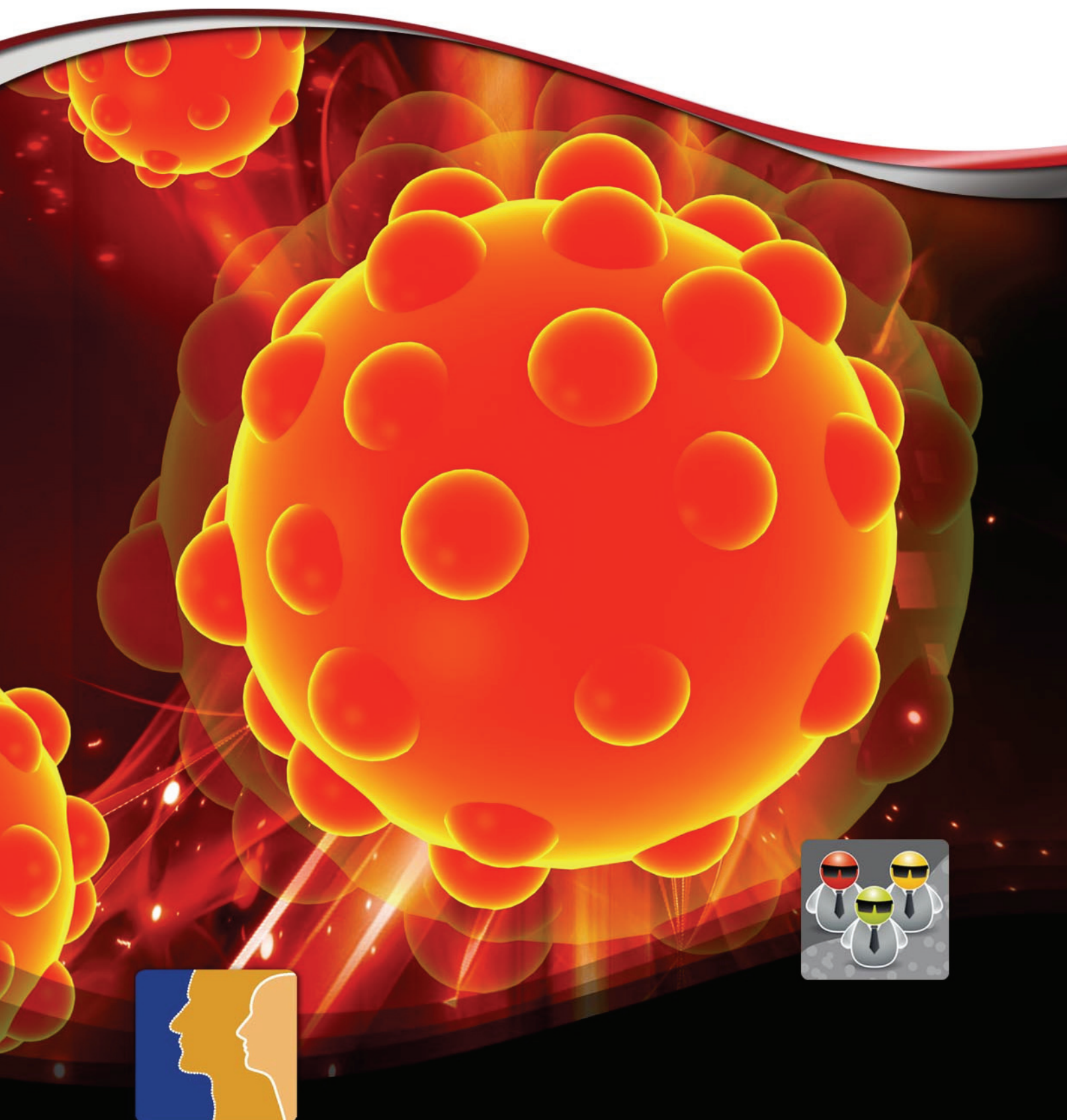




Human Growth





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Human Growth

Introduction

Growth and development are principal features of living organism. These complex processes are closely interconnected.

Growth may be defined as increase of cell amount (hyperplasia) and increase of their size (hypertrophy).

Human growth is pronounced especially in prenatal period, during the first year of the life, and in onset of puberty.

Regulation system of prenatal growth is not completely understood yet, as many maternal and fetal factors are involved in this process.

In postnatal period, the main system controlling the growth of the skeleton is axis – hypothalamus-pituitary gland–chondrocytes, with GH (growth hormone) and IGF-1 (insulin-like growth factor 1) as key agents mediating information.

When information reaches epiphyseal cartilage, longitudinal bone growth occurs. It consists in formation of a new cartilage followed by its calcification and remodeling into bone tissue.

Growth is considered as one of the best indicators of a child's health and deviations from the normal range both for height and for rate of growth may indicate an underlying problem. Although such problem may originate from some endocrine disorder, there are many other factors that play role and must be excluded first, like e.g. nutritional habits, problems with absorption, transport and utilization of nutrients, genetic abnormalities, systemic diseases, family and social factors or emotional deprivation.

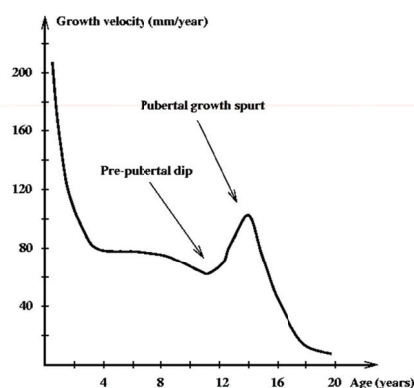
Although children grow at different rates, most reach physical maturity by age 15 to 17. Girls typically finish growing sooner than boys.

Regular measurement of child's height, assessment of growth velocity (see Fig.1), and comparison of both with population-based normative is one of the key aspects of pediatric care.



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Fig.1.: Changes of growth velocity with age



Endocrine control of human growth

Human growth is a complex process requiring contribution and coordination of many factors, including nutritional, mental or social condition. The key element of the whole process is endocrine system. Besides hormones of so called GH-IGF axis (or somatotrophic axis), several other hormones are essential for normal body growth and maturation, including insulin, thyroid hormones, and androgens.

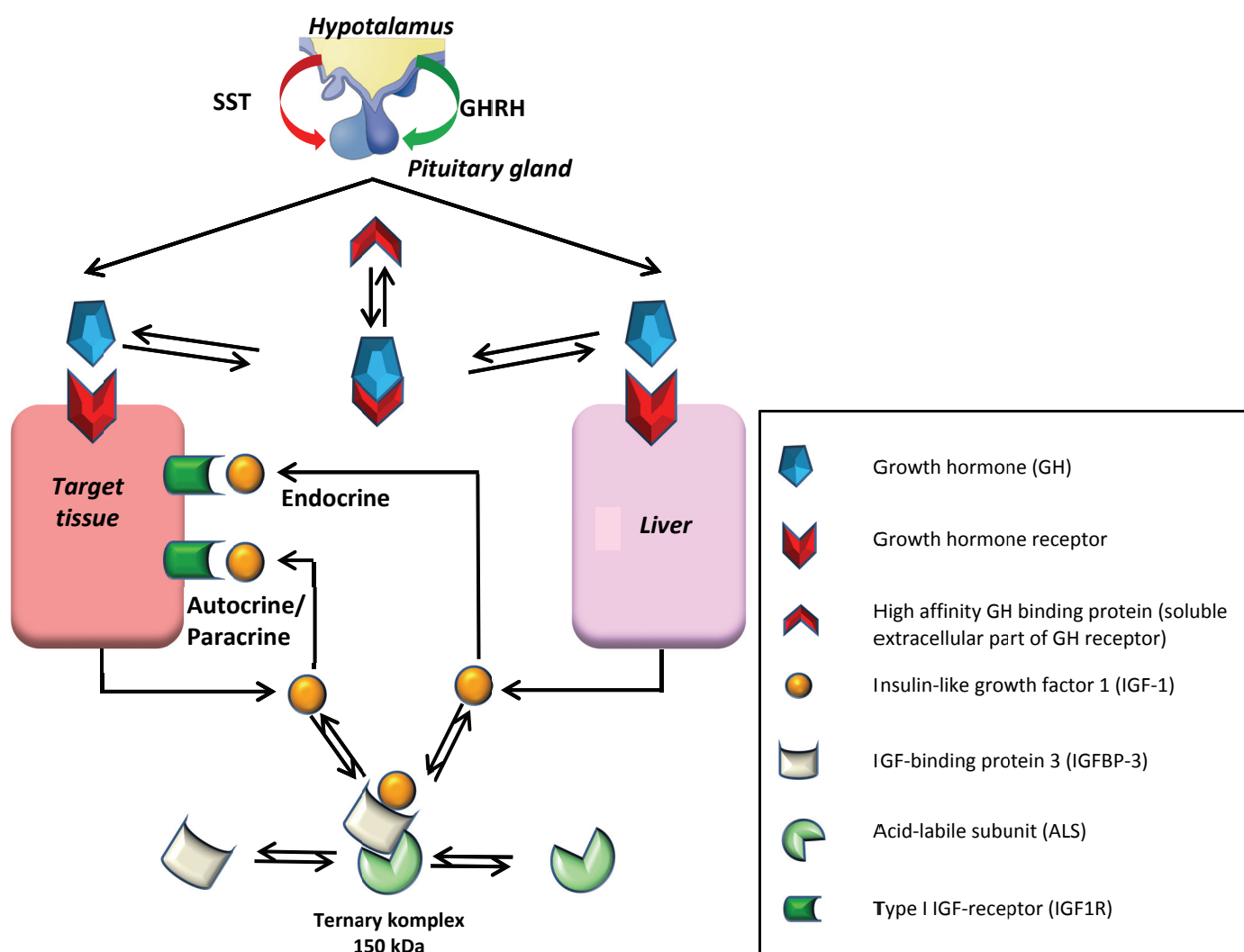
GH-IGF AXIS

Function of the GH-IGF axis (see Fig.2) is dependent on collaboration of various components, including:

- Hypothalamic hormones growth hormone-releasing hormone (GHRH) and somatostatin (SST) and their receptors in pituitary gland
- Pituitary GH, its two binding proteins (high affinity GHBP and low affinity GHBP) and GH receptor in target tissues
- IGF peptides (mainly IGF-1 and IGF-2), two their specific receptors, a family of at least six IGF binding proteins and a glycoprotein named the acid-labile subunit (ALS)



Fig.2.: GH-IGF axis





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GHRH and somatostatin are released by neurosecretory nerve terminals of hypothalamus and they are transferred via hypothalamo-hypophyseal portal system to the anterior pituitary gland. GHRH is a peptide of 44 amino acids, somatostatin may exist in two forms of 14 and 28 amino acids.

GH is a single chain polypeptide, the principal isoform consists of 191 amino acids and has molecular mass 22 kDa. Several other molecular isoforms of GH exist in the pituitary gland and are released to blood.

Approximately a half of monomeric form of GH is bound to carrier proteins. High affinity GH binding protein (high affinity GHBP) is the soluble form of the extracellular part of the GH receptor. Its concentration in serum is relatively low (around 1 nM), whereas the concentration of low affinity GHBP is much higher (around 0.7 μ M).

IGF-1 (insulin-like growth factor 1) is 70 amino acid peptide. It is produced mainly in liver, but also in bone, adipose tissue, muscle, kidney and other tissues in response to GH. Most of IGF-1 in circulation is bound in a ternary complex consisting of IGF-1, IGFBP-3 and acid-labile subunit (ALS).

IGF-1 binds to various highly homologous tyrosine kinase receptors: the two most important are type I IGF-receptor (IGF1R), and the insulin receptor, with significantly higher affinity to IGF1R.

IGF-2 (insulin-like growth factor 2) is a 67 amino acid peptide. Its expression is probably GH-independent. As in case of IGF-1, most of IGF-2 in circulation is bound in a ternary complex consisting of IGF-2, IGFBP-3 and ALS.

IGF-2 binds mainly to type II IGF-receptor; it does not bind to insulin receptor and its binding to type I IGF-receptor is weak.

IGF-binding proteins (IGFBPs) and acid-labile subunit (ALS): The IGFs are found in association with specific IGFBPs in blood and extracellular fluids. Six IGFBPs have been characterized (IGFBP-1 - IGFBP-6). The main functions of this family of proteins are to extend IGFs half-life in the circulation, to transport the IGFs to the target cells, and to modulate the biological actions of the IGFs. 95% of all IGFBPs in circulation is IGFBP-3. Most of the IGFs are bound in a 150 kDa ternary complex consisting of IGF-1 or IGF-2, IGFBP-3 and ALS.



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Approximately 90% of IBFBP-3 and 90% of IGFs are bound in this complex. It is found in blood and milk only.

A small 40 kDa complex is found in many biological fluids including cerebrospinal fluid, amniotic fluid, sperm, milk, urine and blood. It serves mainly for transport and distribution to target cells.

The biological half-life of the 150-kDa ternary complex is approximately 15 hours, much longer than the 40 kDa complex (30 minutes) and free IGF-1 (10 minutes).

REGULATION OF GH SECRETION

GH is synthesized by special cells in the anterior pituitary called somatotropes, where it is stored in secretory granules. It is the most abundant hormone in the pituitary, accounting for 25% of the gland's hormones. GH is synthesized and secreted in a pulsatile manner throughout the day. For most of the time, the levels are relatively low and stable, but there are several secretory peaks occurring approximately 3 hours after meal or physical activity. Marked rise of GH levels appears approximately 90 minutes after the onset of sleep, reaching maximal value during the period of deepest sleep.

Its secretion is regulated by two hypothalamic hormones: GHRH, which increases GH release, and somatostatin, which inhibits. Nevertheless, GH secretion is, in certain extent, influenced by several other factors including various hormones:

GHRH is the most important regulator of GH under physiologic conditions. GHRH binds to its specific receptor in pituitary gland and stimulates GH synthesis by increasing both GH gene transcription and GH release.

Somatostatin binds to a family of specific receptors to inhibit GH release, but not its synthesis.

GH and IGF-1 act on the pituitary and hypothalamus and decrease production of GH by negative feedback mechanism.

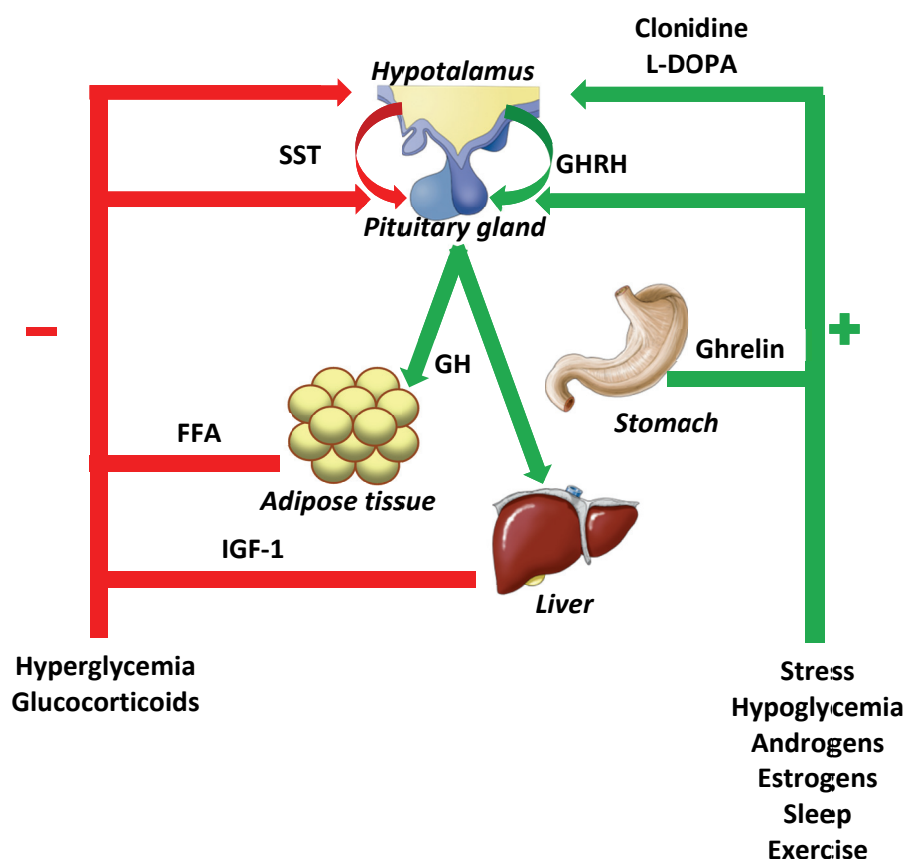


Ghrelin, a small “hunger-stimulating peptide”, is a hormone produced by gastric and pancreas. It is involved in a newly discovered system of regulating GH release. Ghrelin stimulates production of GH through its binding to GH secretagogue receptors (GHSR).

Insulin plays very important role in growth processes, in addition to its actions on carbohydrate and fat metabolism.

Thyroid hormone deficiency is associated with delayed bone growth and epiphyseal closure. Also, GH spontaneous nocturnal secretion is low in hypothyroidism and hyperthyroidism.

Fig.3.: Factors stimulating and inhibiting GH secretion



Abbrev.: FFA – free fatty acids; SST – somatostatin; GH – growth hormone; GHRH - Growth hormone-releasing hormone; L-DOPA - L-3,4-dihydroxyphenylalanine; IGF-1 – insulin-like growth factor-1



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Sex steroids play important role, particularly in puberty. Serum GH concentration rises throughout puberty, in response to increased androgen secretion in both sexes, associated with increase of estradiol in girls. Androgens also exert anabolic growth effects through their actions on protein, but they cannot drive the fully normal tempo of puberty without the actions of GH. Sex steroids are also responsible for the closure of epiphyseal growth plate and thus for inhibition of longitudinal growth in puberty.

Glucocorticoids at excessive levels inhibit growth, apparently because of their antagonistic effect on GH secretion.

Both endocrine and non-endocrine GH stimulating and inhibiting factors are listed in Tab.1, simplified scheme in Fig.3.

Tab.1.: Factors stimulating and inhibiting GH secretion

Stimulators of GH secretion	Inhibitors of GH secretion
<ul style="list-style-type: none"> ○ Peptide hormones <ul style="list-style-type: none"> ○ Growth hormone-releasing hormone (GHRH) through binding to the growth hormone-releasing hormone receptor (GHRHR) ○ Ghrelin through binding to growth hormone secretagogue receptors (GHSR) ○ Sex hormones <ul style="list-style-type: none"> ○ Increased androgen secretion during puberty (in males from testis and in females from adrenal cortex) ○ Estrogen ○ Clonidine and L-DOPA by stimulating GHRH release ○ Hypoglycemia, arginine and propranolol by inhibiting somatostatin release ○ Deep sleep ○ Niacin as nicotinic acid ○ Fasting ○ Vigorous exercise 	<ul style="list-style-type: none"> ○ Somatostatin (SST) from the periventricular nucleus ○ Circulating concentrations of GH and IGF-1 (negative feedback on the pituitary and hypothalamus) ○ Hyperglycemia ○ Glucocorticoids



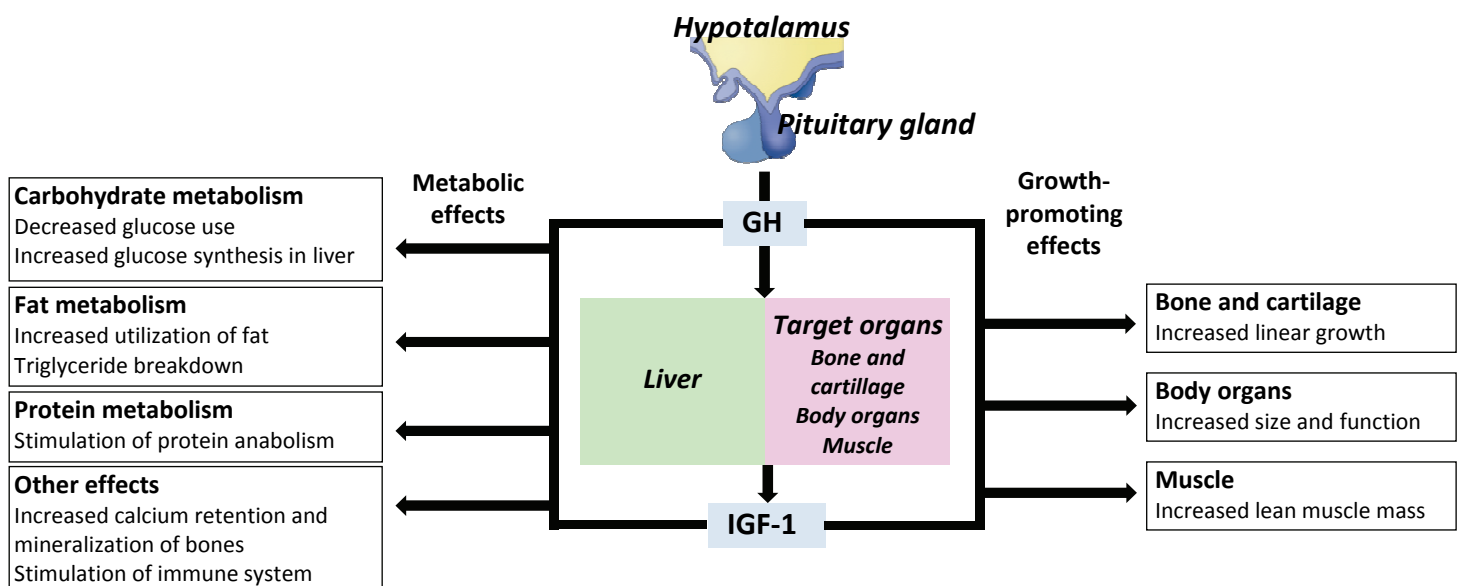
GH AND IGF-1 EFFECTS ON THE BODY

Good function of GH-IGF axis is essential not only for proper growth rate, but it also contributes to the regulation of metabolic functions (Fig.4.).

Although both growth and metabolic action are stimulated by GH, many of its effects are not direct but mediated by IGFs, particularly IGF-1.

IGF-1 is produced primarily by the liver and released in circulation. Such IGF-1 acts as endocrine hormone. But, in contrast to GH, IGF-1 may be also synthesized directly in target organs where it acts in a paracrine/autocrine fashion. Such synthesis by target organs is essential for postnatal organ growth.

Fig.4.: Effects of GH and IGF-1 in the body

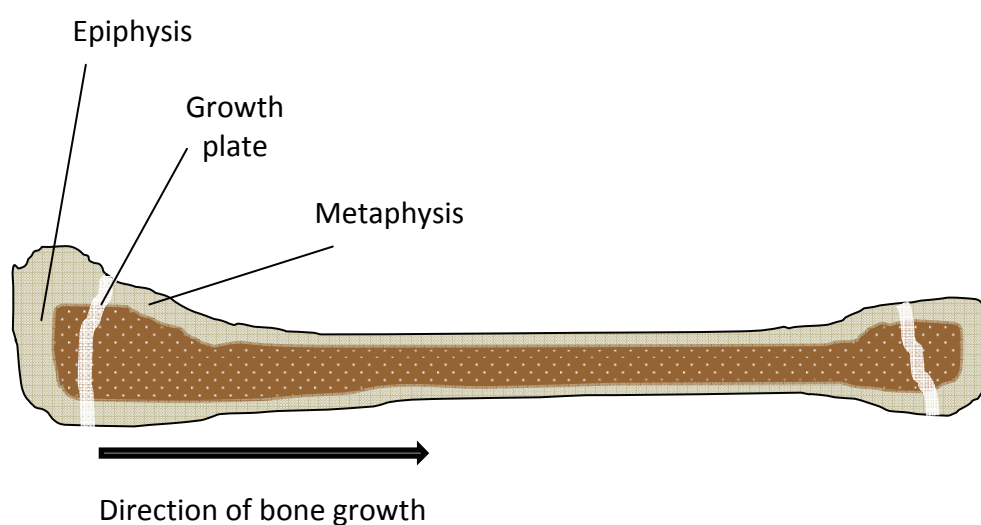




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The most important target organ for linear growth is the epiphyseal growth plate, a layer of cartilage found in growing long bones between the epiphysis and the metaphysis (see Fig.5). Longitudinal bone growth occurs at the growth plate by endochondral ossification, in which cartilage is formed and then remodeled into bone tissue. The cellular distribution is organized according to the stage of cell maturation and differentiation, under a tightly controlled program, and consists of the following cell layers: germinative, proliferative, hypertrophic and degenerative.

Fig.5.: Bone and growth plate



The width of bone increases because of enhanced periosteal growth; visceral and endocrine organs, skeletal and cardiac muscle, skin, and connective tissue all undergo increased growth in response to GH and IGF-1.

In addition to their effects on growth, GH and IGF-1 facilitate the rate of protein synthesis by all of the cells of the body, it enhances fatty acid mobilization and utilization, and it also maintains or increases blood glucose levels by decreasing the use of glucose for fuel.



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ORGANISATION OF GROWTH

GROWTH PHASES

Human growth is a regular process characterized by a pattern of changing growth rate or height velocity from infancy to adulthood (see Fig. 1, page 3).

There are four distinct human growth phases—fetal growth, infancy, childhood, and puberty. Adult shortness may result from subnormal growth during any one or more phases. It seems that growth during the fetal and infancy phases is critical for final height. Children born small for gestational age have a sevenfold increased risk for adult shortness. Growth stunting in early life also increases risk for adult short stature. Nevertheless, the risk for adult shortness associated with subnormal growth during childhood and puberty is known to be important as well.

Rapid growth usually occurs after a period of illness or malnutrition, allowing a child to return to the growth curve he/she had before the illness (so called catch-up growth).

GH AND IGF-1 DYNAMICS DURING THE LIFE

The exact mechanism of fetal growth and its control has not been fully understood yet. In early stages of development, IGF-2 is the coordinating factor of embryonic growth. Later on, its function is undertaken by fetal IGF-1. It is suggested that fetal IGF-1 production is stimulated by fetal insulin at this stage. The fetal pattern of IGF-1 regulation is believed to be dominant until about 6 month of postnatal life.

GH is produced by the pituitary gland of the fetus starting from the end of the 1st trimester of gestation. Despite of relatively high levels, fetal GH does not contribute much to IGF-1 stimulation and to the final size of the fetus. Limited effect of GH is probably due to small number of GH receptors in the tissues. GH-dependent growth dominates in postnatal life when the number of GH receptors increases to the sufficient extent.



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Within the first hours of postnatal life, markedly amplified GH secretory bursts are observed throughout day and night. Such amplified GH response may be due to very low IGF-I levels in early postnatal period.

IGF-I level starts to increase several month after birth and continue to increase until puberty. 24-hour pulsatile GH secretion rates are stable from day to day and are estimated as 200-600 $\mu\text{g/day}$ in the decade before puberty.

The onset of puberty is associated with a marked increase in GH concentration and pulse amplitude, but without changes in pulse frequency or changes in GH half-life. This increase reflects the rise of sex steroid hormone concentrations, and it is associated with a significant increase in IGF-I and IGFBP-3 concentrations. This concomitant rise in GH and IGF-1 appears probably due to changes in in central hypothalamus-pituitary and decrease in feedback loop sensitivity.

In pregnancy, placental form of GH is produced by placenta. It differs in 13 amino acids from 22 kDa pituitary form, and its production is independent on hypothalamus. Production starts at gestation weeks 5-8 and its concentration in maternal blood increases until reaching plateau at week 36. Increase in GH production is accompanied by increase of IGF-1.

Both GH and IGF-1 secretion decrease progressively during adulthood.

The term "somatopause" has been adapted for condition when growth hormone release is diminished due to increased adipose tissue mass, free fatty acid concentration in blood and hyperinsulinism.



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Altered function of the GH-IGF axis

SHORT STATURE STATES IN CHILDREN

Accurate measurement of height is an extremely important part of the physical examination of children. Completion of the developmental history and growth charts is essential. Growth curves and growth velocity studies also are needed. Diagnosis is not made on a single measurement, but is based on actual height and on velocity of growth and parental height¹⁰.

Short stature is a condition in which the attained height is below the fifth percentile or linear growth is below normal for age and sex. Short stature, or growth retardation, has a variety of causes, including GH deficiency, hypothyroidism, panhypopituitarism or chromosomal abnormalities such as Turner's syndrome. Other conditions known to cause short stature include malnutrition, chronic diseases such as renal failure and poorly controlled diabetes mellitus, malabsorption syndromes, and certain therapies such as corticosteroid administration. Emotional disturbances can lead to functional endocrine disorders, causing psychosocial dwarfism. Before searching for the disorders of GH-IGF axis, all other possible cause of retarded growth must be excluded.

Two forms of short stature, genetic short stature and constitutional short stature, are not disease states but rather variations from population norms:

Genetically short children tend to be well proportioned and to have a height close to the midparental height of their parents.

Constitutional short stature is a term used to describe children (particularly boys) who have moderately short stature, thin build, delayed skeletal and sexual maturation, and absence of other causes of decreased growth.

The disorders of growth hormone (GH) in childhood comprise a spectrum of clinical conditions characterized by short stature of varying degrees of severity and slow growth caused by either abnormalities in GH itself, GH-releasing hormone receptor (GHRHR) or the GH receptor (GHR).

Abnormalities in GH production and function include alterations in the production, regulation, secretion or bioactivity of GH and result in **GH deficiency (GHD)**.



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GH insensitivity syndromes (GHIS) connected with abnormalities in the GHR may be due to genetic or acquired defects that cause a state of GH resistance or insensitivity.

Growth hormone deficiency (GHD)

The alterations in the synthesis, secretion and bioactivity of GH are sporadic and heterogeneous (see Tab.2). Its prevalence is approximately of 1:3500.

Tab.2: Causes of GHD

Type	Specification
Genetic	
Congenital	Associated with structural defects Agenesis of corpus callosum Septo-optic dysplasia Holoprosencephaly Arachnoid cyst Associated with midline facial defects Single central incisor Cleft lip/palate Nasal dimple
Acquired	Perinatal trauma Postnatal trauma Central nervous system infections
Primary tumors of hypothalamus or pituitary	Craniopharyngioma Glioma/astrocytoma Germinoma
Secondary tumors of hypothalamus or pituitary	Histiocytosis Lymphoma
Cranial irradiation	
Transient	Psychosocial deprivation



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Majority of GHD patients is still considered as idiopathic in nature, with no apparent cause of the disease. Nevertheless, high incidence of perinatal problems such as breech births or vaginal bleeding has been found in seemingly idiopathic GHD patients when carefully searched for. Children with idiopathic GH deficiency lack the hypothalamic GHRH but have functional somatotropes.

Children with pituitary tumors or agenesis of the pituitary lack somatotropes. GHD can present as an isolated GH deficiency or can be associated with other pituitary hormone deficiencies, most often TSH deficiency and less common gonadotropin or ACTH deficiencies.

During early childhood, isolated GHD can present itself with a classical phenotype of growth failure, protrusion of the frontal bones and poor development of the bridge of the nose. Closure of the anterior fontanel may be delayed and dental eruption and skeletal maturation are usually quite delayed. The penis is often small and this may be accentuated by the presence of truncal obesity. Delay of puberty is frequent. However, if gonadotropin function is intact, puberty will develop.

Congenital GH deficiency is associated with normal birth length, followed by a decrease in growth rate that can be identified by careful measurement during the first year, and that becomes obvious by 1 to 2 years of age.

Acquired GH deficiency develops in later childhood; it may be caused e.g. by infections, trauma, cranial irradiation or hypothalamic-pituitary tumor, and may be accompanied by other pituitary hormone deficiencies.

Rare form may be caused by biologically inactive GH molecule. Low concentrations of IGF-1 and normal to high GH concentrations are found in such cases, similarly to GH insensitivity syndromes (see below).

Another rare form, occurring in some isolated communities, is caused by GHRH receptor mutations.



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Specific form of GHD is so called psychosocial dwarfism. It is seen in emotionally deprived children and involves a functional hypopituitarism. Children usually present with poor growth, potbelly, and poor eating and drinking habits. GH function usually returns to normal after the child is removed from the constraining environment.

Diagnostics

Because of pulsatile nature of GH secretion, GHD cannot be diagnosed with a random blood sample. GH levels are often low during majority of a 24-hour period.

The diagnosis should be confirmed by two GH provocation tests, in which the concentration of GH fails to rise above 20 mIU/L. Arginine, clonidine, glucagon or L-dopa are recommended as stimulation agents.

It is beneficial to determine also IGF-1 and/or IGFBP-3 concentrations. Low levels correspond with diagnosis of GHD.

In case of discordant results of stimulated GH level and IGF-I/IGFBP-3 levels, evaluation of spontaneous GH secretion over time (12 or 24 hours) may help to set up diagnosis.

Radiological investigations include magnetic resonance imaging (MRI) of the brain and determination of skeletal maturation (bone age). Molecular investigations of the GH gene and of other candidate genes such as GHRHR genes should be considered in children with familial GHD or in children with sporadic forms of classical GHD, in particular in children with multiple pituitary hormone deficiency.

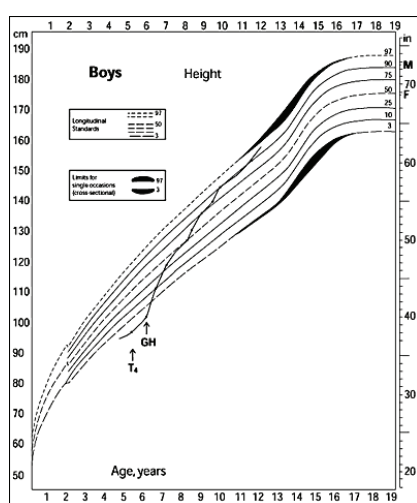
Treatment

After a diagnosis of GHD has been confirmed, the treatment is relatively simple, using a replacement therapy with daily subcutaneous injections of human recombinant GH. If the diagnosis of multiple hormone deficiency has been made, replacement therapy with appropriate doses of hydrocortisone and thyroxine is initiated before starting GH therapy.



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Fig.6: Growth chart of a patient with growth hormone deficiency before and during treatment with GH (Example of catch-up growth).



The aim of GH replacement therapy is to improve height velocity, normalize height during childhood, and restore IGF-1 and IGFBP-3 levels to within the reference range, ideally into the middle third. Higher levels are rarely associated with any further therapeutic gains, but can potentially lead to certain long-term problems associated with an excess of GH.

Children with short stature due to Turner's syndrome and chronic renal insufficiency also benefit from treatment with GH.

GH therapy may be also considered for children without GH deficiency but with short stature.

GH insensitivity syndromes

The term of GH insensitivity syndrome (GHIS) describes a group of inherited disorders characterized by a reduction in the biological effects of GH in the presence of normal or elevated serum GH concentrations.

The first report of GHIS, known as Laron syndrome, is associated with defects of the GHR gene.

The clinical characteristics of the affected patients are very similar to those seen in GH deficiency caused by to mutations in the GH gene, symptoms are namely hypoglycemic episodes, severe growth failure and a typical craniofacial appearance. Growth retardation is clearly visible already during the early post-natal years.



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Diagnostics

Typical signs are severe short stature with or without classical features of Laron syndrome, with normal to high serum GH concentrations, very low serum IGF-1 and IGFBP-3.

Treatment

Children with GHIS are treated with recombinant human IGF-1. Although the recombinant IGF-1 substitutes well the role of liver IGF-1 and its endocrine effect, treatment may not completely compensate the local response of target tissues to locally produced IGF-I.

GROWTH HORMONE DEFICIENCY IN ADULTS

There are two categories of GH deficiency in adults:

- GH deficiency that was present in childhood
- GH deficiency that developed during adulthood mainly as the result of hypopituitarism resulting from a pituitary tumor or its treatment.

Diagnostics is based on stimulation tests. Although spontaneous GH secretion declines with age, response to dynamic tests is not altered and the same cut-off can be used for different age.

GH replacement obviously is important in the growing child, but it seems profitable also in GH deficient adults. Nevertheless, there is an ongoing debate about the correct dose adjustment.

There is also increasing interest in the effects of declining GH levels in elderly persons (described as somatopause). Possible administration of GH still remains a controversial issue.



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TALL STATURE STATES IN CHILDREN

Just as there are children who are short for their age and sex, there also are children who are tall for their age and sex. Normal variants of tall stature include genetic tall stature and constitutional tall stature. Children with exceptionally tall parents tend to be taller than children with shorter parents. The term **constitutional tall stature** is used to describe a child who is taller than his or her peers and is growing at a velocity that is within the normal range for bone age. Other causes of tall stature are genetic or chromosomal disorders such as Marfan's syndrome or XYY syndrome. Endocrine causes of tall stature include sexual precocity because of early onset of estrogen and androgen secretion and excessive GH.

Exceptionally tall children (*i.e.*, genetic tall stature and constitutional tall stature) can be treated with sex hormones—estrogens in girls and testosterone in boys—to effect early epiphyseal closure. Such treatment is undertaken only after full consideration of the risks involved. To be effective, such treatment must be instituted 3 to 4 years before expected epiphyseal fusion.

Growth hormone excess in children

Growth hormone excess occurring before puberty and the fusion of the epiphyses of the long bones results in gigantism. Excessive secretion of GH by somatotrope adenomas causes gigantism in the prepubertal child. It occurs when the epiphyses are not fused and high levels of IGF-1 stimulate excessive skeletal growth. Fortunately, the condition is rare because of early recognition and treatment of the adenoma.

GROWTH HORMONE EXCESS IN ADULTS - ACROMEGALY

Acromegaly is a condition when GH excess occurs in adulthood, after the epiphyses of the long bones have fused. Prevalence of this disease is relatively low, approximately 1: 17 000.

When the production of excessive GH occurs after the epiphyses of the long bones have closed, as in the adult, the person cannot grow taller, but the soft tissues continue to grow, including body organs.



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Acromegaly results from excess levels of GH that stimulate the hepatic secretion of IGF-1, which causes most of the clinical manifestations of acromegaly. Mean age at the time of diagnosis is 40-45 years.

Approximately 75% of persons with acromegaly have a somatotrope macroadenoma at the time of diagnosis, and most of the remainder have microadenomas. The other causes of acromegaly (<5%) are excess secretion of GHRH by hypothalamic tumors, ectopic GHRH secretion by nonendocrine tumors such as carcinoid tumors or small cell lung cancers, and ectopic secretion of GH by nonendocrine tumors¹¹.

The metabolic effects of excess levels of GH include alterations in fat and carbohydrate metabolism, with subsequent GH-induced insulin resistance, and frequently even overt diabetes mellitus. There are many other symptoms including hypertension, excessive sweating, oily skin, heat intolerance, weight gain, muscle weakness and fatigue, menstrual irregularities and decreased libido.

Acromegaly often develops insidiously, and only a small number of persons seek medical care because of changes in appearance. The diagnosis of acromegaly is facilitated by the typical features of the disorder — enlargement of the hands and feet and coarsening of facial features.

Acromegaly (and gigantism) is confirmed if no decrease or a paradoxical increase in GH level after OGTT (oral glucose tolerance test) is found.

MRI and CT scans can detect and localize the pituitary lesions. Because most of the effects of GH are mediated by IGF-1, IGF-1 levels may provide information about disease activity. Pituitary tumors can be removed surgically. Radiation therapy may be used, but remission may not occur for several years after therapy. Radiation therapy also significantly increases the risk for hypopituitarism, hypothyroidism, hypoadrenalism, and hypogonadism. Medical therapy usually has an adjunctive role only.

In well treated acromegaly, IGF-1 level should be within normal range and GH nadir values should be below 0.4 ng/mL during OGTT. IGFBP-3 determination may be useful when GH and IGF-I levels are discordant.



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