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Nutrition and the Insulin-Like Growth Factor System

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Nutritional status is a key regulator of the circulating and tissue insulin-like growth factor (IGF) system. IGF-I mRNA and protein levels decrease in tissues such as liver and intestine with fasting and are restored with refeeding. Additional studies suggest that the level of protein and calorie intake independently regulate plasma IGF-I concentrations in man. The level of nutrition effects the biological actions of recombinant growth hormone (GH) and IGF-I administration in humans. Limited data demonstrate that plasma and tissue levels of the insulin-like growth factor binding proteins (IGFBPs) are also sensitive to nutrient intake. Specific micronutrients, such as potassium, magnesium and zinc also appear to be important for optimal IGF-I synthesis and anabolic effects in animal models. Malnutrition is common in elderly patients, however, the interaction between specific nutrients, general nutritional status and the aging process on the IGF system is incompletely understood. Mechanisms of nutrient-IGF system interactions which may affect the biological actions of IGF-I, IGF-II, and the IGFBPs are increasingly being determined in basic studies. The effects of underlying nutritional status and responses to dietary intake will be important to evaluate in clinical studies of the IGF system and exogenous growth factor therapy.

Key Words: Nutrition; protein; energy; IGF-I; IGF binding proteins.

Introduction

Appropriate administration of nutrient substrates is important for optimal growth factor-induced tissue anabolism in animals and in man. Endogenously-derived and dietary amino acids are utilized as key substrates for new protein and collagen synthesis. Energy sources (amino acids, carbohydrate, fat) support growth processes directly, and indirectly provide fuel for neutrophils, macrophages, lymphocytes, and other cells involved in wound healing and tissue repair. Either generalized protein-energy malnutrition (marasmus-like), protein depletion (kwashiorkor-like) or specific micronutrient deficiency (e.g., zinc) may delay or impair normal tissue regeneration and healing, in association with inhibited production and function of elements of the insulin-like growth factor (IGF) system. Nutritional repletion in these settings often improves wound healing, tissue function, tissue repair and growth, in association with upregulation of plasma and tissue IGF-I and certain IGF binding proteins (IGFBPs).

Endogenous IGF system growth factors, including growth hormone (GH) and IGF-I, appear to mediate many of the key processes required for normal tissue growth and repair. In addition, GH and IGF-I promote tissue amino acid uptake, enhance protein synthesis and/or decrease protein degradation, and thus facilitate tissue anabolic processes. Exogenous administration of recombinant GH, IGF-I, and certain IGFBPs enhance wound healing and tissue repair in animal and human studies. Other studies have demonstrated marked whole-body and tissue-specific anabolic effects of GH and IGF-I when combined with nutritional support.

A large proportion of the data on nutrition-growth factor interactions involve studies on nutritional regulation of the GH-IGF-I axis. Generalized malnutrition or protein depletion diminishes serum IGF-I levels, alters circulating IGF binding proteins, and reduces tissue IGF-I mRNA levels. Depletion of certain micronutrients (e.g., magnesium, thiamine and zinc) also decreases plasma IGF-I levels and reduces tissue IGF-I production in animal models. Additional studies suggest that specific nutrients may upregulate tissue production or secretion of GH, IGF-I and IGFBPs.

Nutrients and growth factors interact to facilitate specific processes critical to tissue growth and wound repair. Several lines of evidence support the concept that nutrient metabolism and IGF system physiology are interactive. The molecular basis for the specific interaction between general nutritional status, single nutrients and the IGF system action pathways is being increasingly investigated. Because malnutrition is very common in elderly populations in the United States and elsewhere, these interac-

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tions may have important implications for therapeutic trials involving growth factor administration in catabolic states and also in understanding age-related changes in the IGF system during health and illness.

Effects of Protein-Energy Malnutrition and Nutritional Repletion

IGF-I synthesis in tissues is dependent upon GH and to a lesser extent insulin secretion, but is also markedly sensitive to nutritional status *(1–3)*. IGF-I circulates in plasma largely bound to one of several IGF binding proteins (IGFBP), with IGFBP-3 being by far the most abundant *(1,2)*. At least seven IGFBPs have been characterized to date, and they are synthesized in multiple tissues throughout the body, including fibroblasts and epithelial cells. IGFBPs appear to variously potentiate or inhibit IGF-I action, and may influence plasma and tissue IGF-I half-life and/or tissue distribution. However,the influence of nutrients, general nutritional status and the aging process on the regulation and biological actions of the IGFBPs are still incompletely understood *(1,2)*.

Proliferation and function of many cell types has been shown to be dependent upon both an appropriate hormonal milieu and an adequate supply of nutrients *(4)*. It has been proposed that hormones influence the external concentrations of specific nutrients in the cellular environment by alternating such control points as cell membrane permeability, local nutrient metabolism and/or nutrient compartmentalization inside the cell *(4)*. For example, insulin and IGF-I are well known to increase tissue uptake and metabolism of glucose in adipocytes and skeletal muscle cells *(1,4)*. In addition, both the quantity and quality of food intake are known to regulate gastrointestinal hormones, including somatostatin, gastrin, EGF and IGF-I that are important in gut growth and repair *(5)*. Milk of various species, including man, is a nutrient source rich in a variety of gut-trophic growth factors, including elements of the IGF system (GH, IGF-I) *(6,7)*. These may interact with receptors in gut mucosa to stimulate regeneration and function of enterocytes or may be absorbed for systemic effects on the whole body. In fact, the gut is a target tissue for nutrient-stimulated IGF-I, which may be derived from the circulation (endocrine route), the gut lumen (via milk, saliva, pancreatic-biliary secretions) and mucosal cells themselves (autocrine/paracrine route).

The mechanisms for nutrient-induced IGF-I production remain elusive. Nutrients and nutritional status may have major effects on the IGF system by several pathways: generalized overnutrition or undernutrition may stimulate or depress IGF/IGFBP synthesis in tissues; specific IGF system elements may require specific cellular nutrient sets for optimal synthesis and/or function; and stimulation of synthesis may be due to the presence or absence of a specific nutrient which corrects an imbalance of that nutrient in the cellular environment. For example, in rats a 3-d total fast reduced jejunal IGF-I mRNA levels to 18% of fed controls, but with enteral refeeding, gut IGF-I mRNA levels were rapidly normalized *(3)*. Similar regulation of IGF-I production are seen in liver cells in response to fasting and refeeding and with the depletion or repletion of specific amino acids *(8–10)*.

It is well documented that nutritional status markedly affects the GH/IGF-I axis in man *(1,2)*. In the 1970s, Grant et al. *(11)* and Hintz et al. *(12)* demonstrated that the bioactivity of somatomedin-C (IGF-I) was significantly reduced in children with primarily protein depletion (kwashiorkor), as well as in those with combined protein-energy malnutrition. In humans and animal models, serum concentrations of total IGF-I are reduced in general proportion to the severity of malnutrition, but rise over time in response to refeeding *(2,11,12)*. In contrast, circulating GH levels are often elevated during starvation and other states of malnutrition, indicative of a GH-resistance state *(2,13–15)*. For example, fasting increases GH pulse amplitude and pulse frequency *(13)*, while after 2 d of fasting endogenous GH production increased 2.4-fold *(15)*.

Fasting in healthy adults causes in a significant decrease in plasma IGF-I concentrations after 2-3 d, in association with negative nitrogen balance *(16)*. In one study, IGF-I levels in plasma continued to decrease steadily over a 9-d period of fasting, but were increased to only 50% of baseline with refeeding for 3 d *(16)*. In obese individuals or patients with hyperphagia, IGF-I levels are either normal or only modestly increased *(2)*. Available data in animal models and in humans suggest that both energy and protein intake are important for IGF-I production. Adequate protein and energy intake was required in order to normalize plasma IGF-I levels after a period of fasting in healthy adults *(17)*. With adequate protein intake, the rise in IGF-I levels after a 5-d fast was proportional to the level of calories provided *(18)*. Further, provision of non-protein calories primarily in the form of carbohydrate has a more potent effect on raising IGF-I levels after a period of undernutrition than isocaloric diets with fat as the primary energy source *(19)*.

The level of protein intake also markedly affects IGF-I mRNA and protein production in rat liver, as well as IGF-I levels in human plasma *(2)*. Enteral protein refeeding with 80% of the dietary protein as essential amino acids significantly increased plasma IGF-I levels (and nitrogen balance) compared to results with diets providing 80% of protein as nonessential amino acids *(20)*. In addition, IGF-I levels in hospitalized patients generally correlate with general nutritional status, protein intake, and nitrogen balance *(2,21)*. Available data suggest that the impact of protein nutritional status on IGF-I production is more marked than the effects of caloric intake *(1,2,11,12)*. In rats, IGF-I clearance from plasma is increased with protein restriction *(2)*, and protein restriction is associated with resistance to the anabolic effects of both GH and IGF-I

infusions. Undoubtedly, the degree of underlying illness affects these relationships in hospital patients, as IGF-I levels are also reduced in proportion to the degree of catabolic stress *(21,22)*.

Decreased serum IGF-I in energy and protein restriction correlates with a decrease in tissue IGF-I mRNA caused by a decreased rate of gene transcription *(2,3)*. Impaired translation of IGF-I mRNA is also presumed because there are discrepancies between serum IGF-I concentrations and liver IGF-I mRNA levels but the mechanisms responsible for these alterations are presently unknown.

Animal studies demonstrated that hepatic mRNA levels for the GH receptor, a proximal mediator of GH-induced IGF-I production, is significantly reduced by fasting *(23)*. Additional studies in rats suggest that protein restriction is associated with normal hepatic GH-receptor binding with a blunted hepatic IGF-I response at the protein and mRNA level *(23,24)*. In malnourished humans, reduced plasma levels of GH binding protein (GHBP) are documented. GHBP is a circulating fragment of the GH receptor extracellular domain and its concentration in serum correlates with the liver GHR abundance *(2)*. Taken together, the available data suggest that malnutrition (protein depletion) induces GH resistance at both receptor and post-receptor sites. Undernutrition may deprive cells of essential nutrients required for IGF-I production *(4)*, and reduce cellular exposure to insulin, a peptide known to be important for IGF-I synthesis *(1,2)*.

The metabolic effects of IGF-I are mediated through its heterotetrameric tyrosine kinase receptor which shares structural and functional homology with the insulin receptor *(3)*. IGF-I, insulin and IGF-II all may bind to the IGF-I receptor in descending order of affinity *(1)*. Fasting for 48 h increased IGF-I binding and IGF-I receptor mRNA levels in several non-intestinal tissues in rats *(25)*. We found a modest, non-significant increase in IGF-I receptor number and mRNA levels in rat jejunum after a 3-d fast *(3)*. However, with 24 to 72 h of enteral refeeding, jejunal IGF-I receptor expression increased significantly (60–80%), at the same time that plasma IGF-I and jejunal IGF-I mRNA levels were increased. This finding suggests that the small intestinal population of IGF-I receptors (and thus the capacity for IGF-I action) is maintained during fasting-induced intestinal atrophy and increased during nutrient-induced intestinal growth with refeeding *(3)*.

Nutritional status also appears to regulate IGFBPs in plasma and in tissues *(2)*. More than 90% of IGFs in serum are bound in a 150 kDa complex that consist of IGF-I or IGF II, IGFBP-3 and an acid-labile subunit (ALS) *(26)*. Less than 5–10% are associated with other IGFBPs within 4 to 50 kDa binary complexes. The functions of the IGFBPs appear to include stabilization of IGFs in the circulation; facilitating passage of IGFs from the intravascular to the extravascular space and regulation of the interaction of free IGFs with their specific receptors, thus enhancing or blunting IGF actions *(26)*. For example, IGFBP-1 and -2 associate with IGF-I in small complexes that have the ability to cross capillary epithelium which may facilitate IGF-I delivery into tissues *(26)*. IGFBPs are produced by a variety of tissues and cell types, where they may be regulated by nutritional and hormonal factors independent of IGFs. Furthermore, IGFBPs may undergo postranslational changes such as phosphorylation or cleavage by specific proteases that change their affinity to IGFs and thus their effect on IGF biological actions *(27)*.

In tissues and cells, IGFBP-3 may exhibit both stimulatory and inhibitory effects on IGF action, depending on the system studied *(26,27)*. IGFBP-3 plasma levels are not markedly affected by acute dietary changes. No significant alteration in plasma levels occurred in healthy adults after short-term 12 to 24 h fasts *(2,28)*, or even after several days of fasting *(29)* or moderate restriction of calories or protein *(30)*. However, plasma IGFBP-3 levels are clearly reduced in states of prolonged protein-energy malnutrition such as anorexia nervosa *(31)*, in undernourished children with shigellosis *(32)*, and also in hospitalized catabolic patients with evidence of mild to moderate malnutrition *(21)*. In rats, the significant decrease in serum IGFBP-3 levels during severe caloric or protein restriction is accompanied by a decrease in liver IGFBP-3 mRNA *(33,34)*. During protein restriction, IGFBP-3 expression in kidney does not change, suggesting that IGFBP-3 regulation by nutrition exhibits organ specificity *(34)*.

Nutritional repletion generally rapidly increases plasma IGFBP-3 in states of undernutrition *(31,32)*. However, decreased plasma IGFBP-3 levels observed in mildly catabolic hospitalized patients receiving parenteral nutrition were unaffected by 14 d of full intravenous feeding *(35)*. Thus, the underlying clinical state of the patient may influence the IGFBP-3 response to nutrient administration.

IGFBP-3 may undergo proteolysis by specific proteases, rendering fragments with lower affinity for IGFs. This effect has been observed in several physiologic and pathological situations, such as pregnancy, post-surgery, and during severe illness and uncontrolled diabetes *(26)*. Data on nutritional regulation of IGFBP-3 protease activity is limited, but protease activity was unaffected by short-term fasting in humans *(28)*, or by protein depletion alone or severe energy/protein restriction in rats *(2,33)*. IGFBP-3 proteolytic activity was high in undernourished children being treated for dysentery, even after 21 d of refeeding with usual amounts of energy and protein *(32)*. However, refeeding with a high protein diet providing twice as much protein significantly reduced proteolytic activity in these subjects *(32)*.

In contrast to changes in plasma IGFBP-3 concentrations, plasma IGFBP-1 and -2 levels are generally increased during malnutrition and reduced by food intake *(2)*. Changes in hepatic IGFBP-1 and IGFBP-2 mRNA parallel changes in circulating plasma levels. IGFBP-1 is very sensi-

tive to acute variations in metabolic status: its plasma levels decrease promptly after meals, and increase markedly after a few hours fasting *(2,36)*. Protein restriction also increases plasma concentrations and hepatic mRNA levels of IGFBP-1 *(33)*. In vivo studies show that insulin is responsible for these fluctuations in circulating IGFBP-1 *(2)*, and in vitro studies demonstrate a direct inhibition of IGFBP-1 release from hepatocytes by insulin *(37)*. GH suppression of plasma IGFBP-1 levels is also mediated indirectly through changes in insulin secretion *(36)*.

IGFBP-1 may be found in a phosphorylated state that has a high affinity for IGF-I and probably inhibits IGF-action, or in a nonphosphorylated, low affinity state *(26)*. During acute fasting, the increase in IGFBP-1 is concomitant with an increase in the phosphorylated form, which may serve to suppress the hypoglycemic effects of free IGF-I *(28)*. However, with a 12-h fast, free and total IGF-I circulating levels were unchanged. Therefore, it is possible that fasting alters the distribution of IGF-I among individual binding proteins rather than diminishing the free IGF-I pool. During fasting, the increase in high affinity, phosphorylated IGFBP-1 may inhibit IGF-I action, and also may serve to bind the peptide for subsequent transport into extracellular tissues after meal-stimulated insulin release *(28)*.

Plasma IGFBP-2 concentrations are more stable and are three to four times greater than those of IGFBP-1. Thus, under normal physiological situations IGFBP-2 may be the most abundant plasma protein available to mediate IGF transport into tissues. IGFBP-2 levels are inversely regulated by dietary protein intake *(32)*, and levels appear to be more sensitive to protein than to caloric restriction. In healthy adults and children, serum concentration of IGFBP-2 did not change with a 50% restriction in caloric intake for 6 d, whereas it increased with mild protein restriction for the same period of time, and rapidly returned to normal during refeeding of a normal diet *(38)*. In other studies, plasma IGFBP-2 levels did not change during overnight fasting *(28)*, but increased after prolonged fasting or in chronic protein-caloric malnutrition *(31,32)*. IGFBP-2 mRNA is increased in liver with fasting, depletion of energy, or depletion of protein *(2)*.

Animal studies have shown that hepatic IGFBP-2 mRNA is increased during nutrient restriction as a result of increased transcription of IGFBP-2 gene. However, in protein restricted rats, IGFBP-2 serum values were decreased compared to control rats, and whereas IGFBP-2 mRNA was increased in liver, it was slightly decreased in kidney. These discrepancies support a differential organ-specific regulation of IGFBP-2 in response to nutritional changes *(34)*.

Little is known regarding the nutritional regulation of IGFBP-4, -5, and -6 in plasma or in tissues. In protein restricted rats, plasma levels for IGFBP-4 plasma levels decreased while liver IGFBP-4 mRNA levels were discoordinately increased *(34)*. IGFBP-5 and -6 mRNAs were unchanged in liver and kidney in this study. We recently documented that a 4-d fast in adult rats does not alter hepatic, jejunal or ileal IGFBP-4 mRNA; in contrast, fasting significantly increased IGFBP-5 mRNA levels in ileum but not in jejunum, suggesting that tissue-specific nutritional regulation of gut IGFBPs occurs *(39)*.

Recombinant GH as an adjunct to nutritional support has been extensively studied in clinically stable and critically ill patients during the post-operative period, in malnourished patients with end-stage renal disease, chronic obstructive lung disease, or the acquired immunodeficiency syndrome, and in gastrointestinal diseases including inflammatory bowel disease, intestinal fistulas, chronic pancreatitis and short bowel syndrome *(21)*. In general, the clinical studies in patients demonstrated markedly improved nutrient utilization efficiency with recombinant GH therapy over a wide range of nutrient intakes and clinical conditions. Significantly increased plasma IGF-I and IGFBP-3 levels are typically observed in patients receiving GH therapy *(21,35)*. In addition, Clemmons et al. documented that parenteral IGF-I could reverse the protein-catabolic and plasma IGF-I-lowering effects of hypocaloric oral diets in healthy adults *(40)*.

Effects of Specific Nutrients

A number of animal studies and limited human data suggest that specific nutrients upregulate the GH/IGF-I axis, and thereby increase IGF-I production and plasma levels of this growth factor. For example, available data indicates that specific dietary amino acids may stimulate GH release and/or IGF-I production. Often these results occur in association with protein anabolism induced by nutrient administration. The role of the aging process on IGF system response to specific nutrients has been little studied.

The GH secretagoge effects of intravenously administered amino acids such arginine and lysine are well documented *(41–43)*. Arginine administration also potently stimulates insulin and prolactin release *(41)*. Few studies have examined the effects of orally administered amino acids on GH secretion in humans. One study evaluated the daily oral administration of arginine aspartate (250 mg/kg) over a one week period. All subjects had a 60% increase in slow wave sleep-related GH peaks as compared with their control periods *(44)*. Oral L-arginine supplements significantly increased plasma IGF-I levels in postoperative and elderly patients, respectively, versus controls given isonitrogenous L-glycine *(45,46)*. In hepatocyte primary culture, tryptophan repletion specifically increased IGF-I production in hepatocytes deprived of this essential amino acid *(8)*.

Several studies suggest that the anabolic and tissue-specific trophic effects of dietary glutamine are enhanced by exogenous GH or IGF-I administration in a synergistic or additive fashion *(40)*. These and other data support the concept that the metabolism of the amino acid glutamine and

the IGF system may be physiologically interactive. In experimental short bowel syndrome in rats, we found that the combination of L-glutamine-enriched enteral diets and sc IGF-I administration synergistically increased ileal protein content, ileal wet weight and plasma IGF-I levels compared to treatment with glutamine or IGF-I alone *(47)*. Dietary glutamine also upregulated hepatic IGF-I mRNA and ileal IGFBP-4 in this study, but had no effect on circu-lating IGFBPs as measured by ligand blotting *(47)*. Glutamine-enriched intravenous nutrition did not alter circulating IGF-I, IGFBP-2 or IGFBP-3 concentrations in catabolic bone marrow transplant recipients, despite improved nitrogen retention with glutamine supplementation *(35)*.

Zinc depletion is common in catabolic and hospitalized patients due to a combination of urinary, gastrointestinal and wound losses, coupled with insufficient intake. Zinc deficiency is associated with poor wound healing, reduced protein synthesis, immunosuppression, diarrhea, dermatitis, and diminished gonadal steroid concentrations *(41)*. Zinc nutritional status has been shown to markedly influence the GH/IGF-I axis *(48–51)*. In rats pair-fed a low zinc-low protein diet, plasma levels of IGF-I fell significantly, but increased in response to the amount of zinc or zinc + protein in the diet. However, no increase in IGF-I occurred when dietary protein alone was increased *(48)*. Growing lambs fed a zinc-deficient diet demonstrated significantly reduced plasma insulin, GH and IGF-I levels, and insulin levels rose significantly more in response to feeding with zinc repletion *(49)*. In rats, experimental zinc deficiency significantly reduced body weight, serum IGF-I and GH concentrations, hepatic GH receptor abundance, and serum GHBP levels (an index of GH receptor number) versus pair-fed controls *(50)*. Liver IGF-I mRNA levels were also specifically reduced by zinc depletion *(51)*. These data suggest that the reduction in IGF-I levels with zinc deficiency is due, in part, to reduced GH concentrations in plasma and reduced GH receptors in tissues. Zinc repletion in zinc deficient animals normalizes the GH/IGF-I axis at both the protein and mRNA level *(51,52)*.

Another example of an interaction between specific nutrients and the IGF system is the reduction in plasma and tissue IGF-I concentrations with potassium or magnesium depletion *(53–55)*. When rats were given magnesium-deficient diets for 12 d, serum magnesium fell markedly, growth and protein synthesis rates diminished and serum IGF-I levels fell markedly versus levels in pair-fed animals *(53)*. Magnesium repletion reversed these alterations. Similarly, potassium depletion in rats led to growth retardation, a fall in protein synthesis and significant fall in serum IGF-I and insulin levels. These effects are reversed with potassium repletion *(53,55)*. Finally, recent data suggest that experimental thiamine deficiency in rats reduces IGF-I levels in plasma and tissues by 40% *(56)*. Thiamine repletion enhanced the IGF-I response to GH administration in this model.

Age-Related Nutritional Regulation of the IGF System

Elements of the IGF system are developmentally regulated. Plasma concentration of IGF-I and IGFBP-3 are very low in the premature infant, show a significant increase in full-term newborns, increase slightly during childhood, peak in puberty and decrease with age *(2,26)*. In contrast, plasma IGFBP-1 levels are very high in premature newborns, fall in full-term and continue to decline during childhood. IGFBP-2 is the dominant IGFBP in fetal serum and at birth and decreases afterwards. Furthermore, age also appears to determine the IGF-I system response to nutrient restriction. Younger (4 wk old) rats exhibited significantly lower serum IGF-I, IGFBP-3, ALS, and GHBP levels than did older (8 wk old) animals in response to calorie restriction; younger rats also had a lower threshold at which caloric restriction affected the plasma IGF-I system *(57)*. When children underwent restricted calorie die-tary regimens for 6 d, plasma IGFBP-3 decreased and IGFBP-1 was unchanged; in contrast in adults IGFBP-3 levels were unchanged and IGFBP-1 concentrations increased *(30)*. During mild protein restriction for 6 d, adult subjects exhibited a significant decrease in plasma IGF-I and IGFBP-3 levels, while these plasma proteins remained unchanged in the pediatric subjects *(30)*.

Summary and Conclusions

Growth factors, general nutritional status, and specific nutrients are interactive in protein and tissue anabolism. Exogenous administration of GH and IGF-I appear to enhance the efficiency of nutrient utilization during cellular growth. Conversely, both general nutritional status and administration of specific nutrients are able to upregulate endogenous production and plasma concentrations of IGF-I and certain IGFBPs (Tables 1 and 2). Adequate intake of certain nutrients, such as zinc, appears to be critical to ensure optimal anabolic responses mediated by GH-IGF-I action. Nutritional status clearly seems to be important for optimal organ function and tissue anabolism. However, dietary intake and underlying nutritional status is often not well controlled or characterized in many published studies on growth factor therapy in clinical settings. The available data suggests that concomitant prevention of malnutrition, treatment of preexisting malnutrition, and/or provision of specific nutrients with growth-promoting effects may influence the tissue and circulating IGF system in humans. The role of aging in nutrient-IGF system interactions has been little studied. The observations on nutrient-IGF system interactions are relevant to future studies in elderly patients on IGF system regulation and potential roles of exogenous GH or IGF-I therapy.

Table 1
Mechanisms Involved in the Regulation of Plasma IGF-I During Nutrient Restriction

Diminished GH receptor number and/or function
Decreased GH receptor binding (calorie-restriction)
Postreceptor defect (protein restriction)
Decreased IGF-gene expression
Reduction in IGF-I gene transcription (calorie restriction)
Reduced stability of IGF-I mRNA (protein restriction)
Possible reduction in IGF-I mRNA translation
Accelerated clearance of IGF-I
Decreased IGFBP-3 levels
Increased proteolysis of IGFBP-3
Increased levels of IGFBP-1 and -2

Table 2
Specific Nutrients That May Influence the Plasma IGF System

Arginine	Magnesium	Thiamine
Glutamine	Potassium	Zinc

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