REVIEW PAPERS

Impact of growth hormone on physical performance

Wpływ hormonu wzrostu na sprawność fizyczną

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- growth hormone
- physical performance
- muscle strength
- sport

ABSTRACT

Growth hormone (GH) is an anabolic hormone produced by the pituitary gland. The action of growth hormone is not only to promote growth in children, but it has a significant effect on metabolism and body composition also in adults. Growth hormone deficiency (GHD) leads to physical impairment (worsening muscle strength and aerobic and anaerobic capacity) and altered body composition – with increased fat and reduced lean body mass, particularly reduced skeletal muscle mass. On the other hand, GH excess in patients with acromegaly impairs physical function, especially aerobic capacity and muscle strength irrespective of GH-dependent muscle hypertrophy. There is unclear data about GH's impact on physical performance among healthy populations. Some studies showed improvement in anaerobic capacity during recombinant human GH (rh-GH) administration, others showed no significant difference. Muscle strength did not improve after rh-GH administration among healthy adults. However, recombinant GH is abused by professional and recreational athletes to improve their physical performance.

SŁOWA KLUCZOWE:

- hormon wzrostu
- sprawność fizyczna
- siła mięśniowa
- sport

STRESZCZENIE

Hormon wzrostu jest hormonem anabolicznym produkowanym przez przysadkę. Działanie hormonu wzrostu nie ogranicza się do promowania wzrastania u dzieci, ale ma istotny wpływ na metabolizm i skład ciała również u osób dorosłych. Niedobór hormonu wzrostu prowadzi do pogorszenia sprawności fizycznej, zmienionej kompozycji ciała ze wzrostem tkanki tłuszczowej i redukcją w zakresie tzw. masy beztłuszczowej (LBM), w szczególności tkanki mięśniowej. Z drugiej strony, nadmiar hormonu wzrostu u pacjentów z akromegalią również pogarsza sprawność fizyczną, szczególnie przez zmniejszenie wydolności tlenowej oraz siły mięśniowej, pomimo ich przerostu pod wpływem GH. Wyniki badań na temat wpływu hormonu wzrostu na wydolność fizyczną u zdrowych osób są niejednoznaczne. Niektóre badania wykazały wzrost anaerobowej wydolności fizycznej podczas suplementacji rekombinowanego hormonu wzrostu (rh-GH), natomiast inne nie wykazały istotnej różnicy w tym zakresie. Nie odnotowano wzrostu siły mięśniowej wśród zdrowej populacji w trakcie stosowania rh-GH. Mimo to, rekombinowany hormon wzrostu jest nadużywany w formie dopingu przez zawodowych sportowców oraz amatorów w celu poprawy osiągnięć sportowych.

Introduction

The importance of the pituitary gland in relation to physical development was first discovered in the 19th century, but the treatment with growth hormone (GH) itself among children with growth deficiency was available from the late 1950s. In the beginning, GH was extracted from human pituitary glands. The first recombinant human GH (rh-GH) was introduced for therapy in the United States in 1985 (1). GH is a polypeptide hormone produced periodically by the pituitary somatotroph cells in response to sleep, exercise, stress, and fasting. It is responsible for growth regulation among children but also has multiple effects on metabolism, muscles, and bones during adulthood (2, 3). Both excess and deficiency in GH can lead to disorders. Acromegaly is a rare condition caused by a GH-secreting pituitary adenoma. Excess

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in GH results in an overgrowth of organs (e.g., heart, liver) and bones especially in the face, hands and feet associated with soft-tissue swelling. It could be complicated by multiple comorbidities such as diabetes, hypertension, arthralgias, heart failure, and increased mortality (4). Growth hormone deficiency (GHD) is an impairment of GH secretion mostly inherited in children and acquired in adults. It could be caused by pituitary and hypothalamic tumors, inflammatory lesions, or pituitary apoplexy or it could develop after neurosurgery performed in the sella turcica area (5). GHD results in abnormal body composition, osteopenia, and increased prevalence of cardiovascular risk factors(6). Due to studies performed among patients with GHD treated with rhGH, it is known that GH has an impact on muscle strength and exercise capacity (6). Because of this fact, GH is widely abused among professional and recreational exercisers (7), even though this effect is not clear among healthy adults. This paper reviews the effect of growth hormone on physical performance, muscle strength, metabolism, and body composition in both healthy adults and patients with either deficiency or excess of GH.

GH influence on metabolism and body composition

GH promotes anaerobic metabolism in skeletal muscles by downregulating genes responsible for oxidative mitochondrial energy production (8, 9). One study revealed increased plasma lactate levels among trained cyclists using GH compared with the placebo group (10). GH stimulates lipolysis and therefore usage of fatty acids for energy production (11). This effect together with a reduction in proteolysis and an increase in protein synthesis leads to a change in body composition (12, 13). In a study by Healy et al., when rhGH was administered during exercise to endurance-trained male athletes, there was less protein oxidation compared to exercise alone (14). Growth hormone had an anabolic effect on whole body protein at rest, during and after exercise. These anabolic effects of GH are observed in adults with GHD as well as in healthy adults (15). However, other investigators showed that although GH induced muscle protein synthesis in untrained men, this effect was not demonstrable in highly trained weight lifters (16). This may be caused by time-dependent changes in protein metabolism. The studies among GHD patients revealed that the anabolic effect was strongest during the first 6 months of therapy. After that time lean body mass (LBM) began to plateau and protein metabolism was set on a new stable level (17).

All of these processes affect body composition in patients with GHD and healthy individuals (7). Growth hormone increases LBM and decreases fat mass. This effect might be greater in recreational athletes than in a non-exercised group (18). What's important, this LBM extension is mostly caused by the expansion of the extracellular water (ECW) volume which is associated with anti-natriuretic properties of GH (19). That can explain the increased proportion of LBM to fat body mass (FBM), as well as oedema and hypertension in patients with GH excess (acromegaly) (20).

GH influence on muscle and strength

Muscle strength depends on muscle size, types, and quality of fibers (21). There are two types of muscle fibers. Type I fibers, also known as slow twitch fibers, rely on aerobic pathways for energy production and are responsible for endurance training. Type II fibers, also known as fast twitch fibers, produce energy from anaerobic pathways and are used for high-intensity exercises such as weight lifting or sprinting and are the ones responsible for muscle strength (8). GH acts indirectly on muscle composition through insulin-like-growth factor-1 (IGF-1) which is produced in the liver (3, 22). It stimulates the formation of new myofibers but does not have an impact on the number and relation between type I and II fibers (23, 24). There is an assumption that the impact of GH on strength depends on muscle size, not myofibers type.

Muscle strength is significantly reduced in patients with GHD (25). Results from the studies prove that this reduction arises from less muscle mass, not from a change in fiber type nor contractile function (26, 27). Strength improves in patients with GHD after receiving rhGH by an increase in muscle mass. Improvement depends on the length of treatment. After 6-months therapy, there was no significant change in force, but over 12 months of treatment, there was an improvement of up to 10% (28, 29). The increase in strength during GH substitution in patients with GHD is associated with a degree of reduction in muscle size and muscle fiber area during deficiency, which improves during treatment.

On the other hand, muscular weakness is one of the factors that might decrease the quality of life among patients with acromegaly (30). However, the results of the studies are conflicting. Some of them showed that those patients had decreased hand grip (strength) (30, 31) or revealed an increase in proximal muscle weakness (31), whereas others showed normal or moderately increased proximal muscle strength that decreased after biochemical improvement and remission of acromegaly (30). Excessive GH secretion and action, directly and indirectly, leads to structural and functional changes in muscle tissue. Amongst them are hypertrophy, which is mentioned in several studies but not all, an increase in intramuscular fat content and insulin resistance, and impaired insulin-stimulated glucose uptake in skeletal muscle (32). In conclusion, it seems that muscles in a course of acromegaly might be weaker despite their bigger mass.

Another question is whether GH affects muscle strength among healthy adults. One study of nearly 100 recreational athletes demonstrated that muscle strength did not improve after 8 weeks of rhGH treatment (18). Another trial performed for 6 months among elderly men and women also failed to show any difference in muscle strength but rhGH treatment improved body composition by reducing fat mass (33, 34). The same results were revealed in a meta-analysis of placebo-controlled trials among healthy young adults (35). In summary, the data do not show notable enhancement in muscle strength in the healthy population.

Growth hormone not only influences muscles but also could be an important factor in building connective tissue. It was shown that GH stimulated collagen synthesis in skeletal muscle and tendon (36). What is more, IGF-1 can improve tendon healing because of its properties to induce cell proliferation and collagen synthesis which is the main component of tendon tissue (37). This knowledge could translate into using GH in rehabilitation programs.

Physical performance

Physical performance refers to the ability of an individual to perform physical tasks or activities. It is a state of health and well-being. It can refer to the motor skills of the whole body when considering speed, stamina, strength, agility,

flexibility, and coordination. However, in relation to diseases or functional limitations, physical fitness is perceived rather as the ability to cope with everyday activities such as walking, climbing stairs, or shopping (38).

Aerobic and anaerobic capacity are two different measures of physical fitness and performance. Aerobic capacity refers to the body's ability to take in, transport, and use of oxygen during exercise. Aerobic exercise, also known as cardiovascular or endurance exercise, is characterized by moderate intensity and sustained activity over an extended period of time. Anaerobic capacity, on the other hand, refers to the body's ability to perform high-intensity exercise without using oxygen.

There is contradictory data about improvement in aerobic capacity in GHD patients after GH supplementation. Some trials showed that GH has a positive influence on aerobic capacity (VO2 max) in patients with GHD. In those studies, the reduction in VO2 max in GHD patients was about 30% in comparison to their predicted values (39, 40). In the same studies after 6 months of supplementation with GH the value of VO2 max nearly normalized. Other trials revealed improvement in aerobic capacity in the time range of 4 to 12 months (41-44). Meta-analysis of 11 randomized placebo-controlled trials showed that the degree of improvement in aerobic capacity is not dependent on the dose of rhGH (45). This effect is not associated with a change in the proportion of muscle fibers with increases in type I fibers as was mentioned before. It is known that an increase in muscle mass during GH replacement in GHD patients is related to an increase in oxygen delivery to muscles and oxygen uptake and that could improve aerobic capacity during exercises (46, 47). This thesis was taken under investigation in a trial that concluded that GH treatment alone without exercise programs will not enhance functional capacity of muscles (48).

Some studies showed that GH treatment did not significantly improve VO2 max in GHD patients, but enhanced anaerobic capacity resulting in an upgrade in quality of life (49, 50). There was a notable advancement in daily-living-like tests such as the stair climb test, the chair stand test, and the average daily step count which resulted in improvement in physical function. As noticed in trials, anaerobic metabolism is the one that plays a great role in initializing movement before aerobic metabolism becomes the predominant energy source (51). That includes activities of daily living and high-intensity physical activity such as sprinting and weight lifting

Unlike GHD patients, healthy recreational athletes did not have any advantage in aerobic capacity during rhGH use (52). Even a high dose of rhGH did not enhance aerobic exercise capacity (53). What is more, GH coadministration with testosterone also failed to increase VO2 max in healthy men (18).

Data about rhGH's impact on anaerobic capacity among healthy adults is limited. There is only one trial among the healthy population that revealed that sprint capacity was improved by about 4% and that effect was no longer detected 6 weeks after rhGH discontinuation. It was speculated that this increase in sprint capacity could translate to an improvement of 0.4 s in a 10-s sprint over 100 m (18).

On the other hand, GH excess leads to worsening in both aerobic and anaerobic capacity as was shown in acromegaly patients. Further, the ventilation threshold, which is a measure of submaximal aerobic capacity, has improved after a reduction in IGF-1 level by treatment with octreotide in patients with acromegaly (54). In another study, it was proved that the anaerobic threshold also improved after such treatment (55).

Table 1. shows comparison of the effect of growth hormone on physical performance and body composition in the groups of patients discussed in the article.

Table 1. Impact of growth hormone on body composition and physical performance in GHD patients before and during GH supplementation, in healthy adults after GH administration and in patients with acromegaly (7, 15, 18, 20, 25, 28-31, 33-35, 39-44, 46-54).

	GHD patients before GH treatment	GHD patients during GH supplementation	GH administration to healthy adults	GH excess (acromegaly)
Fat mass	↑	↓	↓	↓
Lean body mass (LBM)	↓	↑	↑	↑
Muscle strength	↓	↑	↔	↓/↔
Aerobic capacity	↓	↑/↔	↔	↓
Anaerobic Capacity	↓	↑	↑/↔	↓

Even though those reports among the healthy population were not confirmed in other trials, the possibility of enhancement in sports performance during the use of rhGH is the cause of its abuse in sports.

Is GH an elixir of youth?

It is known that the secretion of GH declines with age which is called somatopause (56). Because of possible improvement in physical condition and body composition, rhGH administration is seen as a potential elixir of youth. There are a couple of studies among elderly people with GH deficiency. Although the substitution with rhGH did not improve muscle strength and physical capacity, it had a positive effect on LBM (32, 56). Nevertheless, adverse effects such as carpal tunnel syndrome, gynecomastia, and hyperglycemia were frequent, especially when supraphysiological doses of rhGH were used (57). Side effects exceeded benefits from improvement in LBM. It seems that usage of rhGH among older patients in the case of physical fitness improvement is pointless.

Growth hormone abuse in sport

The knowledge that GH could possibly enhance physical fitness, especially anaerobic capacity, and shorten recovery after injury leads to rhGH abuse in sport although the accessible data about its impact on healthy populations is ambiguous. One of the limitations of such research is that the dose of rhGH used in these trials may differ from the one used by athletes (58). They use supraphysiological doses that are likely ten or more times greater than

typical replacement doses. There are anecdotal reports on increases in muscle mass among bodybuilders who abuse GH (58). What is undeniable is that excess of GH could be damaging to health. Growth hormone excess caused by overtreatment with rhGH generates side effects similar to the clinical signs and symptoms observed in acromegaly. They include metabolic complications such as diabetes or cardiovascular and cerebrovascular disease with hypertension and cardiomyopathy which could even lead to sudden heart failure (4, 57).

The problem of GH abuse in sports has increased since the availability of recombinant GH in the late 1980s. GH is listed in the Prohibited List published by WADA (World Anti-Doping Agency). An exogenous GH is almost the same as the one produced in the pituitary gland and its half-life is short which makes it difficult to detect (7). In recent years, new research has been started to find novel biomarkers in the detection of GH such as fibronectin (59). GH is rarely used alone, usually, it is combined with other doping substances for example androgens and erythropoietin which potentialize an increase in LBM and physical capacity (18, 33, 58), but also increases the risk of side effects.

Conclusions

Growth hormone has an undoubtful anabolic effect and positive impact on lean body mass, whereas its efficacy in the enhancement of athletic performance among healthy adults is unproven. Physical function is impaired in growth hormone deficiency (GHD) and also in growth hormone excess (acromegaly). This suggests that growth hormone influences physical capacity, but a narrow GH/IGF-1 concentration range is required to maintain optimal physical function. Further research is needed to fully acknowledge the impact of GH on physical capacity, with a special focus on possible changes in physical performance parameters during rhGH substitution in GHD patients as well as in the course of acromegaly treatment.

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