TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 17
Number 1 *Fall 2023*

126-132

2023

Do the Benefits of Growth Hormone Outweigh the Risks?

Michael D. Goodstein

Do the Benefits of Growth Hormone Outweigh the Risks?

Michael D. Goodstein

Michael Goodstein graduated with a Bachelor of Science degree in Biology in June 2023

Abstract

Growth hormone treatment was introduced in the 1950s to confront growth hormone deficiency and metabolic irregularities. In 2003, however, the FDA approved growth hormone treatment for patients with abnormal growth rates unlinked to growth hormone deficiency. The treatment has become largely available to the general public, making the safety of growth hormone treatment an extremely important subject. This paper clarifies the benefits and efficacy of growth hormone treatment and analyzes the potential associated risks, including cancer and diabetes.

Introduction

Since the late 1950s, growth hormone-deficient patients have been treated with growth hormones to increase their height. The treatment is commonly administered to children and adolescents since their bones are still susceptible to changes in longitudinal growth. Growth hormones cause tissues to grow primarily by indirectly producing and releasing insulin-like growth factors. Growth hormone treatment is becoming more prevalent and has expanded to non-growth hormone-related disorders such as idiopathic short syndrome.

The potential primary benefit of growth hormone treatment is enhancing the quality of life of adolescents. A study that monitored improvements in behavior and self-esteem of adolescents who received growth hormone treatment concluded that the behavior and depression of prepubertal short children improved to the mean of normal children after three years of treatment (Chaplin et al., 2011).

Since growth hormone treatment became available to the public, the short-term and long-term safety of the treatment has been challenged. One of these concerns is the potentially harmful effect on glucose metabolism. Growth hormone is an adenohypophysic hormone that is part of an extensive network of hormones that work in unison to achieve proper homeostasis in the body. One role of growth hormone is stimulating the release of glucose from liver cells into the blood. Excess growth hormone causes elevated glucose levels in the blood, subsequently triggering beta cells in the pancreas to release an abundance of insulin. Eventually, insulin resistance can occur, potentially leading to diabetes mellitus (Tortora & Derrickson, 2012). For this reason, many people are concerned that interfering with the Growth hormone/insulin-like growth factor axis may adversely affect glucose metabolism and ultimately result in diabetes mellitus.

Since growth hormone induces cell growth, one of the primary concerns of this treatment is an increase in the risk of cancer.

Shen et al., 2007 discovered that growth hormone was the only hormone significantly reduced in parous rats compared with age-matched non-parous rats. Additionally, full-term pregnancy affords women and rats significantly reduced risk for developing breast cancer. Thus, it can be deduced that growth hormone levels are related to cancer-risk (Shen et al., 2007).

The focus of this paper is to explain the benefits and risks of growth hormone treatment clearly and to determine whether the benefits outweigh the risks of the treatment.

Methods

This comprehensive analysis critically evaluated The Touro College Library, PubMed, and ProQuest literature. This paper used solely peer-reviewed academic journals and scientific articles to research growth hormone treatment and its benefits and risks. It used search terms such as "growth hormone benefits," "growth hormone treatment," and "growth hormone therapy." This analysis also relied tremendously on Principles of Anatomy and Physiology 15th edition.

Growth-development Biology

Children born with regular growth patterns begin their lives with rapid growth but then gradually grow until puberty. This height increase is achieved primarily by the lengthwise growth of long bones. Interestingly, bones can only elongate while epiphyseal plates remain active, processing hyaline cartilage into bone tissue. The climax of growth achievement in children occurs at puberty. At this point, sex hormones become plentiful in their bodies, which causes increased osteoblast activity, synthesis of bone extracellular matrix, and a sudden "growth spurt." These hormones also hasten epiphyseal plate closure at about age 18 in women and 21 in men; the later age in men directly results from males producing less estrogen than females.

Sex hormones are not the only hormones instrumental in the growth process. Many other interconnected hormones play essential roles in the development of bones. Thyroid hormones, for example, are also required for proper skeletal system growth. Under the influence of thyrotropin-releasing hormone from the hypothalamus and thyroid-stimulating hormone from the anterior pituitary gland, thyroid hormones have several functions in the growth process. They promote the formation of ossification centers in developing bones, the synthesis of many bone proteins, and the secretion of growth hormones and insulin-like growth factors. Additionally, the hormone insulin from the pancreas promotes bone

growth by increasing the synthesis of bone proteins (Tortora & Derrickson, 2012).

However, growth hormone is the most crucial hormone in bone development and the most plentiful hormone in the body. Controlled by hypothalamic hormones growth hormone-releasing hormone and growth hormone-inhibiting hormone, growth hormone is released from the adenohypophysis in bursts every few hours, especially during deep sleep (Tortora & Derrickson, 2012). Although growth hormone primarily induces its growth-promoting effects indirectly through small protein hormones called insulin-like growth factors, it also acts by binding to its receptor, a homo-dimeric transmembrane receptor belonging to the cytokine receptor superfamily. Growth hormone binding results in the dimerization of the growth hormone receptor and phosphorylation of a tyrosine kinase called JAK2. JAK2 phosphorylation leads to the activation of several intracellular pathways. However, the binding of growth hormone to its receptor is associated chiefly with its metabolic and gene transcription effects, and not its growth effects (Vasques et al., 2019).

Insulin-like growth factors (IGFs) are related to insulin by having similar structures. Although structurally similar, insulin-like growth factors differ in their retention of the C-peptide cleaved from proinsulin to form insulin. Another difference between insulin and insulin-like growth factors is their production location. Insulin is produced by beta cells in the pancreas, whereas the liver and bone tissue produce IGFs. The two main types of IGFs are IGF-1 and IGF-2; IGF-2 has solely prenatal functions, whereas IGF-1 appears to have the predominant role in postnatal growth (Le Roith, 1997). A ternary complex consisting of a molecule of IGF-1, a molecule of IGF binding protein 3 (IGFBP-3), and a molecule of acid-labile subunit (ALS) carries most circulating IGF-1 (Vasques et al., 2019). IGF-binding proteins are essential for preventing IGFs from accessing specific tissues and receptors for IGF-1 and insulin. Serum concentrations of IGF-1 usually parallel 24-hour mean serum concentrations of growth hormone, and IGF-1 inhibits the secretion of growth hormone by the pituitary gland (Le Roith, 1997).

Several mechanisms are responsible for the longitudinal growth-promoting effects of growth hormone and IGF-1 within the growth plate. These mechanisms include progenitor cell recruitment, increased cell division in the resting and proliferative zone, increased chondrocyte cell volume in the hypertrophic zone, and endochondral ossification stimulation (Tidblad, 2021).

Defining Short Stature

The diagnostically accepted definition of short stature is two standard deviations (SD) below the corresponding mean height for a given age, sex, and population group. Children may have short stature for a multitude of reasons. However, in most diagnostic classifications of short stature, three main groups exist: primary growth disorders, secondary growth disorders, and a remaining group with no recognizable cause. Primary growth failure occurs when there is a problem in the genes that directly affect the growth plate (Wit et al., 2008). The gene disorientation causes tissues to grow improperly. This category includes, but is not limited to, Turner syndrome and Prader-Willi syndrome (Tortora & Derrickson, 2012). Secondary growth disorders have identifiable causes rooted outside the growth plate's genes. Secondary growth disorders include growth hormone deficiency, malnutrition, and eating disorders. The last group, idiopathic short stature, has no recognizable cause (Wit et al., 2008).

Endocrinologists and other doctors commonly utilize several tests to determine the source of short stature. For instance, using x-rays on the left hand and wrist is common in determining bone age. Children with secondary growth disorders and idiopathic short stature often have bone age delay, unlike children with most primary growth disorders. An absence of bone age delay thus practically excludes growth hormone deficiency. Other tests include serum IGF-1 and IGFBP-3 screenings. Low serum IGF-1 or IGFBP-3 for age (less than two standard deviations) would indicate a relatively high likelihood of growth hormone deficiency, which a GH stimulation test would commonly confirm. If IGF-1, IGFBP-3, or growth hormone levels are more or less regular and delayed bone age is present, patients are usually diagnosed with idiopathic short stature diagnosis, barring exceptions such as celiac disease or malnutrition (Wit et al., 2008).

Growth Hormone Treatment

When introducing growth hormone therapy as a remedy for short stature, doctors prescribed exclusively pituitary growth hormone to seriously growth hormone deficient patients. These patients were typically relatively old (older than ten years), severely height deficient (below four standard deviations of mean height), and often had combined pituitary hormone deficiencies. In 1979, researchers revealed the DNA sequence encoding human growth hormone through recombinant technology. Soon after, E. Coli and eukaryotic cell systems could express recombinant growth hormones. In 1985, the Food and Drug Administration (FDA) approved the first recombinant growth hormone produced from E. coli in the USA for childhood growth hormone deficiency. At this point, the FDA approved the treatment for less severe cases of

growth hormone deficiency while expanding the diagnosis of growth hormone deficiency to include less extreme cases (Ranke & Wit, 2018). In 2003, the FDA expanded its guidelines to include treating idiopathic short-stature patients with height standard deviation scores 2.25 less than the mean and associated with growth rates unlikely to permit attainment of adult height in the normal range. The height cutoff of –2.25 SD corresponds in adults to 160 cm (63 inches) for men and 150 cm (59 inches) for women. The primary objectives of GH treatment for patients with growth hormone deficiency are acceleration of growth velocity to promote normalization of growth and stature during childhood and attainment of standard adult height appropriate for the child's genetic potential (Grimberg et al., 2016).

In combining ten different reports, a review showed that the mean adult height of 4,520 patients treated with growth hormones was –1.0 SD. Patients were treated for a mean duration of 7 years using a mean growth hormone dose of 0.25 mg/kg/week. The difference between adult height SD and mid-parental height (a child's projected adult height based on the parents' heights) SD, which reflects whether a patient has achieved his or her genetic potential, showed a mean difference of –0.4 SD. In contrast, individuals with untreated growth hormone deficiency had a mean difference of –4.7 SD (Grimberg et al., 2016).

A retrospective study that compared the effect of recombinant growth hormone on height in patients with growth hormone deficiency (GHD) and idiopathic short stature (ISS) after one year of treatment showed that using growth hormone could improve growth velocity in ISS patients as effectively as in GHD patients. At the end of the treatment period, the mean height of both groups showed a significant increase. GHD patients achieved a mean height of 134.23 cm compared to their mean height before the treatment of 125.26 cm, while ISS patients achieved a mean height of 134.04 cm compared to the mean height before the treatment of 125.51 cm (Alzahrani et al., 2020).

Another retrospective study gathered medical records of 95 children (48 males and 47 females) with ISS treated from July 2019 to July 2020. They divided the children into two groups based on their treatment plans. The 41 children who received routine treatment for ISS comprised the first group. The treatment plan consisted of maintaining balanced nutrition, moderate exercise, adequate sleep, calcium and vitamin B12 supplements, and oral glucozone tablets for 12 months. The second group comprised the other 54 children who received growth hormone treatment and routine treatment. IGF-1 concentration, bone age, growth velocity, and height SD were relatively similar in the two groups before the treatment. However, after 12 months of treatment, both groups had notable improvements in all categories, but the degree of improvement in group 2 was significantly higher than in group 1 (Han et al., 2022).

These three studies suggest that recombinant growth hormone successfully treats children with growth hormone deficiency and idiopathic short stature to achieve greater adult height. However, one issue with the two latter studies is that they tested relatively few children. Another problem was that they only documented the effects of growth hormone after one year of treatment, which may not help understand its effects on children with idiopathic short stature and the difference between its effects on ISS and GHD patients long term.

Benefits of Growth Hormone Treatment

Parents deciding whether growth hormone treatment is the best course for their short child need to understand the benefits and risks to weigh against each other. Most of the benefits and risks of treatment on idiopathic short-stature children overlap with those of growth hormone deficiency, but some are syndrome-specific.

Psychological Benefits

One of the more apparent benefits of growth hormone treatment is the potential boost in self-esteem and confidence that achieving standard height could induce in shorter children. This boost in self-esteem would contribute to an overall higher quality of life. Through several methods of quantifying self-esteem and quality of life, a study showed that after three months of treatment, children's self-esteem increased and remained that way throughout treatment. The study noted that patients with ISS increased more dramatically than those with GHD. It attributed this discrepancy to low energy levels inherent to GHD patients, which ISS patients lack (Chaplin et al., 2011). However, research shows that B-endorphin associated with energy enhancement after exercise increases in cerebrospinal fluid via GH treatment in GHD children (Gizli Çoban et al., 2022). That suggests a similarity between ISS and GHD regarding energy levels.

Besides a general boost in self-esteem, growth hormone treatment may have a unique benefit for children diagnosed with GHD. A study showed that among 61 children and adolescents with GHD, about 46% demonstrated at least one psychological disorder, 39.8% of which was associated with social anxiety disorder. Additionally, 28% experienced bullying by their peers (Gizli Çoban et al., 2022). The study attributed these statistics to the lack

of growth hormones. However, these numbers possibly reflect the general population of shorter children, specifically those with idiopathic short stature.

Bone Mineral Density

Whereas hormones such as growth hormones, estrogens, and insulin affect bone growth indirectly, minerals, especially calcium, affect bone growth directly. This is because "bone growth," in the context of minerals, is primarily related to the thickness and density of bones. The extracellular matrix of bone tissue is composed of 55% crystallized mineral salts. Calcium and other minerals strengthen bones and depart from bones into blood circulation when needed by other body parts. Bones and teeth store 99% of bodily calcium. Osteoporosis, a condition of porous bones, affects 10 million people annually in the United States and occurs when bone resorption (breakdown) outpaces bone deposition (formation). Osteoporosis is due primarily to the depletion of calcium from the body— when the urine, feces, and sweat lose more calcium than is absorbed from the diet. A diet high in calcium is vital to reduce the risk of fractures. Parathyroid hormone increases blood calcium levels by increasing bone resorption through the actions of osteoclasts and by decreasing kidney excretion of calcium. Calcitriol, too, promotes the absorption of dietary calcium, increasing blood calcium levels. Conversely, parafollicular cells in the thyroid gland secrete calcitonin, which increases bone deposition through osteoblasts, thereby decreasing blood calcium levels (Tortora & Derrickson, 2012).

The primary non-collagenous protein in the bone matrix is osteocalcin, which osteoblasts secret. Blood osteocalcin levels are, therefore, known to reflect the rate of bone formation. The fact that growth hormone-deficient children show low levels of osteocalcin, whereas acromegalic patients with excess growth hormone display high levels of osteocalcin, supports this presumption. Concentrations of the carboxyl-terminal propeptide of procollagen type I (CPP-I) in the blood are even more reflective of bone synthesis and deposition rates. This is because sizeable soluble propeptide domains are released into the blood circulation from the precursor procollagen type I as it synthesizes into collagen type I, the major extracellular component of bone matrix and soft connective tissues.

A study of 26 children aged 6.5 to 10.7 tested the effects of recombinant growth hormone on mineral metabolism and bone density. Five times over 12 months, these children received growth hormone treatment. Over this time, their ionized calcium, phosphate, parathyroid hormone, calcitonin, 25-hydroxyvitamin D, 1,25-dihydroxy vitamin D, osteocalcin, and CPP-I serum concentrations were measured. Before growth hormone therapy, serum concentrations of osteocalcin and CPP-I were low, indicating low bone density and decreased bone formation. The study found a significant increase in serum osteocalcin levels after three months of treatment. Additionally, levels of CPP-I heightened after just one week and were positively related to growth velocity at 6 and 12 months of treatment (Saggese et al., 1993).

These factors show that growth hormone treatment likely improves mineral metabolism and boosts bone density and growth velocity (Blethen & MacGillivray, 1997). The decrease in blood calcium levels in these children with typical kidney excretion levels of calcium likely reflects the effects of growth hormones on bone density and formation. However, these factors may all be outgrowths of the longitudinal bone growth process unrelated to bone density. Even if that were true, the study would still confirm the efficacy of recombinant growth hormone treatment on bone growth alone. This study, however, has limitations in its sample size and duration of treatment.

Risks of Growth Hormone Treatment

Cancer Risks

The primary long-term concern of growth hormone treatment is its possible contribution to cancer. The basis of this concern is the mitogenic effects of growth hormone and its downstream worker, IGF-1. Since cancer is a group of diseases characterized by uncontrolled or abnormal cell division, it is reasonable to suspect that the administration of exogenous growth hormone into the body could lead to future cancers.

Interestingly, The Nurses Health Studies (NHS), a prospective epidemiological study, reported that serum IGF-1 levels could be a prognostic risk factor for cancer development. Another study reported a 2.4 higher risk of developing prostate cancer in men in the highest quartile of serum IGF-1 versus men with the lowest quartile seven years before the cancers are clinically evident. A separate report found a similar risk of developing premenopausal breast cancer in women two years before diagnosis (Cohen et al., 2000). Growth hormone coincidentally plays an essential role in mammary gland growth and development by supporting duct elongation and alveolar development. GH binds to its receptors in the stromal and epithelial compartment of the mammary gland and stimulates IGF-I mRNA expression. IGF-I then causes the development of terminal end buds, the structures that lead to the mammary gland development during puberty (Shen et al., 2007).

Besides positive correlations found between IGF-1 levels and cancer, negative correlations between IGFBP-3 and cancer also exist. A likely explanation is that IGFBP-3 is a binding protein that inhibits the effects of insulin-like growth factors while attached to a ternary complex. IGFBP-3 also induces apoptosis in prostate and breast cancer cells in vitro (Cohen et al., 2000).

However, other studies suggest no relation between these cancers and IGF-1 and IGFBP-3 concentrations, pointing to possible errors in the first few studies mentioned.

An animal study also shows a correlation between growth hormone administration and cancer risks. Experimenters introduced the cancerogenic N-methyl-N-nitrosourea to spontaneous dwarf rats with a mutation in their growth hormone gene. These rats experienced no cancerous effects. However, the same rats treated with growth hormone developed tumors in the presence of this substance. Additionally, nearly all the developed tumors had left entirely once the hormone treatment terminated (Shen et al., 2007).

What is intriguing about the concerns of growth hormone treatment in cancer development is that the mechanism by which growth hormone treatment would ultimately cause cancer is very unclear. The World Health Organization estimates that carcinogens are associated with 60–90% of all human cancers. Carcinogens, such as hydrocarbons found in cigarette tar or radon gas from the earth, induce mutations and permanent changes in the DNA base sequence of a gene. Oncogenes, cancer-causing genes, can also induce cancer. Cancer seems primarily rooted in genetic factors, not merely the introduction of mitogenic substances. Even if excessive production of growth factors from oncogenes ultimately causes some cancers, it is difficult to ascertain that small growth hormone injections over a short period would compare to a genetic, uncontrollable mutation. The vague hypothesis that introducing small amounts of a "mitogenic substance" could cause cancer seems improbable.

Data released by a cohort called the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE), which involved eight countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK), supports this idea. The cohort merged data from around 24,000 young adults treated with recombinant human growth hormone during childhood and adolescence. It reported that neither cancer nor overall mortality increase occurred in isolated growth hormone deficiency and idiopathic short-stature patients (Sävendahl et al., 2020).

Even if the studies showing IGF-1 levels and cancer-risk correlations are accurate, the GH-IGF axis may not play any role in this correlation. IGFs not part of the growth hormone pathway also exist in the body. The fact that cancer risk has been suggested to be directly related to serum IGF-1 and inversely related to serum IGFBP-3 casts doubt on the role of growth hormone as a driving force in the IGF-cancer equation. Since growth hormone positively influences both parameters in parallel (Cohen et al., 2000), correlations between IGF-1 and cancer risk are unlikely to reflect IGFs from the growth hormone pathway.

Furthermore, concerning the rat experiments and the statistics about parous women mentioned in the introduction, which point toward a connection between growth hormone and cancer risk, a sensible explanation is that growth hormone fosters the ability for cell growth induced by cancer but is not the cause of cancer itself.

Metabolic Risks

Unlike the effects of growth hormone on body growth, which primarily work through insulin-like growth factors, the effects of growth hormone on metabolism are direct. Meaning growth hormone interacts directly with target cells to cause specific metabolic reactions.

One role of growth hormone is stimulating the release of glucose from liver cells into the blood. Similarly, growth hormone also decreases glucose uptake into cells. These actions of growth hormones spare glucose so that it is available to neurons for ATP production in times of glucose scarcity.

Since growth hormone causes elevated amounts of glucose in the blood, excess growth hormone triggers B-cells in the pancreas to release high amounts of insulin. Consequently, insulin resistance may occur (Tortora & Derrickson, 2012). The fact that acromegalics have an increased rate of diabetes illustrates the effects of growth hormones on diabetes. In fact, 12-37.6% of acromegalics have diabetes (Hannon et al., 2017). Once insulin resistance occurs, the body takes an alternate energy path through fatty acids. This process happens when the body is affected by type 2 diabetes mellitus (Tortora & Derrickson, 2012).

For this reason, many people are concerned that interfering with the Gh/IGF axis may adversely affect glucose metabolism and ultimately result in diabetes mellitus.

A study of 23,333 children treated with growth hormone revealed that the incidence of type 1 diabetes mellitus did not increase in growth hormone patients compared to the standard population. However, the study also showed a sixfold increase in type 2 diabetes mellitus cases (Cutfield et al., 2000). This contrast makes

sense since type 1 diabetes is caused by a malfunction in pancreas B-cell function, whereas type 2 diabetes results from insulin resistance caused by a buildup of glucose in the bloodstream (Tortora & Derrickson, 2012). In other words, growth hormone may have caused a glucose build-up in the bloodstream, leading to type 2 diabetes. A second study that monitored fasting glucose, insulin, and hemoglobin (HbA1c) found an increase in HbA1c, insulin, HOMA-IR (insulin resistance), and HOMA-B (beta-cell function) values (Child et al., 2011).

However, in the first study, it is unclear from the paper which patients were the ones who developed diabetes mellitus. The study included growth hormone deficient and idiopathic short-stature children but also included Turner and Prader-Willi syndrome patients who are predisposed to developing type 2 diabetes mellitus (Cutfield et al., 2000). A third study, which confirmed the results of this first study, revealed that all 11 of 11,686 patients who developed diabetes mellitus had predisposing factors towards type 2 diabetes (Pellegrin et al., 2019). So it is likely that growth hormones simply hastened the onset of diabetes in these children. It is also likely that besides an initial uptick in blood glucose and insulin levels, growth hormone has little to no dramatic effects on glucose metabolism in short-statured children who only receive growth hormone for a few years with no risk factors towards diabetes.

Conclusion

Parents of short statured children should meet an endocrinologist to discuss the source of their child's short stature and determine if growth hormone treatment is the best course of action. This is because growth hormone therapy successfully treats both growth hormone deficient and idiopathic short stature children to reach greater adult heights, and in doing so, increases the quality of their lives. Even more encouraging is the seemingly minimal risks of developing cancer and diabetes in children without predispositions towards developing cancer or diabetes. However, more research is necessary to establish concretely that these risks are minimal.

References

Alzahrani, A., Algethami, A. K., Barnawi, G. M., Meftah, I. A., Alshanqiti, A., Al-Hashmi, H., Khan, M., & Felimban, N. (2020). Differences in response to recombinant growth hormone therapy on height gain in patients with idiopathic short stature vs. patients with growth hormone deficiency. Cureus. https://doi.org/10.7759/cureus.7319

Blethen, S. L., & MacGillivray, M. H. (1997). A risk-benefit assessment of growth hormone use in children. Drug Safety, 17(5), 303–316. https://doi.org/10.2165/00002018-199717050-00003

Chaplin, J. E., Kriström, B., Jonsson, B., Hägglöf, B., Tuvemo, T., Aronson, A. S., Dahlgren, J., & Albertsson-Wikland, K. (2011). Improvements in behaviour and self-esteem following growth hormone treatment in short prepubertal children. Hormone Research in Paediatrics, 75(4), 291–303. https://doi.org/10.1159/000322937

Child, C. J., Zimmermann, A. G., Scott, R. S., Cutler, G. B., Battelino, T., & Blum, W. F. (2011). Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: Analysis from the Genesis Observational Research Program. The Journal of Clinical Endocrinology & Metabolism, 96(6). https://doi.org/10.1210/jc.2010-3023

Cohen, P., Clemmons, D. R., & Rosenfeld, R. G. (2000). Does the GH–igf axis play a role in cancer pathogenesis? Growth Hormone & IGF Research, 10(6), 297–305. https://doi.org/10.1054/ghir.2000.0171

Cutfield, W. S., Wilton, P., Bennmarker, H., Albertsson-Wikland, K., Chatelain, P., Ranke, M. B., & Price, D. A. (2000). Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. The Lancet, 355(9204), 610–613. https://doi.org/10.1016/s0140-6736(99)04055-6

Gizli Çoban, Ö., Bedel, A., Önder, A., Sürer Adanır, A., Tuhan, H., & Parlak, M. (2022). Psychiatric disorders and peer-victimization in children and adolescents with growth hormone deficiency. Clinical Pediatrics, 61(10), 684–691. https://doi.org/10.1177/00099228221096654

Grimberg, A., DiVall, S. A., Polychronakos, C., Allen, D. B., Cohen, L. E., Quintos, J. B., Rossi, W. C., Feudtner, C., & Murad, M. H. (2016). Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: Growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Hormone Research in Paediatrics, 86(6), 361–397. https://doi.org/10.1159/000452150

Han, W., Zhang, J., Song, T., & Han, Y. (2022). Significance of recombinant human growth hormone therapy in promoting growth and development of children with idiopathic short stature. Pakistan Journal of Medical Sciences, 38(7). https://doi.org/10.12669/pjms.38.7.6535

Hannon, A. M., Thompson, C. J., & Sherlock, M. (2017). Diabetes in patients with acromegaly. Current Diabetes Reports, 17(2). https://doi.org/10.1007/

s11892-017-0838-7

Le Roith, D. (1997). Insulin-like growth factors. New England Journal of Medicine, 336(9), 633–640. https://doi.org/10.1056/nejm199702273360907

Pellegrin, M. C., Michelon, D., Faleschini, E., Germani, C., Barbi, E., & Tornese, G. (2019). Glucose metabolism evaluated by glycated hemoglobin and insulin sensitivity indices in children treated with recombinant human growth hormone. Journal of Clinical Research in Pediatric Endocrinology, 11(4), 350–357. https://doi.org/10.4274/jcrpe.galenos.2019.2019.0281

Ranke, M. B., & Wit, J. M. (2018). Growth hormone — past, present and future. Nature Reviews Endocrinology, 14(5), 285–300. https://doi.org/10.1038/nrendo.2018.22

Saggese, G., Baroncelli, G. I., Bertelloni, S., Cinquanta, L., & Di Nero, G. (1993). Effects of long-term treatment with growth hormone on bone and mineral metabolism in children with growth hormone deficiency. The Journal of Pediatrics, 122(1), 37–45. https://doi.org/10.1016/s0022-3476(05)83484-5

Shen, Q., Lantvit, D. D., Lin, Q., Li, Y., Christov, K., Wang, Z., Unterman, T. G., Mehta, R. G., & Swanson, S. M. (2007). Advanced rat mammary cancers are growth hormone dependent. Endocrinology, 148(10), 4536–4544. https://doi.org/10.1210/en.2007-0513

Sävendahl, L., Cooke, R., Tidblad, A., Beckers, D., Butler, G., Cianfarani, S., Clayton, P., Coste, J., Hokken-Koelega, A. C., Kiess, W., Kuehni, C. E., Albertsson-Wikland, K., Deodati, A., Ecosse, E., Gausche, R., Giacomozzi, C., Konrad, D., Landier, F., Pfaeffle, R., … Swerdlow, A. J. (2020). Long-term mortality after childhood growth hormone treatment: The saghe cohort study. The Lancet Diabetes & Endocrinology, 8(8), 683–692. https://doi.org/10.1016/s2213-8587(20)30163-7

Tidblad, A. (2021). The history, physiology and treatment safety of growth hormone. Acta Paediatrica, 111(2), 215–224. https://doi.org/10.1111/apa.15948

Tortora, G. J., & Derrickson, B. (2012). Principles of Anatomy & Physiology (15th ed.). John Wiley & Sons.

Vasques, G. A., Andrade, N. L., Correa, F. A., & Jorge, A. A. (2019). Update on new GH-IGF axis genetic defects. Archives of Endocrinology and Metabolism, 63(6), 608–617. https://doi.org/10.20945/2359-3997000000191

Wit, J. M., Clayton, P. E., Rogol, A. D., Savage, M. O., Saenger, P. H., & Cohen, P. (2008). Idiopathic short stature: Definition, Epidemiology, and diagnostic evaluation. Growth Hormone & IGF Research, 18(2), 89–110. https://doi.org/10.1016/j.ghir.2007.11.004