BENEFICIOS NUTRICIONALES DE LA HORMONA DEL CRECIMIENTO Y DE LA TESTOSTERONA EN EL NIÑO Y ADOLESCENTE

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Growth hormone (GH), insulin-like growth factor I (IGF-I), sex steroids, and also insulin, all are potent anabolic hormones. They synergize to develop the full body composition and metabolic changes of puberty and have significant nutritional effects in vivo.

Large bodies of data have accumulated which improve our understanding of these complex and dynamic interactions between hormones and nutrients resulting in an adolescent human. Some of these interactions, both in health and disease, are explored and updated in this clinical review.

Growth and Bone Metabolism: Sex steroids are critical for a normal and timely pubertal growth spurt, and this effect is largely mediated by their impact on GH production. Androgens are anabolic agents in bone and are important in bone remodeling and ample evidence supports the concept that these effects are independent of aromatization to estrogens. Males continue to actively accrue bone mass even after the completion of linear growth, and peak bone mass in males is not achieved until their mid twenties.

Androgen deficiency in males induces an initial, rapid increase in bone loss and increased remodeling, followed by a diminished rates of bone formation. Young boys treated with testosterone have significant increases in intestinal calcium absorption and kinetic measures of bone calcium accretion, contrary to the effects observed in young males treated with a GnRH analogue (GnRHa), whom experienced marked urinary calcium losses after only 10w of sustained hypogonadism. Altogether the data support the anabolic effect of androgens in bone.

The potent growth promoting effect of GH, and of IGF-I are well established and is not the subject of this review. In addition to linear growth, however, GH and IGF-I, have been shown to affect bone mass accrual. Previous studies on the effects of GH on bone mineralization have shown that there is a biphasic response to GH, with an initial decline in bone mineral density (BMD) as resorption exceeds formation, followed by a steady increase in BMD after 12mo of treatment and GH increases bone formation in GH-deficient states only after prolonged treatment (>18mo). GH treatment is clearly important in maintaining the long term mineralization of the skeleton and profound deficiency is associated with osteopenia. In GH deficient children and adolescents both aereal and volumetric BMD are decreased and improve with GH therapy. On the other hand, evidence thus far does not support a role for IGF-I in osteoporosis treatment but, similar to the use of GH chronically, much longer term studies may be needed to demonstrate any potential beneficial effect.

Protein Metabolism/Skeletal Muscle: Androgens have potent effects increasing lean body mass, increasing muscle bulk and skeletal muscle strength in man. Using stable isotopes of leucine and glutamine we have previously shown that testosterone administration to prepubertal males markedly increases whole body protein turnover, decreases protein oxidation, resulting in a net increase in whole body protein synthesis rates. The administration of a GnRH analogue to eugonadal young men resulted in opposite results, i.e., decreased whole body protein turnover and protein synthesis rates with a marked increase in protein oxidation and decreased lean body mass. The latter was observed despite invariant GH and IGF-I concentrations. Testosterone treatment of elderly men, however, is associated with increased mRNA expression of IGF-I in skeletal muscle, effects that mirrored those observed in GnRHa-treated young healthy males whom had decreased mRNA gene expression for IGF-I after induction of testosterone deficiency. Taken collectively, these data suggest that testosterone per se, can affect protein metabolism and body composition, independent of changes in GH production at the systemic level. Yet testosterone is necessary for the normal function of the intramuscular IGF-I system. Data thus far suggest that the anabolic effects of androgens are likely direct and not secondary to aromatization.

The administration of physiological or supraphysiological doses of testosterone has been shown to increase skeletal muscle strength in both elderly and young men, and the induction of a hypogonadal state with GnRHa results in a quantifiable loss of muscle strength as measured by

isokinetic dynamometry. This nutritional effect of testosterone is principally responsible for the marked increase in strength in male puberty. Despite these physiologic effects, the administration of testosterone as an ergogenic agent to young boys is not warranted due to the potentially negative impact accelerating epiphyseal fusion.

GH administration to healthy volunteers results in a selective increase in whole body protein synthesis rates with a net anabolic effect. Because of this significant increase in nitrogen retention, GH has been tried in a variety of catabolic conditions in man and has been shown to improve nitrogen balance in debilitating catabolic conditions such as burned patients, subjects on parenteral nutrition, trauma victims, and after major surgery. However, high-dose GH treatment of critically ill patients resulted in higher mortality than those receiving placebo, causing substantial concern on the use of GH in the intensive care unit setting. On the other hand, GH is clearly a potent protein-anabolic agent which is routinely and safely used to promote growth in children with a variety of other more chronic illnesses such as inflammatory bowel disease, cystic fibrosis or chronic renal failure, as well as in AIDS wasting syndromes. Hence, safety with the use of GH in chronic inflammatory conditions appears to be excellent and different than that in acute severe disease. It is nonetheless prudent to discontinue the use of GH in any patient who develops a severe acute illness necessitating hospitalization and aggressive support.

IGF-I, on the other hand, has very comparable effects as GH enhancing protein anabolism, stimulating protein synthesis, with no effects on proteolysis. However, in high doses, IGF-I suppresses proteolytic rates, effects indistinguishable to those of insulin. GH and IGF-I, when given together, however, do not have more potent protein anabolic effects that when each compound is given separately, whereas in relative caloric deprivation, the co-administration of GH and IGF-I appears to be synergistic enhancing a more positive protein balance. Both GH and IGF-I have been used in severe GH-deficient adults and found to have comparable effects enhancing protein synthesis, this was also observed in post menopausal women treated with either GH or IGF-I for 1 month. Both of these hormones have been tried as protein anabolic agents in a variety of experimental situations in man with very comparable results. Taken in aggregate, the available data suggest that IGF-I mediates the protein-anabolic actions of GH in man. These effects are most evident and magnified during puberty. We have also observed an increase of the effects of combined testosterone and GH to GH deficient boys on IGF-I production, protein synthesis rates and body composition, supporting further the concept that these 2 hormones are synergistic in their metabolic effects during puberty .

Lipid Metabolism: Androgens have been shown to stimulate lipolysis in a variety of experimental situations in both animals and humans. When testosterone is administered to hypophysectomized rats it does not affect lipolysis, however, when given in conjunction with GH, it normalizes rates of lipolysis in vitro more than GH alone. When young men were rendered hypogonadal by the administration of a GnRHa we observed marked changes in body composition with decreased lean body mass and increased adiposity. This was associated with decreased lipid oxidation rates, suggestive of decreased free fatty acid mobilization and substrate availability for oxidation in the absence of testosterone. These and other data support the concept that testosterone and GH have additive effects on lipolysis and helps explain the large changes in body composition, increased lean body mass and decreased adiposity characteristic of the male puberty.

GH receptors are expressed in human adipocytes and GH has been shown to have significant effects on fat metabolism, improving the lipolytic response of isolated adipocytes to epinephrine, improving lipid profiles (although not consistently), and decreasing LPL activity in GH deficient adults and in obese women, hence diminishing the flow of ffa to the adipocyte (antilipogenic). GH therapy in children, is well known to be associated with substantial changes in redistribution of body fat, from abdominal (android) to more peripheral (gynoid) pattern. When given to children with GH deficiency, the classical pudgy appearance on the hypopituitary child changes with a decrease in adiposity, and at times a remarkable "thinning outó of their physique. GH administration, however, typically does not cause weight loss but rather a change in body composition, hence careful discussion with patients needs to include a realistic expectation of the anticipated results of treatment, particularly in adults and in some obese children being treated with GH, such those with Prader Willi syndrome. The effects of GH on lipids/lipolysis, however, are not IGF-I mediated as there are no functional type one IGF-I receptors in adipocytes.

Carbohydrate metabolism: The bulk of available data suggest that androgens are not critical for normal carbohydrate metabolism. GH, on the other hand, is pivotal for the maintenance of normal glucose homeostasis and hepatic glucose production in infancy e.g.. However, this critical role of GH in glu-

cose homeostasis is markedly diminished in older children and adults, a transition which is poorly understood. GH administered chronically results in compensatory hyperinsulinemia and GH treatment is associated with the development of insulin resistance, however, this is typically not associated with clinically significant disease. GH therapy in children is not associated with any increase in the incidence of diabetes. Caution, however, should be exercised when using GH chronically in subjects in whom other risk factors for carbohydrate intolerance or diabetes are present, such as the elderly, the obese, or those on glucocorticosteroids for example.

IGF-I, on the other hand. does not mediate the effects of GH on carbohydrate metabolism as IGF-I has mostly insulin-like effects. During puberty, despite the measurable decrease in insulin sensitivity, carbohydrate tolerance remains normal. Based of these data, it is possible that not only the compensatory hyperinsulinemia but the marked and chronic increase in IGF-I during this period contribute to the maintenance of normoglycemia in adolescence.

Effects of GH depending on gender: GH production rates and IGF-I concentrations are higher in adult females than in males and these differences are apparent in puberty, suggesting lesser sensitivity to GH action in females. We recently conducted studies to assess if the protein-anabolic and lipolytic effects of GH are influenced by gender in children. Using isotope dilution methods and body composition measures, we found that boys had higher rates of protein turnover and synthesis than girls before and after GH Rx, and greater lowering of protein oxidation rates after GH than girls. Boys and girls had similar rates of lipolysis, lipid concentrations and body composition changes after GH Rx. There were no differences in measures of carbohydrate metabolism and insulin sensitivity, nor in lipid concentrations between males and females before or after GH therapy. Boys had higher IGF-I responses to 8w of GH Rx than girls. There were, however, no differential gender effects on the linear growth responses observed after 12mo of Rx. These data suggest that differences in IGF-I and protein metabolism during GH Rx between adolescent boys and girls may account in part for the gender differences in physique and strength that develop during human puberty. Gender differences in IGF-I responses to GH did not translate into differences in the quality of linear growth. Further follow up is needed to better assess the need for differential GH dosing in boys vs. girls in puberty.

Comparison of metabolic effects of GH, IGF-I and sex steroids at whole body level in humans

Effect	GH	IGF-I	Testosterone	Estrogen
Protein Synthesis				No change
Body Composition (FFM/%FM)				Not clear
Insulin Sensitivity			No effect	No effect
Lipolysis/ Lipid Oxidation		Chronically	Facilitates GH effects	Not clear
Bone Density		Not after 12mo		

In conclusion, data summarized give a robust rationale for the use of GH /IGF-I in catabolic conditions in both children and adults and androgenic hormones in adults. Both GH and IGF-I decrease the catabolic states such as the glucocorticosteroid treated patient and the profoundly hypogonadal subject. GH and testosterone both potentiate the development of the full body composition and metabolic changes of male puberty and have significant nutritional effects in vivo.

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