Review Articles
Insulin- Like Growth Factors I- II

Dana Hiyasat and Kamel Ajlouni*

Abstract

IGF- I that is generated in the liver is the anabolic effector and linear growth promoting hormone of the pituitary Growth Hormone (GH). In the tissues, IGFs are important regulators of cell survival, growth, metabolism and differentiated functions.

Prospective studies suggest that individuals with circulating levels of Insulin- like Growth Factor 1 (IGF- I) at the high end of the normal range are exposed to increased risk for several common cancers. This has led to the development of novel IGF- I receptor targeting therapies which have impressive antineoplastic activity in experimental system. This review article will focus on the biology of IGF- I and its role in health and malignant states.

Introduction

Insulin-like growth factors I and II are polypeptide skeletal growth factors secreted by the liver and other tissues in response to stimulation by the growth hormone. These factors are structurally related to insulin. They are partially GH dependent and they mediate many of the anabolic and mitogenic actions of GH.[1, 2]

These growth factors were discovered in late 1950's, and were originally called somatomedian. In 1972, criteria were established and the following features were considered essential to accept growth factor as somatomedian: [2]

- The concentration of this factor in the serum must be GH-dependent.
- It must possess insulin-like activity in extra-skeletal tissues.
- The factor must promote the incorporation of sulfate into cartilage.
- It must stimulate DNA synthesis and cell multiplication.

Since then, many publications appeared in the literature dealing with IGF-I, this review attempts to cover the following aspects:

- The physiology and pathophysiology of IGF-I.
- The use of IGF-I in clinical practices.

The National Center for Diabetes, Endocrinology and Genetics, Amman- Jordan.
* Correspondence should be addressed to:
Prof. Kamel Ajlouni
President, National Center for Diabetes, Endocrinology and Genetics.
P.O. Box: 13165 Amman, Jordan.
E-mail: ajlouni@ju.edu.jo.

IGF-I: IGF-I is a peptide that consists of 70 amino-acids with a molecular weight of 7647 kd, it was originally called (somatomedian C). More than 99% of this peptide is protein-bound, and the liver is the main source of IGF-I; it accounts for 75% of the circulating IGF-I in plasma. [2, 3]

In addition to the liver, IGF-I could be produced locally in other peripheral tissues, such as: bone, cartilage, erythroid cell precursors in response to erythroprotein, central nervous system, skeletal muscle, and the kidney which is another important local source of IGF-I.

IGF-II: It is a peptide that consists of 67 aminoacids. Both IGF-I and IGF-II share 45 amino-acids positions and approximately 50% amino-acid homology with insulin. [2]

IGF-II is secreted by the brain, kidney, pancreas and muscle mammals, it promotes proliferation of many cell types; primarily those that are of fetal origin.

In the fetus, levels of IGF-II are high and it is almost exclusively expressed in embryonic and neonatal tissues.

By 1 year of age, the adult levels of IGF-II are attained with little, if any, subsequent decline, even up to the seventh or eighth decade, so it is less age-dependent and less growth-hormone-dependent than IGF-1, as will be explained later. [2, 3, 4]

IGF-II mRNA is expressed constitutively in a number of mesenchymal and embryonic tumors including:

Wilm's tumor, Rhabdomyosarcoma, Neuroblastoma, Leiomyoma, Leiomyosarcoma, Liposarcoma, in addition to colon cancer-production of a certain variant of IGF-II by these tumors called "Big IGF-II" which may cause Non- Islet- Cell Tumor Hypoglycemia (NICTH). [2]

Regulation of Circulating IGF-I: Several factors are regulating IGF-I levels in plasma, which include:

1- Growth Hormone (GH) [2, 5, 6]

GH stimulates IGF-I production from the liver, while IGF-I had a direct negative feedback effect on the anterior pituitary that inhibits GH release. IGF-I can also Stimulate Somatostation (SS) release by the Hypothalamus, that will in turn inhibit GH secretion from the anterior pituitary. [7] (Fig. 1)

IGF-I is the major mediator of many of the anabolic effects of GH such as protein synthesis and stimulation of epiphyseal growth. However, it is important to remember that certain direct actions of GH such as stimulation of lipolysis and the antagonism of insulin are not shared by IGF-I, on the contrary, IGF-I has both antilipolytic and insulin-like activities [7] (Table 1).

Growth hormone is a major determinant of plasma IGF-I, in addition to its role in stimulating IGF-I gene transcription. IGF-I stimulates the synthesis of IGF-Binding Protein 3 (IGFBP-3), which is a carrier protein, and another 88 kd protein called Acid Labile Subunit (ALS).

In normal adults serum, 75% to 80% of IGF-I peptides are carried in a ternary complex, consisting of one molecule of IGF-I plus one molecule of IGFBP-3 plus one molecule of Acid Labile Subunit (ALS).

Formation of this ternary complex is very important for two reasons:
1) This complex will cause stabilization of IGF-I since it is too large to leave the vascular compartment.
2) It will cause prolongation of IGF-I half-life from 10 minutes for IGF-I alone, to 1-2 hour for IGF-IGFBP-3, to 12-16 hours for the ternary complex. [2, 3]
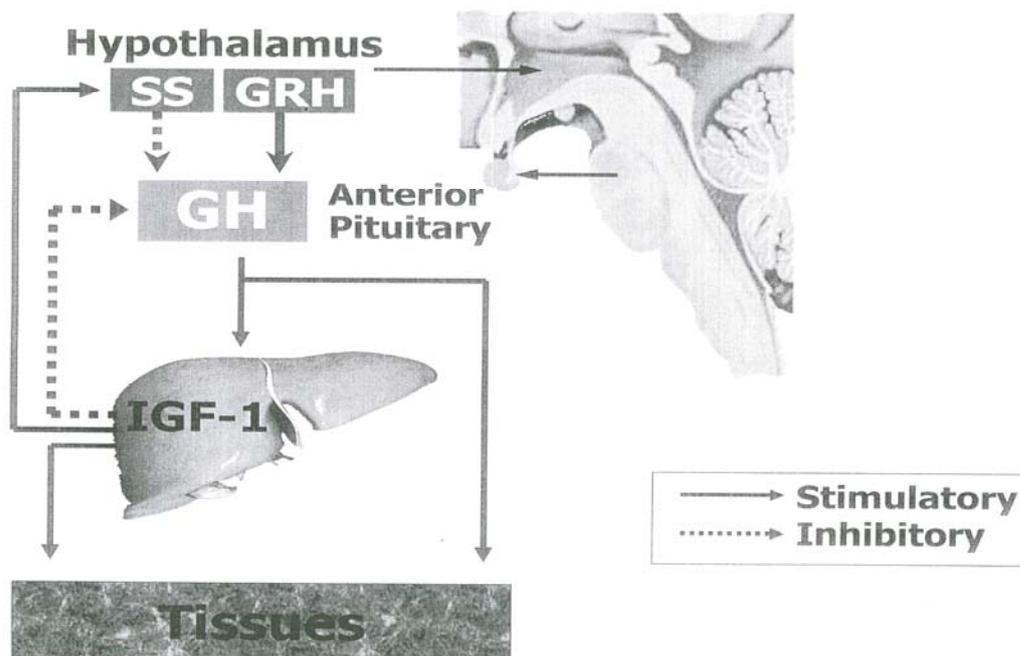
Fig. 1: Feedback control of the Growth Hormone secretion. The dashed arrows indicate inhibitory effects and the solid arrows stimulatory effects .Note that IGF-I stimulates the Secretion of Somatostatin (SS) from the hypothalamus and acts directly on the pituitary to inhibit the Growth Hormone (GH) secretion.

Table (1): Current view of actions mediated by Growth Hormone (GH) and IGF-I:

Actions on	GH	IGF-I
Proteins	*Stimulates protein synthesis*	*Stimulates protein synthesis*
Epiphyseal growth	*Stimulates epiphyseal growth*	*Stimulates epiphyseal growth*
Insulin	*Decreases insulin sensitivity*	*Had insulin-like activity*
Lipids	*Stimulates lipolysis*	*Had antilipolytic activity*

2- Age

In human fetal serum, IGF-I levels are relatively low, but its concentration is positively correlated with gestational age. In newborn infant, IGF-I level is still low at birth and generally it is 30-50% of adult levels. After that, IGF-I increases progressively around sevenfold to reach its peak values at puberty, and here we clearly have an establishing association between pubertal rise in IGF-I and the production of gonadal steroids. [2, 5, 6]

The pubertal rise in gonadal steroids may stimulate IGF-I production indirectly, by first leading to a rise in GH secretion.

However, patients with Growth Hormone insufficiency due to Growth Hormone receptor mutation show also pubertal rise in serum IGF-I, despite the decline in GH levels, suggesting a direct effect of gonadal steroids on IGF-I.

After puberty, the concentration of IGF-I falls rapidly reaching values that are 40-50% of maximum pubertal levels by the age of 20-30 years, then it continues to decline moderately throughout the eighth decade of life. [2, 7]

These changes in IGF-I levels are partially due to age-dependent changes in GH secretion. [15, 12] (Fig 2).
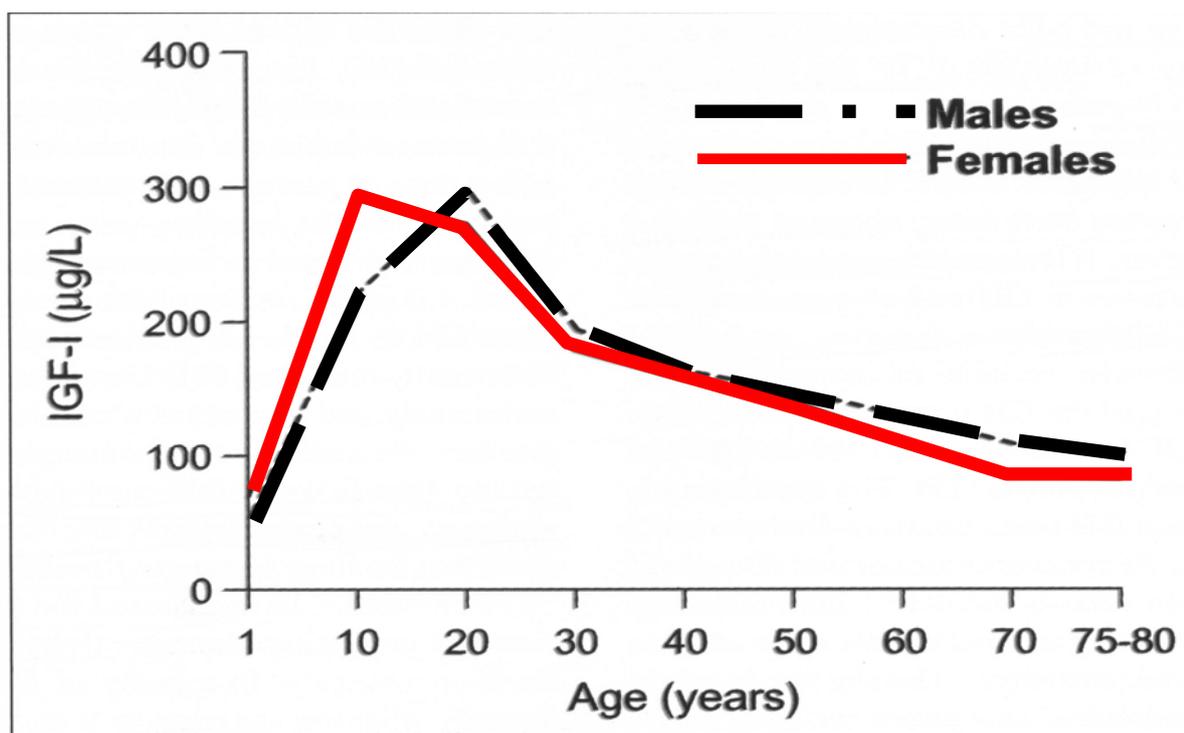
Fig. 2: Mean Insulin-like Growth Factor-I (IGF-I) concentration, shown by age and sex. IGF-I levels in both sexes are relatively low at birth, then it increases progressively to reach its peak values at puberty. After puberty the concentration of IGF-I falls rapidly reaching values that are 40-50% of maximum pubertal levels by the age of 20-30 yrs, then it continues to decline throughout the eighth decade of life.

3- Nutritional Status

Minimum intakes of 20 Kcal/kg/day of energy and 0.6 g/kg of protein are necessary to maintain normal plasma values of IGF-I.

Fasting for seven days will result in 50% decrease in IGF-I values. [11] A decline in IGF-I is also seen in diseases associated with malnutrition; such as hepatic failure, renal failure and inflammatory bowel disease.

Plasma IGF-I is also reduced in hypothyroidism and increased with T_4 replacement. [10]

4- Genetic Determinant

IGF-I concentrations are determined by genetic variables such as polymorphisms in the promoter region of IGF-I gene.

In studies of twins, investigators have estimated that genetic determinants may account for up to 40% of the variation in serum IGF-I concentrations, that occurs in normal individuals. [10, 12]

Actions of IGF-I [3, 7, 14]

IGF-I stimulates muscle growth, and has been shown to benefit the heart as a muscle since it has a direct inotrapic effect on the mammalian myocardium, by augmenting myofilaments responsiveness to Ca^{++}.

- IGF-I encourages the absorption of sulfate into cartilage.
- It improves the production of white blood cells.
- It regenerates nerve tissues.
- It improves parathyroid-vitamin D interaction to produce dense bone matrix.
- It lowers LDL cholesterol.

Also, IGF-I stimulates specialized functions in endocrine tissues including:

- The enhancement of the effects of FSH and LH on the production of:
  A. Steroids by ovarian granulosa cells.
  B. Testosterone by leydig cells.
- The enhancement of the effects of ACTH on adrenal cortical cell steroidogenesis, and increasing the response of thyroid follicular cells to TSH.

IGF Receptors: We have 3 different types of receptors: [2, 3, 13]

- **The first type** is IGF-I Receptors (IGF-IR): these are present in many cell types and tissues. They account for the ability of IGF-I to stimulate balanced and symmetrical growth. The biochemical structure of IGF-I is similar to that of insulin receptor, it consists of 2α and 2β subunits. The α subunit contains the IGF-I binding domain, with an affinity that is maximum for IGF-I, sex fold lower for IGF-II and 200-300 fold lower for insulin. While the β-subunit binds to the enzyme Tyrosine kinase.
- **A second type** of receptors is called IGF-II Mannose-6-phosphate receptor (IGF-II M6p). It is less important for growth but it is important for the regulation of other IGF-I, and IGF-II activities. It consists of a single chain peptide that binds IGF-II with 80-fold greater affinity for IGF-II than IGF-I, but it doesn't bind to insulin.
- **The third type** of receptors is the chimeric receptor that contains α and β dimers of IGF-I and insulin receptors. The physiological significance of this receptor is not well defined, but it may mediate the insulin-like actions of IGF-I. Figure (3) illustrates the 3 different IGF-receptors.

Binding of IGF-I and IGF-II to IGF-IR causes receptor autophosphorylation, and activation of Tyrosine kinase, which subsequently phosphorylates a host of intracellular substrates such as: Insulin-Receptor Substrate I (IRS-I) and others, that will activate multiple signaling pathways, including phosphatidylinositol

3-kinase that stimulates the translocation of glucose- transporter (Glut 4) to cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat cells.

Another important signaling pathway is the Mitogen-Activated protein kinase (MApk) that is important for the stimulation of mitogenesis and inhibition of apoptosis of cells. (Fig. 5).

In addition to these two pathways, binding of IGF-I to its receptor will result in activation of other pathways that are important in the stimulation of protein and glycogen synthesis. (Fig. 4).

IGF-I and its Role in Cell Growth and Cancer Development : [18- 21]

- Several cell types are capable of synthesizing IGF-I and possess IGF-I receptors. Since IGF-I is a potent inhibitor of apoptosis, and at the same time it is a potent stimulator of mitogenesis, DNA synthesis as well as cell multiplication; so definitely, it has a role in cell growth.
- Being an inhibitor of apoptosis could be beneficial in certain systems; for example, in the central nervous system, IGF-I inhibit neuronal myocyte and oligodendrocyte cell death and it also regenerates nerve tissues. However, studies in culture cells have demonstrated that IGF-IR is frequently overexpressed in cancer cell lines, and usually these types of cancer develop due to mutation in certain tumor suppressor gene products, that typically suppress the expression of IGF-IR promoter.
- It appears that elevated plasma IGF-I, as absolute concentrations or relative to the levels of IGFBP-3, may be a risk factor for a number of different tumors, such as breast, prostate, colon, lung and bladder cancers in western societies, and there is some evidence that this relationship may be stronger for tumors that are more advanced or aggressive at the stage of diagnosis. Studies have shown that blockade of IGF/IGF-IR signaling may be a useful therapeutic strategy for human malignancies.

IGF Receptors
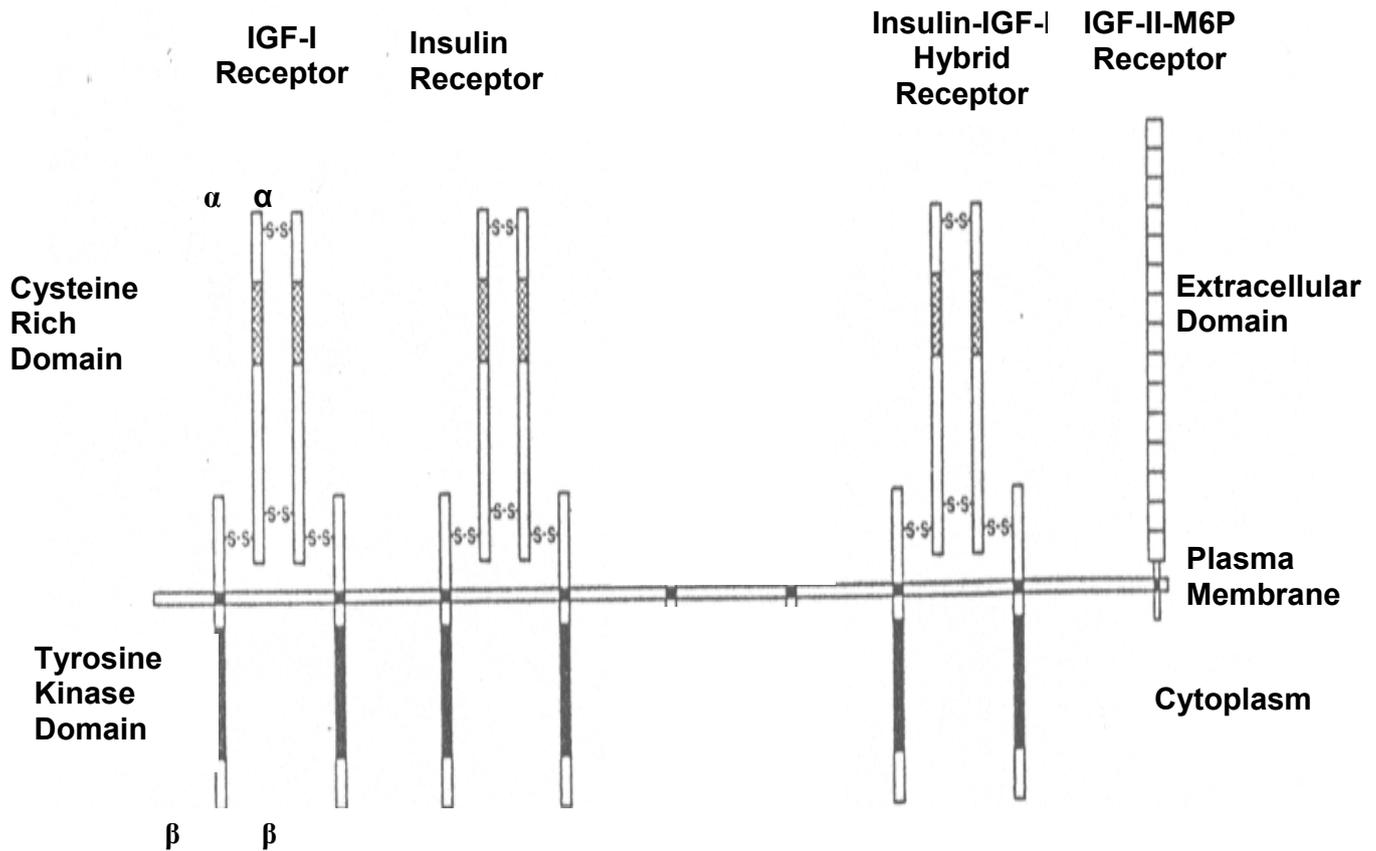
Fig. 3: IGF-Receptors: IGF-I Receptor (IGF-IR) is similar to that of insulin receptor, it consists of 2α and 2β subunits. α subunit contains IGF-I binding site; while β subunit binds to the enzyme Tyrosine kinase. IGF-II Mannose-6-phosphate receptor (IGF-II M6p) consists of single chain peptide. The 3rd type of receptors is the chimeric receptor that contains α and β dimmers of IGF-I and insulin receptor and may mediate the insulin-like actions of IGF-I.
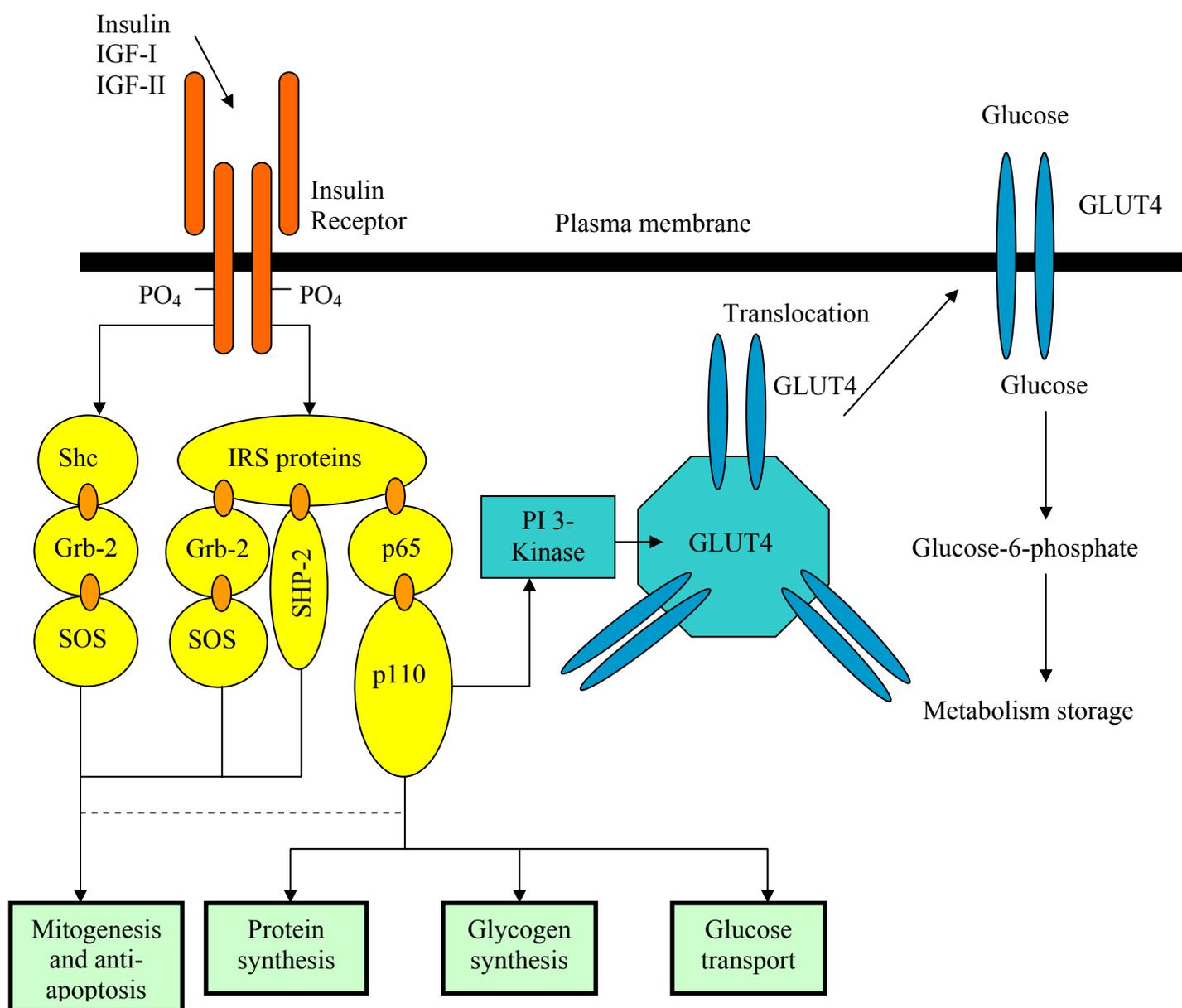
Fig. 4: Insulin signal translation pathway. The insulin receptor has intrinsic tyrosine kinase activity and interactions with Insulin-Receptor Substrates (IRS and Shc) proteins. A number of "docking" proteins bind to these cellular proteins, and initiate the metabolic action of insulin [GrB-2, SOS, SHP-2, P65, P110 and phosphoinositol phosphate 3-kinase (PI 3- kinase)]. Insulin increases glucose transport through PI3-kinase, which promotes the translocation intracellular vesicles containing GluT4 glucose transporter to the plasma membrane.
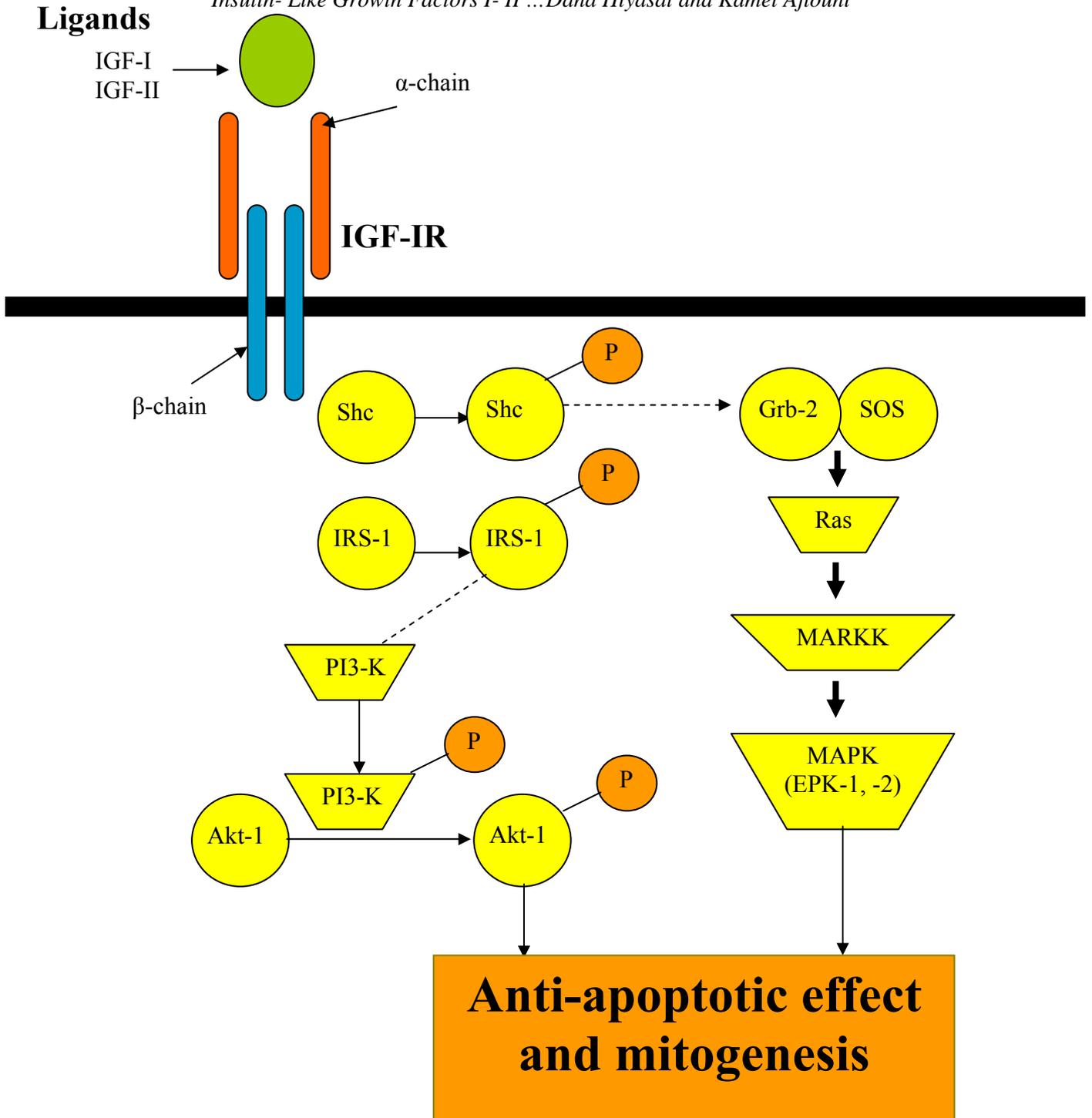
Fig. 5: IGF-IR and malignant transformation. Binding of the ligands, IGF-I and IGF-II, to IGF-IR which is a heterotetramer of two α and two β-chain causes receptor autophosphorylation and activation of tyrosine kinase activity, which subsequently phosphorylates a host of intracellular substrates, including receptor substrate 1 (IRS-1) and Shc. These early events activate multiple signaling pathways, including the Mitogen-Activated Protein Kinase (MAPK; also called Extracellular Signal – Regulated Kinase [ERK]) and Phosphotidyl Inositide 3-Kinase (PI3-K)/AKt-1 (protein kinase B) pathways that result in anti-apoptotic effect and mitogenesis.

Effects of IGF-I Administration to Humans: [15]

- IGF-I infusion into calorically restricted human restores nitrogen balance to normal.
- It will cause a decrease in blood sugar if sufficient concentrations are given.
- It increases glomerular filtration rate by 25%.
- It stimulates the whole body protein synthesis and inhibit proteolysis.
- It causes partial reversal of the catabolic effect of glucocorticoids on protein synthesis.
- It has an anabolic effect on bone, demonstrated by increases in the markers of bone formation.

In patients with Type II D.M, IGF-I administration results in 3.4 fold improvement in insulin sensitivity.

- Injection of IGF-I causes acute dose-dependent side effects, that include the following: [2, 15]
1. Hypoglycemia
2. Hypotension
3. Fluid retention
4. Temporomandibular jaw pain
5. Retinal odema
6. Bell's pulsy
7. Severe myalgias
8. Increased intracranial pressure
9. A vascular necrosis of the head of femur
10. Chronic excess IGF-I administration results in features of acromegaly.

IGF-I therapy may be effective in patients with GH insensitivity due to GH receptors mutations. In one study, IGF-I administration to such patients resulted in growth of approximately 7.5 cm in the first year and 4 cm in the years between 2 and 5, although adverse side effects such as overgrowth of fat mass and facial bones were seen in some children.

IGF-Binding Proteins

6-subtypes of IGF binding protein have been identified 1, 2, 3, 4, 5, 6, which are measured by specific radioimmunoassay. [16]

Functions of IGFBP

- Carrier for IGF-I and II.
- They could either potentiate or inhibit IGF effects.

IGFBPs appear to inhibit IGF action by competing with IGF receptors for binding IGF peptides. Proteolysis of IGFBPs by protease enzyme causes a reduction in their affinity for IGF ligands, resulting in enhanced binding of IGF peptides to its receptors. [4, 16] (Fig. 6 and 7).

IGFBP-3

Is synthesized in hepatic endothelium and kupffer cells. It is the predominant IGFBP in adult serum, since it carries approximately 75% of the total IGF-I. [10]

Serum levels of IGFBP-3 are reduced in patients with GH-deficiency, a condition in which assays for serum IGFBP-3 have important diagnostic values. Measurement of IGFBP-3 appears to have the greatest clinical value because it is GH-dependent. [11]

Blum and colleagues have suggested that serum levels of IGFBP-3 may be superior to IGF-I assays in the diagnosis of GH deficiency, because normal levels of IGF-I are so low in young children and many "normal" short children have low levels of IGF-I. [11]

IGF-I in Clinical Practice

IGF-I Levels in Growth Disorders

IGF-I levels in normal children younger than 5 years of age are low, and there is overlap between the normal range and values in GH-deficient children.

Moore and associates performed GH stimulation tests on 78 children with heights below the 5th percentile, and with serum IGF-I levels lower than 0.5 unit/ml.

Although 19 of these children were subsequently discovered to have GH-deficiency on the basis of standard GH provocative tests, there was an overlap of serum IGF-I levels between GH-deficient children and children with normal provocative GH levels.

Similarly, Reiter and Lovinger found that 4 of 16 children with low provocative GH levels had normal serum IGF-I levels, whereas 7 of 25 children with normal provocative GH levels had low serum IGF-I levels.

Rosenfeld and colleagues, evaluated the efficacy of IGF-I measurements in 68 GH-deficient patients, 197 children with normal stature and 44 normal children with short stature. They found that 18% of GH-deficient children had serum IGF-I levels within the normal range for their age and 32% of normal short children had low IGF-I levels.

In Conclusion: The correlation between IGF-I levels and provocative GH levels is imperfect.[8, 15, 16]

Defects in IGF-I Synthesis

In 1996, Woods et al. reported the case of a 15 year old boy who had the following features due to a homogeneous deletions of exons 4.5 of IGF-I gene: [17, 46]
- Pre and postnatal growth retardation.
- Sensorineural deafness.
- Mental retardation.
- Microcephaly.
- Hyperinsulinemia and insulin resistance due to overproduction of GH.

Use of IGF-I as a Diagnostic Test in Acromegaly:

Several large studies have consistently confirmed the utility of IGF-I as a diagnostic test in acromegaly.[1, 9, 22- 26, 42]

In 57 patients with active acromegaly (43 of whom had never been treated), the mean IGF-I concentration was 10 times greater than the normal mean value, and there was no overlap between these patients and control subjects. [42] Later reports have shown little overlap between IGF-I concentrations in patients with established acromegaly and those in normal adults.[18] The only exception has been observed in one patient who presents during aldolescence. In this situation, overlap has been noted between adolescents with gigantism and normal adolescents because the mean IGF-I concentration for adolescents are substantially higher than the mean concentrations for adults.

The consensus by several expert panels has been that IGF-I should be measured in all patients with suspected acromegaly. [27- 33] GH-suppression testing must be added to the diagnostic strategy in order to confirm acromegaly.

In almost all cases (except for teenage patients), an IGF-I concentration within the normal range excludes the diagnosis of acromegaly.

If IGF-I concentration is outside the normal range then glucose-suppression testing is recommended. After administration of either a 75-g or a 100 g dose of glucose, GH concentrations should be suppressed from the baseline values to less than 0.4 ng/ml, unless a traditional radioimmunoassay is used with such a test, 1.0 ng/ml is the upper limit. [20] With such a test, failure to suppress GH to this level, particularly in the presence of an abnormally increased IGF-I concentration, is diagnostic of acromegaly and this necessitates additional studies including pit. MRI.
- Some physiological conditions can lead to high IGF-I concentrations, e.g.
   1. In the third trimester of pregnancy.

Placental GH $\rightarrow$ increases serum IGF-I to above the normal range.
   2. During adolescence.

- Falsely suppressed IGF-I values in acromegaly have been detected in:
1. States of malnutrition.
2. In the presence of severe hypothyroidism. [30]

The absolute criteria for achieving a cure in acromegaly have always included IGF-I concentrations within the normal range, especially in the lower tertile. Several investigators have found that, in comparison to GH level, the IGF-I concentration is a more sensitive indicator of persistent disease activity in patients with acromegaly.[17, 27, 28] For example:

Freda et al. (1998) evaluated GH and IGF-I concentrations by using a sensitive immunoradiometric assay in 60 patients with acromegaly after transsphenoidal surgical treatment.

As far as this study is concerned, 50% of the patients with active acromegaly had GH nadirs between 0.4 ng/ml and 1.0 ng/ml, and all were associated with high IGF-I concentrations. [25]
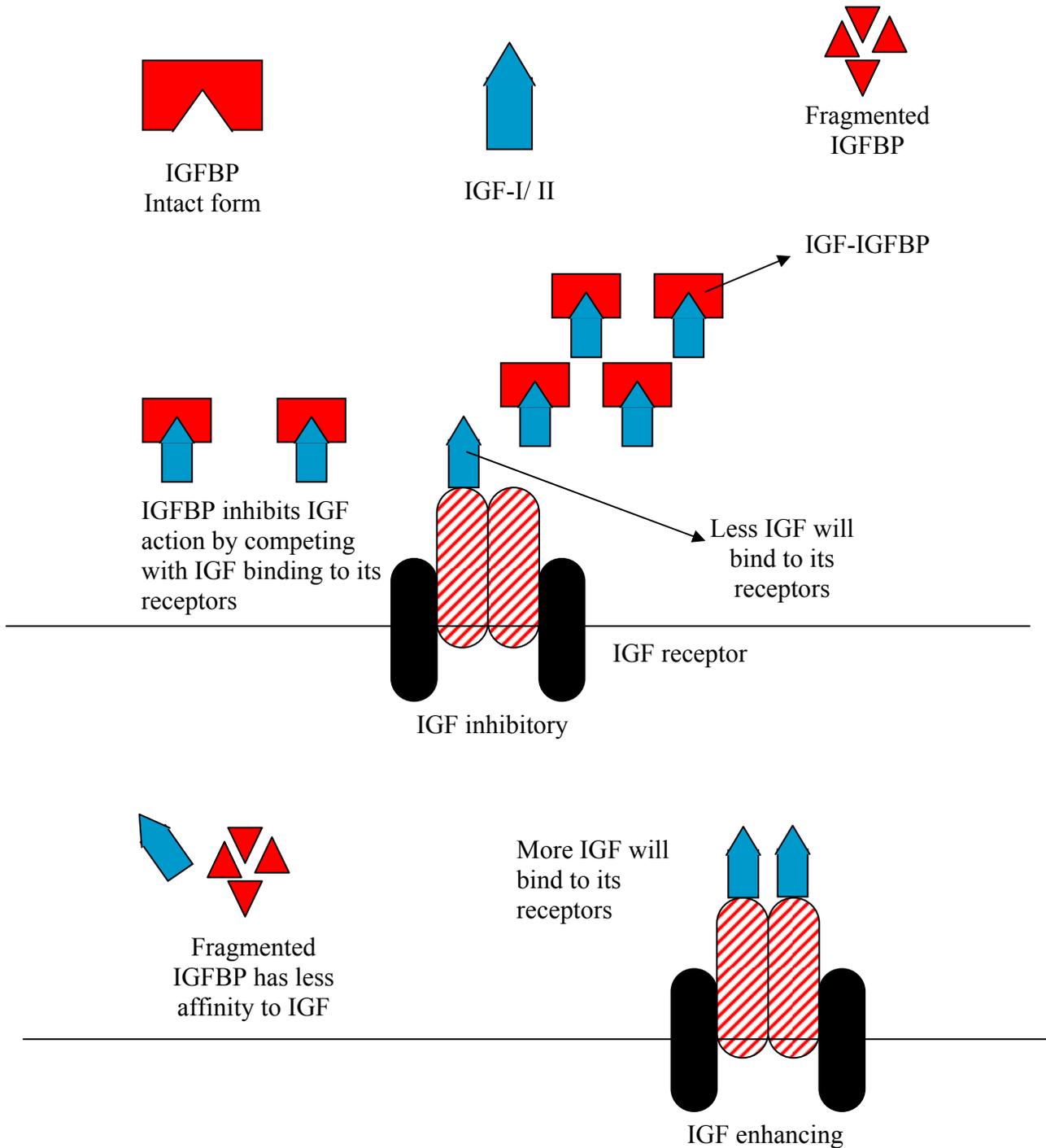
Investigators have observed empirically that several weeks are needed for IGF-I concentrations to reequilibrate with ambient GH secretion. Therefore, IGF-I measurements are not useful if they are obtained during the first 2 to 4 weeks after surgical therapy. [34- 42]

One recommendation is to obtain an IGF-I measurement at least 4 weeks after surgical treatment, before decisions about further therapy are made.
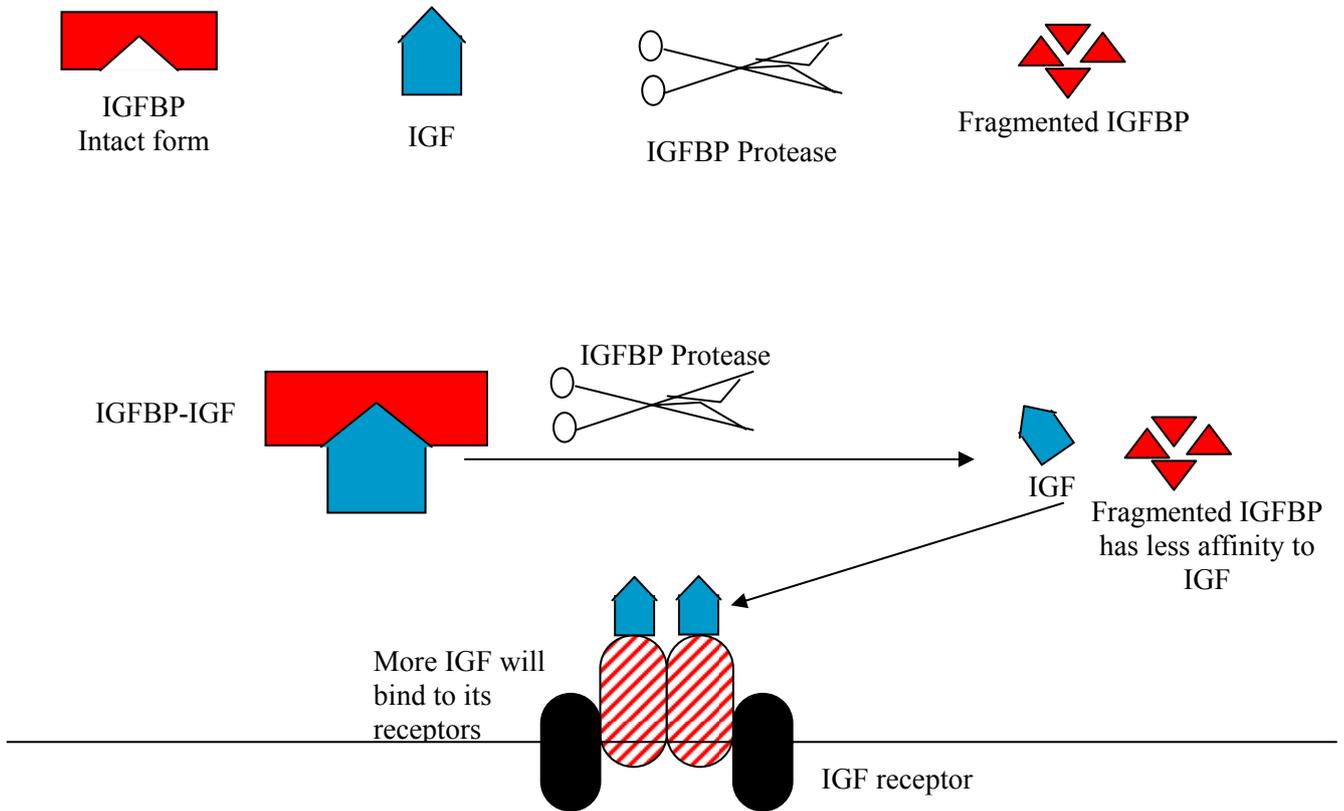
Fig. 6: Proteolysis of IGFBPs by protease enzyme causes a reduction in their affinity for IGF ligands, resulting in enhanced binding of IGF peptides to its receptors.

IGFBP
Intact form

IGF-I/ II

Fragmented
IGFBP

IGF-IGFBP

IGFBP inhibits IGF
action by competing
with IGF binding to its
receptors

Less IGF will
bind to its
receptors

IGF receptor

IGF inhibitory

Fragmented
IGFBP has less
affinity to IGF

More IGF will
bind to its
receptors

IGF enhancing

Fig. 7: IGFBP (IGF-Binding Proteins) appear to inhibit IGF action by competing with IGF receptors for binding IGF peptides.

Conclusion

Insulin and Insulin-like Growth Factors (IGF) I and II belong to a family of peptide hormones and growth factors, that play a fundamental role in the control of essential cellular and physiological processes, such as cell cycle, survival, proliferation, differentiation and metabolism.

With the development of sensitive and specific radioimmunoassay that could distinguish between IGF-I and IGF-II, measurement of each IGF peptide offers its own particular advantages. IGF-I concentrations are more GH-dependent than IGF-II levels, and more likely to identify subtle differences in GH secretory pattern. However, serum IGF-I levels, as stated earlier, are greatly influenced by the chronologic age, degree of sexual maturation and nutritional status. As a result, construction of age- defined normative values is difficult and may be misleading. IGF-I levels in normal children younger than five years old of age may be so low that extensive overlap exists between the normal range and values in GH-deficient children, also, the correlation between IGF-I levels and provocative GH levels is imperfect. Determination of serum IGF-II concentrations has the advantage that it's less age dependent, especially after 1 year of age, but IGF-II is less GH dependent than is IGF-I.

IGF-I is an important indicator of disease activity in acromegaly and it correlates with the development of comorbidities and organs system dysfunction. High IGF-I concentration has been associated with increased mortality, while normalization of IGF-I correlates with a reduced risk of death in patients with acromegaly. Several clinical trails have shown a good correlation between IGF-I and disease activity after treatment.

IGF-I Receptor (IGF-IR) is frequently upregulated in tumors, and mediates many aspects of the malignant phenotype including proliferation, transformation and apoptosis protection.

These properties make the IGF-IR an attractive anticancer treatment and in the next few years we will see the introduction of IGF-IR targeting into the clinic.

References

1. Daughaday WH, Rotwein P. Insulin-like growth factors I and II: peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr Rev. 1989; 10: 68-91.
2. Underwood LE, Van Wyk JJ. Normal and aberrant growth. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. Philadelphia, PA: WB Saunders. 1992; 1079-1138.
3. Jones JI, Clemmons DR. Insulin-like growth factor and their binding proteins: biologic actions. Endocr Rev. 1995; 16: 3- 34.
4. Clemmons DR. Insulin-like growth factor binding proteins. In: Kotyl JL, Goodman HM, eds. Handbook of physiology: Hormonal Control of Growth. Vol 5. New York, NY: Oxford University Press. 1999; 513- 631.
5. Veldhuis JD, Liem AY, South S, et al. Differential impact of age, sex steroid hormones, and obesity on basal versus pulsatile growth hormone secretion in men as assessed in an ultrasensitive chemiluminescence assay. J Clin Endocrinol Metab. 1995; 80: 3209- 3222.
6. Baumann G, Stolar MW, Buchanan TA. The metabolic clearance, distribution, and degradation of dimeric and monomeric growth hormone (GH): implications for the pattern of circulating GH forms. Endocrinology. 1986; 119: 1497-1501.
7. William F. Ganong. The pituitary gland, review of medical physiology. 18th edition. Stamford, Appleton and Lange. 1997; 375-384.
8. Monson JP, Cook DM, eds. Growth Hormone Deficiency in Adults: A Pocket Guide to Clinical Management. Yardley, PA; ApotheCom Associates LLC, 2003.
9. Barkan AL, Beitins IZ, Kelch RP. Plasma insulin-like growth factor– I/somatomedin-C in acromegaly: correlation with the degree of growth hormone hypersecretion. J clin Endocrinol Metab. 1988; 67: 69- 73.

10. Chernausek SD, Underwood LE, Utiger RD, Van Wyk JJ. Growth hormone secretion and plasma somatomedin-C in primary hypothyroidism. Clin Endocrinol (Oxf). 1983; 19: 337-344.

11. Clemmons DR, Klibanski A, Underwood LE, et al. Reduction of plasma immunoreactive somatomedin-C during fasting in humans. J Clin Endocrinol Metab. 1981; 53: 1247-1250.

12. Hall K, Hilding A, Thoren M. Determinants of circulating insulin-like growth factor-I. J Endocrinol Invest. 1999; 22(5 Suppl): 48-57.

13. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol. 1999; 20:157-198.

14. Mark A. Sperling. Disorders of Growth Hormone/Insulin-like growth factor secretion and action. Fiona Foley, Judith Fletcher, ed. Pediatric endocrinology. 2nd ed. Philadelphia, PA: WB Saunders. 2002; 221-288.

15. Michael F. Holick, Stephen M. Krane. Disroders of anterior pituitary and hypothalamus. Eugene Braunwald, Anthony S. Fauci, eds. Harrison's principles of internal medicine. 15th edition. New York McGraw-Hill. 2001; 2: 2041-2047.

16. Kim HJ, Kwon SH, Kim SW, et al. Diagnostic value of serum IGF-I and IGFBP-3 in growth hormone disorders in adults. Horm Res. 2001; 56:117-123.

17. Backeljauw PF, Underwood LE (GHIS Collaborative Group). Prolonged treatment with recombinant insulin-like growth factor –I in children with growth hormone insensitivity syndrome – a clinical research center study. J Clin Endocrinal Metab. 1996; 81: 3312-3317.

18. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science. 1998; 279:563-566.

19. Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet. 1998; 35 (1):1393-1396.

20. Pollak M. Insulin-like growth factor physiology cancer risk. Eur J Cancer. 2000; 36:1224-1228.

21. Grimberg A, Cohen P. Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. J Cell Physiol. 2000; 183:1-9.

22. Freda Pu, Post KD, Powell JS, Wardlaw SL. Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J Clin Endocrinol Metab. 1998; 83: 3808- 3816.

23. Peacey SR, Toogood AA, Veldhuis JD, Thorner MO, Shalet SM. The relationship between 24-hour growth hormone secretion and insulin-like growth factor I in patients with successfully treated acromegaly: impact of surgery or radiotherapy. J Clin Endocrinol Metab. 2001; 86:259-266.

24. Oppizzi G, Petroncini MM, Dallabonzana D, et al. Relationship between somatomedin-C and growth hormone levels in acromegaly: basal and dynamic evaluation. J Clin Endocrinol Metab. 1986; 63:1348-1353.

25. Peacey SR, Shalet SM. Insulin-like growth factor 1 measurement in diagnosis and management of acromegaly. Ann Clin Biochem. 2001; 38(Pt4):297-303.

26. Clemmons DR, Van Wyk JJ, Ridgway EC, Kliman B, Kjellberg RN, Underwood LE. Evaluation of acromegaly by radioimmunoassay of somatomedin-C. *N Engl J Med*. 1979; 301: 1138-1142.

27. Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. J clin Endocrinol Metab. 2000; 85:526-529.

28. Costa AC, Rossi A, Martinelli CE Jr, Machado HR, Moreira AC. Assessment of disease activity in treated acromegalic patients using a sensitive GH assay: should we achieve strict normal GH levels for a biochemical cure? J Clin Endocrinol Metab. 2002; 87:3142-3147.

29. Gama R, Labib M, Teale JD, Marks V. Acromegaly with a misleading normal plasma insulin-like growth factor 1. Ann Clin iochem. 1989; 26(Pt 1):102-103.

30. Dimaraki EV, Jaffe CA, DeMott-Friberg R, Chandler WF, Barkan AL. Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. J Clin Endocrinol Metab. 2002; 87:3537-3542.

31. Oppizzi G, Petroncini MM, Dallabonzana D, et al. Relationship between somatomedin-C and growth hormone levels in acromegaly: basal and dynamic evaluation. J Clin Endocrinol Metab. 1986; 63:1348-1353.

32. Melmed S. Acromegaly. N Engl J Med. 1990; 322:966-977.

33. Bates AS, Van't Hoff W, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. Q J Med. 1993; 86: 293-299.

34. Fahlbusch R, Honegger J, Buchfelder M. Surgical management of acromegaly. Endocrinol Metab Clin North Am. 1992; 21:669-692.

35. Swearingen B, Barker FG II, Katznelson L, et al. Longterm mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab. 1998; 83:3419-3426.

36. Lindholm J, Giwercman B, Giwercman A, Astrup J, Bjerre P, Skakkebaek NE. Investigation of the criteria for assessing the outcome of treatment in acromegaly. Clin Endocrinol (Oxf). 1987; 27:553-562.

37. Wass JA, Clemmons DR, Underwood LE, Barrow I, Besser GM, Van Wyk JJ. Changes in circulating somatomedin-C levels in bromocriptine-treated acromegaly. Clin Endocrinol (Oxf). 1982; 17:369-377.

38. Rieu M, Girard F, Bricaire H, Binoux M. The importance of insulin-like growth factor I (somatomedin) measurements in the diagnosis and surveillance of acromegaly. J Clin Endocrinol Metab. 1982; 55:147-153.

39. Roelfsema F, Frolich M, Van Dulken H. Somatomedin C levels in treated and untreated patients with acromegaly. Clin Endocrinol (Oxf). 1987; 26:137-144.

40. Melmed S, Jackson I, Kleinberg D, Klibanski A. Current treatment guidelines for acromegaly. J Clin Endocrinol Metab. 1998; 83: 2646-2652.

41. Acromegaly Therapy Consensus Development Panel. Consensus Statement: benefits versus risks of medical therapy for acromegaly. Am J Med. 1994; 97:468-473.

42. Melmed S, Casanueva FF, Cavagnini F, et al. (Acromegaly Treatment Consensus Workshop Participants). Guidelines for acromegaly management. J Clin Endocinol Metab. 2002; 87:4054-4058.

43. Quarmby V, Quan C, Ling V, Compton P, CanovaDavis E. How much insulin-like growth factor I (IGF-I) circulates? Impact of standardization on IGF-I assay accuracy. J Clin Endocrinol Metab. 1998; 83:1211-1216.

44. Powell-Braxton L, Hollingshead P, Warburton C, et al. IGF-I is required for normal embryonic development in mice. Genes Dev. 1993; 7:2609-2617.

45. Roberts CT Jr, Lasky SR, Lowe WL Jr, Seaman WT, LeRoith D. Molecular coding of rat insulin-like growth factor I complementary deoxyribonucleic acids: differential messenger ribonucleic acid processing of regulation by growth hormone in extrahepatic tissue. Mol Endocrinol. 1987; 1: 243-248.

46. Marzullo P, Di Somma C, Pratt KL, et al. Usefulness of different biochemical markers of the insulin-like growth factor (IGF) family in diagnosing growth hormone excess and deficiency in adults. J Clin Endocrinol Metab. 2001; 86:3001-3008.