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

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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

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 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...
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
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 isofrom 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, Aylng 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 (Aylng 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
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). Dagaard 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, Dagaard 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).

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.
(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: OGDH, oxoglutarate dehydrogenase; SDHB, succinate dehydrogenase complex B. Mitochondrial chain: OXA, oxidase; NDU, NADH dehydrogenase; ATPS, ATP synthase.
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. (1991a,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, Gullesstad 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. (1991a,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. 1991a,b, Whitehead et al. 1992, Gullesstad 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. 1991a,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
<table>
<thead>
<tr>
<th>Study</th>
<th>GHD patients</th>
<th>Diagnosis of GHD</th>
<th>Study design</th>
<th>GH dose</th>
<th>Method</th>
<th>Effects of GH</th>
</tr>
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<tbody>
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<td>Jorgensen et al. (1989)</td>
<td>n = 22, CO</td>
<td>Peak GH &lt; 5 µg/l after clonidine stimulation test</td>
<td>4 months DBPC crossover</td>
<td>2 IU/m²</td>
<td>Cycle ergometer</td>
<td>Increase in exercise capacity (kJ) in GH group</td>
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<td></td>
<td>M:F 14:8</td>
<td>23.8 ± 1.2</td>
<td></td>
<td>Median 2.9 IU/m² (1.2–3.8 IU/m²)</td>
<td>Cycle ergometer</td>
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<td>Jorgensen et al. (1991)</td>
<td>n = 13, CO</td>
<td>Peak GH &lt; 5 µg/l after clonidine stimulation test</td>
<td>16 months open label, continuation of the above study</td>
<td>2 IU/m²</td>
<td>Cycle ergometer</td>
<td>Further increase in exercise capacity</td>
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<td></td>
<td>M:F 9:4</td>
<td>24.4 ± 1.7</td>
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<td>Jorgensen et al. (1994)</td>
<td>n = 10, CO</td>
<td>Peak GH &lt; 5 µg/l after clonidine stimulation test</td>
<td>37.6 months open label, continuation of the above study</td>
<td>2 IU/m²</td>
<td>Cycle ergometer</td>
<td>Increase in exercise capacity observed at 16 months was sustained</td>
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<td>M:F 7:3</td>
<td>28.4 ± 2.3</td>
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<td>Cuneo et al. (1991a,b)</td>
<td>n = 24, AO</td>
<td>Peak GH &lt; 3.0 mU/l during insulin-induced hypoglycaemia</td>
<td>0.07 U/kg per day</td>
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<td>Cycle ergometer</td>
<td>Increase in VO₂ max (mL/kg per min) and maximal power output (W) in GH group compared with placebo</td>
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<td></td>
<td>M:F 16:8</td>
<td>39 ± 2</td>
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<td>Jorgensen et al. (1996)</td>
<td>n = 29, AO</td>
<td>Peak GH &lt; 10.0 µg/l during insulin-induced hypoglycaemia</td>
<td>2 IU/m²</td>
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<td>Cycle ergometer</td>
<td>Increase in exercise capacity (kJ) in GH group compared with placebo</td>
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<td></td>
<td>M:F 19:10</td>
<td>45.5 ± 2</td>
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<td>Nass et al. (1995)</td>
<td>n = 20, AO</td>
<td>Peak GH &lt; 2 ng/ml during insulin-induced hypoglycaemia</td>
<td>12.5 µg/kg per day</td>
<td></td>
<td>Cycle ergometer</td>
<td>Increase in VO₂ max (L/min) in GH group from baseline; VO₂ max (mL/min per kg LBM) remained unchanged</td>
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<td>M:F 15:5</td>
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<tr>
<td>Caidahl et al. (1994)</td>
<td>n = 10, AO</td>
<td>Peak GH &lt; 5.0 mU/l during insulin-induced hypoglycaemia</td>
<td>0.5 U/kg per week</td>
<td></td>
<td>Cycle ergometer</td>
<td>No significant difference in maximal power output (W) compared with placebo</td>
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<td>M:F 9:1</td>
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<td>Whitehead et al. (1992)</td>
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<td>0.5 U/kg per week</td>
<td></td>
<td>Cycle ergometer</td>
<td>Increase in exercise capacity (W) and VO₂ max (L/min) in GH group compared with placebo</td>
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<td></td>
<td>M:F 9:5</td>
<td>29.4 ± 2.7</td>
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<td>Rodriguez-Arnao et al. (1999)</td>
<td>n = 35, mixed M:F 18:17</td>
<td>Peak GH &lt; 10.0 mU/l after glucagon or insulin-induced hypoglycaemia</td>
<td>0.125 IU/kg per week for first 4 weeks; thereafter 0.25 IU/kg per week</td>
<td>Treadmill</td>
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<td>DBPC: VO₂ max (mL/kg per min) decreased in placebo and remained unchanged in GH group</td>
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<td></td>
<td></td>
<td>39.8</td>
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<td>Open label: increase in VO₂ max (mL/kg per min) previously placebo treated group but no change in GH group VO₂ max increased by 6 and 9% when expressed in absolute value (L/min) and relative to body weight (mL/kg per min) respectively</td>
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<td>Bollerslev et al. (2005)</td>
<td>n = 55, AO</td>
<td>Peak GH &lt; 3 µg/l to insulin hypoglycaemia (&lt; 2.2 mmol/l)</td>
<td>1.2 IU/day for men, 1.8 IU/day for women</td>
<td></td>
<td>Treadmill</td>
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<td>M:F 31:24</td>
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VO₂ 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 VO₂ 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

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**Table 1 Continued**

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<th>Study</th>
<th>Age (years)</th>
<th>GHD patients</th>
<th>Diagnosis of GHD</th>
<th>Study design</th>
<th>GH dose</th>
<th>Method</th>
<th>VO₂ maxmaximal oxygen uptake: CO, adult onset; GH, growth hormone deficiency; LBM, lean body mass.</th>
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<td>Woodhouse et al (1999)</td>
<td>18–68</td>
<td>n=38, AO M:F 15:13</td>
<td>Peak GH &lt; 3.0 mU/L during insulin-induced hypoglycaemia</td>
<td>3 months DBPC crossover, 1 month washout</td>
<td>6.25-12.5 μg/kg LBM for first month 6.0 μg/kg LBM thereafter</td>
<td>Treadmill</td>
<td>Increase in VO₂ max was significant within the GH group but the change was not significantly different between the two groups.</td>
</tr>
<tr>
<td>Beshyah et al. (1995)</td>
<td>19–67</td>
<td>n=40, mixed M:F 19–21</td>
<td>Peak GH &lt; 6.0 mU/L during insulin-induced hypoglycaemia or oral clonidine</td>
<td>6 months DBPC followed by 12 and 18 months open label</td>
<td>DBPC: 0.02–0.05 IU/kg Open label: 0.05 IU/kg</td>
<td>Treadmill</td>
<td>Exercise time increased within the GH group but the change was not significantly different between the two groups.</td>
</tr>
<tr>
<td>DBPC, double-blind placebo-controlled; VO₂ maxmaximal oxygen uptake: CO, adult onset; GH, growth hormone deficiency; LBM, lean body mass.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**References**

- Green 1994
- Vandewalle et al. 1987
- Cahill et al. 1997
- Van Praagh 2007
- Meinhardt et al. 2010
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 a 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 (cm²) or volume (cm³) 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 compared with those of age- and height-matched controls. 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).
Jorgensen et al. (1998) 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, 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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no.</th>
<th>Mean age (years)</th>
<th>Gender (M:F)</th>
<th>Type</th>
<th>Diagnostic criteria</th>
<th>Control</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson et al. (1997)</td>
<td>56</td>
<td>45 ± 2</td>
<td>35:21</td>
<td>Mixed</td>
<td>Peak GH &lt;1.7 μg/l during insulin-induced hypoglycaemia</td>
<td>Reference population of Goteborg, n = 144, age 40–79 years matched for mean Ht and Wt</td>
<td>Lower isometric muscle strength in quadriceps and hamstring muscles</td>
</tr>
<tr>
<td>Rutherford et al. (1995)</td>
<td>14</td>
<td>41.8 ± 17.3</td>
<td>9:5</td>
<td>Mixed</td>
<td>Peak GH &lt;6.0 mU/l during insulin-induced hypoglycaemia or oral clonidine</td>
<td>14 age- and gender-matched controls</td>
<td>Lower isometric strength</td>
</tr>
<tr>
<td>Janssen et al. (1999)</td>
<td>28</td>
<td>49 ± 2</td>
<td>28:0</td>
<td>Mixed</td>
<td>Peak GH &lt;7.0 mU/l during insulin-induced hypoglycaemia</td>
<td>20 age- and Wt-matched controls</td>
<td>Lower maximal isometric strength</td>
</tr>
<tr>
<td>Cuneo et al. (1990)</td>
<td>24</td>
<td>39 ± 2</td>
<td>16:8</td>
<td>AO</td>
<td>Peak GH &lt;3.0 mU/l during insulin-induced hypoglycaemia</td>
<td>41 age-, gender- and Wt-matched controls</td>
<td>Maximal isokinetic strength tended to be lower (P = 0.06)</td>
</tr>
<tr>
<td>Sartorio &amp; Narici (1994)</td>
<td>8</td>
<td>29.6 ± 3.4</td>
<td>8:0</td>
<td>CO</td>
<td>Peak GH &lt;5.0 ng/ml to GHRH plus galanin and also to l-DOPA plus propranolol</td>
<td>Eight age- and gender-matched controls</td>
<td>Lower quadriceps force/body Wt (N/kg). Lower quadriceps force/quadriceps area (N/cm²)</td>
</tr>
<tr>
<td>Degerblad et al. (1990)</td>
<td>6</td>
<td>29 ± 3</td>
<td>3:3</td>
<td>CO</td>
<td>Peak GH &lt;3.4 μg/l to insulin plus arginine stimulation test</td>
<td>Published normal values</td>
<td>Lower torque at speed of 30/8 and angular position of 45° during knee flexion/extension</td>
</tr>
</tbody>
</table>

Wt, weight; Ht, height; CO, childhood onset; AO, adult onset; N, Newton; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone releasing hormone.
### Table 3 The effects of GH on muscle strength in adults with GHD

<table>
<thead>
<tr>
<th>Study</th>
<th>GHD patients</th>
<th>Diagnosis of GHD</th>
<th>Study design</th>
<th>GH dose</th>
<th>Effects of GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorgensen et al. (1989)</td>
<td>n = 22, M:F 14:8, CO, mean age 23.8 ± 1.2 years</td>
<td>Peak GH &lt; 5 μg/l after clonidine stimulation test</td>
<td>4 months DBPC crossover</td>
<td>2 IU/m²</td>
<td>No significant difference in isometric strength between GH and placebo group</td>
</tr>
<tr>
<td>Jorgensen et al. (1991)</td>
<td>n = 13 M:F 9:4, CO, mean age 24.4 ± 1.7 years</td>
<td>Peak GH &lt; 5 μg/l after clonidine stimulation test</td>
<td>16 months open label, continuation of the above study</td>
<td>Median 2.9 IU/m² (1.2–3.8 IU/m²)</td>
<td>Biometric strength of quadriceps increased compared with placebo, but remained lower than the control group. Increased isometric strength observed at 16 months was sustained</td>
</tr>
<tr>
<td>Jorgensen et al. (1994)</td>
<td>n = 10 M:F 7:3, CO, mean age 28.4 ± 2.3 years</td>
<td>Peak GH &lt; 5 μg/l after clonidine stimulation test</td>
<td>37.6 months open label, continuation of the above study</td>
<td>2 IU/m²</td>
<td>No significant change in isokinetic knee extensor strength, concentric knee extensor strength and left handgrip strength remained unchanged</td>
</tr>
<tr>
<td>Svensson et al. (2003)</td>
<td>n = 109 M:F 61:48, AO, mean age 50 years</td>
<td>Peak GH &lt; 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)</td>
<td>5 years open label</td>
<td>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</td>
<td>10% increase in isometric quadriceps strength</td>
</tr>
<tr>
<td>Sartorio &amp; Narici (1994)</td>
<td>n = 8 M:F 8:0, CO, mean age 29.6 ± 3.4 years</td>
<td>Peak GH &lt; 5 ng/ml during two stimulation tests, GHRH plus galanin and L-DOPA plus propranolol</td>
<td>6 months open label</td>
<td>0.5 IU/kg per week</td>
<td>No significant change in isokinetic knee extensor strength</td>
</tr>
<tr>
<td>Bollerslev et al. (2005)</td>
<td>n = 55 M:F 31:24, AO, mean age 49 years</td>
<td>Peak GH &lt; 3 μg/l to insulin-induced hypoglycaemia</td>
<td>9 months DBPC crossover, 4 months washout</td>
<td>1.2 IU/day for men</td>
<td>No significant change in isokinetic knee extension strength</td>
</tr>
<tr>
<td>Bell et al. (1999)</td>
<td>n = 53 M:F 23:20, mixed age 21–60 years</td>
<td>Peak GH &lt; 5 mg/l during insulin-induced hypoglycaemia or GHRH stimulation test</td>
<td>6 months DBPC followed by 6 months open label</td>
<td>0.125 IU/kg per week for first week; thereafter 0.25 IU/kg per week</td>
<td>DBPC: no significant change in strength</td>
</tr>
<tr>
<td>Woodhouse et al. (1999)</td>
<td>n = 28 M:F 15:13, AO age 18–68 years</td>
<td>Peak GH &lt; 3.0 μg/l during insulin-induced hypoglycaemia</td>
<td>3 months DBPC crossover, 1 month washout</td>
<td>6.25 μg/kg LBM for first month</td>
<td>DBPC: no significant change in maximal voluntary strength in any muscle group</td>
</tr>
<tr>
<td>Beshyah et al. (1995)</td>
<td>n = 40 M:F 19:21, mixed age 19–67 years</td>
<td>Peak GH &lt; 6.0 μU/l during insulin-induced hypoglycaemia or oral clonidine</td>
<td>6 months DBPC followed by 12 and 18 months open label</td>
<td>DBPC: 0.02–0.05</td>
<td>Open label: 0.05 IU/kg IU/kg</td>
</tr>
<tr>
<td>Rutherford et al. (1995)</td>
<td>n = 6 M:F 3:3, mixed mean age 41.8 ± 17.3 years</td>
<td>Peak GH &lt; 6.0 μU/l during insulin-induced hypoglycaemia or oral clonidine</td>
<td>6–24 months open label</td>
<td>0.04 ± 0.01 IU/kg per day</td>
<td>Significant increase in maximal voluntary isometric strength</td>
</tr>
<tr>
<td>Study</td>
<td>GHD patients</td>
<td>Diagnosis of GHD</td>
<td>Study design</td>
<td>GH dose</td>
<td>Effects of GH</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wallymahmed et al. (1997)</td>
<td>n = 30 M:F 10:20, mixed age ~ 35 years</td>
<td>Peak GH &lt; 10.0 mU/l after glucagon or insulin-induced hypoglycaemia</td>
<td>6 months DBPC followed by 6 months open label (n = 12)</td>
<td>0.125 U/kg per week for first month; thereafter 0.25 U/kg per week</td>
<td>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</td>
</tr>
<tr>
<td>Jorgensen et al. (1996)</td>
<td>n = 29 M:F 19:10, AO, mean age 45.5 ± 2 years</td>
<td>Peak GH &lt; 10.0 μg/l during insulin-induced hypoglycaemia</td>
<td>12 months DBPC</td>
<td>2 IU/m²</td>
<td>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)</td>
</tr>
<tr>
<td>Cuneo et al. (1991a,b)</td>
<td>n = 24 M:F 16:8, AO, mean age 39 ± 2 years</td>
<td>Peak GH &lt; 3.0 mU/l during insulin-induced hypoglycaemia</td>
<td>6 months DBPC</td>
<td>0.07 U/kg per day</td>
<td>Increase in strength of only one (hip flexion) out of nine muscle groups</td>
</tr>
<tr>
<td>Janssen et al. (1999)</td>
<td>n = 28 M:F 28:0, mixed mean age 49 ± 2 years</td>
<td>Peak GH &lt; 7.0 μU/l during insulin-induced hypoglycaemia</td>
<td>12 months open label</td>
<td>First 24 week, 0.6, 1.2 or 1.8 U and thereafter individualized dosing to normalize IGF1</td>
<td>Significant increase in isokinetic muscle strength</td>
</tr>
<tr>
<td>Johannsson et al. (1997)</td>
<td>n = 56 M:F 35:21, mixed mean age 45 ± 2 years</td>
<td>Peak GH &lt; 1.7 μg/l during insulin-induced hypoglycaemia</td>
<td>2 years open label</td>
<td>Individualized according to IGF1 level. Mean GH dose 0.62 ± 0.03 mg/day</td>
<td>Significant increase in isometric knee extension and flexion strength</td>
</tr>
<tr>
<td>Rodriguez-Arnao et al. (1999)</td>
<td>n = 35 M:F 18:17, mixed mean age 39.8 years</td>
<td>Peak GH &lt; 10.0 μU/l after glucagon or insulin-induced hypoglycaemia</td>
<td>6 months DBPC followed by 6 months open label</td>
<td>0.125 IU/kg per week for first 4 weeks; thereafter 0.25 IU/kg per week</td>
<td>Significant increase in isokinetic knee extension strength at angular velocity of π/3 rad/s Significant increase in isokinetic knee flexion strength at angular velocity of π/3 rad/s and π rad/s</td>
</tr>
<tr>
<td>Whitehead et al. (1992)</td>
<td>n = 14 M:F 9:5, AO, mean age 29.4 ± 2.7 years</td>
<td>Peak GH &lt; 7.0 mU/l during insulin-induced hypoglycaemia</td>
<td>6 months DBPC crossover with 1 month washout</td>
<td>0.5 IU/kg per week</td>
<td>No change in handgrip strength</td>
</tr>
<tr>
<td>Degerblad et al. (1990)</td>
<td>n = 6 M:F 3:3, CO, mean age 29 ± 3 years</td>
<td>Peak GH &lt; 3.4 μU/l during insulin plus arginine stimulation test</td>
<td>3 months DBPC crossover with 3 month washout</td>
<td>0.5–0.6 IU/kg per week</td>
<td>No significant change in isokinetic knee flexion and extension strength</td>
</tr>
</tbody>
</table>

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.

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