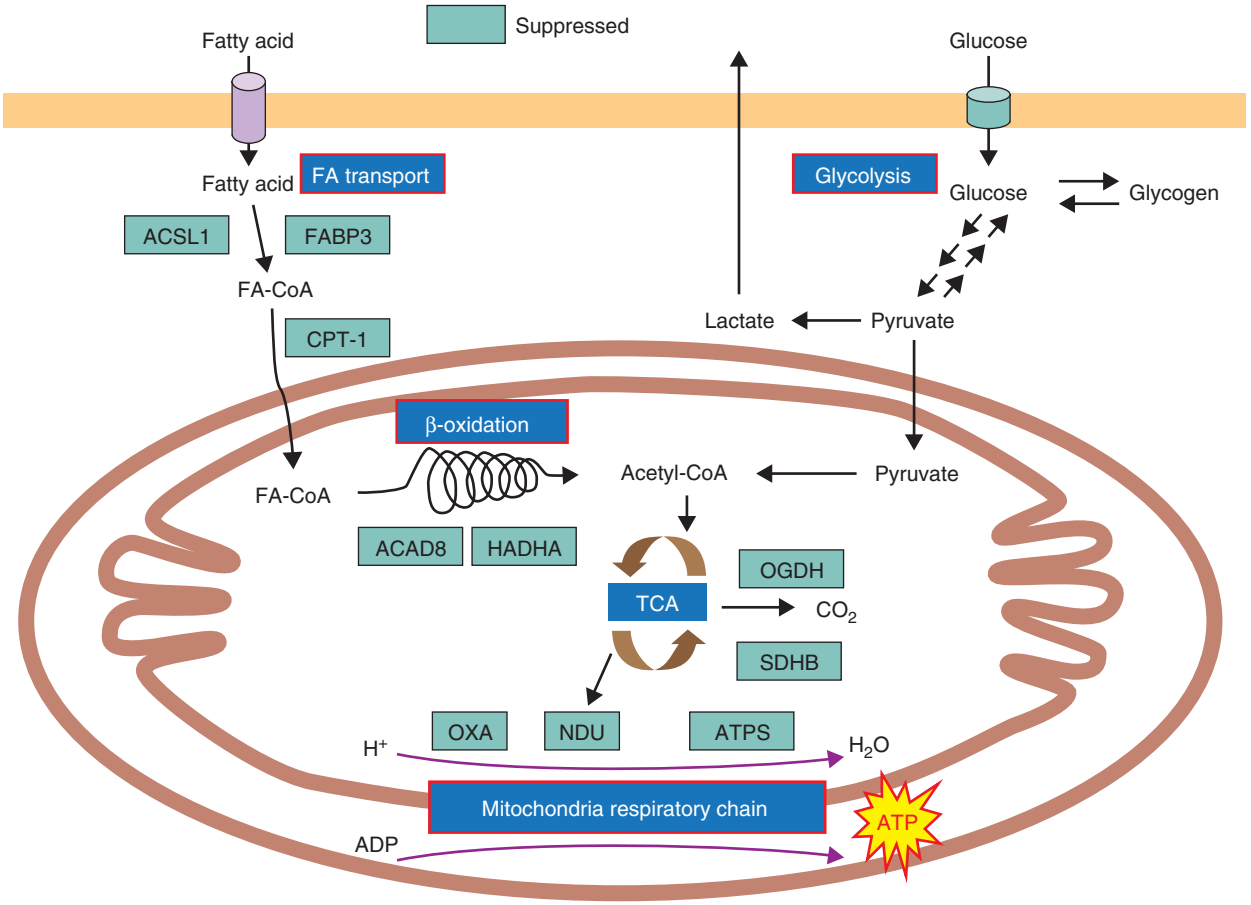

Figure 2

Schematic diagram of changes in the expression of key genes in the skeletal muscle governing the oxidative metabolism of FAs and glucose after GH therapy (data from Sjogren *et al.* (2007)). Metabolic genes that were downregulated by GH in the skeletal muscle are boxed in green with the abbreviated names expanded below. FA, fatty acid; TCA, tricarboxylic acid cycle. Lipid metabolism: FABP3, fatty acid-binding protein-3; ACSL, acyl-CoA synthetase, long-chain; CPTI, carnitinepalmitoyl-transferase I; ACAD8, acyl-CoA dehydrogenase, family member 8; HADHA, hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase. TCA cycle: OGHD, oxoglutarate dehydrogenase; SDHB, succinate dehydrogenase complex B. Mitochondrial chain: OXA, oxidase; NDU, NADH dehydrogenase; ATPS, ATP synthase.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

favour non-oxidative (anaerobic) pathways for ATP synthesis in the skeletal muscle. This is supported by a study in trained cyclists, in which GH use was associated with increased plasma lactate levels during moderate to intense exercise compared with placebo, implying an increased rate of anaerobic disposal of pyruvate (Lange *et al*. 2002).

In summary, GH effects on substrate metabolism are tissue-specific. Recent evidence has suggested that GH may promote non-oxidative or anaerobic substrate metabolism in skeletal muscle for ATP synthesis, findings contrary to its effects on whole-body metabolism.

GH effects on muscle power

Muscle power is defined as work performed per unit of time and is expressed in joules per second or watts. It is described in terms of aerobic and anaerobic power, depending on which energy source is predominantly utilised to do the work. Thus, muscle power can be assessed by measuring aerobic exercise capacity and anaerobic exercise capacity.

Aerobic exercise capacity

Aerobic exercise capacity is a measure of endurance i.e. the muscle's ability to sustain work for prolonged period with energy provided principally from oxidation of carbohydrates or lipids in the mitochondria. In the athletic world, it determines performance in sports such as marathon, football, tennis, etc., while in day-to-day life, it relates to activities such as walking. Aerobic exercise capacity is a stronger predictor of mortality in men than any other established risk factors for cardiovascular disease such as hypertension, smoking and diabetes (Myers *et al*. 2002). It is determined by the measurement of maximal oxygen uptake ($VO_{2\ max}$) in l/min or ml/kg per min or maximal aerobic power output in watts or kilojoules during an incremental exercise test on a cycle ergometer or a treadmill (Astrand 1976).

Studies on GHD subjects have provided strong evidence that GH is a significant positive regulator of aerobic exercise capacity. Cuneo *et al*. (1991*a*,*b*) reported a reduction of 28% in $VO_{2\ max}$ in adults with GHD compared with their maximum predicted value based on age, weight and height. Many studies have reported a similar degree of impairment in aerobic exercise capacity in these individuals (Whitehead *et al*. 1992, Nass *et al*. 1995, Gullestad *et al*. 1998).

Numerous double-blind placebo-controlled and long-term open-label trials have investigated GH effects on aerobic exercise capacity in adults with GHD (Table 1). In a study on 22 adults with GHD, aerobic exercise capacity increased significantly after 4 months of GH therapy and was sustained for up to 38 months of GH treatment (Jorgensen *et al*. 1989, 1994). Cuneo *et al*. (1991*a*,*b*) observed a near normalisation of $VO_{2\ max}$ over a period of 6 months with GH replacement in a study involving 24 adults with GHD. Most of these studies show an improvement in $VO_{2\ max}$ and/or maximal aerobic power output following GH therapy of the duration from 4 to 12 months (Jorgensen *et al*. 1989, 1991, 1994, 1996, Cuneo *et al*. 1991*a*,*b*, Whitehead *et al*. 1992, Gullestad *et al*. 1998, Bollerslev *et al*. 2005). A few studies failed to show a positive effect of GH on aerobic exercise capacity in comparison with placebo (Degerblad *et al*. 1990, Caidahl *et al*. 1994, Woodhouse *et al*. 1999). This is likely due to the small number of participants in these trials or related to a type II statistical error.

The underlying mechanisms responsible for the improvement in aerobic performance during GH replacement are multifactorial. Oxygen delivery to exercising muscles depends on cardiac function, lung capacity and oxygen-carrying capacity of the blood (Saltin & Strange 1992). Adults with GHD have impaired cardiac function (Colao *et al*. 2001), diminished lung capacity (Merola *et al*. 1996) and reduced red cell mass (Christ *et al*. 1997). These deficits are restored with GH replacement. In adults with GHD, GH replacement increases i) cardiac output, which arises from enhancement of heart rate and stroke volume (Jorgensen *et al*. 1989, Cuneo *et al*. 1991*a*,*b*, Nass *et al*. 1995, Maison & Chanson 2003); ii) lung capacity by increasing respiratory muscle strength and lung volumes (Nass *et al*. 1995, Merola *et al*. 1996); and iii) red cell mass, which determines oxygen-carrying capacity of the blood (Claustres *et al*. 1987, Vihervuori *et al*. 1996, Christ *et al*. 1997). As discussed previously, biopsy data in humans do not provide evidence that GH increases the number of oxidative type I muscle fibres. However, studies uniformly show that the increase in muscle mass is associated with an increase in oxygen consumption during GH replacement (Whitehead *et al*. 1992, Nass *et al*. 1995). These observations are consistent with the delivery of a greater amount of oxygen to an increased muscle mass as a result of GH replacement in adults with GHD, leading to an increase in aerobic capacity of exercising muscles.

Several studies have failed to show any significant effects of GH on $VO_{2\ max}$ in healthy adults (Liu *et al*. 2008). Berggren *et al*. (2005) observed no significant increase in

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

Table 1 The effects of GH on aerobic exercise capacity in adults with GHD

Study	GHD patients	Age (years)	Diagnosis of GHD	Study design	GH dose	Method	Effects of GH
Jorgensen *et al.* (1989)	$n=22$, CO M:F 14:8	23.8±1.2	Peak GH <5 μg/l after clonidine stimulation test	4 months DBPC crossover	2 IU/m^2	Cycle ergometer	Increase in exercise capacity (kJ) in GH group
Jorgensen *et al.* (1991)	$n=13$, CO M:F 9:4	24.4±1.7	Peak GH <5 μg/l after clonidine stimulation test	16 months open label, continuation of the above study	Median 2.9 IU/m^2 (1.2–3.8 IU/m^2)	Cycle ergometer	Further increase in exercise capacity
Jorgensen *et al.* (1994)	$n=10$, CO M:F 7:3	28.4±2.3	Peak GH <5 μg/l after clonidine stimulation test	37.6 months open label, continuation of the above study	2 IU/m^2	Cycle ergometer	Increase in exercise capacity observed at 16 months was sustained
Cuneo *et al.* (1991*a*,*b*)	$n=24$, AO M:F 16:8	39±2	Peak GH <3.0 mU/l during insulin-induced hypoglycaemia	6 months DBPC	0.07 U/kg per day	Cycle ergometer	Increase in $VO_{2\ max}$ (ml/kg per min) and maximal power output (W) in GH group compared with placebo
Jorgensen *et al.* (1996)	$n=29$, AO M:F 19:10	45.5±2	Peak GH <10.0 μg/l during insulin-induced hypoglycaemia	12 months DBPC	2 IU/m^2	Cycle ergometer	Increase in exercise capacity (kJ) in GH group compared with placebo
Nass *et al.* (1995)	$n=20$, AO M:F 15:5	~45	Peak GH <2 ng/ml during insulin-induced hypoglycaemia	6 months DBPC	12.5 μg/kg per day	Cycle ergometer	Increase in $VO_{2\ max}$ (l/min) in GH group from baseline; $VO_{2\ max}$ (ml/min per kg LBM) remained unchanged Increase in maximal power output (W) in GH group
Caidahl *et al.* (1994)	$n=10$, AO M:F 9:1	47	Peak GH <5.0 mU/l during insulin-induced hypoglycaemia	6 months DBPC crossover	0.5 U/kg per week	Cycle ergometer	No significant difference in maximal power output (W) compared with placebo
Whitehead *et al.* (1992)	$n=14$, AO M:F 9:5	29.4±2.7	Peak GH <7.0 mU/l during insulin-induced hypoglycaemia	6 months DBPC crossover with 1 month washout	0.5 U/kg per week	Cycle ergometer	Increase in exercise capacity (W) and $VO_{2\ max}$ (l/min) in GH group compared with placebo
Rodriguez-Arnao *et al.* (1999)	$n=35$, mixed M:F 18:17	39.8	Peak GH <10.0 mU/l after glucagon or insulin-induced hypoglycaemia	6 months DBPC followed by 6 months open label	0.125 IU/kg per week for first 4 weeks; thereafter 0.25 IU/kg per week	Treadmill	DBPC: $VO_{2\ max}$ (ml/kg per min) decreased in placebo and remained unchanged in GH Open label: increase in $VO_{2\ max}$ (ml/kg per min) previously placebo treated group but no change in GH group
Bollerslev *et al.* (2005)	$n=55$, AO M:F 31:24	49	Peak GH <3 μg/l to insulin hypoglycaemia (<2.2 mmol/l)	9 months DBPC crossover, 4 months washout	1.2 IU/day for men 1.8 IU/day for women	Treadmill	$VO_{2\ max}$ increased by 6 and 9% when expressed in absolute value (l/min) and relative to body weight (ml/kg per min) respectively

Table 1 *Continued*

Study	GHD patients	Age (years)	Diagnosis of GHD	Study design	GH dose	Method	Effects of GH
Woodhouse *et al.* (1999)	$n=28$, AO M:F 15:13	18–68	Peak GH <3.0 μg/l during insulin-induced hypoglycaemia	3 months DBPC crossover, 1 month washout	6.25 μg/kg LBM for first month 12.5 μg/kg LBM thereafter	Treadmill	Increase in $VO_{2\ max}$ (l/min) was significant within GH group but not significantly different between the two groups
Beshyah *et al.* (1995)	$n=40$, mixed M:F 19:21	19–67	Peak GH <6.0 mU/l during insulin-induced hypoglycaemia or oral clonidine	6 months DBPC followed by 12 and 18 months open label	DBPC: 0.02–0.05 IU/kg Open label: 0.05 IU/kg	Treadmill	Exercise time increased within the GH group but the change was not significantly different between the two groups Open label: exercise time continued to increase at 6, 12 and 18 months

DBPC, double-blind placebo-controlled; $VO_{2\ max}$, maximal oxygen uptake; CO, childhood onset; AO, adult onset; GH, growth hormone; GHD, growth hormone deficiency; LBM, lean body mass.

$VO_{2\ max}$ following 28 days of low (0.033 mg/kg per day) and high dose (0.067 mg/kg per day) of GH in a double-blind placebo-controlled trial involving 30 healthy adults. These findings were supported by the lack of improvement in $VO_{2\ max}$ of 96 recreational athletes, following 8 weeks of GH administration (2 mg/kg per day) (Meinhardt *et al.* 2010). Thus, GH does not enhance aerobic exercise capacity in healthy adults.

Collectively, these results indicate that GH enhances aerobic exercise capacity in GHD subjects, but not in healthy adults. The improvement can be explained by effects on muscle mass, cardiorespiratory function and haematological parameters.

Anaerobic exercise capacity

Anaerobic exercise capacity is defined as the total amount of work during a maximal exhausting exercise of a short duration, which is underpinned by anaerobic ATP supply (Green 1994). This work is executed by fast twitch type II muscle fibres. Various exercise tests have been used in the assessment of anaerobic exercise capacity (Vandewalle *et al.* 1987). In sporting activities that involve short-term high intensity physical activity, such as sprinting, baseball, gymnastics, etc., the main energy source is anaerobic ATP. All physical activities including activities 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, Van Praagh 2007). Thus, it is conceivable that a suboptimal anaerobic energy system impairs muscle function leading to chronic fatigue in patients and diminished performance in athletes.

Factors other than physical training that regulate anaerobic exercise capacity are largely unknown (Cahill *et al.* 1997). To our knowledge, only one study has investigated the effects of GH on anaerobic exercise capacity (Meinhardt *et al.* 2010). This double-blind placebo-controlled study in a large group of recreational athletes showed a significant improvement in anaerobic exercise capacity after GH therapy for 8 weeks, as assessed by the Wingate test. GH did not increase body cell mass, the functional compartment of LBM that is predominantly composed of muscle, nor standard measures of muscle strength (dynamometry) and power (jump height) (Fig. 3). These findings suggest that muscle anabolism is unlikely to explain the improvement in the Wingate test. Jump height represents instantaneous work, whereas the Wingate test involves all-out intensive exercise on a cycle ergometer for 30 s. Although both tests measure anaerobic

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

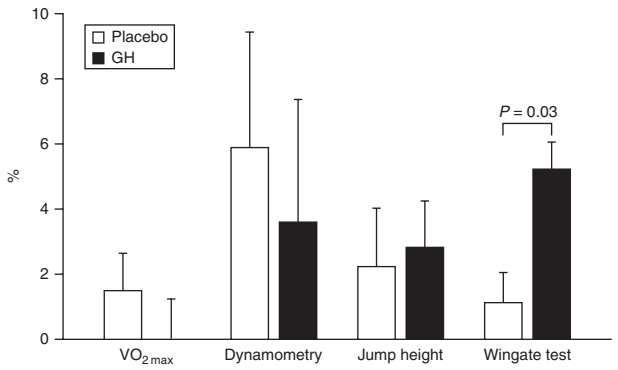

Figure 3
GH effects on physical performance in recreational athletes (data from Meinhardt *et al.* (2010)). This figure illustrates the percent change after GH or placebo treatments in four measures of physical performance: VO_2 max, strength (dynamometry), jump height and Wingate test.

power, the energy required for jumping is drawn from PCr stores while that for the longer Wingate test, from PCr stores and that derived from glycolysis. A likely explanation is a GH effect on energy supply stimulating ATP production from glycolysis, leading to an increase in anaerobic exercise capacity in skeletal muscle. In this study, the effects were assessed in GH-replete individuals treated with a supraphysiological dose of GH. To address the physiological significance, we are undertaking studies on subjects with GHD treated with a physiological replacement dose of GH.

Most sports involve repeated bouts of high-intensity exercise, interspersed with short recuperation periods. The athletes' physical performance may also rely on the ability to replenish PCr stores repeatedly, for repeated high-power outputs over a long duration. There is evidence that both aerobic and anaerobic metabolism contribute significantly to the replenishment of depleted PCr stores (Baker *et al.* 2010). A recent study has reported an association between PCr recovery after submaximal exercise and serum IGF1 and peak-stimulated GH levels (Makimura *et al.* 2011). However whether GH plays a role in the replenishment of PCr stores has not been investigated.

The anaerobic energy system provides energy for the initiation of all biological activities, including activities of daily living and powers short-term high-intensity physical activity (Cahill *et al.* 1997, Van Praagh 2007). Hence, the finding that GH may regulate the anaerobic energy system has potential therapeutic implications not only in the GHD population but also possibly in accelerating physical rehabilitation and improving physical function in the frail elderly. It also provides further justification of GH prohibition in sports.

GH effects on muscle mass and strength

Muscle strength is defined as maximal force (in newtons, N) or torque (in newton-metres, Nm) that is generated by a muscle or a group of muscles during maximal voluntary contraction (MVC; Abernethy *et al.* 1995). This force is determined by fast twitch type II muscle fibres and relies on preformed ATP for energy (Wells *et al.* 2009). Muscle strength is commonly assessed by measuring the force or torque produced during an isometric or isokinetic contraction. Isometric strength is the MVC that can be developed against an immovable object without a change in joint angle, whilst isokinetic strength is a measure of torque/force through a range of motion, in which limb is moving at a constant velocity (Abernethy *et al.* 1995).

Muscle strength is significantly reduced in adults with GHD (Rutherford *et al.* 1995, Johannsson *et al.* 1997; Table 2). It is usually expressed in absolute values (N or Nm), corrected for muscle area (cm^2) or volume (cm^3) to distinguish between the contributions of muscle mass and contractile quality. Janssen *et al.* (1999) reported a significant reduction in strength and volume of quadriceps muscle in adults with GHD compared with those of age- and height-matched controls. These findings suggest that diminished strength in GHD arise from reduced muscle mass rather than from reduced contractile function. Sartorio & Narici (1994) found that the strength of quadriceps muscle in adults with GHD was reduced in proportion to a reduction in muscle mass. These results stand in contrast to those of Cuneo *et al.* (1990), which found that quadriceps muscle force was reduced in adults with GHD when corrected for muscle area. These authors hypothesised that contractile properties, energy metabolism or neuromuscular function of skeletal muscle is impaired in the GH-deficient state. Janssen *et al.* (1999) attributed the disagreement to the possible inaccurate muscle mass assessment from a single slice computerised tomography scan (Cuneo *et al.* 1990) as opposed to a more precise method from using multiple magnetic resonance imaging slices in their study. As discussed in the previous section, muscle biopsy studies on adults with GHD also failed to identify any qualitative differences in fibre types compared with healthy adults. Thus, it is likely that muscle strength in GHD is reduced from diminished mass rather than a change in contractile quality.

Studies investigating the effects of GH replacement on muscle strength have provided conflicting results (Table 3).

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

Table 2 Studies comparing muscle strength of adults with GHD with healthy controls

Study	Total no.	Mean age (years)	Gender (M:F)	Type	Diagnostic criteria	Control	Outcome
Johannsson *et al.* (1997)	56	45±2	35:21	Mixed	Peak GH <1.7 μg/l during insulin-induced hypoglycaemia	Reference population of Goteborg. $n=144$, age 40–79 years matched for mean Ht and Wt	Lower isometric muscle strength in quadriceps and hamstring muscles The peak handgrip strength was 83% and average 10-s handgrip strength was 81% of healthy control
Rutherford *et al.* (1995)	14	41.8±17.3	9:5	Mixed	Peak GH <6.0 mU/l during insulin-induced hypoglycaemia or oral clonidine	14 age- and gender-matched controls	Lower isometric strength (84% of maximal predicted value for age gender and Ht)
Janssen *et al.* (1999)	28	49±2	28:0	Mixed	Peak GH <7.0 mU/l during insulin-induced hypoglycaemia	20 age- and Wt-matched controls	Lower maximal isometric strength Maximal isokinetic strength tended to be lower ($P=0.06$)
Cuneo *et al.* (1990)	24	39±2	16:8	AO	Peak GH <3.0 mU/l during insulin-induced hypoglycaemia	41 age-, gender- and Wt-matched controls	Lower quadriceps force/body Wt (N/kg). Lower quadriceps force/quadriceps area (N/cm^2)
Sartorio & Narici (1994)	8	29.6±3.4	8:0	CO	Peak GH <5.0 ng/ml to GHRH plus galanin and also to L-DOPA plus propranolol	Eight age- and gender-matched controls	Lower quadriceps isometric strength (63% of the controls)
Degerblad *et al.* (1990)	6	29±3	3:3	CO	Peak GH <3.4 μg/l to insulin plus arginine stimulation test	Published normal values	Lower torque at speed of 30°/s and angular position of 45° during knee flexion/extension

Wt, weight; Ht, height; CO, childhood onset; AO, adult onset; N, Newton; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone releasing hormone.

Journal of Molecular Endocrinology

Jorgensen *et al.* (1989) observed that muscle strength did not change significantly after GH replacement for 4 months in 22 adults with GHD. However, muscle strength improved significantly after 12 months, with the improvement sustained at the end of 38 months of treatment (Jorgensen *et al.* 1991, 1994). Similarly, a number of other investigators have observed a lack of effect in the short-term but a significant increase in muscle strength after extended treatment (Beshyah *et al.* 1995, Wallymahmed *et al.* 1997, Bell *et al.* 1999, Rodriguez-Arnao *et al.* 1999). In an open label prospective study of 109 adults with GHD, GH therapy normalised the strength of different muscle groups over 10 years of therapy (Gotherstrom *et al.* 2009). The majority of studies assessing GH effects beyond 12 months have reported a significant improvement in muscle strength (Rutherford *et al.* 1995, Johannsson *et al.* 1997, Janssen *et al.* 1999, Svensson *et al.* 2003, Gotherstrom *et al.* 2009), whereas trials of less than 6 months duration have not (Jorgensen *et al.* 1989, Whitehead *et al.* 1992, Beshyah *et al.* 1995, Wallymahmed *et al.* 1997, Bell *et al.* 1999, Rodriguez-Arnao *et al.* 1999, Woodhouse *et al.* 1999). The studies that show an increase in strength also report a concomitant increase in muscle mass after long-term GH therapy (Jorgensen *et al.* 1991, 1994, Janssen *et al.* 1999). The collective findings indicate that GH replacement beyond 12 months is required to improve muscle strength in adults with GHD, reflecting the time taken to restore muscle mass towards normal. In summary, the collective evidence indicates that GH increases muscle strength by increasing muscle mass.

Implicit in these studies of GH and muscle strength is the mediatory role of IGF1, which stimulates proliferation and differentiation of satellite cells into myoblasts and formation of new myofibres (Florini *et al.* 1996, Adams 2002). IGF1 knockout mice exhibit muscle hypoplasia (Liu *et al.* 1993), whereas overexpression of IGF1 leads to muscle hypertrophy (Coleman *et al.* 1995) and accelerates

Published by Bioscientifica Ltd.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

Table 3 The effects of GH on muscle strength in adults with GHD

Study	GHD patients	Diagnosis of GHD	Study design	GH dose	Effects of GH
Jorgensen *et al.* (1989)	$n=22$, M:F 14:8, CO, mean age 23.8±1.2 years	Peak GH <5 μg/l after clonidine stimulation test	4 months DBPC crossover	2 IU/m^2	No significant difference in isometric strength between GH and placebo group
Jorgensen *et al.* (1991)	$n=13$ M:F 9:4, CO, mean age 24.4±1.7 years	Peak GH <5 μg/l after clonidine stimulation test	16 months open label, continuation of the above study	Median 2.9 IU/m^2 (1.2–3.8 IU/m^2)	Isometric strength of quadriceps increased compared with placebo, but remained lower than the control group
Jorgensen *et al.* (1994)	$n=10$ M:F 7:3, CO, mean age 28.4±2.3 years	Peak GH <5 μg/l after clonidine stimulation test	37.6 months open label, continuation of the above study	2 IU/m^2	Increased isometric strength observed at 16 months was sustained
Svensson *et al.* (2003)	$n=109$ M:F 61:48, AO, mean age 50 years	Peak GH <3 μg/l during insulin hypoglycaemia ($n=95$); two additional hormone deficiency plus 24 h GH profile ($n=9$); one additional hormone deficiency plus 1 stimulation test ($n=4$)	5 years open label	First 80 patients, starting dose 0.25 IU/kg per week and individualized when Wt based regimen abandoned. In other patients, individualized from the beginning	Isometric knee flexor strength, concentric knee flexor strength and right handgrip strength increased. Isometric knee extensor strength, concentric knee extensor strength and left handgrip strength remained unchanged
Sartorio & Narici (1994)	$n=8$ M:F 8:0, CO, mean age 29.6±3.4 years	Peak GH <5 ng/ml during two stimulation tests, GHRH plus galanin and L-DOPA plus propranolol	6 months open label	0.5 IU/kg per week	10% increase in isometric quadriceps strength
Bollerslev *et al.* (2005)	$n=55$ M:F 31:24, AO, mean age 49 years	Peak GH <3 μg/l to insulin-induced hypoglycaemia	9 months DBPC crossover, 4 months washout	1.2 IU/day for men 1.8 IU/day for women	No significant change in isokinetic knee extensor strength
Bell *et al.* (1999)	$n=53$ M:F 23:20, mixed age 21–60 years	Peak GH <5 mg/l during insulin-induced hypoglycaemia or GHRH stimulation test	6 months DBPC followed by 6 months open label	0.125 IU/kg per week for first week; thereafter 0.25 IU/kg per week	DBPC: no significant change in strength Open label: significant increase in knee extension strength in previously GH-treated males. Significant increase in arm flexion in previously GH as well as placebo-treated females
Woodhouse *et al.* (1999)	$n=28$ M:F 15:13, AO age 18–68 years	Peak GH <3.0 μg/l during insulin-induced hypoglycaemia	3 months DBPC crossover, 1 month washout	6.25 μg/kg LBM for first month 12.5 μg/kg LBM thereafter	No significant change in isometric handgrip strength, isotonic arm, leg or chest press or isokinetic knee flexion/extension strength in GH group compared to placebo
Beshyah *et al.* (1995)	$n=40$ M:F 19:21, mixed age 19–67 years	Peak GH <6.0 mU/l during insulin-induced hypoglycaemia or oral clonidine	6 months DBPC followed by 12 and 18 months open label	DBPC: 0.02–0.05 Open label: 0.05 IU/kg IU/kg	DBPC: no significant change in maximal voluntary strength in any muscle group Open label: significant increase in neck flexion and elbow extension at 6 and 18 months; neck flexion, elbow flexion and extension, and hip flexion and extension at 12 months
Rutherford *et al.* (1995)	$n=6$ M:F 3:3, mixed mean age 41.8±17.3 years	Peak GH <6.0 mU/l during insulin-induced hypoglycaemia or oral clonidine	6–24 months open label	0.04±0.01 IU/kg per day	Significant increase in maximal voluntary isometric strength

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

Table 3 *Continued*

Study	GHD patients	Diagnosis of GHD	Study design	GH dose	Effects of GH
Wallymahmed *et al.* (1997)	$n=30$ M:F 10:20, mixed age ~35 years	Peak GH <10.0 mU/l after glucagon or insulin-induced hypoglycaemia	6 months DBPC followed by 6 months open label 2 years open label ($n=12$)	0.125 U/kg per week for first month; thereafter 0.25 U/kg per week	DBPC and open label: no significant change in isometric quadriceps muscle strength over 12 months 2 years open label: significant improvement in quadriceps muscle strength from baseline at 12 months and at 24 months
Jorgensen *et al.* (1996)	$n=29$ M:F 19:10, AO, mean age 45.5±2 years	Peak GH <10.0 μg/l during insulin-induced hypoglycaemia	12 months DBPC	2 IU/m^2	No significant increase in isometric quadriceps strength in GH group, owing to a small increase in the placebo group (placebo: 89.6±12.4 (baseline) vs 113.4±12.3 (12 months) ($P=0.08$); GH: 98.2±10.5 (baseline) vs 136.5±13.1 (12 months) ($P=0.003$); Δ GH vs placebo: 14.5±16.5, $P=0.39$)
Cuneo *et al.* (1991*a*,*b*)	$n=24$ M:F 16:8, AO, mean age 39±2 years	Peak GH <3.0 mU/l during insulin-induced hypoglycaemia	6 months DBPC	0.07 U/kg per day	Increase in strength of only one (hip flexion) out of nine muscle groups
Janssen *et al.* (1999)	$n=28$ M:F 28:0, mixed mean age 49±2 years	Peak GH <7.0 mU/l during insulin-induced hypoglycaemia	12 months open label	First 24 week, 0.6, 1.2 or 1.8 U and thereafter individualized dosing to normalize IGFI	Significant increase in isokinetic muscle strength No change in isometric muscle strength
Johannsson *et al.* (1997)	$n=56$ M:F 35:21, mixed mean age 45±2 years	Peak GH <1.7 μg/l during insulin-induced hypoglycaemia	2 years open label	Individualized according to IGFI level. Mean GH dose 0.62±0.03 mg/day	Significant increase in isometric knee extension and flexion strength Significant increase in isokinetic knee extension strength at angular velocity of π rad/s Significant increase in isokinetic knee flexion strength at angular velocity of π/3 rad/s and π rad/s No change in handgrip strength
Rodriguez-Arnao *et al.* (1999)	$n=35$ M:F 18:17, mixed mean age 39.8 years	Peak GH <10.0 mU/l after glucagon or insulin-induced hypoglycaemia	6 months DBPC followed by 6 months open label	0.125 IU/kg per week for first 4 weeks; thereafter 0.25 IU/kg per week	DBPC: no significant change in isometric quadriceps muscle strength between GH and placebo groups Open label: significant increase in isometric quadriceps muscle strength in previously GH-treated group but not in previously placebo-treated group
Whitehead *et al.* (1992)	$n=14$ M:F 9:5, AO, mean age 29.4±2.7 years	Peak GH <7.0 mU/l during insulin-induced hypoglycaemia	6 months DBPC crossover with 1 month washout	0.5 U/kg per week	No significant change in isokinetic knee extension strength
Degerblad *et al.* (1990)	$n=6$ M:F 3:3, CO, mean age 29±3 years	Peak GH <3.4 μg/l during insulin plus arginine stimulation test	3 months DBPC crossover with 3 month washout	0.5–0.6 IU/kg per week	No significant change in isokinetic knee flexion and extension strength

DBPC, double-blind placebo-controlled; Wt, weight; Ht, height; CO, childhood onset; AO, adult onset; GH, growth hormone; GHD, growth hormone deficiency; IGF1, insulin-like growth factor 1; GHRH, growth hormone-releasing hormone; LBM, lean body mass.

muscle regeneration after disuse atrophy (Ye *et al*. 2013). Kim *et al*. (2005) observed a significantly increased muscle mass and stimulation of satellite cells and myofibre hypertrophy in the skeletal muscle of WT mice treated with GH, but these effects were absent in mice that lacked a functioning IGF1 receptor in the skeletal muscle. These studies indicate that the action of GH on muscle growth and strength are mediated via IGF1.

Only a few double-blind placebo-controlled studies have investigated the effect of GH on muscle strength in healthy adults (Yarasheski *et al*. 1992, Deyssig *et al*. 1993, Papadakis *et al*. 1996, Blackman *et al*. 2002, Meinhardt *et al*. 2010). A 6-week GH administration failed to demonstrate any effect on maximal muscle strength in 8 healthy males (Deyssig *et al*. 1993). Similarly, in a study on nearly 100 recreational athletes, muscle strength did not increase after 8-week of GH treatment (Meinhardt *et al*. 2010). GH administration in 16 healthy men combined with resistance exercise did not further enhance muscle strength more than exercise alone after 3 months (Yarasheski *et al*. 1992). Studies on healthy elderly subjects have also failed to observe any increase in muscle strength following 6 months of GH therapy (Papadakis *et al*. 1996, Blackman *et al*. 2002). These studies suggest that short-term GH therapy does not enhance muscle strength in healthy adults; however, the effects of long-term GH treatment are yet to be evaluated in this population.

In summary, GH increases muscle strength by increasing muscle mass in adults with GHD, an effect that is IGF1 mediated. At present, there is no evidence to support a role of GH in the enhancement of contractile function of skeletal muscle.

Conclusion

GH stimulates whole-body anabolism with protein accretion occurring in muscle and extra-muscular tissues. GHD results in a reversible loss of aerobic capacity arising secondarily from impaired cardiopulmonary and haematological status. GH regulates the bioenergetics of muscle that enhance anaerobic performance. GH increases muscle strength by increasing muscle mass without affecting contractile force or fibre composition.

In conclusion, GH is an anabolic hormone, which positively regulates muscle function. The contractile function of skeletal muscle is dependent on muscle size, fibre types and the availability of energy. Muscles utilise different forms of energy to carry out specific function. The effects on skeletal muscle bioenergetics highlight a novel aspect of GH metabolic action that provides a new direction for future research in this field.

Declaration of interest

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

Funding

K K Y H is supported in part by the National Health and Medical Council of Australia. V C is supported by the Princess Alexandra Hospital Research Support Scheme.

References

Abernethy P, Wilson G & Logan P 1995 Strength and power assessment. Issues, controversies and challenges. *Sports Medicine* **19** 401–417. (doi:10.2165/00007256-199519060-00004)

Adams GR 2002 Autocrine and/or paracrine insulin-like growth factor-I activity in skeletal muscle. *Clinical Orthopaedics and Related Research* **403S** S188–S196. (doi:10.1097/00003086-200210001-00022)

Aroniadou-Anderjaska V, Lemon PW & Gilloteaux J 1996 Effects of exogenous growth hormone on skeletal muscle of young female rats. *Tissue & Cell* **28** 719–724. (doi:10.1016/S0040-8166(96)80074-7)

Astrand PO 1976 Quantification of exercise capability and evaluation of physical capacity in man. *Progress in Cardiovascular Diseases* **19** 51–67.

Ayling CM, Moreland BH, Zanelli JM & Schulster D 1989 Human growth hormone treatment of hypophysectomized rats increases the proportion of type-1 fibres in skeletal muscle. *Journal of Endocrinology* **123** 429–435. (doi:10.1677/joe.0.1230429)

Baker JS, McCormick MC & Robergs RA 2010 Interaction among skeletal muscle metabolic energy systems during intense exercise. *Journal of Nutrition and Metabolism* **2010** 905612. (doi:10.1155/2010/905612)

Barroso O, Mazzoni I & Rabin O 2008 Hormone abuse in sports: the antidoping perspective. *Asian Journal of Andrology* **10** 391–402. (doi:10.1111/j.1745-7262.2008.00402.x)

Bell W, Davies JS, Evans WD & Scanlon MF 1999 Strength and its relationship to changes in fat-free mass, total body potassium, total body water and IGF-1 in adults with growth hormone deficiency: effect of treatment with growth hormone. *Annals of Human Biology* **26** 63–78. (doi:10.1080/030144699282985)

Berggren A, Ehrnborg C, Rosen T, Ellegard L, Bengtsson BA & Caidahl K 2005 Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH–insulin-like growth factor I axes. *Journal of Clinical Endocrinology and Metabolism* **90** 3268–3273. (doi:10.1210/jc.2004-1209)

Beshyah SA, Sharp PS, Gelding SV, Halliday D & Johnston DG 1993 Whole-body leucine turnover in adults on conventional treatment for hypopituitarism. *Acta Endocrinologica* **129** 158–164. (doi:10.1530/acta.0.1290158)

Beshyah SA, Freemantle C, Shahi M, Anyaoku V, Merson S, Lynch S, Skinner E, Sharp P, Foale R & Johnston DG 1995 Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. *Clinical Endocrinology* **42** 73–84. (doi:10.1111/j.1365-2265.1995.tb02601.x)

Bigard AX, Lienhard F, Merino D, Serrurier B & Guezennec CY 1994 Effects of growth hormone on rat skeletal muscle after hindlimb suspension. *European Journal of Applied Physiology and Occupational Physiology* **69** 337–343. (doi:10.1007/BF00392040)

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

Binnerts A, Swart GR, Wilson JH, Hoogerbrugge N, Pols HA, Birkenhager JC & Lamberts SW 1992 The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. *Clinical Endocrinology* **37** 79–87. (doi:10.1111/j.1365-2265.1992.tb02287.x)

Birzniece V, Nelson AE & Ho KK 2011 Growth hormone and physical performance. *Trends in Endocrinology and Metabolism* **22** 171–178. (doi:10.1016/j.tem.2011.02.005)

Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD *et al.* 2002 Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *Journal of the American Medical Association* **288** 2282–2292. (doi:10.1001/jama.288.18.2282)

Bollerslev J, Hallen J, Fougner KJ, Jorgensen AP, Kristo C, Fagertun H, Gudmundsen O, Burman P & Schreiner T 2005 Low-dose GH improves exercise capacity in adults with GH deficiency: effects of a 22-month placebo-controlled, crossover trial. *European Journal of Endocrinology* **153** 379–387. (doi:10.1530/eje.1.01971)

Bonora M, Patergnani S, Rimessi A, De Marchi E, Suski JM, Bononi A, Giorgi C, Marchi S, Missiroli S, Poletti F *et al.* 2012 ATP synthesis and storage. *Purinergic Signalling* **8** 343–357. (doi:10.1007/s11302-012-9305-8)

Bottinelli R, Schiaffino S & Reggiani C 1991 Force-velocity relations and myosin heavy chain isoform compositions of skinned fibres from rat skeletal muscle. *Journal of Physiology* **437** 655–672.

Bottinelli R, Narici M, Pellegrino MA, Kayser B, Canepari M, Faglia G & Sartorio A 1997 Contractile properties and fiber type distribution of quadriceps muscles in adults with childhood-onset growth hormone deficiency. *Journal of Clinical Endocrinology and Metabolism* **82** 4133–4138. (doi:10.1210/jc.82.12.4133)

Brooke MH & Kaiser KK 1970 Muscle fiber types: how many and what kind? *Archives of Neurology* **23** 369–379. (doi:10.1001/archneur.1970.00480280083010)

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

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. (doi:10.1177/036354659702500623)

Caidahl K, Eden S & Bengtsson BA 1994 Cardiovascular and renal effects of growth hormone. *Clinical Endocrinology* **40** 393–400. (doi:10.1111/j.1365-2265.1994.tb03937.x)

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. (doi:10.1210/jc.82.9.2985)

Claustres M, Chatelain P & Sultan C 1987 Insulin-like growth factor I stimulates human erythroid colony formation *in vitro*. *Journal of Clinical Endocrinology and Metabolism* **65** 78–82. (doi:10.1210/jcem-65-1-78)

Colao A, Marzullo P, Di Somma C & Lombardi G 2001 Growth hormone and the heart. *Clinical Endocrinology* **54** 137–154. (doi:10.1046/j.1365-2265.2001.01218.x)

Coleman ME, DeMayo F, Yin KC, Lee HM, Geske R, Montgomery C & Schwartz RJ 1995 Myogenic vector expression of insulin-like growth factor I stimulates muscle cell differentiation and myofiber hypertrophy in transgenic mice. *Journal of Biological Chemistry* **270** 12109–12116. (doi:10.1074/jbc.270.20.12109)

Copeland KC & Nair KS 1994 Acute growth hormone effects on amino acid and lipid metabolism. *Journal of Clinical Endocrinology and Metabolism* **78** 1040–1047. (doi:10.1210/jc.78.5.1040)

Cuneo RC, Salomon F, Wiles CM & Sonksen PH 1990 Skeletal muscle performance in adults with growth hormone deficiency. *Hormone Research* **33** (Suppl 4) 55–60. (doi:10.1159/000181585)

Cuneo RC, Salomon F, Wiles CM, Hesp R & Sonksen PH 1991*a* Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. *Journal of Applied Physiology* **70** 688–694.

Cuneo RC, Salomon F, Wiles CM, Hesp R & Sonksen PH 1991*b* Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. *Journal of Applied Physiology* **70** 695–700.

Cuneo RC, Salomon F, Wiles CM, Round JM, Jones D, Hesp R & Sonksen PH 1992 Histology of skeletal muscle in adults with GH deficiency: comparison with normal muscle and response to GH treatment. *Hormone Research* **37** 23–28. (doi:10.1159/000182276)

Danieli Betto D, Zerbato E & Betto R 1986 Type 1, 2A, and 2B myosin heavy chain electrophoretic analysis of rat muscle fibers. *Biochemical and Biophysical Research Communications* **138** 981–987. (doi:10.1016/S0006-291X(86)80592-7)

Daugaard JR, Bramnert M, Manhem P, Endre T, Groop LC, Lofman M & Richter EA 1999 Effect of 6 months of GH treatment on myosin heavy chain composition in GH-deficient patients. *European Journal of Endocrinology* **141** 342–349. (doi:10.1530/eje.0.1410342)

Daughaday WH, Hall K, Raben MS, Salmon WD Jr, van den Brande JL & van Wyk JJ 1972 Somatomedin: proposed designation for sulphation factor. *Nature* **235** 107. (doi:10.1038/235107a0)

Degerblad M, Almkvist O, Grunditz R, Hall K, Kaijser L, Knutsson E, Ringertz H & Thoren M 1990 Physical and psychological capabilities during substitution therapy with recombinant growth hormone in adults with growth hormone deficiency. *Acta Endocrinologica* **123** 185–193. (doi:10.1530/acta.0.1230185)

Deyssig R, Frisch H, Blum WF & Waldhor T 1993 Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. *Acta Endocrinologica* **128** 313–318. (doi:10.1530/acta.0.1280313)

Dubowitz V & Pearse AG 1960 A comparative histochemical study of oxidative enzyme and phosphorylase activity in skeletal muscle. *Zeitschrift für Zellforschung und Mikroskopische Anatomie. Abteilung Histochemie* **2** 105–117. (doi:10.1007/BF00744575)

Everitt AV, Terry V, Phillips MJ, Kerry HM & Shorey CD 1996 Morphometric analysis of gastrocnemius muscle fiber size and fiber proportions in the hypophysectomized rat after prolonged administration of growth hormone or thyroxine. *Growth, Development, and Aging* **60** 85–93.

Florini JR & Ewton DZ 1989 Skeletal muscle fiber types and myosin ATPase activity do not change with age or growth hormone administration. *Journal of Gerontology* **44** B110–B117. (doi:10.1093/geronj/44.5.B110)

Florini JR, Ewton DZ & Coolican SA 1996 Growth hormone and the insulin-like growth factor system in myogenesis. *Endocrine Reviews* **17** 481–517.

Fryburg DA & Barrett EJ 1993 Growth hormone acutely stimulates skeletal muscle but not whole-body protein synthesis in humans. *Metabolism: Clinical and Experimental* **42** 1223–1227. (doi:10.1016/0026-0495(93)90285-V)

Fryburg DA, Gelfand RA & Barrett EJ 1991 Growth hormone acutely stimulates forearm muscle protein synthesis in normal humans. *American Journal of Physiology* **260** E499–E504.

Fukagawa NK, Minaker KL, Rowe JW, Goodman MN, Matthews DE, Bier DM & Young VR 1985 Insulin-mediated reduction of whole body protein breakdown. Dose–response effects on leucine metabolism in postabsorptive men. *Journal of Clinical Investigation* **76** 2306–2311. (doi:10.1172/JCI112240)

Ghanaat F & Tayek JA 2005 Growth hormone administration increases glucose production by preventing the expected decrease in glycogenolysis seen with fasting in healthy volunteers. *Metabolism: Clinical and Experimental* **54** 604–609. (doi:10.1016/j.metabol.2004.12.003)

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. (doi:10.1152/ajpendo.00483.2004)

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

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. (doi:10.1210/jc.2008-1538)

Gravholt CH, Schmitz O, Simonsen L, Bulow J, Christiansen JS & Moller N 1999 Effects of a physiological GH pulse on interstitial glycerol in abdominal and femoral adipose tissue. *American Journal of Physiology* **277** E848–E854.

Green S 1994 A definition and systems view of anaerobic capacity. *European Journal of Applied Physiology and Occupational Physiology* **69** 168–173. (doi:10.1007/BF00609411)

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 & IGF Research* **8** 377–384. (doi:10.1016/S1096-6374(98)80307-9)

Hansen TK, Gravholt CH, ØRskov H, Rasmussen MH, Christiansen JS & Jorgensen JO 2002 Dose dependency of the pharmacokinetics and acute lipolytic actions of growth hormone. *Journal of Clinical Endocrinology and Metabolism* **87** 4691–4698. (doi:10.1210/jc.2002-020563)

Healy ML, Gibney J, Russell-Jones DL, Pentecost C, Croos P, Sonksen PH & Umpleby AM 2003 High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. *Journal of Clinical Endocrinology and Metabolism* **88** 5221–5226. (doi:10.1210/jc.2002-021872)

Healy ML, Gibney J, Pentecost C, Croos P, Russell-Jones DL, Sonksen PH & Umpleby AM 2006 Effects of high-dose growth hormone on glucose and glycerol metabolism at rest and during exercise in endurance-trained athletes. *Journal of Clinical Endocrinology and Metabolism* **91** 320–327. (doi:10.1210/jc.2005-0916)

Hoffman DM, Pallasser R, Duncan M, Nguyen TV & Ho KK 1998 How is whole body protein turnover perturbed in growth hormone-deficient adults? *Journal of Clinical Endocrinology and Metabolism* **83** 4344–4349. (doi:10.1210/jc.83.12.4344)

Holt RI & Sonksen PH 2008 Growth hormone, IGF-I and insulin and their abuse in sport. *British Journal of Pharmacology* **154** 542–556. (doi:10.1038/bjp.2008.99)

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. (doi:10.1172/JCI114694)

Jacob R, Barrett E, Plewe G, Fagin KD & Sherwin RS 1989 Acute effects of insulin-like growth factor I on glucose and amino acid metabolism in the awake fasted rat. Comparison with insulin. *Journal of Clinical Investigation* **83** 1717–1723. (doi:10.1172/JCI114072)

Janssen YJ, Doornbos J & Roelfsema F 1999 Changes in muscle volume, strength, and bioenergetics during recombinant human growth hormone (GH) therapy in adults with GH deficiency. *Journal of Clinical Endocrinology and Metabolism* **84** 279–284. (doi:10.1210/jc.84.1.279)

Johannsson G, Grimby G, Sunnerhagen KS & Bengtsson BA 1997 Two years of growth hormone (GH) treatment increase isometric and isokinetic muscle strength in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* **82** 2877–2884. (doi:10.1210/jc.82.9.2877)

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. (doi:10.1016/S0140-6736(89)92328-3)

Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Moller J, Muller J, Skakkebaek NE & Christiansen JS 1991 Long-term growth hormone treatment in growth hormone deficient adults. *Acta Endocrinologica* **125** 449–453. (doi:10.1530/acta.0.1250449)

Jorgensen JO, Moller J, Alberti KG, Schmitz O, Christiansen JS, Orskov H & Moller N 1993 Marked effects of sustained low growth hormone (GH) levels on day-to-day fuel metabolism: studies in GH-deficient patients and healthy untreated subjects. *Journal of Clinical Endocrinology and Metabolism* **77** 1589–1596. (doi:10.1210/jc.77.6.1589)

Jorgensen JO, Thuesen L, Muller J, Ovesen P, Skakkebaek NE & Christiansen JS 1994 Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. *European Journal of Endocrinology* **130** 224–228. (doi:10.1530/eje.0.1300224)

Jorgensen JO, Vahl N, Hansen TB, Thuesen L, Hagen C & Christiansen JS 1996 Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition. *Clinical Endocrinology* **45** 681–688. (doi:10.1046/j.1365-2265.1996.8720883.x)

Kim H, Barton E, Muja N, Yakar S, Pennisi P & Leroith D 2005 Intact insulin and insulin-like growth factor-I receptor signaling is required for growth hormone effects on skeletal muscle growth and function *in vivo*. *Endocrinology* **146** 1772–1779. (doi:10.1210/en.2004-0906)

Krag MB, Gormsen LC, Guo Z, Christiansen JS, Jensen MD, Nielsen S & Jorgensen JO 2007 Growth hormone-induced insulin resistance is associated with increased intramyocellular triglyceride content but unaltered VLDL-triglyceride kinetics. *American Journal of Physiology. Endocrinology and Metabolism* **292** E920–E927. (doi:10.1152/ajpendo.00374.2006)

Lange KH, Larsson B, Flyvbjerg A, Dall R, Bennekou M, Rasmussen MH, Orskov H & Kjaer M 2002 Acute growth hormone administration causes exaggerated increases in plasma lactate and glycerol during moderate to high intensity bicycling in trained young men. *Journal of Clinical Endocrinology and Metabolism* **87** 4966–4975. (doi:10.1210/jc.2001-011797)

Larsson L, Li X, Teresi A & Salviati G 1994 Effects of thyroid hormone on fast- and slow-twitch skeletal muscles in young and old rats. *Journal of Physiology* **481** 149–161.

Le Roith D, Bondy C, Yakar S, Liu JL & Butler A 2001 The somatomedin hypothesis: 2001. *Endocrine Reviews* **22** 53–74. (doi:10.1210/er.22.1.53)

Liu JP, Baker J, Perkins AS, Robertson EJ & Efstratiadis A 1993 Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). *Cell* **75** 59–72. (doi:10.1016/S0092-8674(05)80084-4)

Liu H, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B, Bendavid E, Saynina O, Salpeter SR, Garber AM *et al*. 2008 Systematic review: the effects of growth hormone on athletic performance. *Annals of Internal Medicine* **148** 747–758. (doi:10.7326/0003-4819-148-10-200805200-00215)

Loughna PT & Bates PC 1994 Interactions between growth hormone and nutrition in hypophysectomised rats: skeletal muscle myosin heavy chain mRNA levels. *Biochemical and Biophysical Research Communications* **198** 97–102. (doi:10.1006/bbrc.1994.1014)

Lucidi P, Laureti S, Santoni S, Lauteri M, Busciantella-Ricci N, Angeletti G, Santeusanio F & De Feo P 2000 Administration of recombinant human growth hormone on alternate days is sufficient to increase whole body protein synthesis and lipolysis in growth hormone deficient adults. *Clinical Endocrinology* **52** 173–179. (doi:10.1046/j.1365-2265.2000.00910.x)

Maison P & Chanson P 2003 Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* **108** 2648–2652. (doi:10.1161/01.CIR.0000100720.01867.1D)

Makimura H, Stanley TL, Sun N, Hrovat MI, Systrom DM & Grinspoon SK 2011 The association of growth hormone parameters with skeletal muscle phosphocreatine recovery in adult men. *Journal of Clinical Endocrinology and Metabolism* **96** 817–823. (doi:10.1210/jc.2010-2264)

Mauras N, O'Brien KO, Welch S, Rini A, Helgeson K, Vieira NE & Yergey AL 2000 Insulin-like growth factor I and growth hormone (GH) treatment in GH-deficient humans: differential effects on protein, glucose, lipid, and calcium metabolism. *Journal of Clinical Endocrinology and Metabolism* **85** 1686–1694. (doi:10.1210/jc.85.4.1686)

Meinhardt U, Nelson AE, Hansen JL, Birzniece V, Clifford D, Leung KC, Graham K & Ho KK 2010 The effects of growth hormone on body

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

composition and physical performance in recreational athletes: a randomized trial. *Annals of Internal Medicine* **152** 568–577. (doi:10.7326/0003-4819-152-9-201005040-00007)

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. (doi:10.1530/eje.0.1350553)

Moller N, Jorgensen JO, Alberti KG, Flyvbjerg A & Schmitz O 1990 Short-term effects of growth hormone on fuel oxidation and regional substrate metabolism in normal man. *Journal of Clinical Endocrinology and Metabolism* **70** 1179–1186. (doi:10.1210/jcem-70-4-1179)

Moller N, Jorgensen JO, Abildgard N, Orskov L, Schmitz O & Christiansen JS 1991 Effects of growth hormone on glucose metabolism. *Hormone Research* **36** (Suppl 1) 32–35.

Moller N, Schmitz O, Porksen N, Moller J & Jorgensen JO 1992 Dose–response studies on the metabolic effects of a growth hormone pulse in humans. *Metabolism: Clinical and Experimental* **41** 172–175. (doi:10.1016/0026-0495(92)90147-3)

Myers J, Prakash M, Froelicher V, Do D, Partington S & Atwood JE 2002 Exercise capacity and mortality among men referred for exercise testing. *New England Journal of Medicine* **346** 793–801. (doi:10.1056/NEJMoa011858)

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. (doi:10.1210/jc.80.2.552)

Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GA, Schambelan M & Grunfeld C 1996 Growth hormone replacement in healthy older men improves body composition but not functional ability. *Annals of Internal Medicine* **124** 708–716. (doi:10.7326/0003-4819-124-8-199604150-00002)

Porter MM, Vandervoort AA & Lexell J 1995 Aging of human muscle: structure, function and adaptability. *Scandinavian Journal of Medicine & Science in Sports* **5** 129–142. (doi:10.1111/j.1600-0838.1995.tb00026.x)

Rodriguez-Arnao J, Jabbar A, Fulcher K, Besser GM & Ross RJ 1999 Effects of growth hormone replacement on physical performance and body composition in GH deficient adults. *Clinical Endocrinology* **51** 53–60. (doi:10.1046/j.1365-2265.1999.00737.x)

Roy RR, Tri C, Grossman EJ, Talmadge RJ, Grindeland RE, Mukku VR & Edgerton VR 1996 IGF-I, growth hormone, and/or exercise effects on non-weight-bearing soleus of hypophysectomized rats. *Journal of Applied Physiology* **81** 302–311.

Russell-Jones DL, Weissberger AJ, Bowes SB, Kelly JM, Thomason M, Umpleby AM, Jones RH & Sonksen PH 1993 Protein metabolism in growth hormone deficiency, and effects of growth hormone replacement therapy. *Acta Endocrinologica* **128** (Suppl 2) 44–47.

Russell-Jones DL, Bowes SB, Rees SE, Jackson NC, Weissberger AJ, Hovorka R, Sonksen PH & Umpleby AM 1998 Effect of growth hormone treatment on postprandial protein metabolism in growth hormone-deficient adults. *American Journal of Physiology* **274** E1050–E1056.

Rutherford OM, Beshyah SA, Schott J, Watkins Y & Johnston DG 1995 Contractile properties of the quadriceps muscle in growth hormone-deficient hypopituitary adults. *Clinical Science* **88** 67–71.

Saltin B & Strange S 1992 Maximal oxygen uptake: "old" and "new" arguments for a cardiovascular limitation. *Medicine and Science in Sports and Exercise* **24** 30–37. (doi:10.1249/00005768-199201000-00007)

Sartorio A & Narici MV 1994 Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size, strength and neural activation. *Clinical Physiology* **14** 527–537. (doi:10.1111/j.1475-097X.1994.tb00411.x)

Schaefer AM, Taylor RW & Turnbull DM 2001 The mitochondrial genome and mitochondrial muscle disorders. *Current Opinion in Pharmacology* **1** 288–293. (doi:10.1016/S1471-4892(01)00051-0)

Shi J, Sekhar RV, Balasubramanyam A, Ellis K, Reeds PJ, Jahoor F & Sharma MD 2003 Short- and long-term effects of growth hormone (GH) replacement on protein metabolism in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* **88** 5827–5833. (doi:10.1210/jc.2002-021943)

Shorey CD, Everitt AV, Armstrong RA & Manning LA 1993 Morphometric analysis of the muscle fibres of the soleus muscle of the ageing rat: long-term effect of hypophysectomy and food restriction. *Gerontology* **39** 80–92. (doi:10.1159/000213518)

Sjogren 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. (doi:10.1152/ajpendo.00054.2007)

Staron RS & Johnson P 1993 Myosin polymorphism and differential expression in adult human skeletal muscle. *Comparative Biochemistry and Physiology. B, Comparative Biochemistry* **106** 463–475. (doi:10.1016/0305-0491(93)90120-T)

Svensson J, Sunnerhagen KS & Johannsson G 2003 Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. *Journal of Clinical Endocrinology and Metabolism* **88** 2061–2069. (doi:10.1210/jc.2002-020901)

Tessari P, Trevisan R, Inchiostro S, Biolo G, Nosadini R, De Kreutzenberg SV, Duner E, Tiengo A & Crepaldi G 1986 Dose–response curves of effects of insulin on leucine kinetics in humans. *American Journal of Physiology* **251** E334–E342.

Tollet-Egnell P, Parini P, Stahlberg N, Lonnstedt I, Lee NH, Rudling M, Flores-Morales A & Norstedt G 2004 Growth hormone-mediated alteration of fuel metabolism in the aged rat as determined from transcript profiles. *Physiological Genomics* **16** 261–267. (doi:10.1152/physiolgenomics.00093.2002)

Ullman M & Oldfors A 1989 Effects of growth hormone on skeletal muscle. I. Studies on normal adult rats. *Acta Physiologica Scandinavica* **135** 531–536. (doi:10.1111/j.1748-1716.1989.tb08612.x)

Vandewalle H, Peres G & Monod H 1987 Standard anaerobic exercise tests. *Sports Medicine* **4** 268–289. (doi:10.2165/00007256-198704040-00004)

Van Praagh E 2007 Anaerobic fitness tests: what are we measuring? *Medicine and Sport Science* **50** 26–45. (doi:10.1159/000101074)

Vihervuori E, Virtanen M, Koistinen H, Koistinen R, Seppala M & Siimes MA 1996 Hemoglobin level is linked to growth hormone-dependent proteins in short children. *Blood* **87** 2075–2081.

Wagenmakers AJ 1999 Tracers to investigate protein and amino acid metabolism in human subjects. *Proceedings of the Nutrition Society* **58** 987–1000. (doi:10.1017/S0029665199001305)

Wallymahmed ME, Foy P, Shaw D, Hutcheon R, Edwards RH & MacFarlane IA 1997 Quality of life, body composition and muscle strength in adult growth hormone deficiency: the influence of growth hormone replacement therapy for up to 3 years. *Clinical Endocrinology* **47** 439–446. (doi:10.1046/j.1365-2265.1997.2801076.x)

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

Whitehead HM, Gilliland JS, Allen IV & Hadden DR 1989 Growth hormone treatment in adults with growth hormone deficiency: effect on muscle fibre size and proportions. *Acta Paediatrica Scandinavica. Supplement* **356** 65–67 discussion 68, 73–64. (doi:10.1111/j.1651-2227.1989.tb11246.x)

Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB & Hadden DR 1992 Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. *Clinical Endocrinology* **36** 45–52. (doi:10.1111/j.1365-2265.1992.tb02901.x)

Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M & Ho KK 2001 Oral estrogen antagonizes the metabolic actions of growth

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.

hormone in growth hormone-deficient women. *American Journal of Physiology. Endocrinology and Metabolism* **281** E1191–E1196.
Woodhouse LJ, Asa SL, Thomas SG & Ezzat S 1999 Measures of submaximal aerobic performance evaluate and predict functional response to growth hormone (GH) treatment in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* **84** 4570–4577. (doi:10.1210/jc.84.12.4570)
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. (doi:10.1210/er.2004-0022)
Yamaguchi A, Sakuma K, Morita I, Soya H, Takeda H & Katsuta S 1996 Changes in fibre types in rat soleus and plantaris muscles following hypophysectomy and compensatory overload. *Acta Physiologica Scandinavica* **158** 89–95. (doi:10.1046/j.1365-201X.1996.532277000.x)
Yarasheski KE, Campbell JA, Smith K, Rennie MJ, Holloszy JO & Bier DM 1992 Effect of growth hormone and resistance exercise on muscle growth in young men. *American Journal of Physiology* **262** E261–E267.
Yarasheski KE, Zachweija JJ, Angelopoulos TJ & Bier DM 1993 Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. *Journal of Applied Physiology* **74** 3073–3076.
Ye F, Mathur S, Liu M, Borst SE, Walter GA, Sweeney HL & Vandenborne K 2013 Overexpression of insulin-like growth factor-1 attenuates skeletal muscle damage and accelerates muscle regeneration and functional recovery after disuse. *Experimental Physiology* **98** 1038–1052. (doi:10.1113/expphysiol.2012.070722)

Received in final form 14 October 2013
Accepted 25 October 2013
Accepted Preprint published online 25 October 2013

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0208

Published by Bioscientifica Ltd.