The consequences of growth hormone deficiency in adults

Skutki niedoboru hormonu wzrostu u dorosłych

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• growth hormone deficiency
• recombinant human growth hormone

Abstract
Adult growth hormone deficiency (GHD) is a result of the decreased growth hormone (GH) production and secretion from the anterior pituitary gland in adulthood, that cannot be explained by the physiological aging process. GHD is associated with numerous deleterious consequences such as adverse changes in body composition, carbohydrate and lipid metabolism, alterations in the cardiovascular system, and deterioration in the quality of life (QoL). Most of these complications are at least partially reversible during recombinant human growth hormone (rhGH) replacement therapy. Thus, physicians and particularly endocrinologists, should consider GHD diagnosis and select patients who could benefit from rhGH therapy.

Słowa kluczowe:
• niedobór hormonu wzrostu
• rekombinowany ludzki hormon wzrostu

Streszczenie
Niedobór hormonu wzrostu (GHD) u dorosłych jest skutkiem spadku produkcji i sekrecji tego hormonu przez komórki somatotropowe przedniego płata przysadki, który nie wynika z fiziologicznego procesu starzenia. Konsekwencjami GHD są: niekorzystna zmiana składu ciała, zaburzenia metabolizmu węglowodanów i lipidów, powikłania dotyczące układu sercowo-naczyniowego oraz upośledzona jakość życia. Wiele z tych następstw może być, przy najmniej częściowo odwraconych podczas leczenia rekombinowanym ludzkim hormonem wzrostu (rhGH). Dlatego lekarze wielu specjalności, w szczególności endokrynologowie powinni diagnozować pacjentów z podejrzeniem GHD, a w przypadku potwierdzenia diagnozy rozważyć substytucję rhGH.

Introduction
Growth hormone (GH) is produced and secreted by somatotroph cells of the anterior pituitary gland, and it influences synthesis of the insulin-like growth factor 1 (IGF-1) by the liver and other tissues. Subsequently, GH directly and indirectly (by IGF-1 action) exerts numerous effects on organs and tissues, leading to an increase in linear bone growth in childhood, regulation of protein, lipid, and carbohydrate metabolism, and stimulation and preservation of peak bone mass both in children and adults (1-3). Growth hormone deficiency (GHD) can arise at any age. Depending on the age of onset, patients present different signs and symptoms. Thus, two populations of patients with GHD can be distinguished: with adult-onset GHD (AO-GHD) or childhood-onset GHD (CO-GHD) (1-3). Childhood-onset GHD can be characterized by growth impairment, short stature, and craniofacial deformities, accompanied by the complications that are typical also for AO-GHD. In patients with AO-GHD metabolic disorders dominate and alterations in body composition are common, with an increase in total fat and visceral fat mass, as well as a reduction in lean body and bone mass. In the adult population only severe GHD is a well-defined clinical entity as opposed to partial GHD, which is used only in children (2).

Long-lasting severe GHD in the adult population may lead to an increased risk of cardiovascular events, osteoporotic bone fractures and decreased quality of life (2-4). The transition period between the completion of linear bone growth and the acquisition of peak bone mass seems to be especially vulnerable and untreated GHD could negatively impacts not only bones but also other physiological processes (5). It should be emphasized that an adult patient can be diagnosed with adult-onset GHD as well as childhood-onset GHD. CO-GHD affects developmental years and adult patients with CO-GHD might have experienced longer periods of GH deficiency than individuals with AO-GHD.
GHD should be suspected when a patient presents with a history of hypothalamic-pituitary disease. The most common cause of GHD in children is an isolated idiopathic GHD, while in adults more often there are the tumors of the hypothalamic and pituitary region and their treatment (surgery or radiotherapy). Nontumoral aetiology such as traumatic brain injury, subarachnoid haemorrhage, ischemic stroke, and central nervous system infections are other, less common causes of GHD.

Growth hormone obtained from human pituitary glands was first discovered in the 1950s in California and Massachusetts and by 1985 it was widely used in North America. In 1985 the Food and Drug Administration suspended the use of pituitary GH in the United Stated due to cases of Creuzfeldt Jacob disease in patients treated with pituitary GH. This led to prompt approval of synthetic methionyl GH, which is used to this day as somatropin. Its use in the treatment of GHD adults was approved in 1996 (6). For a long time in Poland it was commonly used only in children due to the lack of reimbursement for adult patients. Finally, in 2020 the program of severe adult GHD treatment was initiated in Poland granting wider access to recombinant human growth hormone (rhGH) therapy. Moreover, adults with Prader-Willi’s syndrome who received rhGH as a children could be treated with rhGH due to already existing reimbursement program. Current recommendations do not support rhGH therapy in adults in other disease entities.

Adult populations at risk of growth hormone deficiency

The exact number of patients with GHD is difficult to calculate, though it is estimated that 2-3 per 10,000 are affected (7, 8). Adult GHD occurs at an annual incidence of 12-19 cases per million (9, 10). However, precise data for the Polish population is lacking.

It is crucial to recognize groups of patients who are at risk of developing GHD. Pituitary adenomas ablate surgical interventions or radiotherapy of the sellar region are the most common causes of AO-GHD. Young adults with a history of rhGH replacement treatment in childhood can also suffer from GHD later in life. It may also occur as a result of primary hypophysitis or pituitary infarctions secondary to systemic inflammatory diseases. Examples may include sarcoidosis, lupus erythematosus and Langerhans cell histiocytosis. The somatotropic axis is the first to be affected after cranial or total body radiotherapy since it is the most susceptible to radiation damage. Multiple pituitary axis deficiencies might also become more common due to the complications of more widespread use of immunotherapy that may induce hypophysitis (11). GHD may arise due to traumatic brain injury or subarachnoid hemorrhage. Approximately 16% of GHD cases are diagnosed as idiopathic (12). The proportions of AO-GHD and CO-GHD differ among medical centers, and it depends on local referral practice; however, about 27% of adult patients are diagnosed with CO-GHD (10, 13).

Diagnosis of GHD

It is important to establish the diagnosis of GHD if it is suspected based on medical history of pituitary disease or signs and symptoms of GH deficiency, before initiating rhGH treatment. Complete anterior pituitary function should be assessed. Confirmed dysfunction of three or more pituitary axes together with decreased IGF-1 concentration (below the normal range for age and sex) is sufficient for GHD diagnosis. If those conditions are not fulfilled, then a GH stimulation testing should be performed. Provocative tests are necessary because basal GH levels might be low also in healthy individuals due to its pulsatile pattern of secretion. On the other hand, IGF-1 levels might be within normal range in about 20% of adults with GHD, especially males (3, 12). It is imperative to provide adequate hormonal substitution of other axes such as hydrocortisone and levothyroxine replacement before performing the dynamic tests. The insulin-induced hypoglycaemia is considered to be the gold standard test, as it provides the most reliable stimulus of GH secretion. Other options are stimulation testing with glucose, macimorelin, or GH-releasing hormone and arginine (1-3, 14). Only patients who meet the criteria of severe GHD (with GH cut off in most stimulation tests <3 ug/dl) can be qualified for rhGH treatment (2).

Patients with isolated CO-GHD who have been treated with rhGH during childhood should be retested as adults with two stimulation tests before decision of continuing rhGH replacement, as many of those patients might not require such treatment later in life.

Furthermore, stimulation tests allow to distinguish between severe GHD and age-related reduction in GH secretion, thus allowing to identify and treat elderly patients with severe GHD according to the general criteria (15).

Clinical features of GHD

GHD in adults causes many unspecific signs and symptoms such as depressed mood, anxiety, fatigue, decreased muscle strength, increased fat mass especially visceral fat, thinning of hair on the scalp, decreased sweating, and reduced energy level. In patients with hypopituitarism the quality of life is decreased if they are not treated with rhGH, despite adequate substitution of other hormones (2, 3). Exercise capacity is significantly reduced due to adverse effect on heart muscle. GHD may lead to impaired left ventricular systolic function and increased risk of cardiovascular disease (16). Thus, in some patients signs of heart failure might coexist. These symptoms significantly impair patient quality of life and worsen long-term prognosis (17).

Body composition and metabolism

GHD leads to adverse changes in body composition such as increased body fat mass, particularly visceral fat, and decreased lean body mass, including muscle mass, together with the impaired muscle strength. GH directly antagonizes the effects of insulin and indirectly exerts insulin-like effects mediated by IGF-1. Adult GHD patients have on average 7-10% higher total body fat than general population, with android type obesity predomination, which may lead to insulin resistance (2, 18). The influence of GH on carbohydrate metabolism is complex. Short-term treatment with GH may exacerbate insulin resistance in the peripheral tissues, including skeletal muscles (19). In long-term therapy the beneficial reduction of visceral fat mass predominates, partially reversing the cardio-metabolic disturbances (2, 19). Numerous studies have shown significant improvement in body...
Virtually all patients undergoing rhGH replacement therapy manifest a marked subjective improvement in QoL during the first 6-12 months of treatment. However, this effect wanes over time. Studies that have followed up patients for 5-10 years show that improvements in QoL are maintained within the normal range for age and sex (38). The beneficial effects of rhGH and normalization of QoL are maintained over several years of therapy.

Bone metabolism

GH and IGF-1 regulate bone remodelling by increasing bone mineral content (BMC) and bone mineral density (BMD), which can be demonstrated by dual-energy x-ray absorptiometry (DXA). Patients with GHD suffer from decreased bone turnover as measured by bone biomarkers and shown in histomorphometric analyses. In childhood GHD leads to growth impairment and later in life it may prevent adults from acquiring peak bone mass and increase the risk of osteoporosis. Thus, adult GHD patients have an increased fracture risk and subsequently increased mortality. The prevalence of fractures is 2-7.4 times higher than in a normal population (23). Particularly, the risk of vertebral fractures (VF) is increased in patients with GHD. Symptomatic VFs occur in over 30% of patients with AO-GHD, even those with normal BMD (24). The risk might be exacerbated by overtreatment of coexistent hypoadrenalism and hyperthyroidism (1, 3, 25). Furthermore, BMD measured by DXA may provide unreliable and underestimated results, since CO-GHD patients have a smaller bone size and volume and altered bone composition with reduced muscle mass (26, 27). Assessment of bone microarchitecture might be useful in those patients, so a high-resolution peripheral quantitative computed tomography (HR-pQCT) at the distal radius and tibia might be performed. However, that method is not commonly accessible, and the trabecular bone score (TBS) remains a reasonable and more available alternative that enables better fracture risk prediction.

Therapy with rhGH not only improves body composition, but also bone metabolism and it reduces fracture risk, especially VF risk. Bone resorption predominates in the first 6-12 months of treatment, leading to an initial decrease in BMD, followed by its increase after 12 months of continuous rhGH replacement when bone formation prevails (28, 29). As mentioned before, long-term effects of rhGH treatment have also been studied. The beneficial effects were observed with a sustained increase in total body and lumbar spine BMC and BMD, without a significant change in the femoral neck (30, 31). Most studies showed that rhGH therapy in patients suffering from GHD decreased the risk of vertebral and non-vertebral fractures (32, 33).

Cardiovascular risk

Adverse changes in lipoprotein and carbohydrate metabolism, altered body composition and increased vascular resistance contribute to atherosclerosis in GHD. Both GH and IGF-1 play crucial roles in the regulation of vascular tone, endothelial and cardiac function (47). GHD promotes the formation and progression of atherosclerosis through disrupting nitric oxide secretion. Nitric oxide protects the endothelium, inhibits the proliferation and migration of smooth muscle cells, reduces LDL-C oxidation, inhibits platelet activation (48-50) and favors angiogenesis and vascular repair (51). Thus, in GHD patients all those processes are disrupted. Furthermore, GH decreases sympathetic activity and vascular resistance through its peripheral action (48). Numerous studies have shown that long-term rhGH

Quality of life

Adult patients with GHD have impaired quality of life compared to general population. They often complain about the lack of energy and motivation, fatigue, anxiety, impaired self-care, decreased emotional and cognitive functions, social isolation, weight gain, and other disease-specific and unspecific signs and symptoms, which can be measured by numerous quality of life (QoL) indices (34). Diminished cognitive performance can be explained by the direct effects of GH and IGF-1 on the brain (35). It has been proven that rhGH therapy can improve QoL in GHD and even older patients can reach the QoL of the general population in 2 years of therapy. Moreover, psychological benefits may also impact positively the cardiovascular risk through stress reduction and improvement of general well-being and compliance (36, 37). The positive effects of rhGH and normalization of QoL are maintained over several years of therapy (38).

Carbohydrate metabolism, lipid profile, inflammatory markers

GHD is associated with an atherogenic lipid profile with increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and apolipoprotein B levels, together with reduced high-density lipoproteins cholesterol (HDL-C) (7, 39). In addition, concentrations of pro-inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL-6) tend to be increased in patients with GHD and these parameters improve after initiating rhGH therapy (4, 40, 41). Two meta-analyses showed a significant reduction in LDL cholesterol and in total cholesterol during rhGH treatment, however, none of them demonstrated an increase in HDL cholesterol concentrations (42, 43).

The effects of GH on carbohydrate metabolism are two-directional: it acts directly antagonizing insulin action and indirectly through IGF-1 exerting insulin-like effect (44). GH suppresses the utilization of glucose in the liver and other tissues and increases liver glucose production. It also stimulates lipolysis and increases free fatty acids concentration, which may be among the mechanisms for impaired insulin sensitivity observed during rhGH replacement therapy (45). On the other hand, IGF-1 mediated effect inhibits insulin secretion and reverses GH-induced insulin resistance. GHD patients experience decreased fasting glucose concentrations, which are accompanied by impaired glucose tolerance, decreased insulin secretion and decreased insulin sensitivity. Treatment with rhGH reverses these effects and in the first 6-12 months transient deterioration of glucose metabolism may be observed. These negative effects are not further observed after 12 months of rhGH replacement (46). A potential explanation may involve the reduction of visceral fat mass and therefore the reduction in insulin resistance. An increase in muscle mass, together with increased strength and physical activity may contribute to the improvement of glucose and lipid metabolism (46, 47).
replacement led to lowered diastolic blood pressure (42, 52). Increased carotid intima-media thickness (IMT), commonly observed in GHD, was considered to be one of the earliest signs of atherosclerosis and increased cardiovascular risk (53, 54). It was shown that the changes in IMT cannot be explained only by the lipid anomalies observed in GHD. It was suggested that GH acts on the vascular wall directly or through IGF-1, or via NO secretion (49, 50). Moreover, rhGH has been shown to reduce the carotid artery IMT (55).

The myocardial structure also tends to be altered in GHD with left ventricle (LV) mass reduction and impaired LV function being the most common. Magnetic resonance imaging reveals significantly smaller LV end-systolic and end-diastolic volumes (56). Positive effects of rhGH treatment on cardiac muscle and improvement of the systolic function have been found in several studies (52, 56).

Consequences of GHD and benefits of rhGH treatment are summarized in Table 1.

### Mortality

GHD patients have increased mortality, however, the aetiology is multifactorial. Numerous studies have confirmed this finding but also shown that the risk of death might be associated with panhypopituitarism and both unreplaced GHD as well as inadequate hormonal replacement of other pituitary axes. Mortality may depend on the aetiology of GHD, treatment applied for underlying disease and its possible complications (57). Interestingly, there are also gender differences, and a standardized mortality ratio in GHD female patients was 1.73±2.17 higher than in male patients (58, 59).

The most common causes of death in GHD group were cardiovascular diseases. Some researchers found that excess mortality is also due to infections and inadequately treated secondary adrenal insufficiency during stress (60). Many studies are inconclusive, however, most authors agree that rhGH therapy decreases the deleterious impact of hypopituitarism on survival (59). Data regarding isolated GHD are very scarce, however, one study concerning untreated isolated GHD caused by a GHRH receptor mutation found no change in longevity (61).

### Conclusions

GHD is a clinical entity which results in adverse body composition changes, metabolic abnormalities that predispose to the increased cardiovascular risk and mortality. The most prominent consequences of GHD in adults are cardiovascular complications, osteoporotic bone fractures, and lower quality of life. All patients with multiple pituitary hormone deficiencies, or with a history of cranial surgery or irradiation, traumatic brain injury, and infiltrative central nervous system diseases should be suspected of GHD. Diagnosing and treating adult GHD patients with rhGH might be beneficial by improving body composition, muscle strength, lipid profile, general well-being and thus decreasing cardiovascular risk.

### References

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