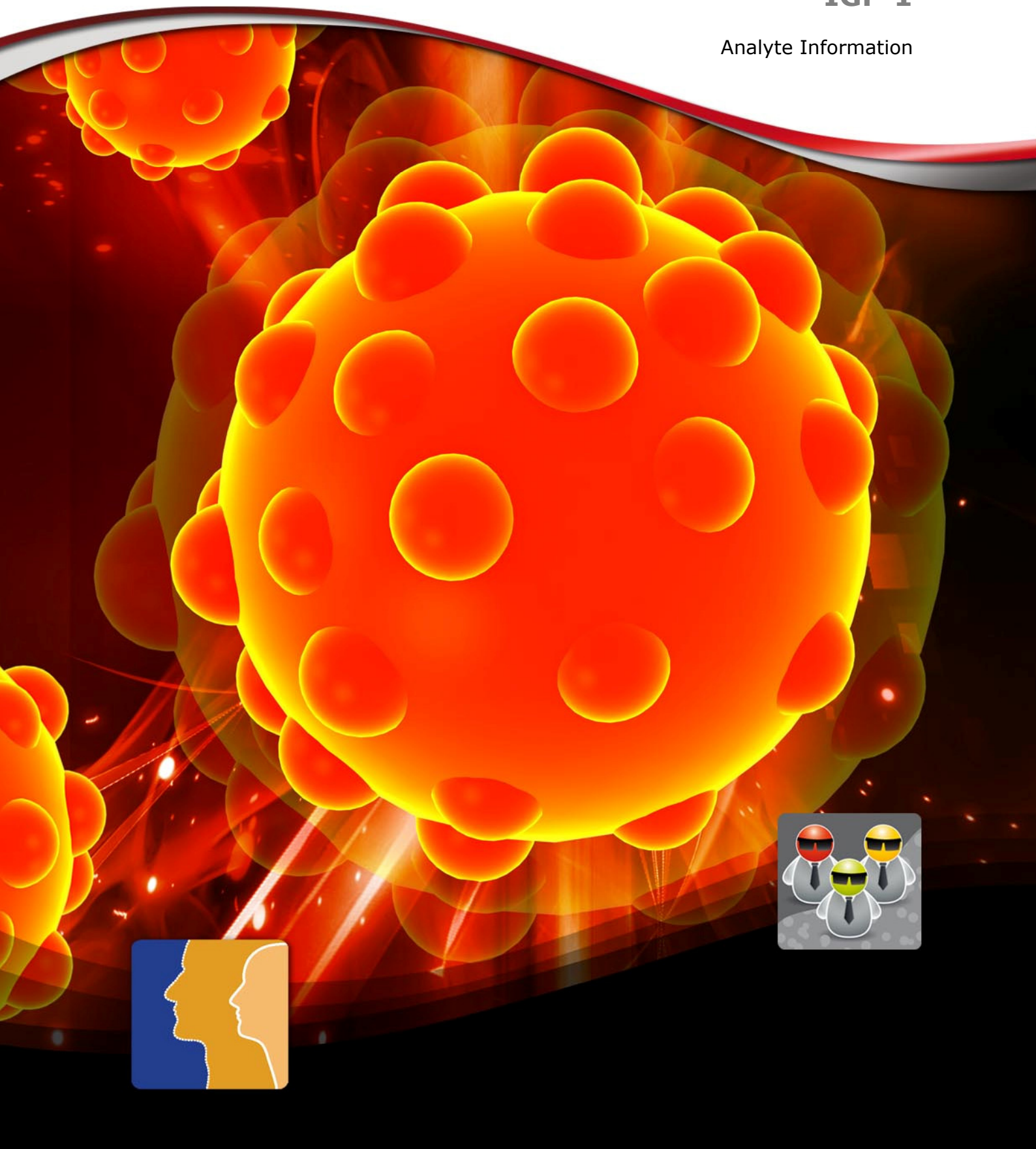
Growth

IGF-1

Analyte Information



IGF-1

Introduction

Insulin-like growth factor 1 (IGF-1, IGF-I) is a single chain polypeptide containing 70 amino acids and three disulfide bridges. It is structurally similar to proinsulin. Its molecular weight is 7649 daltons.

IGF-1, together with structurally similar IGF-2, belongs to so called insulin-like growth factor family. Its main biological function is to promote growth in cartilage, bone and soft tissue. Besides growth-promoting effects, it has also insulin-like activity in many tissues.

Its older name is somatomedin C, it was also called sulfatation factor in the past.

Biosynthesis

IGF-1 is produced primarily by the liver as an endocrine hormone. Approximately 55% of serum concentration is derived from liver production. IGF-1 is also produced in target organs like kidney, adrenal glands, mammary glands, pancreas and others, acting in a paracrine/autocrine fashion.

Production is stimulated by growth hormone (GH), both in liver and target organs. On the other hand, IGF-1 affects GH production by negative feedback.

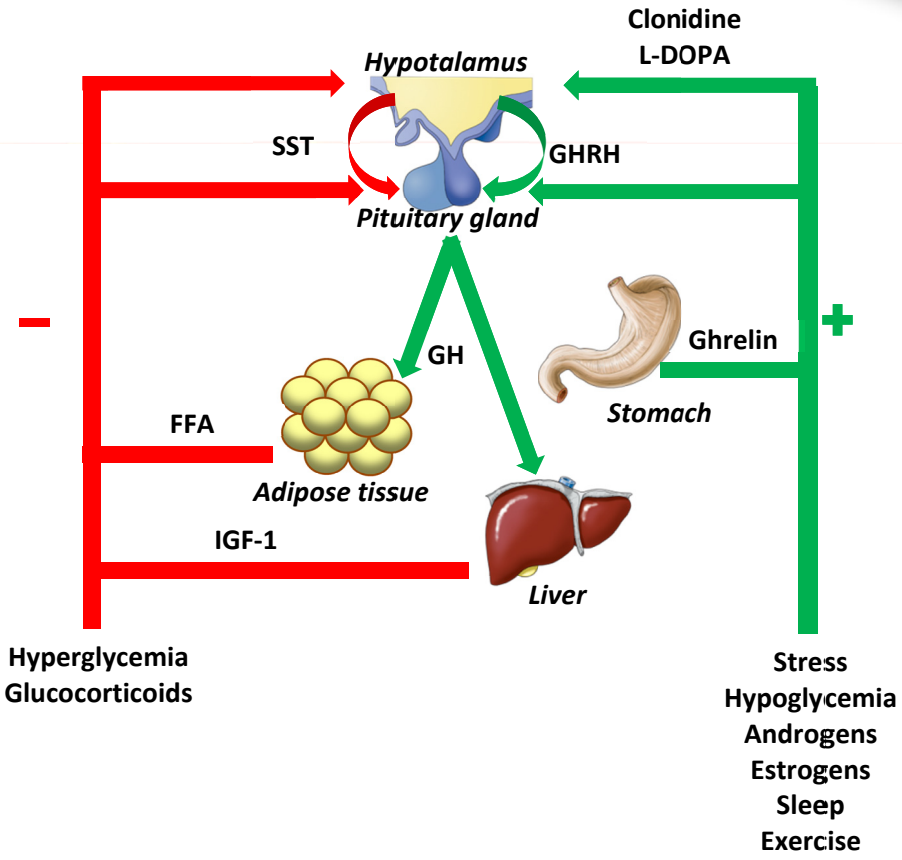
IGF-1 production can be retarded by malnutrition, GH insensitivity, lack of G receptors, or failures of the downstream signalling pathway post GH receptor. Other factors like sex steroids, thyroid hormones and some paracrine factors are involved, too.

Simplified scheme of IGF-1 production under the control of GH is in Fig. 1.

Metabolism

IGF-1 is metabolized by both liver and kidneys. Biological half-life of IGF-1 complex with IGFBP-3 and ALS is 12-15 hours, whilst free IGF-1 half-life is only 5-10 minutes[3].

Fig.1.: Factors stimulating and inhibiting GH and IGF-1 production

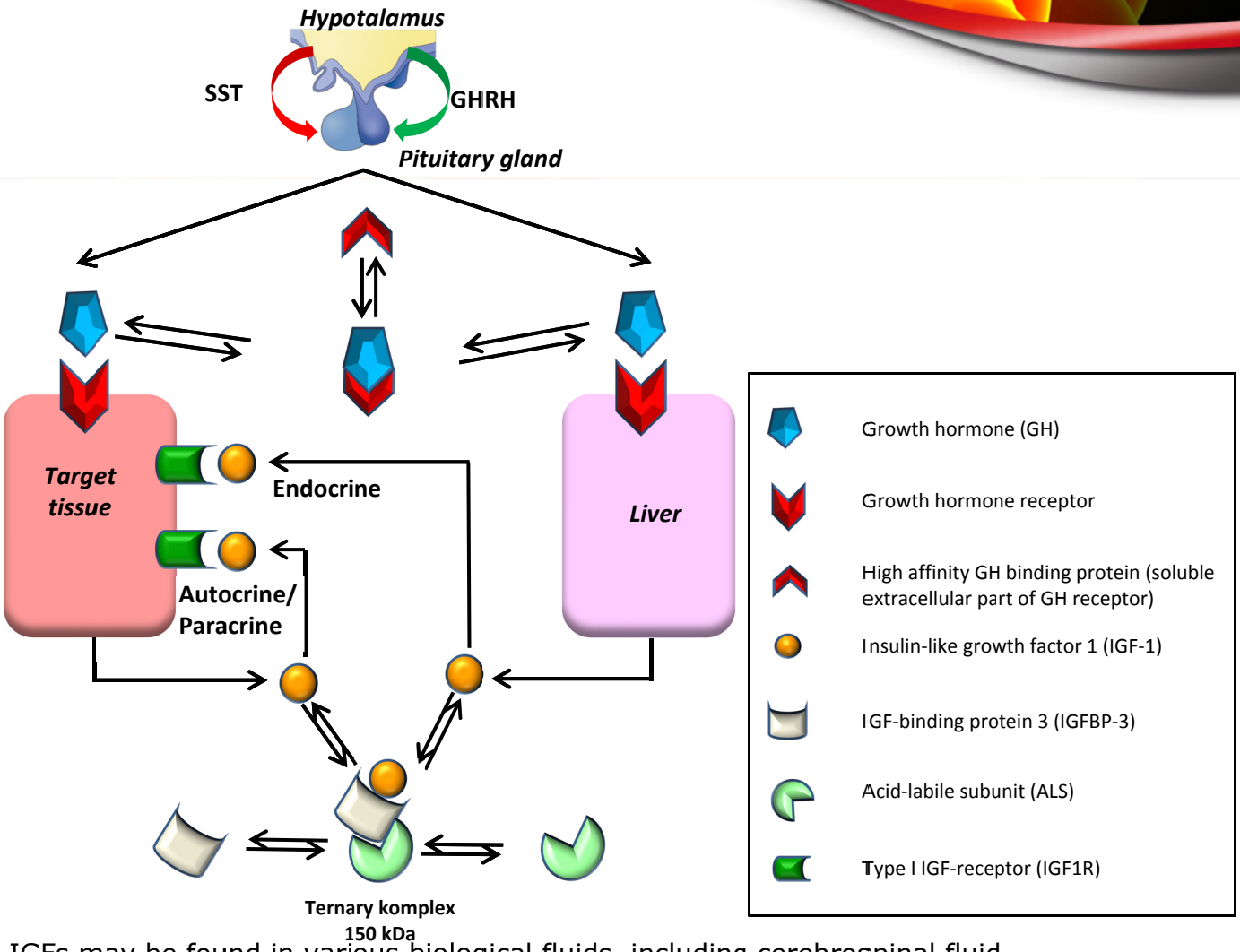


Abbrev.: FFA – free fatty acids; SST – somatostatin; GH – growth hormone; GHRH - Growth hormone-releasing hormone; L-DOPA - L-3,4-dihydroxyphenylalanine; IGF-1 – insulin-like growth factor-1

Physiological function

The IGF system is composed of two main IGF peptides (IGF-1 and IGF-2), two specific receptors, a family of IGF binding proteins and a glycoprotein named the acid-labile subunit. Both insulin-like growth factors are single chain polypeptides with structural similarity to proinsulin. Both IGF-1 and IGF-2 have certain effects similar to those of insulin, therefore the name insulin-like growth factors. Structural analogy of IGF-1 and IGF-2 is 62%, analogy of IGF-1 with proinsulin is 42%.

Fig.2.: GH-IGF axis



IGFs may be found in various biological fluids, including cerebrospinal fluid, amniotic fluid, sperm, saliva, or milk. Approximately 98% of IGF-1 in blood is bound to one of six specific binding proteins called insulin-like growth factor binding proteins (IGFBPs). The role of IGFBPs is to moderate biological availability of IGFs.

IGFBP-3, the most abundant protein of all IGFBPs, accounts for 80% of all IGF binding. Most of IGF-1 in blood is bound in 150 kDa tertiary complex consisting of one molecule of IGF-1 bound to IGFBP-3 and of a protein ALS (acid-labile subunit), which does not bind directly to IGF-1.

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.

Its primary action is mediated by binding to IGF-1 receptor, which is present on various cell types in many tissues. IGF-1 is one of the most potent natural activators of the AKT signalling pathway, a stimulator of cell growth and proliferation, and a potent inhibitor of apoptosis (programmed cell death).

Ability of IGF-1 to activate the insulin receptor is approximately ten times lower than that of insulin.

IGF-1 is produced primarily by the liver as an endocrine hormone, but also in target organs where it acts in a paracrine/autocrine fashion. Target organ synthesis is essential for postnatal organ growth.

The IGF-1 effects are very complex (see also Fig. 3.):

Biological effects

IGF-1 is the principal mediator of GH.

It stimulates the proliferation of different cell types: fibroblasts, chondrocytes, hematopoietic and mammary cells.

Effects on cellular differentiation

IGF-1 stimulates the differentiation of chondrocytes, osteoblasts, adipocytes and of muscular tissue.

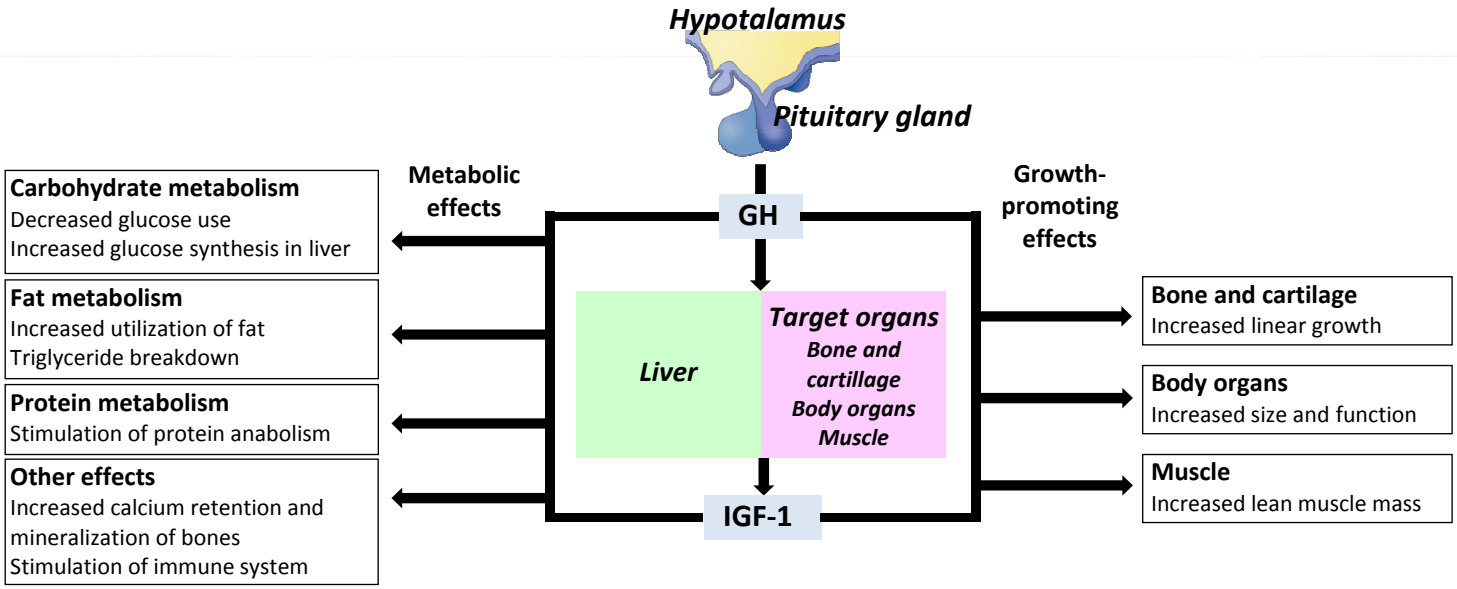
Insulin mimetic effects

IGF-1 stimulates the transport of glucose and amino acids, and the synthesis of glycogen and proteins, it inhibits lipolysis.

Potentiation of the effect of other hormones

IGF-1 acts on the cells of the granulosa by potentiating the effects of FSH on progesterone synthesis and inducing the LH receptors. It exerts similar effects on the Leydig cells (potentiation of FSH), Sertoli cells (potentiation of LH) and on the corticoadrenals (potentiation of ACTH).

Fig.3.: Effects of GH and IGF-1 in the body



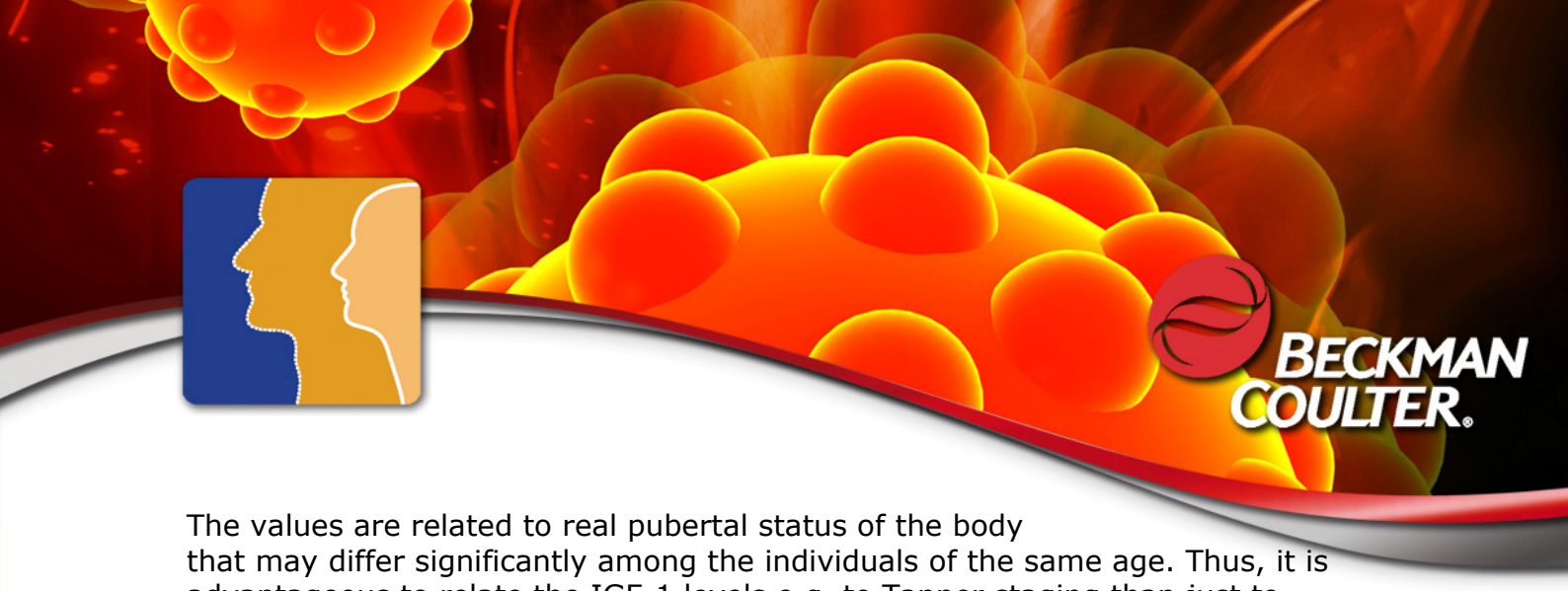
Levels

IGF-1 level in the blood is stable during the day and after eating, as a results of its binding to IGFBP-3.

Great differences may be seen during the life. In early stages of development, IGF-2 is the coordinating factor of embryonic growth. Later on, its function is undertaken by fetal IGF-1[9].

In contrast to GH, postnatal levels of IGF-1 are very low, and they start to increase several months after birth.

They continue to increase until puberty. The onset of puberty is associated with a marked increase in all GH, IGF-1 and IGFBP-3 levels, in response to increased levels of sex steroid hormones. This concomitant rise in GH and IGF-1 appears probably due to changes in hypothalamus and pituitary gland, resulting in decreased feedback loop sensitivity.



The values are related to real pubertal status of the body that may differ significantly among the individuals of the same age. Thus, it is advantageous to relate the IGF-1 levels e.g. to Tanner staging than just to chronological age.

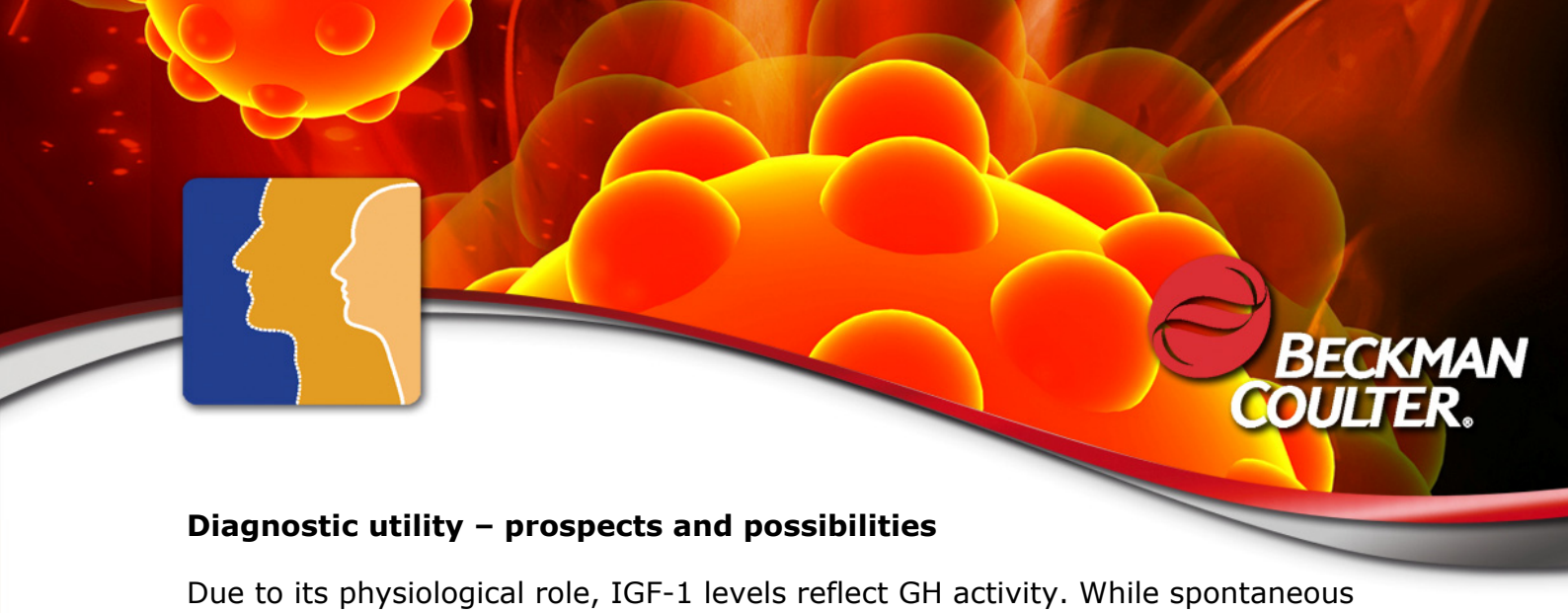
After reaching maximum values during puberty, IGF-1 levels decrease progressively during adulthood.

IGF-1 values are significantly higher during pregnancy.

Typical IGF-1 levels[2] of children and adult males and females are given in Tab. 1. For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Tab.1.: Typical IGF-1 levels

Serum		**Reference interval** (ng/mL)*
Male;	1–2 years	31–160
Female;	1–2 years	11–206
Male;	3–6 years	16–288
Female;	3–6 years	70–316
Male;	7–10 years	136–385
Female;	7–10 years	123–396
Male;	11–12 years	136–440
Female;	11–12 years	191–462
Male;	13–14 years	165–616
Female;	13–14 years	386–660
Male;	15–18 years	134–836
Female;	15–18 years	152–660
Male;	19–25 years	202–443
Female;	11–25 years	231–550
Adult;	26–85 years	135–449



Diagnostic utility – prospects and possibilities

Due to its physiological role, IGF-1 levels reflect GH activity. While spontaneous GH secretion is episodic, there is no diurnal variation in IGF-1 levels — they depend only on age, sex and pubertal status.

Therefore, its measurement is more useful tool for evaluation of GH-IGF axis than random determination of GH itself. In practice, the IGF- levels are often determined in combination with stimulated or suppressed GH values.

IGFBP-3 may be used in addition to IGF-1 and GH determinations, too, especially in cases when GH and IGF-1 levels are discordant.

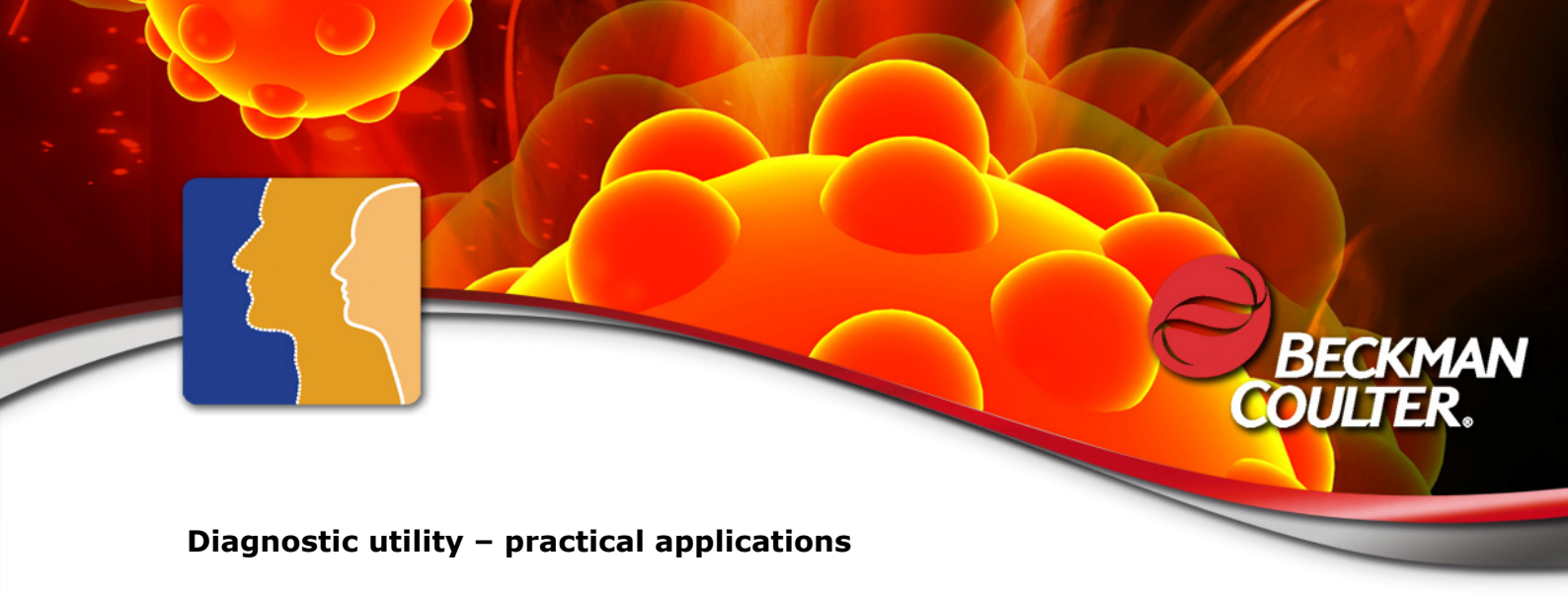
Altered IGF-1 levels can be found in a broad spectrum of conditions, e.g.:

Elevated IGF-1 levels

- gigantism
- acromegaly
- ectopic GH secretion (neoplasms of stomach, lung)

Decreased IFG-1 levels

- dwarfism (both Laron and pituitary dwarfism)
- malnutrition, prolonged fasting, anorexia nervosa
- emotional deprivation syndrome
- hypopituitarism
- hypothyroidism
- cirrhosis of liver, other hepatocellular diseases



Diagnostic utility – practical applications

IGF-1 measurement is used, either alone or in conjunction with other tests (GH after stimulation or suppression, IGFBP-3) to diagnose diseases of GH-IGF axis and to monitor their treatment.

GH deficiency (GHD) in childhood and in adults[5,8]

The evaluation for GHD in a short child should be initiated when other possible causes like hypothyroidism, chronic systemic disease etc. are excluded. 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.

Both GH deficiency and mild-to-moderate GH-resistance is treated with recombinant human GH (rhGH) injections.

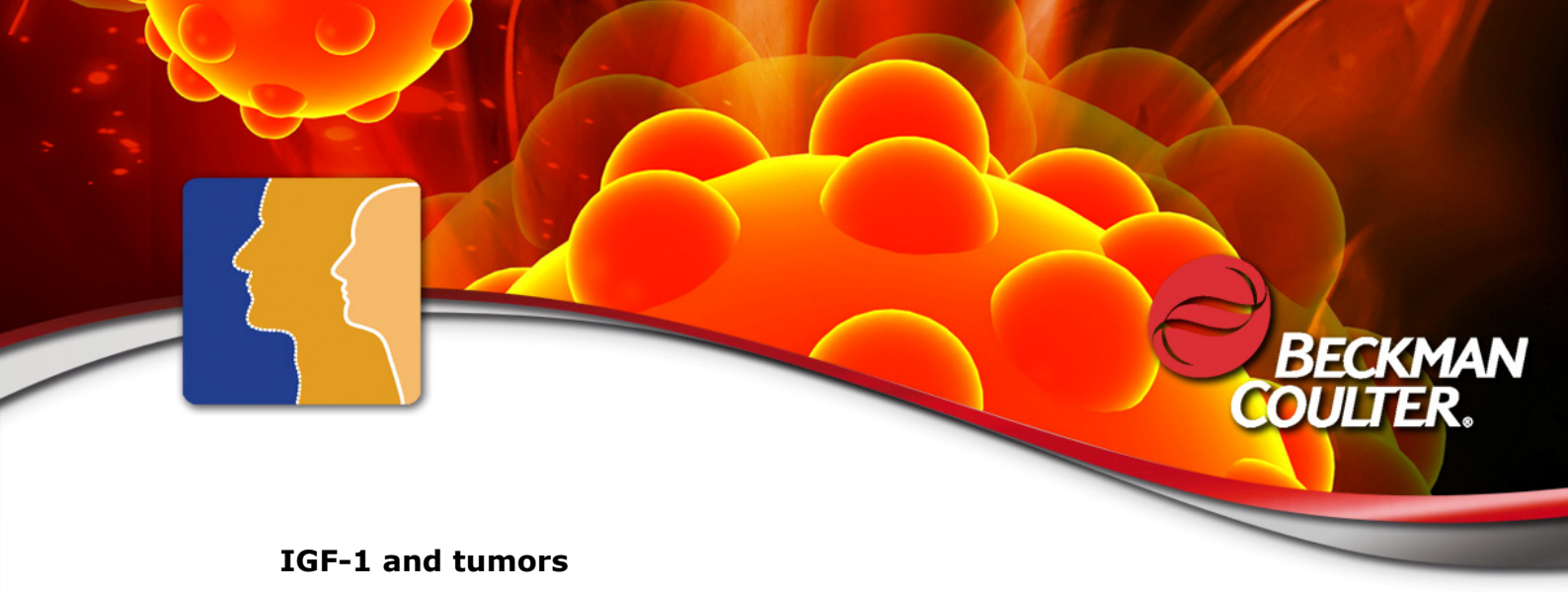
IGF-1, alone or in combination with IGFBP-3, is also used to monitor treatment. IGF-1 levels should fall within the reference range, ideally into the middle third. Higher levels are rarely associated with any further therapeutic gains, but can potentially lead to certain long-term problems associated with an excess of GH.

GH replacement therapy is also profitable in GH deficient adults. Nevertheless, there is an on-going debate about the correct dose adjustment.

Acromegaly[6]

Glucose normally suppresses GH production (<1-2 ng/mL). Individuals with acromegaly or gigantism show no decrease or a paradoxical increase in hGH level after OGTT (oral glucose tolerance test). IGF-1 may be used in diagnosing patients who have relatively low basal levels of GH and patient suspect of acromegaly who have suppression of GH to normal after glucose administration.

IGF-1 and GH are used also for monitoring. 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-1 levels are discordant.



IGF-1 and tumors

Many studies concerning this topic IGF-1 levels and their association with several types of tumors have been published recently, and a lot of interest is still devoted to this topic. IGF-1 has been proposed as a predictor of prostate cancer, but there is still controversy about the benefits of IGF-1 determination for other possible applications in this field.

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