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REVIEW ARTICLE

Insulin like Growth Factor-1 as a Marker of Nutritional Status and Health

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Abstract: Insulin like growth factor-1 (IGF-1) is a peptide hormone that is secreted from liver and is known to mediate many somatotrophic changes. Since IGF-1 has a wide range of metabolic effects, it becomes important to study its relationship with nutrition and health. It seems to be responsive and selective biomarker of energy status due to its rapid response to depletion and repletion.
Keywords: IGF-1, nutrition, health, biomarker

Insulin like growth factor-1 (IGF-1) is a key peptide hormone, which regulates human growth and development [1]. Primarily liver in response to growth hormone secreted from pituitary or high calorie intake secretes IGF-1[2]. IGF-1 is present in its highest concentration in blood largely in association with binding proteins IGFBP's [3]. IGF is considered to be a major regulator of childhood growth [4-6] and mediates most of the anabolic actions of growth hormone [5] . In the circulation IGF-1 is mostly bound to IGFBP-3 which regulates IGF-1 bioavailability [2]. IGF-1 has both immediate and long term effects on various cellular activities e.g. IGF-1 exerts an acute anabolic action on protein and carbohydrate metabolism by increasing the cellular uptake of amino acids and glucose and by stimulating glycogen and protein synthesis. IGF-1 has long term impact on cell proliferation, differentiation and apoptosis [7].

IGF-1 plays a central role in the regulation of prenatal and postnatal growth and also exerts a growth promoting effect by decreasing apoptosis and increasing cell proliferation and angiogenesis [8]. Studies [9-13] have been carried out regarding its therapeutic utility in conditions such as type 1 and possibly type 2 diabetes, osteoporosis, protein metabolism in critically ill patients, disease induced catabolic states and age associated tissue degeneration. However, the ideal dosage for these is yet to be established. IGF-1 has been shown to increase bone mass [14-15] and evidence has shown that IGF-1 has direct effects on bone forming cells [16]. IGF-1 exhibits direct influence on maintenance of normal immune function [17-18]. The combined mitogenic and antiapoptopic effects have been found to have profound effect on tumor growth [19].

Factors affecting IGF-1 levels: There are several factors that affect IGF-1 levels viz., energy intake, body mass index (BMI), physical activity but the intimate relationship among these variables restricts the identification of their independent effects [1].

Diet: Dietary energy intake and nutritional status are critical regulators of IGF-1 level [20]. In case of protein calorie malnutrition the IGF-1 levels decrease but with improvement in energy intake, levels increase [21]. Fasting also causes a decrease in IGF-1 levels [22] and the effect is smaller in obese subjects [23] plausibly of their less dependency on energy intake to maintain IGF-1 levels. On the other hand, overnutrition has been found to result in increased IGF-1 [24]. It has been seen that protein restriction reduces plasma levels of IGF-1 by inducing resistance to the action of growth hormone in liver and increases the metabolic clearance rate of the growth factor [20, 25-26]. Thissen *et al* [20] observed that protein depletion could blunt the effect of IGF-1 on target organs. Therefore low protein intake in elderly people could prove to be detrimental to skeletal integrity, muscle strength and immune response [27-31] possibly due to the decreased production of IGF-1[32-37]. Study by Devine *et al* [38] on normal adults revealed a positive correlation between protein intake and serum IGF-1 levels. Smith and Castro [39] conducted studies to determine the influence of dietary factors on these proteins in children and to compare the responses in children to those in adults. They observed that protein restriction caused negative nitrogen balance in both children and adults and decrease in mean IGF-1 concentration in adults. Another study by Smith *et al* [26] revealed that a 50% reduction in calorie intake or a 30% reduction in protein intake could result in a decline in serum IGF-1 levels and IGFBP3 levels and an increase in IGFBP-2 level.

Studies [40-45] that examined the association of total fruit, total vegetables, legumes, tomatoes and their related antioxidant states with IGF-1 and IGFBP3 concentration found inconsistent results. However, studies [46-47] have shown lower IGF-1 concentration and higher concentration of both IGFBP-1 and IGFBP-2 in meat eaters and vegetarians. Milk has been found to have positive association with plasma IGF-1 concentrations in cross-sectional [40, 48-50] and experimental studies of adults [51] and children [4, 50]. On the other hand inverse associations between milk intake in childhood and IGF-1 concentration in adulthood have been reported in prenatal and postnatal milk supplementation [52]. Tran et al [53] conducted a study on 1542 healthy women to investigate whether fruits, vegetables and antioxidant intakes are associated with plasma IGF-1 and IGFBP-3 concentrations and concluded that women with higher intakes of citrus fruits or dietary vitamin C tend to have higher plasma concentrations of IGFBP-3.

Height: Children with short stature have low circulating IGF-1 levels [54-55] and individuals with acromegaly have elevated serum IGF-1 levels [37, 56]. Zhang *et a*l [57] reported height to be either weakly correlated or uncorrelated with adult IGF-1 level suggesting that the determinants of pre adult IGF-1 differs from adult IGF-1 levels. Therefore, adult height could be an indirect marker of IGF-1 levels during growth period. Some studies [58-61] reported no association between the level of IGF-1 and height.

Different studies conducted on the association between IGF-1 and BMI revealed different results. Some studies [60-63] showed no association with total IGF-1 whereas others [62, 64] showed inverse association with total or with free IGF-1.

Physical Activity: Cross-sectional studies have shown no association between physical activity and IGF-1 levels [59-61, 65], positive association with leisure time exercise [66], general physical activity [67], physical fitness [68] and training [69]. Nicklas *et al* [70] carried out a non randomized study that involved a 16-week physical training program but found no change in IGF-1 levels. On the other hand, randomized trials have shown that IGF-1 levels increase in association with a two-week training intervention [71] or a strength test [72] but decrease in IGF-1 after a 5-week period of training in adolescents has been reported in some studies [73-75]. Study by Bermon *et al* [72] reported no association of IGF-1 level with strength training.

Alcohol consumption: Clear relationship between alcohol consumption and IGF levels has not been reported. Different levels of alcohol consumption could have opposite effects on IGF levels [59, 61, 76-78]. Barni *et al* [79] reported that long term and heavy consumption of alcohol could cause severe damage to liver function that could result in a decline in production of IGFs. Laboratory experiments by Tomono and Kiss [77] and Srivastava *et al* [78] exhibited that alcohol enhances IGF-1 action and expression. Cross sectional study by Barret-Connor [61] reported a positive association between moderate alcohol consumption in elderly women and serum IGF-1 levels but study by Ma *et al* [80] have reported opposite results.

Age: Studies have demonstrated inverse relationships between circulating levels of IGF-1 in childhood and birth weight [81-82] and these suggest that IGF-1 levels may be influenced by early life events [81]. IGF-1 levels are regulated by nutrition during infancy [83] and transition towards GH regulation occurs as number of hepatic GH receptor increase during the first two years of life [84]. Ong *et al* [85] carried out a study on 497, children who were followed closely from birth to five years of age and reported that circulating IGF-1 levels in childhood are influenced by growth rate and possibly mediate the effects of early postnatal nutrition on later rates of growth and maturation.

Insulin: Acute elevation in plasma insulin suppresses the hepatic production and circulating level of IGFBP-1 which in turn increases the bioavailability of free IGF-1[86]. Liew *et al* [87] reported that ethnicity, fasting insulin, fasting leptin and insulin sensitivity can independently affect fasting IGFBP-1 levels. Rapid changes in serum IGFBP-1 concentrations are regulated primarily by changes in insulin levels and several studies [88-89] have shown that insulin inhibits the synthesis of IGFBP-1 in liver. Low insulin levels associated with long and short term fasting or poorly controlled type 1 diabetes are characterized by elevated serum IGFBP-1 levels [24, 26, 88, 90]. Conversely, individuals with chronic hyperinsulinemia or whose serum insulin concentration is temporarily raised as during the post prandial stage, during insulin infusions in healthy control individuals and among people with obesity, insulinomas or congenital hyperinsulinism with hypoglycemia all show significantly lower serum IGFBP-1 levels than control subjects [24,91]. Studies [89-90] of patients with type 1 diabetes have shown that insulin levels are positively correlated with serum IGF-1 that can be reversed following insulin infusion. Insulin may also indirectly increase the circulating IGF-1/IGFBP-3 ratio [89].

*High levels of IGF-1:*A number of epidemiological studies have shown consistently that high circulating levels of IGF-1 are associated with increased risk for several common cancers such as prostate [58], colorectum [80] and breast [92]. Higher IGF-1 levels have also been associated with decreased risk of heart disease and osteoporosis [93].

Gene Polymorphism: Karlowatz *et al* [94] analyzed the polymorphisms in the genes of IGF-1, IGF-1 receptor (IGF-1R) and the negative regulator of the cardiac IGF-1 signalling pathway and their relation to left ventricular mass of endurance athletes and reported polymorphisms in IGF-1 and IGF-1R gene showed a significant relation to the left ventricular mass for male but not for female atheletes. It has been reported that polymorph variants of IGF genes may serve as a susceptibility factor for pancreatic cancer [95]. Although common genetic variations in IGF-1 alters IGF-1 concentration but is not associated with growth, glucose metabolism or type 1 diabetes [96]. Pechlivanis *et al* [91] studied the polymorphisms in the insulin like growth factor-1 and IGF binding protein 3 genes and risk of colorectal cancer suggested no major role of the assessed genetic variation within the IGF-1 and the IGFBP3 genes in colorectal cancer risk. The data collected [97-99] on physiological responses under combat stress in military population supports the utility of IGF-1 as a marker of energy status. IGF-1 declines rapidly to energy restriction and is a sensitive marker for adequacy of protein intake. IGF-1 may also have merit in evaluation of health status provided a simple test to measure its levels is developed as in case of glucose. At present measurement requires immunoassay or radioimmunoassay.

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