Acta Salus Vitae, Vol 12, No 2 (2024)
ISSN 1805-8787 actasalus@palestra.cz

GROWTH HORMONE AS A CONDITION FOR HEALTHY DEVELOPMENT

Martina MUKNŠNÁBLOVÁ

Abstract

Growth hormone is produced by the endocrine system from early intrauterine development, because without it there would be no tissue development and healthy development of the human organism. Production changes alternately with age, and if it is insufficient, it can manifest itself not only in insufficient body height, but also metabolically, which will affect the overall state of health. This review study points to insufficient natural production, which can be monitored prenatally, followed by accurate dynamic laboratory tests, and early replacement home injection treatment can be initiated in order to eliminate the symptoms of limited biological secretion of growth hormone.

Keywords

growth hormone, organism development, somatotropin

INTRODUCTION

Hormones are biologically active substances, carrying important information for the activity of individual tissues. Their function is to support or, conversely, dampen the activity of organs or the entire organism. Hormones are produced by the endocrine system, which in its endocrine glands produces hormones that are carried directly into the blood, which then distributes them throughout the body to the target site of action. The endocrine system is connected to the nervous system, to which it is subordinate. The synthesis of somatotropin (growth hormone) is ensured by the pituitary gland, specifically adenohypophyseal somatotropes. Other hormones are also produced in the adenohypophysis, e.g. adrenocorticotropic, thyrotropic, gonadotropic or melano-stimulating.

Growth hormone production

The regulation of somatotropin secretion is controlled by the hormone GHRH (growth hormone-releasing hormone), which can be demonstrated in the human hypothalamus between the 18th and 29th week of intrauterine development, specifically, it is produced in the arcuate nucleus of the hypothalamus. As stated by Bengi (2012), several neuroendocrine neurons can be found in this nucleus. However, GHRH, also known as somatoliberin, is primary for growth. Somatoliberin has a stimulating function, the opposite is somatostatin (growth hormone inhibiting hormone, GIH), which has an inhibitory effect. Somatoliberin and somatostatin influence the regulation of somatotropin secretion. After somatotropin enters the bloodstream, it is bound to a carrier protein called growth hormone-binding protein, or GHBP for short.

The action of somatotropin is closely related to two peptides (IGF 1 and IGF 2), which are part of the physiological control of growth, metabolism and cell survival. They are insulin-like factors. IGF 1 is a polypeptide similar to proinsulin, composed of 70 amino acids. Its action in the body is focused primarily on cell growth and differentiation, IGF 1 ensures the progression of the cell from the G1 phase to the next phases of the cell cycle. IGF 1 also has the ability to delay cell death. It

has an effect on the metabolism of virtually all essential nutrients. IGF2 is a peptide formed by 67 amino acids. It increases during early development and then decreases during adulthood. It plays an important role in the regulation of cell growth, differentiation and metabolism the ability to act on adipose tissue, liver and skeletal muscles. In the liver, it suppresses glucose production and increases glycogen synthesis. An important difference between IGF 1 and IGF 2 is the time when they are applied to human growth. While IGF 1 acts more in the postnatal period, IGF 2 is mainly applied in the prenatal period. Both peptides circulate in the blood, they are bound to specific binding proteins called IGFBP (insulin-like growth factor binding proteins, whose synthesis takes place mainly in the liver.

Human growth is ensured by somatotropin through somatomedins, which stimulate the growth plates of long and short bones, thereby ensuring bone growth to length (in childhood before ossification of the growth cartilages after puberty). According to Bláhová & Fencl & Lebl (2019), another important task for growth is the direct stimulation of division and multiplication of cartilage chondrocytes. Therefore, somatotropin is also used in treatment to improve the patient's body height and strengthen muscles.

The effect of growth hormone is also proven in various metabolic processes. An example is the ability to increase the release of glycogen from the liver, thereby affecting carbohydrate metabolism. In children with Prader-Willi syndrome, its effect on the reduction of body fat and on the better development of muscle mass is used, thanks to which subsequent psychomotor development takes place better. But the growth of the organism is not only influenced by the growth hormone, circumstances such as: diet (sufficient amino acids as building blocks for building the organism, optimal supply of vitamin D[1]), genetic predisposition (homeobox genes, represented by the SHOX gene, if abnormalities occur) also come to the fore. there are organ defects, Madelung's deformity (wrist deformity), goth palate, shortening of the length of long bones or noticeable muscle enlargement), chronic diseases (chronic intestinal inflammation with impaired absorption of nutrients, celiac disease or food intake disorders, chronic kidney disease), the course of pregnancy (lifestyle of the mother, intrauterine infection, duration and course of pregnancy and childbirth), other hormonal factors, for example thyroid hormones (triiodothyronine, thyroxine), sex hormones (gestagens, androgens), and hormones from the adrenal cortex (corticosteroids).

Monitoring the effect of growth hormone

The overview study shows that the growth of each child is monitored according to the prescribed growth curve, which is one of the indicators of the successful development of an individual, taking into account the connection between physical growth and mental health, especially in the post-pubertal period. The pediatrician is responsible for monitoring the growth curve during regular preventive examinations. The data is recorded in the child's vaccination card and plotted in so-called percentile graphs. These charts are a tool for comparing a child's growth with values common in the entire population aged 0-18 years. flight. It is important to pay attention to the gender difference. The resulting height percentile

[1] Vitamin D is obtained from sunlight, diet or vitamin supplements. Its effect is crucial for proper growth, because it has the ability to support the absorption of calcium and phosphorus in the intestine, which helps the formation and growth of bones. Sufficient daily intake of vit. D is 600-800 units, individually according to the current blood level. Its active form is calcitriol, which ensures the differentiation and mineralization of newly growing bone. The most common problems include its insufficient intake or resistance to it.

value means that a given percentage of children achieve the same or lower result. The 50th percentile corresponds to the mean value of the monitored physical property. We always measure infants and toddlers lying down using a so-called body meter. We use the stadiometer for children who are already standing on their own, which is around 2 years old.

The medical field - auxology - deals with the ICP growth model. Loosely translated from the Greek auxó= growth. The founder of the ICP model is the Swedish auxologist Johan Karlberg, who divided the mouth curve into three components that overlap and add up. ICP is an abbreviation - infancy, childhood and puberty. Each of these periods is controlled hormonally differently. The I-infancy period smoothly follows fetal growth, when insulin-like growth factors (IGF) play a significant role in development, but IGF 1 the most. Between the first and second year of life, the onset of the C-childhood period begins, which is dominantly controlled by growth hormone, which acts through the liver to stimulate the formation of somatomedins, which will allow the hormone to act on the tissues. The C period of the model lasts until the end of body growth. The last component is the P period - Puberty is characterized by a large action of sex hormones, when individuals reach sexual maturity and gain the last 15% of their final height. This model is also referred to as a sandwich model and is recognized worldwide. It is another indicator of a possible problem with the child's development.

Thanks to knowledge about the growth rate, or the so-called skeletal linear growth, we know when growth ends and when to stop the already synthesized growth hormone. Growth rate peaks before the juvenile reaches full sexual maturity. Then it gradually decreases. It is therefore estimated that roughly 80% of growth occurs before puberty. An important term is the so-called growth spurt. A spurt is a term for a period of sudden acceleration of a child's growth. When it comes to the pubertal spurt, the child should reach their final adult height.

The field of auxology deals with the possibilities of proving the specific biological maturation (age, stage of development or growth) of an individual. This is done by assessing dental age, sexual maturity, anthropometric characteristics (height, weight, length, head circumference...) and bone age. Bone age indicates the state of maturity of the skeleton, indicating the degree of maturity of the skeleton, determined by the degree of ossification. It is not a measurement of bone length, but the conversion of cartilage to bone. According to Igaz (2022), an auxologist is able to evaluate the degree of maturation from an x-ray of the wrist and distal forearm. Knowledge of the location of ossification centers is important for his work. For a right-handed person, the left hand is always X-rayed and vice versa. It is advantageous because of the large number of ossification centers in a small area that is easily accessible. When examining an X-ray image, an auxologist is able to detect various abnormalities in addition to the state of skeletal maturity and also has the opportunity to evaluate the width of the epiphyseal fissures. The result of the auxologist's work is information on a relatively accurate prediction of the final height in adulthood.

It also assesses whether the child's height is small or large in the family. Important information for the doctor is specifically the assessment of the closure of the growth fissures. Once the complete closure of the growth cracks is detected, it is no longer effective to administer the growth hormone, the child will no longer grow even despite its effects.

Among the current methods for evaluating bone age in our country and in the world,

the following are used: Greulich-Pyle (G-P) methods, Tanner Whitehouse methods (TW1, TW2, TW3) The G-P method is referred to as a faster method, but at the same time less accurate. In the 1950s, anthropologist William Bill Greulich and Stanford Anatomy Institute researcher Mr. Idell Pyle established the Radiological Atlas of Hand and Wrist Skeletal Development. The G-P method is therefore based on comparing images from the atlas and the image of the patient that is most similar to it. The Tanner and Whitehouse (TW) methods are based on the assessment of the shape and size of the ossification centers of the 20 bones of the hand and distal forearm and their relationship with neighboring bones. The approach is done very carefully bone by bone. Each bone is assigned 8-9 stages of maturity that the bone passes through.

When evaluating sexual maturation and puberty as an indicator of phase and growth potential, the proportionality of the figure, the child's psychological state, the state of nutrition, physical deviations and the development of secondary sexual characteristics are monitored. The doctor evaluates the degree of development of secondary sexual characteristics according to Tanner. It is a scale of physical development of children, adolescents and adults. In girls, the development of the mammary glands (mamma) is evaluated at M1-M5, the scale of pubic hair is marked P1-P5, and in girls and boys, the development of the genitals is also evaluated at G1-G5. The markings are from 1 to 5, with 1 being the stage of the child where no signs of pubertal development are evident. Stage 5 corresponds to a fully developed adult. For boys, an orchidometer is required for examination. It is a tool used for an indicative examination of the volume of the testicles. The development of the testicles is an important milestone for boys, it is the first sign of their puberty. At around 11.5 years of age, the testicles usually begin to enlarge. The first sign of puberty in girls is the enlargement of the mammary glands. It usually starts at the age of 11, and menarche starts at an average of 12.5 years.

Intrauterine growth restriction (IUGR) is supported by diagnostics using ultrasound, on which the fetus is characterized by a significant delay in growth, or a deviation from the so-called genetic growth rate. This serious situation can occur from the very beginning of pregnancy or it can begin to manifest itself only after a few months. That is why ultrasound examinations in the gynecologist's office are very important. The cause of IUGR can be inappropriate lifestyle of the mother (nutrition, drug abuse), age and height of both parents, pregnancy infection and chronic diseases, gestosis, various anomalies of the uterus, insufficiency of the placenta, e.g. as a result of preeclampsia, gestational diabetes or hypertension. In the event of insufficient placental function in an attempt to reduce metabolic demands, the movement of the fetus is stopped, as well as its growth. If a genetic or otherwise caused congenital growth disorder is suspected, a karyotype examination using cordocentesis (puncture of the umbilical cord) is possible.

Among the most frequently used examination methods for the diagnosis of growth disorders, the examination of blood parameters is also used - blood count, liver and kidney function, IGF-1 in urine, erythrocyte sedimentation, CRP, celiac disease antibodies, thyrostimulating hormone, free thyroxine, genetic examination - karyotype, SHOX gene and, last but not least, brain and pituitary MRI.

The effects of growth hormone are mainly mediated by the IGF 1 factor, which has a constant level in the serum. Therefore, if it is found during blood sampling that the child has significantly lower IGF 1 values, the production of STH is determined in more detail using dynamic or functional

tests. The level of IGF 1 is found to increase after the administration of growth hormone, so it is assumed that the levels of IGF 1 reflect the levels of growth hormone in the blood. Tests are divided into stimulatory and inhibitory.

Stimulating influences and substances include stress, hypoglycemia, arginine, dopamine and food intake. The opposite is the effect that inhibits secretion, among them is the action of glucose. Clonidine, arginine or insulin tests are most often used to determine STH levels. The clonidine test for detecting growth hormone secretion is performed on an outpatient basis, fasting and in bed. First, blood is collected before stimulation, then clonidine chloride is given by mouth in the form of a clear solution, and then blood is collected again at 30, 60 and 90 minutes of the test. The insulin tolerance test is also an invasive examination in which insulin is administered into the venous circulation, thereby inducing hypoglycemia, during which the secretion of growth hormone increases. The arginine test for growth hormone stimulation in the pituitary gland is also performed on an outpatient basis, fasting and at bed rest. Before starting the test, the child is examined by a doctor, blood pressure is measured and an EKG is recorded. After the initial blood sampling and determination of the blood sugar level, the test substance Arginine chloride 21% (the dosage is based on the patient's weight) is administered as an intravenous infusion for 30 minutes, followed by further blood sampling after the end of the infusion at regular 30-minute intervals for 90 minutes.

Growth hormone therapy

If the pituitary gland is unable to produce enough growth hormone, there is a possibility of treatment with its synthesized form. Currently, the biosynthetic hormone is produced by the recombinant DNA method. Wright (2011) describes a process where initially there was an effort to obtain the necessary material from animal pituitary glands. It was soon discovered that it does not affect humans. In 1957, the hormone was first used when it was working properly. The manufacturing process at the time was based on extracts from cadaveric human pituitary glands. Therefore, the product was called cadaver-GH. An unfortunate milestone in the development of a drug against short stature was the death of a patient. Most likely, there was an error in the processing of the material when it was contaminated. Subsequently, a prion disease called Creutzfeldt-Jakob disease began to develop in the organism. Unfortunately, this is a disease for which the causal treatment is unknown and always ends in death. An important turning point in the development of growth hormone treatment occurred in 1985.

Recombinant preparations have become available, which is artificially synthesized DNA that is created by inserting the entire gene or a certain part of it into the genome of another organism. The basis is the use of an organism that is capable of rapid reproduction, for example the bacterium E. Coli. The gene for human growth hormone is inserted into the cell. Everything takes place in the conditions of a nutrient solution, as soon as the number of cells increases, the amount of growth hormone produced also increases. After the end of cell multiplication, the next phase occurs, which is purification. Remains of cell walls are removed and ingredients are added, important for a longer life of the resulting product. In the final stage, the drug is prepared in ampoules, which are inserted into application pens. There is no risk of transmission of a fatal disease with recombinant preparations. In addition, synthesizing solves the problem with the amount of the drug, which is now unlimited (but the selling price is still high). Growth hormone in recombinant form has been on the market for more than 30 years.

The following preparations are approved for treatment in the Czech Republic (Škvor, 2012): Genotropin (Pfizer), NgenLa (Pfizer), Humatrope (Eli Lilly), Norditropin (Novo Nordisk), NutropinAq (Ipsen), Omnitrope (Sandoz), Saizen (Merck Serono) and Zomacton (Ferring). These products are available in the Czech Republic with a doctor's prescription and only in some pharmacies. Each medical facility providing growth hormone treatment usually works with several of the companies listed above. Company representatives also supply all accessories such as application pens, growth charts, supplies for transporting growth hormone (thermal bags) and needles that are compatible for the given pen. All applicators are for s.c. use. (subcutaneous), in addition to the pen, Zomacton works as a needle-free transdermal applicator. The choice of the preparation and thus the application pen is up to the attending physician. According to workplace customs, training takes place with an educational nurse or company representative. Thus, the child and his parents always leave the surgery instructed and equipped for the home application of growth hormone. If the patient has an application pen with a needle, he must set the dose prescribed by the attending physician before use.

The application takes place s.c. every day, or just once a week in the case of NgenLa. The preparation NgenLa is specific in its composition, it contains somatrogon[2] instead of somatotropin, which allows application only once a week. For the correct effect, the substance is applied in the evening before going to bed to imitate the natural nocturnal peak of the hormone (Pomahačová & Kalvachová, 2017). It is necessary to store the drug in a refrigerator at a temperature of +2 to +8°C to prevent its deterioration. The ideal injection sites are the front of the thighs or the gluteal muscle. If it is a daily application, the patient must alternate injection sites to avoid the formation of hematomas. The application procedure is similar to, for example, insulin administration. The injection site must be disinfected and allowed to dry, after creating a skin fold, the needle is inserted at an angle of 45°, growth hormone pens cannot be aspired. After inserting the needle and pressing the application button, the patient must wait about 10 seconds for the medicine to be applied in full.

Since the patient applies the growth hormone at home without the supervision of a health professional, it is important that he keeps a record of the application of the drug and its possible omission. Currently, phone applications are available to help the patient monitor the treatment. So far, Merck Serono is the only company that provides the option of treatment through the Easypod smart applicator. This applicator has a great advantage in pre-setting the dose, the child just puts on the needle and can apply himself without daily adjustment of the dose. It also has an intelligent data transmitter. At the next check-up, when the patient comes to the doctor for a check-up, the nurse downloads all the data into the system and has an overview of when the application was missed.

CONCLUSION

It is necessary to control the use of growth hormone not only in the context of comparison with the growth curve of a specific user, but also due to overuse or abuse by a person other than the one indicated (doping athletes, acceleration of the growth of farm animals). Given the

[2] Somatrogon is a protein made from human growth hormone and a small part of human chorionic gonadotropin.

high financial demands of the treatment (financed by public health insurance), it is also necessary to eliminate missing doses due to forgetfulness and their unnecessary expiration, which is facilitated by patient mobile applications.

REFERENCES

Bengi, K., (2012). *Growth Hormone*. Springer Verlag.

Bláhová, K., Fencl, F. & Lebl, J. (2019). *Pediatrická propedeutika*. Galén.

Igaz, P. (2022). *Practical Clinical Endocrinology*. Springer Nature Switzerland.

Pomahačová, R., & Kalvachová, B. (2017). *Dětská endokrinologie do kapsy*. Mladá fronta.

Škvor, J. *Selhání tělesného růstu: praktický průvodce nejen pro dětské lékaře.* (2012). Mladá fronta.

Wright, Y.L. (2011). *Secrets About Growth Hormone To Build Muscle Mass, Increase Bone Density, And Burn Body Fat!.* Lulu.com

CONTACT

PhDr. Martina Muknšnáblová, Ph.D., MBA

College of Physical Education and Sport PALESTRA, Ltd.

e-mail: m.muknsnablova@tiscali.cz