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The Insulin-Like Growth Factor System in the Human Pathology

Emrah Yerlikaya and Fulya Akin

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<http://dx.doi.org/10.5772/55213>

1. Introduction

1.1. Physiology

Insulin-like growth factors are single chain polypeptides. There are two principle IGFs referred to as IGF-I and IGF-II. IGF-1 is a polypeptide hormone with a molecular weight of 7.6-kDa structurally similar to insulin. In 1957, it is identified by Salmon and Daughaday. Because of its ability to stimulate the sulfation of the cartilage proteoglycans, it was regarded as a sulphation factor [1]. The IGF-1 gene is on the long arm of chromosome 12q23–23. IGF-1 gene contains 6 exons [2, 3]. The alternate extension peptide at carboxy terminal, encoded by exons 5 and 6 determines the subforms of IGF-1: IGF-1B and IGF-1A. The most abundant isoform of the IGF-1 (153 aminoacid) is IGF-1A [4, 5]. IGF1B peptide (195 amino acids) is a less abundant IGF1 isoform. IGF-2 is also a peptide with 67 amino acids and molecular weight of 7.4-kDa. IGF-2 is encoded by a gene on the short arm of chromosome 11 at position 15.5. This gene consists of nine exons [6]. In the plasma, 99% of IGFs are bound to a family of binding cysteine-rich proteins. There are six binding proteins (IGFBP-1 to IGFBP-6) [7]. They act as carriers for IGFs in the circulation, regulate the bioavailability of IGFs to specific tissues and modulates the biological activities of IGF proteins. Six IGF-binding proteins (IGFBPs) can inhibit or enhance the actions of IGFs [8]. Potentiation of IGF activity by some of the IGFBPs, described for IGFBP-1 and IGFBP-3, is also documented for IGFBP-5. Each of IGFBPs is the product of a separate gene. These genes share a common structural organization in which four conserved exons are located within genes ranging from 5 kb (IGFBP-1) to more than 30 kb (IGFBP-2 and IGFBP-5) [9]. IGFBPs contain N terminal and C terminal domains which are similar in aminoacid sequence. Post-translational modifications of IGFBP, including glycosylation, phosphorylation and proteolysis modify the affinities of the binding proteins to IGF. IGFs mediate their action on target cells by three

receptors that bind IGFs with differing affinities. These receptors are type 1 IGF receptor, type 2 IGF receptor and Insulin receptors. The type 1 IGF receptor (IGF-1R), structurally homologous to the insulin receptor, exhibits four transmembrane spanning subunits and an intracellular tyrosine kinase domain [10]. The IGF-1R and IR are both synthesized as a precursor that is glycosylated on the extracellular regions, dimerized and proteolytically processed to yield separate α and β chains [11]. IGF-1R binds insulin, IGF-1, or IGF-2. IGF1R binds to IGF1 with greater affinity than IGF-2. IGF-1R affinity for insulin is lower than for IGF-1. Type 2 IGF receptor is structurally and functionally different from the IGF-1R. The receptor is a 250-kDa protein with a large extracellular domain, which binds M6P, lysosomal enzymes, and IGF-2 [12]. IGF-2R binds to IGF-2 with high affinity whereas IGF-1 binding is weak and insulin does not bind at all [13]. Binding of IGF-1 and IGF-2 to the cognate IGF-1R stimulates the intrinsic tyrosine kinase activity of this receptor [14]. Upon IGF binding, the tyrosine kinase activity of IGF-1 receptor leads to the phosphorylation of several substrates, including the insulin receptor substrate family of proteins (such as Insulin receptor substrate 1 (IRS-1), SHC (Src homology 2 domain containing) transforming protein 1 (Shc) and some others. Once phosphorylated, these docking proteins activate downstream intracellular signaling through the Phosphatidylinositol 3-kinase (PI3K) or Growth factor receptor-bound protein 2 (GRB2)/ Son of sevenless homolog (SOS) / v-Ha-ras Harvey rat sarcoma viral oncogene homolog (H-Ras) pathways that ultimately leads to cellular proliferation [15,16].

Ligand binding to IGF-1R activates the tyrosine kinase higher concentration of the anti-apoptotic proteins bcl-2 and bcl-XL, a lower level of the apoptotic proteins bax and bcl-xs activates phosphatidylinositol 3-kinase (PI3-K), and activates protein kinase B (PKB/Akt) that also prevent apoptosis. Activation of PI 3-kinase generates inositol triphosphate activation of protein tyrosine kinase-B activate mTOR, p70/S6 kinase and GSK-3 β results in protein glucose uptake, glycogen synthesis. Most IGF-1 is secreted by the liver and is transported to other tissues, acting as an endocrine hormone. IGF-1 is also secreted by other tissues, including cartilagenous cells, and acts locally as a paracrine hormone. In response to GH, IGF-1 synthesis is increased in connective tissues. Growth hormone released from the anterior lobe of the pituitary binds to receptors on the surface of liver cells which stimulates the synthesis and release of IGF-1 from them. STAT5B is a transcription factor mediating effect of GH on liver. Low IGF-1 and IGFBP-3 levels in cirrhosis occurs due to decreased hepatic synthesis [17, 18]. IGFBP-3 that binds 95% of circulating IGFs is also produced by the endothelial lining and Kupffer cells in the liver.

2. Factors affecting IGF system

IGF-1 peaks during puberty. Advanced age is associated with a progressive decrease in serum IGF-1 because GH secretion declines; 14% per decade of life [19, 20]. During lifetime, GH production is reduced nearly 30-fold. This decrement in IGF-1 is attributable to increased somatostatinergic tone and a generalized reduction in the pulses of GH-releasing hormones and GH-releasing peptides [21]. Although GH may be responsible for the decre-

ment it is not the only factor responsible for the increment in childhood. Serum estradiol concentrations correlate with IGF-1 in both men and women [22]. Stimulated and spontaneous GH secretion is higher in young women than in postmenopausal women or young men, with the difference strongly correlated with circulating estradiol levels [23, 24, 25]. Use of oral estrogen resulted in a significant reduction in IGF1 levels but no effect of transdermal estrogen was shown in patients with hypopituitarism [26]. Transdermally delivered estrogen stimulates IGF-1 production. When delivered orally, estrogen reduces IGF-1 [27]. IGF-1 mRNA expressed by endometrium. Progesterone increases IGF-1 expression in the endometrial stroma. There is circumstantial evidence to suggest a positive association between circulating levels of testosterone and IGF-1. Administration of testosterone to younger men with hypogonadism and boys with isolated gonadotropin-releasing hormone deficiency increases serum IGF-1 [28]. Endogenous testosterone levels correlate with IGF-1 in hypopituitary women with unsubstituted growth hormone deficiency [29]. Serum dehydroepiandrosterone concentrations decline with age, and absolute concentrations in postmenopausal women correlate with serum IGF-1 [30]. Thyroxine is also another hormone affecting IGF-1 levels. In patients with T4 deficiency due to primary and central hypothyroidism IGF-1 and ALS are low at baseline. In most of these T4-treated patients, T4 therapy increased IGF-1 and ALS concentrations [31]. The major effect of thyroid hormones on IGF-1 and IGFBP-3 in vivo has been considered to occur by increased expression and secretion of growth hormone by the pituitary gland [32]. IGFBP-3 also increases with thyroxine replacement in primary hypothyroidism [33]. One key function of IGF-1 is the stimulation of anabolic processes and body growth. Protein and energy content of the diet influence plasma IGF-1 concentrations [34]. IGF-1 is reduced in conditions of energy restriction, such as short-term fasting [35] and malnutrition [36]. Zinc deficiency is a common component of protein-calorie malnutrition. IGF-1 synthesis can be impaired by zinc deficiency. A reduction in circulating IGF-1 concentrations has been proposed as a potential mechanism for growth retardation induced by zinc deficiency [37]. Significant elevation in the IGF-1 level after zinc supplementation occurs [38]. Similarly, nutritional deprivation results in a major decrease in IGF-1 mRNA that can be restored with refeeding. In the population of healthy well-nourished men, greater dietary intakes of protein, zinc, red meat, and fish and seafood were associated with higher IGF-1 concentrations [39]. The anabolic effect of PTH may be mediated by local growth factors. PTH has been shown to stimulate IGF-1 production at the transcriptional and polypeptide levels [40]. Low IGF-1 and IGFBP-3 levels occur in liver cirrhosis due to decreased synthesis and low IGF-1 levels may be involved in the development of cirrhotic complications including malnutrition, insulin resistance, impaired immunity, and osteoporosis [41].

Any factors affecting IGFBP concentrations in blood and extracellular fluids also affects the IGF levels and its availability to tissues. Binding of IGF-1 to ALS and IGFBPs form ternary complexes. Acid Labile Subunit (ALS) is a liver-derived protein that exists in a ternary complex with IGFBP-3 also with IGFBP-5. Formation of the ternary complexes restricts the IGFs to the circulation prolongs their half-lives and allows them to be stored at high concentration in plasma. ALS is a single-copy gene, and was mapped to bands A2-A3 of mouse chromosome 17 and to the short arm of human chromosome 16 at p13.3 [42, 43]. ALS has no affinity for free

IGF-1 or IGF-2 and very low affinity for uncomplexed IGFBP-3. Main binding protein of IGFs is IGFBP-3 and its synthesis is mainly determined by growth hormone. IGFBP-3 is the most abundant form of the IGFBPs. IGFBP-3 concentrations decreases in patients with growth hormone deficiency and increases by GH secretion. Testosterone administration increases IGFBP-3 levels in serum. IGFBP-3 level is also affected by thyroid hormone levels. Low IGFBP-3 levels were found in hypothyroid patients and IGFBP-3 levels are increased by thyroxine replacement in hypothyroid patients. The IGFBP-1 that is present in the circulation is also synthesized in the liver. At concentrations higher than IGF-1, IGFBP-1 inhibits DNA synthesis, glucose transportation [44]. Postprandial increase in serum insulin concentrations results in a four- to five-fold decrease in IGFBP-1 [45]. Intrauterine growth retardation correlates with high levels of serum IGF binding protein-1 (IGFBP-1). Overexpression of IGFBP-1 may affect body growth and skeletal formation as well as biomineralization. IGFBP-1 overexpression may also reduce carbohydrate resources necessary for growth and survival [46]. IGFBP-1 plays roles in the endometrial and ovarian physiology. The IGFBP-2 that is present in the circulation originates from hepatocytes, GH is a main determinant of IGFBP-2 levels in circulation. IGF-1 is a potent stimulant of IGFBP-2 concentrations in serum. IGFBP-2 gene transcription is increased in starved rodents and plasma concentrations are increased in fasted humans [47]. IGFBP-2 has mostly inhibitory effects. IGF-1 stimulated collagen synthesis is inhibited by IGFBP-2.

The serum concentrations of intact IGFBP-4 are quite low. IGFBP-4 level is increased with low bone turnover and low parathyroid hormone levels. Sunlight exposure, vitamin D or its active metabolites also may regulate serum IGFBP-4. It may play a role in bone metabolism. IGFBP-5 circulates as incomplete fragments, intact IGFBP-5 is at very low levels. Its concentration is also regulated with GH and IGF-1. IGFBP-6 inhibits the effects of IGF-2 in several tissues and cell types. IGFBP-6 differs from the other IGFBPs, it has a markedly higher affinity for IGF-2 than for IGF-1, whereas the other IGFBPs bind the two IGFs with similar affinities and IGFBP-2 has a slight IGF-2 binding preference [48, 49, 50].

However, IGF bioactivity in tissues is not determined by the circulating levels of IGFs, IGFBPs, or ALS. Proteases that digest IGFBPs are also important in determining the actions of IGFs at tissue level. In addition, IGFBPs have their own separate roles in the extravascular tissue compartment.

3. IGFs and bone

Osteoblasts and preosteoblasts secrete IGF-1. Several bone trophic factors, estrogens, PTH stimulate the synthesis of the IGF-1 while glucocorticoids, FGF, PDGF, TGF- β decreases IGF1 expression.

IGF-1 released from the bone matrix during bone remodeling stimulates osteoblastic differentiation of recruited mesenchymal stem cells by activation of mammalian target of rapamycin (mTOR), thus maintaining proper bone microarchitecture and mass. It is well known that both BMD and serum concentration of IGF-1 decrease with age, in age-related osteoporosis in

humans, it is found that bone marrow IGF-1 concentrations were 40% lower in individuals with osteoporosis than in individuals without osteoporosis [51]. As compared to healthy controls, total bone mass was found lower in men with GH deficiency and The total BMD was found positively related to plasma IGF-1 and median of GH values [52]. GH deficiency in adulthood is associated with reduced BMD. IGF-1 may be an early marker for low bone mass [53]. Short term treatment with recombinant human IGF-1 in healthy postmenopausal women resulted in increases in bone turnover markers [54]. However, certain effects of the long-term treatment with IGF-1 is unknown.

4. IGFs and growth

Linear bone growth at the epiphyseal plate occurs by a process that is similar to endochondral ossification. The epiphyseal plate between the epiphysis and the metaphysis grows by mitosis. This process continues throughout childhood and the adolescent years until the cartilage growth slows and finally stops. GH may act directly at the growth plate to amplify the production of chondrocytes from germinal zone precursors and then to induce local IGF-1 synthesis, which is thought to stimulate the clonal expansion of chondrocyte columns in an autocrine/paracrine manner [55, 56]. IGF-2 mRNA expression is higher in the proliferative and resting zones than the hypertrophic zone. IGF-1 and GH receptors are expressed throughout the growth plate. Molecular studies revealed that the causes of GH resistance are deletions[57] or mutations [58] in the GH receptor gene, resulting in the failure to generate IGF-1 and a reduction in the synthesis of several other substances, including IGFBP-3.

The expression of IGF-I, IGF-II, IGFBP-3, and ALS is tightly controlled by GH. STAT5B is a transcription factor mediating effect of GH on liver. Six cases of homozygous mutations of the signal transducer and activator of transcription STAT5B gene have also been described [59]. These mutations result in a type of dwarfism characterised by high serum GH values. Studies revealed that these patients cannot generate IGF-1. Several cases have been reported of mutations of the gene for the ALS, which encodes a protein which forms part of the ternary complex that transports IGF-1 in serum [60, 61]. These cases have markedly low serum IGF-1 concentrations and modest growth failure. Syndrome of GH resistance (insensitivity) was named by Elders et al as Laron dwarfism, a name subsequently changed to Laron syndrome [62]. Long term treatment of patients with LS promotes growth and, if treatment is started at an early age, there is a considerable potential for achieving height normalisation [63]. The recently available recombinant human insulin-like growth factor I has shown promise as a promoter of growth in children with Laron syndrome. Main adverse effects with IGF-1 treatment is hypoglycemia. Other adverse effects of IGF-1 treatment appear to be related to hyperstimulation of lymphoid tissue growth: tonsillar growth, snoring, sleep apnea, recurrent ear infections, thymic hypertrophy, and splenic enlargement [64, 65, 66, 67]. Injection site hypertrophy has been observed, but is generally amenable to proper rotation of injection sites. Arthralgias and myalgias have been reported in as many as 20% of recipients in uncontrolled studies, but are usually transient. Benign intracranial hypertension has been reported in ~4% of recipients. Although this number appears somewhat larger than that observed with GH

treatment, it is usually transient, disappearing following temporary cessation of treatment. Craniofacial growth, sometimes with coarsening of features, has been described in a number of patients [64, 65, 66, 67].

5. IGFs and cancer

The IGF-1R can regulate cell-cycle progression through control of several cycle checkpoints. It can facilitate G0-G1 transition through activation of p70S6K, leading to phosphorylation of the S6 ribosomal protein and an increased ribosomal pool necessary for entry into the cycle [68]. It can promote G1-S transition by increasing cyclin D1 and CDK4 gene expression, leading to retinoblastoma protein phosphorylation, release of the transcription factor E2F, and synthesis of cyclin E [69, 70]. Alterations in cyclin D1 expression to play a role in tumor formation. IGF's are also important for the development and progression of angiogenesis in tumors. Tumor-induced neovascularization is one of the pathologic mechanisms lying underlying cancer metastasis. IGF-1 and IGF-2 can induce angiogenesis by stimulating the migration and morphological differentiation of endothelial cells [71, 72]. Hypoxia is a major trigger for tumor-dependent angiogenesis. IGF-1 and IGF-2 can induce the expression of hypoxia-inducible factor 1 α and this can lead to the formation of the HIF-1/arylhydrocarbon receptor nuclear translocator complex which is involved in transcriptional regulation of hypoxia response element-containing genes such as VEGF [73], a major tumor-derived angiogenic factor. The IGF system can cooperate with other tyrosine kinase receptors such as the EGFR in the induction of angiogenesis [74].

Accumulating evidence has suggested that GH and IGF-1 may be important components of the pathophysiologic mechanisms that underlie the growth of neoplasms, including colorectal carcinoma [75, 76, 77, 78]. Many epidemiology studies have indicated that high levels of IGF - I or altered levels of its binding proteins, or both, are associated with an increased risk of the most common cancers, including cancers of the lung [79], colon and rectum [80], prostate, and breast [81].

Patients with acromegaly, who have elevated levels of circulating GH and IGF-1, may be at increased risk of developing colorectal adenoma and carcinoma [82, 83].

Two prospective epidemiologic studies [84, 85] have shown that higher plasma IGF-1 and lower plasma IGFBP-3 concentrations are associated with an increased risk of colorectal adenoma and cancer among both men and women. These observations suggest that the ratio of circulating IGF-1/IGFBP-3 may be a marker of circulating and tissue IGF-1 bioavailability. Cancer can cause proteolysis of insulin-like growth factor binding protein-3 and affect concentrations of IGFBP-2. These changes in IGF system can affect distribution and clearance of IGFs, thus bioavailability of IGFs to specific tissues. In vitro studies on human colon cancer cells, which showed that IGF-1 promoted cell proliferation, IGF-1 receptors were frequently overexpressed on colon cancer cells and IGF-1R blockade with a monoclonal antibody inhibited cell proliferation [85]. A larger case-control study from Sweden reported a similar positive association between IGF-1 level and prostate cancer risk [86]. In the Physicians' Health

Study, a prospective epidemiological study, the associations between IGF-1 and IGFBP-3 levels and subsequent prostate cancer risk among 152 patients and 152 age-matched controls were investigated. There was a significant linear trend between IGF-1 and prostate cancer risk [87]. Strong association between IGF-1 and IGFBP-3 levels and the risk of advanced prostate cancer but no association with early stage disease was found. Measurement of IGF-1 and IGFBP-3 levels may predict the risk of advanced stage prostate cancer years before the cancer is actually diagnosed and may be helpful in aiding decision making about treatment [88]. No trend in the relative risk of prostate cancer with increasing IGF-1 was found in another study; rather, the highest incidence of prostate cancer was in the lowest quartile of IGF-1, and the incidence in the other quartiles of IGF-1 was slightly lower but not statistically significantly different from incidence rates in the lowest quartile [89]. A multiethnic study was performed to determine the associations between prediagnostic levels of IGF-1 and IGFBP-3 and risk of prostate cancer. In this study no association was observed for levels of IGF-1 or IGF-to-IGFBP-3 ratio and prostate cancer risk [90]. In one metaanalyze including included both retrospective and prospective studies and demonstrated that average 21% increase risk of prostate cancer per standard deviation increase in IGF-1. A stronger association of IGF-1 was found in more aggressive and advanced cancers in comparison to nonaggressive and localized ones [91]. Considerable evidence has accumulated that suggests that the IGF system is involved in the pathophysiology of prostate cancer. GH is believed to be the pituitary factor responsible for mammary ductal morphogenesis [92, 93]. It has been reported that IGF-1 or amino-terminally truncated IGF-1, des(1–3) IGF-1, mimic the action of GH on mammary development in hypophysectomized gonadectomized rats [94, 95]. IGF-1 mRNA is localized to stromal fibroblasts surrounding normal breast epithelium while high levels of IGF-2 mRNA are found in fibroblasts adjacent to malignant epithelium [96, 97]. Malignant breast epithelial cells can induce expression of IGF-2 in the stroma in vitro [98]. IGF-1R has been found on the surface of malignant breast epithelial cells [99] and IGFs provide radioprotection and resistance of breast cancer cells to chemotherapeutic agents [100, 101]. Some epidemiologic studies have associated high circulating levels of IGF-1 with increased risk of breast cancer among premenopausal women. In a meta-analysis, circulating levels of IGF-1 were not significantly higher in breast cancer patients than in controls for all women and for the postmenopausal group but were significantly higher for the premenopausal group [102]. Literature on the relationship between breast cancer risk and circulating concentrations of IGF-1 and IGFBP-3 showed an increased risk for premenopausal women with increasing levels of IGF-1 and IGFBP-3. More prospective studies are needed to clarify the association between IGF-1 and IGFBP-3 and breast cancer.

Overexpression of IGF-2 mRNA and peptide has been described in human pheochromocytomas [103, 104]. Despite to this finding, very little tumoral IGF-2 is released into the circulation, unlike catecholamines [104]. IGF-1 also seems to be secreted by pheochromocytoma cells in an autocrine or paracrine manner. In rat pheochromocytoma PC12 cells IGF-1R has been shown to be important for the stimulation of cell replication [105]. Significant overexpression of the IGF-1R in human pheochromocytomas was found. [106]. IGF-1 was 10 times more potent in stimulating DNA synthesis than IGF-2, suggesting that these effects are mediated by the IGF-1R [107, 108]. In Wilms' tumor, a childhood kidney neoplasm expresses IGF-2 mRNA and protein [109]. Wilms' tumors contain receptors that recognize and respond to exogenous IGF

[110]. Deletions or point mutations of the Wilms tumor suppressor gene-1 (WT-1) on chromosome 11p13 are associated with Wilms' tumors. WT1 binds to multiple sites in the promoter region of the IGF-2 gene, and that it acts as a potent repressor of IGF-2 transcription [111]. A molecular basis for the overexpression of IGF-2 in Wilms' tumor may have autocrine effects in tumor progression.

IGF-1R is expressed in pancreatic cancer cell lines and human pancreatic cancers and also IGF-1 is markedly overexpressed in these cancers [112]. The anti-IGF-1R antibody inhibited the action of IGF-1 on cell proliferation. Moderately strong IGF-2R immunoreactivity was present in the cytoplasm of islet cells and mild cytoplasmic immunoreactivity was evident occasionally in ductal and acinar cells. In the pancreatic cancers, regions of strong IGF-2R immunoreactivity were present in the duct-like cancer cells within the tumor mass often exhibiting nuclear localization [113].

IGF-2R may contribute to the pathobiology of pancreatic cancer. Insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP-3) was found to be selectively overexpressed in pancreatic ductal adenocarcinoma tissues but not in benign pancreatic tissues. The highest rate of expression was seen in poorly differentiated cancers. Overall survival was found to be significantly shorter in patients with IGF2BP-3 expressing tumors [114]. Enhanced expression of IGF-1 and IGF-2 mRNA transcripts has been demonstrated in gliomas, meningiomas, and other tumours [115]. Patients with malignant CNS tumours showed increased IGFBP-2 concentrations in CSF. Patients with CNS tumours and microscopically detectable malignant cells in their CSF had the highest IGFBP-2 values [116]. The IGFs have important roles in the normal ovary and exert intra-ovarian control in the replication and differentiation processes of folliculogenesis. [117, 118]. The IGFs, their receptors and IGFBPs were identified in ovarian tumours. IGFBP-2 levels are high in the sera of patients with epithelial ovarian cancer and they may be useful as a possible tumour marker [119, 120]. Primary ovarian epithelial cell lines derived from previously untreated ovarian cancers expressed all major components of the IGF system and were able to demonstrate functional responses to exogenous IGFs [121]. Expression of the IGF-2 gene was more than 300-fold higher in ovarian cancers compared with normal ovarian surface epithelium samples. High IGF-2 expression was associated with advanced stage disease at diagnosis, high-grade cancers and sub-optimal surgical cytoreduction. Relative IGF-2 expression was regarded as an independent predictor of poor survival [122]. IGF-1 mRNA expression and peptide concentrations were also analyzed in epithelial ovarian cancer. High levels of free IGF-1 peptide were associated with elevated risk of disease progression. Women with high IGF-1 mRNA and peptide were found to be at greater risk for disease progression compared to those with low in both [123].

6. IGFs and hypoglycemia

Hypoglycaemia from malignant tumours is rare. This is the only paraneoplastic syndrome caused by the IGF2 overproduction. This phenomenon, referred to as non islet cell tumour hypoglycaemia (NICTH). Hypoglycaemia secondary to mesenchymal tumours account for

64% of the cases with hepatomas, adrenal carcinomas, and gastrointestinal malignancies accounting for others [124, 125]. Endogenous IGFs which circulate in adults fail to exert their immense potential hypoglycaemic activity because they are largely trapped within the vascular space due to their sequestration in a high molecular weight protein complex. IGF-2 leads to an increased peripheral glucose uptake in different tissues as well as inhibition of hepatic gluconeogenesis and lipolysis [126]. IGF-2 has also been shown to have high affinity binding with the insulin receptor. The insulin receptor exon 11+ (IR-B) isoform is the form best known for the classic metabolic responses induced upon insulin binding and this isoform has low affinity for the IGFs. IGF-2 binds with high affinity to the insulin receptor exon 11- (IR-A) isoform of the IR. Activation of IR-A leads to mitogenic responses similar to those described for the IGF-1R [127]. IGF-2 gene can be expressed to produce proteins of various molecular weights. The most active form, with regard to binding of IGF receptors, is 7.5kDa [128]. IGF-2 gene expression regulation, post-translational processing of the 156-amino acid IGF-2 precursor is abnormal in tumors [129]. Larger forms lack posttranslational cleavage plays role in hypoglycemia. Incompletely processed IGF-II (Big-IGF-II) has a strongly reduced affinity for ALS. Impaired formation of the 150 kDa complex, tumour-derived 'big'-IGF-II primarily forms smaller binary complexes with IGFBPs and a greater fraction may stay in the free unbound form [130, 131, 132]. These smaller complexes have a greater capillary permeability and thus are thought to increase IGF bioavailability to the tissues, resulting in hypoglycaemia through action on the insulin receptors and IGF1R [133]. Patients whose underlying condition is one of GH resistance, especially if it is complete and at the level of the GHR, having lost the counter-regulatory effects of GH, are susceptible to hypoglycemia with the IGF-1 treatment [134]. Administration of IGF-I with meals may overcome with this problem.

7. IGFs and diabetes

Reduced IGF-1 levels have been proposed to have a role in diabetes [135]. In animal studies deletion of IGF-1 gene expression in liver caused increased GH secretion and reduced insulin sensitivity. A positive association between low IGF-1 levels and glucose intolerance/diabetes in a sample of 615 subjects aged 45-65 years was found [136]. In contrast, recently Rajpatak et al did not find an independent association between IGF-1 and diabetes among 922 subjects aged ≥ 65 yrs from the Cardiovascular Health Study [137]. In a study was to evaluate the association between IGF-1 level and insulin resistance, both low and high normal IGF-1 levels are found to be related to insulin resistance [138]. A study in 7,665 subjects showed that low and high baseline IGF-1 serum concentrations were both related to a higher risk of developing type 2 diabetes within 5 years [139]. This U-shaped association seems to be likely in face of a higher prevalence of metabolic syndrome or type 2 diabetes in patients with GH deficiency [140]. A state of low IGF-1 levels, as well as with acromegaly [141], a disease characterized by high IGF-1 levels, although endogenous GH secretion may confound short-term glucose homeostasis in these patients. IGF-1 administration reduces the GH hypersecretion of adolescents and adults with type 1 diabetes [142, 143]. IGF-1 administration increases systemic IGF-1 levels, resulting in reduced GH secretion

and improves insulin sensitivity in adults with type 1 diabetes [144]. Also in patients with types 2 diabetes, glycemic control improves with IGF-1 treatment [145]. In one study, subcutaneous administration of recombinant human IGF-1 (for 6 weeks) significantly lowered blood glucose. Glycosylated hemoglobin, which was 10.4% pretreatment, declined to 8.1% at the end of therapy and this improvement in glycemic control was accompanied by a change in body composition with a 2.1% loss in body fat without change in total body weight [146]. Paracrine or autocrine effects of IGF-1 may play a role in the pathogenesis of diabetic complications. Hyperglycemia and IGF-1 stimulate the endothelial cell migration, and tubular formation is induced by a combination of IGF-1 and hyperglycemia [147]. Animal models have provided direct evidence that IGF-1 contributes to the development of retinopathy induced by retinal ischemia. Active capillary proliferation has been documented after implantation of intracorneal pellets containing IGF-1 [148]. The progression of retinopathy is slowed in diabetic patients with hypopituitarism who have low serum IGF-1 levels [149, 150]. Patients with more rapid progression of their retinopathy had the highest levels of IGF-1 in the vitreous [151]. However, Data concerning the relationship between serum IGF-1 levels and diabetic retinopathy is contradictory. Some studies have shown no association between serum IGF-1 levels and the development or progression of diabetic retinopathy. In patients with diabetic retinopathy IGF-1 reducing treatment strategies with either somatostatins or pegvisomant have been tried. Glomerular hypertrophy is thought to be one of the key early changes in the development of diabetic nephropathy. IGF-1 has been associated with renal/glomerular hypertrophy and compensatory renal growth. Epithelial, mesangial, and endothelial cells derived from the kidney respond to IGF-1 binding with increased protein synthesis, migration, and proliferation. Both GH and IGF-1 increase renal plasma flow and glomerular filtration rate. Microalbuminuric patients display higher levels of urinary IGF-1, urinary GH, and plasma IGF-1 than normoalbuminuric diabetic subjects [152]. Patients with microalbuminuria had higher levels of urinary IGFBP-3 even when compared to patients without microalbuminuria matched for metabolic control [152, 153, 154]. Hyperglycemic conditions limit the protective role of IGF-1 against podocyte apoptosis. IGFBP-3 can facilitate podocyte apoptosis. Podocyte structural changes also contribute to the pathogenesis of albuminuria in diabetes. IGF-1 binding to its type 1 receptors stimulates mesangial cell proliferation [155]. Mesangial cell proliferation is one of the factors that contributes diabetic nephropathy.

Higher IGF-1 bioavailability may protect against the onset of ischemic heart disease [156, 157]. Potential beneficial actions of IGF-1 in cardiovascular physiology include increased nitric oxide synthesis and K⁺ channel opening [158,159] and this may explain the impaired small-vessel function associated with low IGF-1 levels in patients with cardiovascular syndrome X [159]. Higher IGF-1 bioavailability may offer improved metabolic control and prevent vascular complications in type 2 diabetic patients. In contrast to this finding, posttranslational phosphorylation of IGFBP-1 increases its affinity for IGF-1 and modify IGF bioavailability. Low circulating levels of hpIGFBP-1 are found to be closely correlated with macrovascular disease and hypertension in type 2 diabetes [160]. further studies are needed to better understand the true value of the IGF-1/IGFBP axis in macrovascular complications of diabetes.

Author details

Emrah Yerlikaya* and Fulya Akin

Pamukkale University Division of Endocrinology and Metabolism, Denizli, Turkey

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