Basal metabolic rate in adults with growth hormone deficiency and in patients with acromegaly: relationship with lean body mass, plasma insulin level and leucocyte sodium pump activity

Franco SALOMON, Ross C. CUNEO, Richard HESP*, Jenny F. MORRIS†, Lucilla POSTON† and Peter H. SÖNKSEN

Endocrine and Diabetic Unit and †Renal Laboratory, Department of Medicine, UMDS, St Thomas's Hospital, London, U.K., and *Radioisotopes Division, MRC Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex, U.K.

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1. The relationship of lean body mass, plasma insulin concentration and leucocyte active sodium transport with basal metabolic rate was investigated in 24 adults with growth hormone deficiency before and after treatment with recombinant human growth hormone and in 10 patients with untreated acromegaly.

2. Based on total-body potassium determined by whole-body 40K counting, patients with acromegaly had increased lean body mass, whereas lack of growth hormone was associated with decreased lean body mass.

3. By indirect calorimetry, patients with acromegaly had increased basal metabolic rates and patients with growth hormone deficiency had decreased values when expressed as percentages of values predicted from the WHO/FAO/UNU equations. Basal metabolic rate expressed in terms of lean body mass was similar in acromegaly and growth hormone deficiency, but was higher than normal in both patient groups.

4. The leucocyte ouabain-sensitive sodium efflux rate constant was decreased in both patients with acromegaly and patients with growth hormone deficiency, and there was no correlation with basal energy expenditure, fasting plasma insulin level or serum growth hormone level.

5. There was no increase in the sodium efflux rate constant in patients with growth hormone deficiency after 1 month on treatment with recombinant human growth hormone.

6. Apparent differences in basal metabolic rate in growth hormone deficiency and acromegaly are due to changes in lean body mass. Both adults with growth hormone deficiency and patients with acromegaly have increased energy expenditure, probably owing to changes in fuel metabolism which are not reflected in the leucocyte sodium pump activity.

INTRODUCTION

A mild increase in resting energy expenditure in acromegaly and during short-term growth hormone [GH] treatment is well described [1–4]. Recently, increased sodium pump activity has been reported in patients with acromegaly [5] and the authors have speculated on its possible relationship with the increased energy expenditure. Stimulation of the sodium pump by GH has also been reported in the liver and kidney of hypophysectomized rats [6]. Similar stimulation occurred with tri-iodothyronine [6], suggesting a common site for the thermogenic action of thyroid hormone and GH [6, 7]. The contribution of Na+/K+-ATPase activity to basal metabolic rate (BMR) in vivo has been estimated to be about 20% in man [8]. The main determinant of BMR is lean body mass (LBM) [9–12]. Through its anabolic and lipolytic actions, GH has a substantial effect on body composition and energy expenditure, as shown in adults with GH deficiency (GHD) during treatment with GH [13].

To investigate the effect of GH on the relationship between resting energy production, body composition and sodium pump activity, we performed indirect calorimetry, total-body 40K counting and the estimation of leucocyte glycoside-sensitive sodium efflux rate constants (ERCs) in patients with acromegaly and in adults with GHD before and after GH treatment.

This study was presented in part at the 7th Joint Meeting of the British Endocrine Societies, Exeter, U.K., April 1988 [13a].

Key words: acromegaly, body composition, energy expenditure, growth hormone, growth hormone deficiency, lean body mass, sodium/potassium-adenosine triphosphatase.

Abbreviations: BMR, basal metabolic rate; ERC, efflux rate constant; GH, growth hormone; GHD, growth hormone deficiency; LBM, lean body mass; rhGH, recombinant human growth hormone.

Correspondence: Dr Franco Salomon, Department of Medicine, University Hospital, University of Zürich, Rämistrasse 100, 8091 Zürich, Switzerland.
METHODS

Patients

Thirty-four adult patients and 14 normal subjects agreed to participate in this study, which was approved by the Ethics Committee of the West Lambeth Health Authority. Ten were non-diabetic patients with acromegaly (Table 1) and 24 had longstanding GHD. The patients with GHD were the same as those reported in a previous paper [13]. Fourteen normal control subjects, who were not on drug treatment and had no history of endocrine diseases, were members of laboratory and medical staff recruited from within the Department (Table 2). GHD was documented for at least 1 year and approval by the Ethics Committee of the West Lambeth Health Authority. Ten were non-diabetic patients with GHD. The patients with GHD were the same as those reported in a previous paper [13]. Patients with GHD were on appropriate treatment had been discontinued 4 and 5 years ago. The patients with GHD took part in a double-blind, placebo-controlled study on the effects of replacement treatment with human recombinant GH (rhGH) [13]. Patients were treated with 0.07 unit of rhGH day\(^{-1}\) kg\(^{-1}\) body weight given subcutaneously at bedtime. Sodium pump activity in leucocytes was measured after 1 month of treatment. The effect of rhGH treatment on BMR has been reported previously [13].

Body surface area was calculated using the formula of Du Bois & Du Bois [14].

Indirect calorimetry

Patients were studied using indirect calorimetry to measure O\(_2\) consumption and CO\(_2\) production after an overnight fast. Normal pituitary hormone replacement treatment was continued, except that cortisone acetate (12.5 mg) was taken 2 h before the beginning of the study in the place of other glucocorticoids.

After cannulation of an antecubital vein for blood sampling, the patients rested for 60 min in an air-conditioned room at 22°C. O\(_2\) consumption and CO\(_2\) production were measured using an open-loop system (Metabolic Measurement Cart; Horizon, Beckman Instruments Inc., Anaheim, CA, U.S.A.) with a mouthpiece and a nose clip, with the patient in a semi-recumbent position. The use of a mouthpiece has been shown to give similar results to other techniques [15]. The cart was calibrated against standardized gases, 900 ml volume syringe, operating temperature and ambient barometric pressure before each study, and additional gas calibration was performed during the study. Three measurements were made over a 90 min period each lasting about 12–14 min. After 2 min of equilibration, respiratory gases and ventilation were analysed continuously and averaged over intervals of 3 min. The values reported for O\(_2\) consumption and CO\(_2\) production were standardized for temperature and pressure and represent the mean of all readings. BMR was predicted using the FAO/WHO/UNU equations [16].

Total-body potassium

On the same day the total-body potassium of the patients was measured in a whole-body counter [17], and the results were compared with normal values based on sex, age, height and weight [18]. LBM was calculated assuming 60 mmol of K\(^+\)/kg LBM in female subjects and 66 mmol of K\(^+\)/kg LBM in male subjects [19]. The validity of this assumption in adults with GHD has been confirmed by the tight correlation between LBM and total thigh muscle area determined by computed tomography before \((b = 0.28, r = 0.94)\) and after \((b = 0.32, r = 0.93)\).
Treatment with rhGH which were indistinguishable from values in normal control subjects ($b = 0.28, r = 0.92$) as reported previously [20].

**Estimation of leucocyte sodium pump rate constants**

Leucocytes were isolated from 50 ml of peripheral blood. Sodium ERCs were estimated as previously described [21] by measuring residual $^{22}$Na activity against time in leucocytes preloaded with $^{22}$Na as tracer. Sodium ERC was estimated in the presence and absence of the cardiac glycoside, ouabain. Total, ouabain-sensitive and ouabain-insensitive sodium ERCs were evaluated in leucocytes incubated with Earle’s buffer.

**Statistical analysis**

All values are given as means±SEM. Measured values for total-body potassium and BMR were compared with the expected values using a one-sample t-test. For comparing the three groups, unweighted one-way analysis of variance was used. When significant at the 5% level, orthogonal contrasts were used post hoc to look for differences between groups. Simple linear and stepwise regression analyses for BMR were performed using the Number Cruncher Statistical System (NCSS, Kaysville, UT, U.S.A.).

**RESULTS**

**Body composition**

The patients in both groups with abnormal GH status were moderately overweight (Table 2). In absolute terms, their mean body weight and mean total-body potassium were not significantly different, but when the measured total-body potassium was expressed as a percentage of the predicted value patients with GHD had a significantly reduced LBM ($92.6±2.0\%$, $P<0.001$), whereas patients with acromegaly had an increased LBM ($107.9±2.9\%$, $P<0.02$).

**BMR**

BMR was $6870±310\text{kJ/day}$ in patients with GHD, $6732±393\text{kJ/day}$ in normal subjects and $8201±456\text{kJ/day}$ in patients with acromegaly (analysis of variance, $P<0.035$, patients with acromegaly versus normal subjects, $P<0.05$). BMR, expressed as a percentage of the predicted value, was increased in patients with acromegaly and decreased in patients with GHD (Fig. 1a).

Total daily basal energy expenditure expressed per kg body weight (analysis of variance, $P<0.001$) was significantly lower in patients with GHD ($84.5±2.5\text{kJ day}^{-1}\text{kg}^{-1}$, $P<0.001$ versus normal subjects) than in normal subjects ($100.4±3.3\text{kJ day}^{-1}\text{kg}^{-1}$) or patients with acromegaly ($99.2±3.8\text{kJ day}^{-1}\text{kg}^{-1}$), who in turn did not differ significantly from each other. BMR related to body surface area (analysis of variance, $P<0.01$) was similar in patients with GHD ($3548±88\text{kJ day}^{-1}\text{m}^{-2}$) and normal subjects ($3745±117\text{kJ day}^{-1}\text{m}^{-2}$) but was increased in patients with acromegaly ($4142±146\text{kJ day}^{-1}\text{m}^{-2}$, $P<0.05$ versus normal subjects). However, when energy expenditure was expressed in terms of LBM, patients with GHD and patients with acromegaly had similar values, and both had significantly higher values than normal subjects (Fig. 1b).

**Sodium ERCs**

The ouabain-sensitive sodium ERC was decreased both in patients with acromegaly and in adults with GHD (Table 3). After 1 month of rhGH treatment in 11 patients with GHD, no significant change in the ouabain-sensitive sodium ERC was observed (ouabain-sensitive sodium ERC $3.04±0.10$ versus $2.98±0.15\text{h}^{-1}$, not significant; ouabain-insensitive sodium ERC $0.39±0.03$ versus $0.51±0.05\text{h}^{-1}$, $P =$
Hormones

Fasting plasma insulin concentrations were elevated in patients with acromegaly and in patients with GHD (Table 4). Plasma insulin-like growth factor-1 levels were increased in patients with acromegaly and decreased in patients with GHD (Table 4). Serum free tri-iodothyronine levels were similar and within the normal range in the three groups studied.

Correlation analysis

Patients with GHD. BMR was highly correlated with body weight \( r = 0.86, P < 0.0001 \), body surface area \( r = 0.92, P < 0.0001 \) and LBM \( r = 0.86, P < 0.0001 \). Fasting plasma insulin concentration was positively correlated with BMR \( r = 0.53, P < 0.01 \), but not with LBM \( r = 0.26, P < 0.05 \) and with LBM \( r = 0.48, P < 0.05 \). In a multiple regression analysis of BMR versus LBM, height, plasma insulin, serum tri-iodothyronine and leucocyte ouabain-sensitive sodium ERC, an overall significant correlation was found \( r^2 = 0.79, P < 0.0001 \) with LBM \( P < 0.0001 \) and plasma insulin concentration \( P = 0.05 \) still significantly correlated. BMR expressed per kg LBM was negatively correlated with height \( r = -0.54, P = 0.049 \), but not with age or gender. In a multiple regression analysis of BMR/LBM versus height, body weight, plasma insulin, and serum free tri-iodothyronine level, there was no significant correlation.

Patients with acromegaly. BMR was significantly correlated with body weight \( r = 0.99, P < 0.0001 \), body surface area \( r = 0.97, P < 0.0001 \) and LBM \( r = 0.99, P < 0.0001 \). Plasma insulin level was also significantly related with BMR \( r = 0.79, P = 0.02 \), but no correlation was found with serum free tri-iodothyronine level, leucocyte ouabain-sensitive sodium ERC or serum GH level. In a multiple regression analysis of BMR versus LBM, plasma insulin level, serum GH level during an oral glucose tolerance test and leucocyte ouabain-sensitive sodium ERC, an overall significant correlation was found \( r^2 = 0.97 \), with only LBM \( P < 0.001 \) remaining significantly correlated with BMR. BMR expressed per kg LBM showed no correlation with height, age or gender.

Normal subjects. In normal subjects BMR was significantly correlated with LBM \( r = 0.79, P < 0.01 \), but not with body weight \( r = 0.36, P < 0.05 \) or body surface area \( r = 0.49, P = 0.07 \). When BMR was expressed per kg LBM, there was no correlation with age, height or gender.

DISCUSSION

The lack and the excess of GH are associated with hypermetabolism. The fact that adults with GHD had increased energy consumption in relation to their reduced LBM was unexpected and is surprising. The increase in patients with acromegaly confirms previous data [2]. The mechanisms for the increase in basal energy expenditure are unlikely to be the same in patients with acromegaly and patients with GHD.

The present study confirms that LBM is the appropriate reference standard for the expression of energy expenditure [9–12], especially in the presence of altered body composition [22]. In patients with GHD, LBM was decreased [13], whereas it was increased in patients with acromegaly [23]. LBM was the only measurement of body size showing a
significant correlation with BMR in all three groups studied.

In children, height is negatively correlated with BMR expressed per LBM, explaining 66% of the variance in energy expenditure related to LBM [24]. A weak negative correlation \( r = -0.40 \) between BMR per LBM and height was also present in patients with GHD, but was no longer significant in a multiple regression analysis taking into account height, age and plasma insulin level. No detailed analysis of the composition of LBM in patients with GHD is available, but correlation between LBM measured by total-body \( ^{40} \text{K} \) counting and muscle mass determined by computed tomography of the thigh indicates that there is no difference in the non-muscle compartment in GHD [20].

Factors leading to an increased energy consumption which need to be considered in the present context include the calorigenic effect of GH, effects associated with hyperinsulinaemia, changes in intermediary metabolism or stimulation of \( \text{Na}^+ / \text{K}^+ \text{-ATPase} \). Multiple regression analysis of the factors determining resting energy expenditure in GHD showed that about 80% of the variation in BMR could be explained by variation in LBM and the rest by fasting plasma insulin levels. In acromegaly, however, LBM seemed to be the sole determinant of BMR. In acromegaly the calorigenic effect of GH may contribute to the hypermetabolism. Increased \( \text{O}_2 \) consumption has been demonstrated [3, 4, 13, 25] and is probably mainly related to the protein anabolic action of GH [13, 25]. Whether this is also present in chronic GH excess is not established. Hyperinsulinaemia is present in patients with acromegaly. Insulin has been shown to have a negligible thermic effect on its own and the increase in energy expenditure during glucose/insulin infusion is due to changes in glucose metabolism [26]. Indeed, patients with acromegaly have elevated glucose turnover and increased glucose cycling in the liver has been found [27], which could in part explain the calorigenic effect of GH.

The high energy expenditure in adults with GHD may also be related to changes in the intermediate metabolism. Children with GHD become hypoglycaemic after an overnight fast owing to low hepatic glucose production [28]. Our patients had a normal fasting plasma glucose concentration, which may be the result of increased glucoseogenesis. An investigation into glucose metabolism in adults with GHD is reported in a separate paper [29].

Recently, much interest has been expressed in the contribution that \( \text{Na}^+ / \text{K}^+ \text{-ATPase} \) may make to BMR [5, 8, 30]. Ng & Evans [5] reported increased activity of the sodium pump in leucocytes of patients with acromegaly [5] and obesity [30], and stimulation of leucocyte sodium transport \textit{in vitro} by human GH [5] and insulin [30]. We have been unable to confirm these observations in patients with acromegaly. The leucocyte ouabain-sensitive ERC was decreased in patients with acromegaly. This would be in keeping with the presence of an endogenous digitalis-like factor in the plasma of patients with acromegaly proposed by Deray et al. [31]. They also found a relationship between the increase in plasma volume [31] and inhibition of \( \text{Na}^+ / \text{K}^+ \text{-ATPase} \) activity, suggesting that a factor might be released in response to extracellular fluid expansion [32].

Adults with GHD had reduced activity of the leucocyte sodium pump and there was no change after 1 month of replacement treatment with rhGH. In hypophysectomized rats treatment with bovine GH increases \( \text{Na}^+ / \text{K}^+ \text{-ATPase} \) activity in liver, kidney and brain [6]. A stimulatory effect of human GH on human leucocytes \textit{in vitro} has also been reported [5]. Low activity of the sodium pump has also been reported in adrenocortical insufficiency [33], which is unlikely in our patients who had normal serum cortisol levels at the time of testing (data not shown). Suppression of active sodium transport by a digitalis-like factor is associated with volume expansion. Adults with GHD have decreased extracellular fluid volume [34]. Moreover, Deray et al. [31] have speculated that the pituitary may be involved in the production or control of a digitalis-like substance. If this were so, stimulation rather than suppression, of active transport might have been anticipated in our patients with GHD, who had lost most of their anterior pituitary function.

No correlation between BMR and leucocyte sodium pump activity was present in normal subjects, in patients with longstanding GHD and in patients with acromegaly. A similar lack of correlation between erythrocyte \( \text{Na}^+ / \text{K}^+ \text{-ATPase} \) and BMR has been reported in normal subjects [35].

In summary, we confirm that LBM is a main determinant of basal energy expenditure. The apparent differences in BMR seen in patients with GHD and patients with acromegaly when expressed as a percentage of the predicted value are largely due to changes in LBM, and both groups have significantly increased energy expenditure when related to LBM compared with normal subjects. The calorigenic effect of GH is not reflected by the leucocyte sodium pump activity. The increase in energy expenditure in patients with GHD and patients with acromegaly may be due to changes in intermediary metabolism associated with excess or lack of GH.

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REFERENCES


