

RESEARCH ARTICLE**Insulin-Like Growth Factor I (IGF-I); cytoprotective effects, idea of replacement therapy in the healthy elderly subjects****Authors*****Hakki Dalcik**

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Insulin-like growth factor-I (IGF-I) is one of the important molecule that has driven great interest in gerontology. The connection between IGF-I and the replacement therapy has been the center for many investigations for the past decade. IGF-I levels decline with age and has been considered to contribute to age-related decline in body activities. As adults age, there is a decline in the concentration of IGF-I. It has been postulated that the declines in both growth hormone (GH) and IGF-I, as it is evident in aged adults, may be associated with increased body fat, reduced muscle strength, decreased bone mass, and reduced lean body mass. This reduction may lead to overall body performance and thus may decrease the quality of life. In the present review, we have viewed the past history of the relevant publications to find a perception that would lead us to come close to the idea of the therapeutic step and provide a view of a possible IGF-I replacement therapy in the healthy elderly subjects. More specifically, this review will summarize and help to understand the effects and benefits of IGF-I system impacting on the aged organ systems. In addition, we aim to discuss the general functional properties of IGF-I and implications of its possible use as a replacement to the healthy elderly subjects and we will emphasis its downfalls and new perceptions.

1. Introduction

IGF-I and IGF-II were first identified by Salmon and Daughaday in 1957 and was named as “sulphation factor”¹ and renamed by Rinderknecht and Humbel in 1976 as “insulin-like growth factor I and II”.² IGF-I is a 70 amino acid polypeptide structurally resembles to IGF-II. IGF-I and IGF-II have 60% amino acid homology to insulin and has low affinity to bind to insulin receptors.³ IGF-I is produced by many tissues in the body and the liver. The production of IGF-I by the liver is by the effect of growth hormone (GH), forming the GH/IGF-I axis.⁴ Therefore, the main source of circulating IGF-I is GH-dependent. IGF-I is also present in the local tissue having a paracrine/autocrine effect is widely GH-independent.⁵ It has been demonstrated that in the GH-deficiency both in humans and in the mouse models, there is a clear decrease in plasma IGF-I levels and prominent symptom is short height⁶ however, local expression of IGF-I is normal or elevated.⁷ These finding suggests that, growth regulation is also effected by extrahepatic IGF-I actions by means of paracrine/autocrine effect and the locally produced IGF-I is also involved in growth, protein synthesis, and survival.⁴ The prepro-IGF-I gene consists of six exons and is located on chromosome 12 in humans. IGF-I gene expression has been shown to be controlled by regional hormones such as; estradiol in the endometrium⁸ or TSH in thyroid⁹, etc.

2. IGF-Binding proteins (IGFBPs)

Six high-affinity IGFBPs have been identified; IGFBP-1 through IGFBP-6; exhibit widespread distribution including serum, tissue, and extravascular fluid.^{10,11,12} IGFBPs are produced by many organs but

the majority are produced by the liver. In humans, IGFBP-3 is the most abundant binding protein in the serum that coordinates the actions of IGF-I.¹³ IGF/IGFBP complex upon reaching the target tissue local proteases releases IGF-I from its IGFBP making it available for binding to its receptor (IGF-IR). Therefore, IGFBPs increase or inhibit the actions of IGF-I by modulating the interaction of IGF-I/IGF-IR complex. It has been demonstrated that IGFBPs also exhibit IGF-independent activities.¹⁴ Upon action of the local proteases IGF/IGFBP complex disconnects and specific fragments of IGFBP dissociates and exhibits IGF-I independent cellular activity,¹⁴ which include cellular migration, control proliferation, and proapoptotic activities.^{14,15}

3. IGF-I Receptor (IGF-IR)

The biological activity of IGF-I is transduced by the IGF-IR, a member of the family of transmembrane tyrosine kinase receptors,¹⁶ IGF-I can act also through the insulin receptor. The IGF-IR consist of two α - and two β -subunits. There is 60% sequence homology between the IGF-IR and the insulin receptor, both of which have tyrosine kinase activity. The IGF ligands and insulin have weak affinities for each other's receptors. The β -subunit has a extracellular domain, a transmembrane domain, and an intracellular domain, which forms the signal transduction component. The signal transduction include phosphorylation of insulin receptor substrate-1 (IRS-1), activation of phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinases (MAPK).^{17,18,19} The highest levels of IGF-IR mRNA expression is present in the fetal and early postnatal period, showing that

IGF-I is primarily involved in growth.²⁰ IGF-I receptor expression is significantly down-regulated in the adults.^{17,18,20}

4. Antiapoptotic, Survival and Beneficial Effects of IGF-I

There is a wide acceptance of IGF-I being crucial molecule for maintenance and survival of the human body.²¹ Results has demonstrated that IGF-I, through Akt or MAPK pathways, can induce cell survival by inhibiting BAD, the proapoptotic member of the Bcl-2 family,^{22,23} and inducing phosphorylation of Bcl-2, which stabilizes the Bcl-2-Bax heterodimerization and support survival.²⁴ In one of the studies, treatment with IGF-I reduced the percentage of cells killed by FasL by 51%.²⁵

The growth-promoting actions of IGF-I is attributed to their mitogenic property.²⁶ The pro-differentiation effects of IGF-I has been demonstrated in many cell types including cells of the central nervous system, osteoblasts, adipocytes, myoblasts and, hemopoietic cells.²⁷ IGF-I also has an insulin effect, that include glucose uptake, glycolysis, and glycogen synthesis.²⁸ In our study, we demonstrated that chronic ethanol reduced the levels of IGF-I in various brain areas causing the formation of gliosis, indicating that IGF-I may have a protective role in the CNS.^{29,30} In addition, we demonstrated the differential change in the expression of IGF-I in the preeclamptic and in the small for gestational age fetal placenta,^{31,32} this change in the expression may act to protect and or to restore the impaired tissue function.

Several studies and review articles have suggested that, IGF-I protects and prevents cell death in a number of cell types.^{33,34} IGF-I was found to be a potent survival factor in neuronal,^{35,36} renal

tissues,³⁷ and testicular germ cells.³⁸ Furthermore, IGF-I was demonstrated to improve cardiomyocyte contractility as evidenced by an increase in sarcomere shortening and a decrease in the relaxation constant.³⁹ In addition, IGF-I was shown to regulate the survival pathway by stimulating the antiapoptotic signaling and suppress apoptosis.^{40,41,42,43} In our previous research, we demonstrated that IGF-I treatment improves the liver function and decreases oxidative liver damage of rats with liver cirrhosis.⁴⁴

In one of the replacement therapy studies, low doses of IGF-I was administered to aged rats, there was a reduced oxidative damage in the brain and liver, normalizing antioxidant enzymes, reduced mitochondrial dysfunction, improved glucose and lipid metabolism, and increased testosterone levels.⁴⁵ In addition, it has been demonstrated that IGF-I administration can reduce brain cell loss due to hypoglycemic injury,⁴⁶ and reduce the risk of cognitive decline, dementia,⁴⁷ and maintaining brain microcirculation.⁴⁸

In the elderly rats similar to humans, IGF-I protein and receptor concentration is decreased, this decline is most pronounced in the hippocampus and had a negative effect in the learning process, however, after increasing the IGF-I levels learning was shown to be improved.^{49,50} Moreover, in a study performed on human subjects, two injections of human recombinant IGF-I (rhIGF-I) (0.1 mL Increlex) 24-h apart, was administered to twelve healthy nonsmoking men (age 62 ± 1 years), and a significant increase in tendon collagen synthesis was demonstrated.⁵¹

5. Ageing and Anti-Aging Interventions

Ageing can be regarded as a decline in the functional capacity of the cells and

organs along with the changes in body composition and metabolism. Aging is also associated with a decline of the activity of the GH/IGF-I axis,⁵² contributing to a significant change in the body composition. However, the driving force of the ageing process is not known. There is an understanding that DNA damage may be a cause of gene regulation present in the aging events. The telomere hypothesis of aging gained great importance.^{53,54} According to this hypothesis the enzyme responsible for adding the telomere ends, which have been reduced with each cell division, is not expressed or expressed in low levels in human tissues.

It has been demonstrated that there is a increase at puberty and progressive decline of IGF-I plasma levels in the aged population including in the humans.⁵⁵ The levels in the aged population has been reported to be similar to those recorded in adult patients with GH deficiency.^{56,57} It has been speculated that, by restoring the IGF-I levels in the healthy aged individuals it may be possible to counterbalance or prevent the age-related alterations. In addition, there is a wide range of interpretation regarding IGF-I may be used as a marker and a regulator of the aging process, and the benefits of treatment of healthy aged individuals may appear to be promising^{55,58,59} however, the side effects are the main concerns.⁶⁰

6. IGF-I and Neoplasia

Although there may be health benefits to prevent the possible deficiencies of the decline of IGF-I in the elderly individuals, studies have suggested that high levels of IGF-I may course increase risk of several cancer types. It has been demonstrated that there is an association between IGF-I and neoplasia, such as;

central nervous system neoplasm,^{61,62} gastrointestinal neoplasm,^{63,64} pulmonary neoplasm,⁶⁵ reproductive neoplasms.^{25,66} However, in the psoriatic patients there was no evidence for involvement of IGF-I in the proliferation of the skin cells.⁶⁷ Besides its neoplastic effects, in the healthy elderly individuals by stimulating the GH/IGF-I axis, adverse effects such as fluid retention, carpal tunnel syndrome and gynecomastia was reported.^{68,69}

7. IGF-I as a Potential Therapeutic Agent

Therapeutic approach of IGF-I is very much limited to Laron Dwarfism.⁷⁰ In one of the studies, once daily dose of IGF-I administration raised serum alkaline phosphatase an indicator of osteoblastic activity, and serum procollagen in children and adults with Laron Dwarfism.^{71,72} On the other hand, to establish wellbeing, quality of life and to increase cognition of the healthy elderly subjects, IGF-I replacement therapy to the normal elderly individuals has become a potential concern. In recent clinical trials, rhIGF-I have been used in insulin-dependent diabetes and patients with anorexia nervosa.^{73,74} The findings of these studies demonstrated that, rhIGF-I (40 microgram/kg s.c.) reduced the dose of insulin and HbA1c in the insulin-dependent diabetes mellitus patients.⁷³ The study of women with anorexia nervosa, demonstrated that short term administration of rhIGF-I (100 or 30 microgram/kg s.c.) have increased markers of bone turnover in severely osteopenic women.⁷⁴ In one of the studies, IGF-I has been shown to increase wound-healing processes and, IGF-I levels in human wound fluid are at maximum levels 24 h post injury, and return to baseline levels upon the completion of healing.⁷⁵ Moreover, it has been demonstrated that IGF-I increases

myelination by promoting oligodendrocyte proliferation and cell survival, and stimulating myelin-specific protein expression, this results in an increased number of thickened myelin sheaths and increased activity of the neuronal cells.⁷⁶

IGF-I administration has been demonstrated to increase cardiac functions and restore ventricular function in ischemic cardiomyopathy and heart failure.^{77,78,79,80} Animal and *in vitro* studies have shown that, IGF-I administration exerts neurotrophic and neuroprotective effects in the hippocampus,^{81,82} involved in reducing the formation of neurofibrillary tangles of the Alzheimer's disease.⁸³ Moreover, in cases in GH deficient children with low levels of IGF-I, cognitive impairment has been reported.⁸⁴ In the studies on few of the elderly subjects that presented high total IGF-I levels showed better cognitive performance.⁸⁵ These findings suggests the potential usefulness of IGF-I in neurodegenerative diseases. However, more studies needs to be done to prove its usefulness in cognition, memory and mood performances and other actions on the central nervous system.

Systemic administration of IGF-I cause hypoglycemia due its binding to insulin receptors. I has been suggested that, IGF-I therapy at low doses improves insulin resistance and lipid metabolism, exerts mitochondrial protection, has a hepatoprotective, neuroprotective, antioxidant and antifibrogenic effects.⁸⁶ In another study, GH-releasing peptide was administered to aged human individuals (25mg/day; 64-81 yr) for 14/28 days, serum IGF-I concentration was increased into the normal range for young adults (265 mg).⁸⁷ This study suggested that, the decline of IGF-I possibly contributed to adverse body

composition changes and increased incidence of cardiovascular diseases.⁸⁷

Moreover, rhGH was administered to healthy aged subjects, possibly activated the GH/IGF-I axis, demonstrated an increase in lean body mass and decrease in fat mass both in women and men subjects.⁸⁸ In addition, rhIGF-I administration in physiologic replacement doses increased bone formation in adults.⁸⁹ In a study done on 5 healthy elderly subjects (age range 71-86 years), rhGH (0.03 mg/kg/week) was administrated for 6 months, the investigators demonstrated an increase in IGF-I levels, increased body mass composition, and muscle strength, without producing any side effects.⁹⁰

Due to short half-life of the unbound IGF-I in the circulation, administration of the IGF-I/IGFBP-3 complex results in a 6 hour longer duration in the circulation extending the half-life, also, it has been demonstrated that administration of IGF-I/IGFBP-3 has a higher therapeutic index than free IGF-I.^{91,92} In a recent study, patients was treated with twice daily injections of rhIGF-I and metformin for more than 5 years and improvement in acanthosis nigricans, hyperkeratosis and hypertrichosis was demonstrated, in addition, a dramatic fall in fasting insulin, HOMA-IR and HbA1c was maintained without any adverse effects.⁹³

8. Conclusion

Both animal and human studies have demonstrated the beneficial effects including cytoprotective and survival functional effects of IGF-I in a variety of tissues and organs. As IGF-I declines with age this wide range of benefits also declines. It is important to realize that, as age increases the functional integrity of the muscles, bones, liver, brain, heart, and other

vital organ decreases therefore, the quality of life also decreases. In this respect, rejuvenating and improving the quality of life both the physical and cognitive performance of the healthy elderly subjects became a great concern for many investigators. The evidence of the benefits of IGF-I raised the possibility of IGF-I replacement to the healthy elderly subjects

by restoring IGF-I levels to those present in the younger individuals. However, the mitogenic and other adverse effects are the pitfalls in this area. Moreover, low doses of IGF-I administration received great attention to overcome these adverse effects. However, IGF-I interventions to healthy aged subjects should be applied in a controlled and measured approach.

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