生長激素對身體組成的影響

The effects of growth hormone on body composition

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The action of growth hormone (GH) on longitudinal bone growth is well known and easily recognized. GH also has profound effects on body composition. Generally, GH increases the amount of body cell mass and extracellular water and decreases body fat. The lipolytic effect of GH was demonstrated in the 1930s when it was shown that pituitary extracts reduced body fat in rats. Recently, GH treatment has been shown to promote a redistribution of adipose tissue from the abdominal (android) to a more peripheral (gynoid) distribution. The reverse change has been demonstrated in patients with acromegaly after successful treatment. The anabolic action of GH was first demonstrated when nitrogen retention was observed after GH administration. GH seems to stimulate cell division and increase the amount of DNA in the muscle. In patients with acromegaly the overweight is partly explained by a significant increase in body cell mass and muscle volume, compared to matched controls, demonstrated by several independent methods of determining body composition. In GH-deficient patients, however, the overweight is due to an increase in adipose tissue mass and the body cell mass seems only decreased in subjects below the age of 55. The anabolic action of GH is accompanied by sodium and fluid retention, due to increased sodium pump activity. In acromegalic subjects extracellular water has been shown to be increased by up to 25%. However, in GH-deficient adults the extracellular fluid volume is markedly decreased by approximately 15%. Replacement therapy with recombinant human GH in patients with GH deficiency restores the extracellular fluid volume by an initial rapid expansion of the fluid volume, followed by a slight decrease towards a new steady-state level.

GH has profound effects on body composition. Although body composition is determined by many factors including age and physical activity, changes in body composition can be helpful parameters in following the effect of GH in various body compartments.

Introduction

Growth hormone (GH) has profound effects not only on longitudinal bone growth, but also on body composition. GH is not only secreted during childhood but also during the entire adult life. In general, GH increases the amount of body cell mass and extracellular water and decreases body fat[1].

The advent of recombinant human GH (rhGH) has increased the supply of GH and made it possible to treat not only children but also adults with GH deficiency (GHD). Body composition studies in various GH-related disorders may yield important information about the physiological role of GH in different body compartments and can be helpful in assessing the effects of treatment.

This review will focus on the effects of GH on body composition on the basis of studies performed in patients with GH-related disorders and on the validation of the different methods to determine body composition in these patients.

Metabolic actions of growth hormone

Growth hormone at cellular level

GH exerts is biological effect on the target cell by binding to specific GH receptors, which are abundantly present throughout the body[2,3]. The GH receptors are hormonally regulated by, for example, insulin and GH itself[4].

GH has been shown to express different effects in different target issues[5]. These differences may be explained by different GH receptors in the various tissues.

Moreover, several specific human binding proteins have been discovered in plasma[6]. These binding proteins interrelate with the bioactivity of GH, partly by competition with the receptor[7,8].

Insulin-like growth factor-I (IGF-I) is generated locally and in the liver by GH induction. Based on the dual effector theory of GH action[9] it has been proposed that GH directly promotes the differentiation of precursor cells such as preadipocytes and pre-chondrocytes. During this process the cells become responsive to IGF-I, which results in an increased production of IGF-I in these differentiating cells and further autocrine and paracine actions of IGF-I are exerted[5,10].

Lipolytic effect

The lipolytic action of GH was demonstrated in the 1930s when it was shown that pituitary extracts reduced body fat in rats. Lipolysis was the first metabolic effect of GH to be described in humans[11]. GH opposes the actions of insulin on the adipocytes resulting in an increase in plasma free fatty acids[12], except during the initial approximately two hours fasting period, which is characterized by a fall in free fatty acid concentration[13]. Nocturnal GH peaks seem to activate the mobilization of fat stores[14].

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At the cellular level GH promotes the differentiation of pre-adipocytes into adipocytes, thereby increasing the number of cells in adipose tissue[9]. Furthermore, GH treatment has been shown to promote a redistribution of adipose tissue from an abdominal (android) towards a more peripheral (gynoid) distribution[15]. Concordingly, GH administration in GH-deficient children has been shown to result in both a reduction of the amount of lipid per cell in the abdominal adipocyte as well as a reduction of lipogenesis[16]. This study indicates anatomical site-specific GH-mediated changes in insulin responsiveness.

The effect of GH on body fat and fat distribution has recently been reviewed[17].

Anabolic effect

The anabolic actions of GH in man were demonstrated in the 1950s when Ikkos and colleagues observed nitrogen retention after GH administration[18]. In the rat, the rate of cell division in muscle declines after hypophysectomy, and subsequent treatment with GH stimulates cell division and increases the amount of DNA in the muscle[19]. A study in adult patients with growth hormone deficiency (GHD) receiving GH therapy indicated that the observed increase in lean body mass resulted from increased protein synthesis rather than decreased protein degradation[20].

Several studies have been performed investigating the potency of GH to reverse catabolism in trauma, burns, sepsis, etc. Post-traumatic protein catabolism in muscle seems to be attenuated by GH administration[21,22]. Probably this anabolic effect of GH is caused by an increase of hepatic glutamine transport to the muscle while urea synthesis is reduced[23,24].

The administration of IGF-I does not exert similar effects as GH on the muscle[25]. Also trangenic animals expressing IGF-I do not develop changes characteristic of acromegaly[26]. Hence, the action of GH on muscle is probably a direct one not mediated by IGF-I. However, a paracrine effect of IGF-I is possible[27].

Antinatriuretic action

Early in the 1950s it was demonstrated that GH administration resulted in sodium retention, accompanied by a marked expansion of the extracellular fluid volume[28]. The mechanism of this effect is still unclear, though evidence exists for both a direct renal action as well as an indirect effect mediated via the renin-angiotensin system[29].

The direct antinatriuretic action of GH may be acted on the tubular cell by increasing the sodium pump activity[30,31].

Administration of recombinant human growth hormone (rhGH) to healthy adult subjects has been reported to result in an acute activation of the renin-angiotensin system[29]. Interestingly, in acromegaly, evidence is found for an alleged sodium transport inhibitor to counteract the volume expansion at high GH levels[32]. In contrast to adult subjects, treatment with GH in childhood is not associated with activation of the renin-angiotensin system[33].

Bone metabolism

Bone formation and resorption after longitudinal bone growth has finished. The mechanism behind the effect of GH on bone metabolism is not clear yet, but probably GH increases both the availability of minerals as well as osteoblast proliferation. GH stimulates, mediated by IGF-I, renal 25-hydroxyvitamin D-1α-hydroxylase activity, thus increasing intestinal calcium and phosphate absorption. Furthermore GH promotes renal reabsorption of phosphate[34]. The direct effect of GH on osteoblast proliferation is mediated by GH receptors on these cells.

Body composition in acromegaly

The first systematic studies of body composition in acromegaly, a disorder due to hypersecretion of GH by a pituitary adenoma, were performed in the mid-1950s[35]. An excess of total body water (TBW) and especially the extracellular water (ECW) component was shown.

Before treatment

In a retrospective study comprising 189 patients it was shown that patients with untreated acromegaly were heavier than matched controls. Moreover, profound alterations in body composition were found[36]. Body composition was determined on basis of measuring TBW and total body potassium (TBK) using a four-compartment model. Observed body weight (BWT) in male acromegalics was 8.1 kg higher than predicted from healthy subjects of the same height, a difference explained by an average increase of 4.7 kg in body cell mass (BCM) and 7.1 kg in ECW, simultaneously, with a mean decrease of 3.7 kg in body fat (BF). Female acromegalics weighed on average 6.4 kg more than healthy women, a difference explained by an increase in BCM of 3.3 kg and ECW of 4.6 kg concomitant with a decrease in BF of 1.5 kg. Furthermore, a significant negative correlation between GH concentration and % BF in both male and female patients was observed.

Effect of treatment

Interestingly, treatment of acromegaly seems not to affect BWT, although changes in body composition can be observed[37]. GH concentration after treatment correlated significantly with excess ECW and inversely with BF deficit. After treatment a normalization of TBW and BF was observed in the group of patients with a GH concentration below 5 mU/l.

Using a multiscan computed tomography (CT) technique in 15 patients before and one year after surgical therapy, it was shown that muscle and skin mass, as well as visceral organ mass, were decreased and adipose tissue (AT) mass was increased after treatment[38]. Furthermore, the fractions of AT in the subcutaneous trunk and the intra-abdominal depots increased after treatment, while the AT fractions in the limbs and the head and neck region decreased. In males, these alterations resembled a change of AT distribution towards an abdominal predominance.

Growth hormone deficiency (GHD)

Body composition studies in GH-deficient (GHD) children showed a loss of AT after initiation of GH treatment[39]. These changes were reversed after treatment withdrawal[40]. Until recently, body composition studies in GHD adults have received little attention. After the advent of rhGH and the recognition of the various negative effects of GHD on the body such as increased mortality[41], studies concerning GH replacement therapy have increased using body composition as one of the important outcome parameters.

GHD adults

Body composition in GHD adults is characterized by an increase in BF, and decrease in fat-free mass (FFM) and ECW, the inverse alterations as seen in acromegaly.

In a study comprising 106 subjects with GHD, it was shown that GHD adults are overweight[42]. Males were found

7.5 kg heavier than predicted, a difference mainly explained by an average increase of 6.6 kg in BF. Female subjects weighed 3.6 kg more than the healthy controls, a difference explained by an increase of BF of 6.0 kg with a simultaneous decrease of 2.4 kg of ECW. Similar findings in a smaller population of GHD adults were reported earlier[43].

The impression that lean body mass is replaced by AT in GHD adults is supported by a study determining muscle and AT area in the thigh using computed tomography[44]. The muscle to AT ratio, as well as the muscle area to BWT ratio, were significantly reduced in GHD adults.

Recently, consistent data suggesting reduced bone mineral content in GHD adults have emerged[45,46].

The effect of GH replacement therapy

Treatment with rhGH over 6–12 months results in marked changes in body composition, without a clear change of BWT.

In a 6-month double-blind placebo-controlled trial of adults with GHD, acquired during adult life, body composition was studied by measuring TBK and skinfold thickness[43]. In response to 6 months treatment with rhGH, body fat decreased by 20% and lean body mass increased about 10%.

Estimates of BF from measurements of skinfold thickness (SFT) in 14 GHD adults after 6 months of rhGH therapy showed a 10% decrease of fat mass[47].

Another trial showed an 5% increase of CT-determined muscle area of the thigh and a 7% decrease of AT area and 16% decrease of SFT after 4 months of rhGH treatment[44]. After proceeding with treatment in a open setting, these changes seemed to be progressive[48].

In a recent double-blind cross-over placebo-controlled trial in ten patients with adult-onset GHD, body composition was studied by various independent techniques during 6 months therapy with rhGH[49]. BF estimations based either on TBK and TBW measurements, using a four-compartment model, or bio-electrical impedance analysis resulted in a near 25% decrease after 6 months treatment. Simultaneously a significant 5% increase of BCM based on TBK measurement was observed. Whole body CT scans revealed that rhGH replacement therapy results in differential rates of AT loss from different regions of the body: subcutaneous AT decreased by 13%, while visceral AT decreased 30%.

GH administration in the absence of GHD

In a placebo-controlled study of young, well-trained, exercising adults, body composition was studied by hydrodensitometry[50]. A continued high-protein diet and physical training was combined with the administration of supraphysiological doses of rhGH, which resulted in a decrease of BF and an increase of FFM. In another double-blind placebo-controlled study without cross-over design rhGH was administered during a 6-week period to male power athletes[51]. Unfortunately, body composition was only estimated by the measurement of SFT at ten sites. No significant change of BF could be showed by this probably insufficient method.

Also GH administration in obesity has been studied. Moderate doses of rhGH were given to obese subjects during an 11-week period if diet restriction[52]. This did not result in an accelerated BF loss as determined by hydrodensitometry.

Three weeks of the GH treatment in patients with chronic obstructive pulmonary disease caused initial weight gain – possibly due to fluid retention — and signs of nitrogen retention[53].

Aging is associated with decreased GH secretion and low IGF-I levels[54]. Body composition alterations comparable to those seen in GHD can also be observed. In a study comprising elderly healthy men with subnormal IGF-I concentrations, 6 months of rhGH administration was accompanied by a 9% increase in lean body mass[55].

Appropriate body composition techniques

The primary problem in comparing different methods of determining body composition is the lack of a 'gold standard'. All methods of measuring body composition in humans are based on a body composition model with a specific set of assumptions and errors. As a result, the validity of any methods of assessing body composition has to be determined from the agreement between it and a reference method, rather than by trying to determine the real accuracy. This demands an appropriate statistical approach[56].

Because of the aberrant body composition caused by abnormal secretion of GH, as described earlier in this report, with the associated change of water distribution between the intracellular and extracellular spaces, the assumptions of a standard two-compartment system are not valid.

Recently, comparative studies of determining body composition by applying various body composition techniques in either acromegaly or GHD have been reviewed[57]. Paired comparison of TBW predicted by bio-electrical impedance analysis and TBW measured by isotope dilution in patients with acromegaly displayed good agreement[58]. TBW and BF predictions from anthropometric variables alone showed, in relation to bio-electrical impedance analysis, poor agreement with the values obtained by a four-compartment model based on the measurement of TBW and TBK.

In 10 patients with untreated acromegaly, paired comparisons between CT-determined AT and BF measurements according to a four-compartment model, various two-compartment models based on isotope dilution and by various bio-electrical impedance equations were performed[59]. There was a reasonable agreement between the CT-estimated AT volume converted to BF mass (as the reference method) and the four-compartment model, as well as bio-electrical impedance estimations using standard equations. Equations described by van Loan[60], Segal[61] and Deurenberg[62] oversetimated BF dramatically.

In adults with GHD receiving rhGH therapy over 26 weeks, the increase of CT-determined muscle volume as well as the increase of BCM based on TBK measurement were 5%, while TBN,determined by in vivo neutron activation, had increased by 13%[49]. This difference may indicate a changed N:K ratio induced by treatment.

A preliminary analysis, performed by the authors, of comparative body composition determinations in more than 90 adults with GHD confirms the results as obtained in patients with acromegaly[57].

Conclusion

Body composition studies yield important information about physiological changes induced by GH and the effect of treatment of patients with either GH deficiency or acromegaly. GH induces an increase of BCM and ECW and a decrease of BF, mainly due to reduction of abdominal and visceral AT depots.

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