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Insulin Sensitivity and Glucose Effectiveness Measured with the Minimal Model in Adults with GH Deficiency

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ABSTRACT

Insulin sensitivity (SI) and glucose effectiveness (Sg) were evaluated with the minimal model in growth hormone-deficient adult patients (GHD): six men and seven women, age: 19–51 years, body mass index 20.6–28.3 kg/m^2) compared with 13 matched controls (eight men, five women, age: 21–45 years, body mass index 19.1–29.4 kg/m^2). GHD had a higher waist-to-hip ratio than the control subjects ($P<0.02$). They had also, as measured by bioelectrical impedance, a higher percentage of fat ($P<0.02$) a lower percentage of lean body mass ($P<0.02$) and a lower percentage of body water ($P<0.02$). Their glucose tolerance was assessed by minimal model analysis of a frequent sampling IV glucose tolerance test (FSIVGTT). GHD patients had a higher basal insulin (Io) (9.54 ± 0.86 vs 7.08 ± 0.37 μU/ml $P<0.02$), a lower HDL cholesterol (-35% $P<0.01$), a higher insulin first phase response ($+150\%$ $P<0.05$) and a lower insulin sensitivity [4.9 ± 1.06 vs 10.36 ± 1.7/min/(μU/ml) $\times 10^{-4}$ $P<0.02$] than the control subjects resulting in a lower basal insulin effectiveness ($P<0.02$). In the whole sample of 26 subjects (GHD + controls), there was a negative correlation between I_{1+3} (being the sum of insulinemia at the first and the third minute after i.v. glucose) and the percentage of body water ($r=-0.542$, $P=0.0042$). In GHD considered alone Io was negatively correlated with SI ($r=-0.560$, $P=0.047$). Thus GHD have a lower insulin sensitivity as well as a diminished basal action of insulin, compensated by a higher basal insulinemia and a higher insulin peak. This pattern may be due to higher total body fat and may be involved in lipid disorders and increased cardiovascular risk.

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INTRODUCTION

While the importance of growth hormone in children is well known, biological and clinical features of growth hormone deficiency (GHD) syndrome in adults have been neglected until recently. This syndrome includes alterations in body composition (that is an increase in fat relatively to lean mass), a deterioration of lipid metabolism, and decreased psychosocial well-being. Carbohydrate homeostasis in this syndrome is poorly understood. However, first reports on this subject gave unexpected results, since excess GH is well known to be diabetogenic, while GHD infants frequently suffer from hypoglycemia. There is increasing evidence that GHD adults are insulin resistant [1–3], probably because of their modified body composition [1,3]. Insulin re-

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sistance is suggested by impaired glucose tolerance after an oral glucose tolerance test, and has been more precisely measured with a glucose clamp technique which does not differentiate insulin sensitivity itself (SI, that is the responsiveness of glucose assimilation to an increase in insulinemia) from glucose effectiveness (Sg, that is the ability of tissues to assimilate glucose without any increase in insulinemia). Nonetheless, this latter parameter which has not been previously studied in adult GHD compared to a matched control group, may be influenced by the hormonal and metabolic status [4]. Since it is responsible for one-third of the total glucose tolerance [4,5], it may be expected to explain a part of the previously reported decrease in glucose clearance in such patients. In addition, the pathophysiological significance of changes in Sg and changes in SI may be different. We have studied adult GHD patients with the minimal model in order to determine: (a) whether this procedure detects results consistent with the clamp study; (b) the influences of SI and Sg on glucose assimilation in these subjects; (c) the relationships between these parameters and body composition.

MATERIALS AND METHODS

Subjects

Thirteen GHD patients were selected from an initial sample of 17 subjects, after excluding markedly obese patients (BMI>40). GH deficiency was defined according to a GH serum peak below 5 ng/ml on two provocative tests (levodopa, ornithine or glucagon-propranolol). Four had isolated GH deficiency and the nine others had well equilibrated substitutive treatment of their other hormonal axes. Seven out of the nine patients had hydrocortisone substitutive therapy (10 to 25 mg per day) and six took it in the morning 1 h before the test (10 to 15 mg). Clinical data concerning these patients are given in Table 1. Study subjects were six men and seven women (age: 19–51 years, body mass index 20.6–28.3 kg/m^2. They were compared with a control group of 13 healthy control subjects (eight men, five women, age: 21–45 years, body mass index 19.1–29.4 kg/m^2 who were matched for age, sex, weight and body mass index as shown on Table 2.

Bioelectrical impedance measurements

Body composition was assessed with a four terminal impedance plethismograph BIA 101/s from Akern RJL Systems (Detroit, MI, USA). The four electrode method minimizes contact impedance and skin-electrode interactions. Measurements were made in fasting subjects after 15 min resting in a supine position. A current of 800 μA and 50 kHz is introduced into the subject and the measurement of the voltage drop allows the determination of total body reactance and impedance. These values are used with software provided by the manufacturer for calculating body water, fat mass, fat-free mass, and body cell mass [6].

Intravenous glucose tolerance test (IVGTT)

Subjects were asked to fast for 12 h before the test which began at 09.00 am. A cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose injection was administered via the contralateral cephalic vein. Glucose (0.5 g/kg, solution at 30%) was slowly injected over 3 min. Insulin (0.02 units/kg body weight that is 1–2 units) was injected intravenously immediately after 19 min. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min following glucose injection. Times 1 and 3 min were used for the determination of insulin early secretory phase [7]. The other times were necessary for minimal model calculations [8,9].

Laboratory measurements

Serum cholesterol and triglycerides were measured with the kits PAP and PAP1000 from Biomérieux, Marcy L'Etoile, France. HDL-cholesterol was measured with the kit CHOD PAP Cholesterol C system from Boehringer-Mannheim GmbH Diagnostica. Samples were analysed for plasma insulin by a radioimmunoassay (kit SB-INSI-5 from the international CIS) and plasma glucose with a Beckman glucose analyser. The within assay coefficient of variation (CV) for insulin was determined by repetitive measurements of the same sample and was between 8.6% (low values) and 9.7% (high values). The between assay CV for insulin was between 12.5% (low values) and 14.4% (high values). The sensitivity (lowest detectable value) was 2 μU/ml.

Glucose assimilation coefficient 'K_g'

The least square slope of the log of the absolute glucose concentration between 4 and 19 min after the glucose bolus was used as an index of glucose tolerance K_{g4-19}. This K_g value describes glucose assimilation by tissues and depends on three factors: insulin release, insulin sensitivity, and glucose effectiveness independent of insulin [4,5].

Table 1 Clinical characteristics and treatment of GHD patients

Patients	Sex	GHD onset	Aetiology	Treatment
1	M	Ch	Idiopathic	LT4, SS
2	M	Ch	Craniopharyngioma	LT4, SS, D, HC (15+5 mg/day)
3	M	Ch	Idiopathic	isolated GHD
4	M	Ch	Craniopharyngioma	LT4, SS, D, HC (15+5 mg/day)
5	M	Ad	Idiopathic	isolated GHD
6	F	Ch	Idiopathic	LT4, SS
7	F	Ad	Idiopathic	isolated GHD
8	F	Ad	Cushing	LT4, SS, HC (15+5 mg/day)
9	M	Ad	Craniopharyngioma	LT4, SS, D, HC (15+5 mg/day)
10	F	Ad	Pituitary adenoma	LT4, SS, HC (15+5 mg/day)
11	F	Ad	Sheehan	LT4, SS, HC (10 mg/day)
12	F	Ad	Sheehan	LT4, SS, HC (10+5 mg/day)
13	F	Ad	Idiopathic	isolated GHD

M=male, F=female, Ch=childhood, Ad=adulthood, SS=sex steroids, D=desmopressin, HC=Hydrocortisone, LT4=L thyroxine.

Table 2 Clinical and body composition data in growth hormone-deficient (GHD) adults and control subjects (mean±SEM). The two groups are matched for age, sex, weight and body mass index. All body composition data are expressed as percentages of total body weight.

	Sex (M/F)	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	WHR	LBM (% weight)	FM (% weight)	TBW (% weight)
GHD	6/7	35.1 ±3	160.4 ±2.4	64 ±3	24 ±0.7	0.89 ±0.02	67.1 ±2.7	32.9 ±2.7	51.6 ±1.6
Controls	8/5	30.7 ±2.1	168.5 ±1.7[a]	63.4 ±2.5	22.5 ±0.9	0.81 ±0.02[a]	76.3 ±2.1[a]	23.7 ±2.1[a]	57.8 ±1.7[a]

BMI: body mass index; WHR: waist to hip ratio; LBM: lean body mass; FM: fat mass; TBW: total body water. [a]$P<0.02$.

Measurement of insulin sensitivity and glucose effectiveness

Minimal model analysis of IVGTT was according to Bergman [10] with the software 'TISPAG' from the Department of Physiology of the University of Montpellier I, France [9,11,12] which uses a non-linear least square estimation. This program gave the values of insulin sensitivity (SI) and glucose effectiveness (Sg). Sg is the fractional disappearance rate of glucose, independent of any insulin response. SI is an index of the influence of plasma insulin to change glucose's own effect on glucose concentration. Sg was divided into its two components [4]: the contribution of hyperglycemia per se to tissue glucose utilization and the effect of basal insulin on glucose uptake. The basal insulin component of Sg is termed the basal insulin effect (BIE) and can be calculated as the product of basal insulin Ib and SI. Thus the contribution of non-insulin-dependent glucose uptake (glucose effectiveness at zero insulin, GEZI) to glucose uptake is the difference between total Sg and the BIE.

Assessment of beta-cell function

First phase insulin secretion [7] was calculated by the sum of insulin concentration at the first and the third min after the end of glucose injection (I_{1-3}). Since exogenous insulin was added at 19 min, the second phase insulin secretion could not be measured.

Statistics

Results are presented as mean±the standard error of the mean (SEM). Comparison of parameters of glucose assimilation between controls and patients were performed with the Mann–Whitney non-parametric test for unpaired data. Correlations were determined by least squares fitting. Significance was defined as $P<0.05$.

RESULTS

As shown in Table 2, subjects were matched for age, sex, weight and BMI. However GHD compared to con-

Table 3 Data calculated from IVGTT in growth hormone-deficient adults and control subjects (mean ± SEM).

	K_g (%/min)	I_{1+3} (μU/ml)	SI (/min/(μU/ml) × 10^{-4})	Sg (%/min)	BIE (%/min)	GEZI (%/min)
GHD	2.3 ±0.2	183.5 ±45.2[a]	4.9 ±1.1[b]	2.9 ±0.3	0.4 ±0.1[b]	2.51 ±0.3
Controls	2.7 ±0.3	73.8 ±8.2	10.4 ±1.7	3.5 ±0.4	0.8 ±0.1	2.6 ±0.4

K_g: slope of exponential decrease in blood glucose between 4 and 19 min after glucose infusion; I_{1+3}: sum of plasma insulin at 1 and 3 min after i.v. glucose; SI: insulin sensitivity; Sg: glucose effectiveness; BIE: basal insulin effectiveness; GEZI: glucose effectiveness at basal insulin.
[a] $P<0.05$
[b] $P<0.02$.

Table 4 Lipid parameters in growth hormone-deficiency adults and control subjects of the study (mean ± SEM).

	Cholesterol (mmol/l)	Triglycerides (mmol/l)	HDL Cholesterol (mmol/l)	LDL Cholesterol (mmol/l)
GHD	5.84 ±0.4	3.29 ±1.5	1.1 ±0.1[a]	3.42 ±0.3
Controls	4.93 ±0.4	0.74 ±0.1	1.77 ±0.2	3.27 ±0.4

[a] $P<0.01$.

trols were slightly shorter ($P<0.02$) and their waist to hip ratio was higher ($P<0.02$). They had also, as shown on Table 2, a higher percentage of fat ($P<0.02$) and thus a lower percentage of lean body mass ($P<0.02$) while their percentage of body water was also lower ($P<0.02$).

Baseline blood glucose was similar in the two groups (4.3 ± 0.2 vs 4.55 ± 0.12 mmol/l), but GHD patients had a higher basal insulin (9.54 ± 0.86 vs 7.08 ± 0.37 μU/ml $P<0.02$).

Compared to the control subjects, the GHD patients of this study had a similar value of the glucose tolerance parameter K_g. However, they had a higher insulin first phase response I_{1+3} (+150% $P<0.05$) and a lower insulin sensitivity (SI) (−53% $P<0.02$) resulting in a lower basal insulin effectiveness (BIE) (−50% $P<0.02$). Glucose effectiveness at both basal insulinemia (Sg) and zero insulinemia (GEZI) were not different from controls (Table 3).

GHD subjects had a lower HDL cholesterol (−35% $P<0.02$), while their values of LDL cholesterol and total cholesterol were not different (Table 4). A tendency to higher triglyceride levels in GHD was not significant because values overlapped considerably between the two groups.

Differences between isolated GHD subjects and subjects with multiple teated hormonal deficiency were investigated. There was no difference in basal insulin (9.18 ± 1.5 vs 9.44 ± 0.98 μU/ml), I_{1+3} (225 ± 114 vs 165 ± 35 μU/ml) or SI [5.5 ± 2.55 vs 4.72 ± 0.93/min/(μU/ml).10^{-4}). Six patients had taken hydrocortisone (10 to 15 mg 1 h before the IVGTT) and no consecutive hyperinsulinemia was found when compared to the other GHD subjects [basal insulin 9.2 ± 0.9 μU/ml vs 9.4 ± 1; SI 4.75 ± 0.9 vs 4.72 ± 0.9/min/(μU/ml).10^{-4}].

In the whole sample of 26 subjects there was a negative correlation between I_{1+3} and the percentage of body water (r −0.542 $P=0.0042$) while other measurements of body composition were not significantly correlated with IVGTT parameters. When GHD were considered alone a negative correlation was found between (Io) and SI ($r=-0.560$ $P=0.047$). Parameters of body composition were not correlated with blood lipids.

DISCUSSION

The importance of investigating insulin sensitivity in GHD adults is underlined by the high rate of early mortality in these patients [13]. Insulin resistance is now a well-documented factor of increased vascular risk [14]. Another study has investigated insulin sensitivity with the glucose clamp technique [15] and showed that it was impaired in adult GHD patients. The effects of 3 months GH treatment in such patients has been studied

recently with the minimal model [16]. However, our study seems to be the first report of minimal model measurements of insulin sensitivity in adult GHD patients before treatment, compared to a matched control group.

We observed that glucose tolerance in a group of GHD adults compared to a matched control group was maintained in a physiological range (as evidenced by the similar values of K_g), but that these patient had a 50% reduction in insulin sensitivity compensated by an increase in basal insulin and first phase insulin response. Non-insulin dependent glucose uptake was not different from controls. In addition, these patients had some characteristics of 'Syndrome X' [14] such as a higher percentage of body fat and a lowered HDL cholesterol.

In this study markedly obese patients were excluded since obesity by itself results in impaired glucose tolerance [14] and can be a confounding factor. We therefore focused on the metabolic effects of GH deficiency in patients without marked obesity. Obveously, further studies on obese GHD subjects will be also required, since obesity is a common feature of adult GH deficiency.

Another problem with GHD subjects is the possible confounding effect of other hormonal deficiencies and their substitutive treatments. Alterations of glucocorticoid status have been reported to modify minimal model parameters. Corticosteroid excess (e.g. Cushing's disease) is associated with a reduction in both SI and Sg in the presence of enhanced insulin secretion [15]. In the present study, patients with hydrocortisone or sex steroid substitutive treatment did not however have a different basal insulin or insulin sensitivity compared with patients with isolated GH deficiency.

The finding of a reduced insulin sensitivity in GHD is in accordance with several recent studies. Fowelin and coworkers [18] demonstrated with the euglycemic clamp that GH treatment in adults, when compared to placebo, had a biphasic effect on glucose disposal. After 6 weeks, there was a decrease (−45%) in glucose infusion rates, probably related to a rise in insulin resistance, as expected from the classical effects of GH. However, there was a reversal of this effect after 26 weeks with a rise in glucose infusion rates (and thus probably increased insulin sensitivity) which was in parallel with a profound modification of body composition, that is an increase in lean body mass and a decrease in fat mass. This is consistent with the concept of a reduction in insulin sensitivity in GHD, as found in the present study. However, since the study of Fowelin *et al.* [18] included no matched control group it could not determine whether there was insulin resistance in GHDs. Beshyah *et al.* [18] studied 63 GHDs and found impaired carbohydrate and lipid metabolism with a decreased total cholesterol to HDL cholesterol ratio, comparable blood glucose levels but higher insulin levels after an oral glucose tolerance test, when compared to control subjects. This pattern was also highly suggestive of an insulin-resistant state. Finally, Johansson *et al.* [15] reported a euglycemic clamp study in 15 adults with GHD compared to matched controls. When results were corrected for body fat, GHD patients had a 50% lower glucose infusion rate for an insulinemia of 80 μU/ml than the control subjects. This latter study thus provides unequivocal evidence that there is a reduction in insulin sensitivity in GHD patients. A 50% decrease in insulin sensitivity is similar to the findings of the present study. Although the techniques used are quite different, they have been shown to give equivalent data [20]. However, the clamp experiment was performed at only one level of insulinemia, so that no dose–response relationship could be calculated between insulinemia and blood glucose disposal. The non-insulin-dependent component of glucose clearance was also not determined, although it may theoretically explain a part of the defect in glucose disposal [4,5]. Thus, it was interesting to characterize insulin sensitivity further in a GHD adult population, in the present study, with a well-validated method.

The reduction in insulin sensitivity, although representing a −50% decrease when compared to controls, is relatively moderate when compared to the range of values observed in NIDDM subjects or in marked insulin resistant states, where values are lower than 0.1/min/(μU/ml) $\times 10^{-4}$ [10,21,22]. The values for SI are more comparable with the range of values of SI found in obese non-diabetic subjects, i.e. around 3/min/(μU/ml) $\times 10^{-4}$ [10,22].

The defect in GHD patients in the present study was confined to insulin sensitivity itself, since the non-insulin-dependent component represented by Sg and GEZI remained unaltered. This was important to assess, because this parameter, which is modified by regular exercise [9,12], is a major component of glucose disposal [4,5]. Since the effects of GH deficiency on glucose homeostasis are likely to result from body composition changes and metabolic abnormalities, modifications in Sg could be expected. The correlation between SI and insulin levels at baseline (I_0) indicates that there was some degree of homeostatic compensation for the reduction in insulin sensitivity. The physiological balance between SI and insulin secretion is to some extent maintained, since I_{1+3} increases when SI decreases, resulting in values of K_g which remain within a normal range. According to the concept of the feedback between SI and the insulin peak [10,23] a compensatory increase in insulin secretion tends to

protect from a reduction of glucose uptake when SI is decreased.

Further studies will be necessary to elucidate the pathophysiological mechanism of this reduction of insulin sensitivity. However, as postulated by other investigators, changes in body composition probably play a role [1,15], since lean mass is a determinant of glucose disposal and fat mass induces metabolic abnormalities which impair glucose tolerance. It is now well known that GHD subjects have an increase in abdominal fat [24]. In this study, we found a higher percentage of body fat and a higher waist to hip ratio in GHD patients when compared to controls. It is unlikely that a difference in sex ratio between the two groups could explain this difference, since the comparison of sex ratios with the Fisher's test gives a significance level of $P=0.46$, suggesting a correct matching for sex. The negative correlation between the insulin peak (I_{1+3}) and the percentage of body water further supports the hypothesis of a link between body composition alterations and metabolic disturbances resulting in insulin resistance and hyperinsulinemia.

In conclusion in this study, GHD were shown to have a higher basal insulinemia and a lower insulin sensitivity with a disminished basal action of insulin, as well as a lower HDL-cholesterol than a matched control group. These results may be explained by the alteration of body composition since a higher total body fat and a higher waist-to-hip ratio were found in GHD.

REFERENCES

1. Salomon F, Cuneo R, Sönksen PH. Insulin sensitivity and insulin resistance in growth hormone deficient adults. Horm. Res. 1993; 40: 34–36.
2. Salomon F, Cuneo R, Sönksen PH. Glucose metabolism in adults with growth hormone deficiency. Acta Paediatr. Scand. (Suppl. 377) 1991: 64–68.
3. Fédou C, Boyer P, Brun JF, Orsetti A. Tolérance au glucose et composition corporelle chez les adultes déficients en hormone de croissance (GH). (abstract) Diabetes Metab. 1994, 20:4A.
4. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Nieffing JL, Ward K, Beard JC, Palmer JP, Porte D, Jr: The contribution of insulin-dependent and insulin independent glucose to intravenous glucose tolerance in healthy human subjects. Diabetes 1994; 43: 587–592.
5. Ader MA, Pacini G, Yang YJ, Bergman RN. Importance of glucose per se to intravenous glucose tolerance. Comparison of the minimal-model prediction with direct measurements. Diabetes 1985; 34: 1092–1103.
6. Lukaski HC, Johnson PE, Bolonchuch WW, Lykken GE: assessment of fat free mass using bioelectrical impedance measurements of the human body. Am. J. Clin. Nutr. 1985; 41: 810–817.
7. Bouix O, Brun JF, Orsetti A. The magnitiude, the kinetics and the metabolic efficiency of first-phase insulin response to intravenous glucose are related. Horm. Metab. Res. 1993; 25: 312–316.
8. Steil GM, Bergman RM. Reduced sampling for the minimal model estimate of insulin sensitivity from the modified and standard frequently sampled IVGTT. (Abstract) Diabetes (Suppl. 1) 1991; 40: 38A.
9. Brun JF, Guintrand-Hugret R, Boegner C, Bouix O, Orsetti A. Influence of short submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. Metabolism 1995; 44: 833–840.
10. Bergman RN. Toward physiological understanding of glucose tolerance. Minimal model approach. Diabetes 1986; 38: 1512–1527.
11. Brun JF, Guintrand-Hugret R, Fons C, Carvajal J, Fédou C, Fusselier M, Bardet L, Orsetti A. Effects of oral zinc gluconate on glucose effectiveness and insulin sensitivity in humans. Biol. Trace. Elem. Res. 1995; 47: 385–392.
12. Brun JF, Boegner C, Orsetti A. Le minimal model: un nouvel outil pour l'étude des hypoglycémies du sportif. Science & Sports 1994; 9: 47–49.
13. Rosén T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 1990; 336: 285–288.
14. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595–1607.
15. Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA. Insulin resistance in adults with growth hormone deficiency. Endocrinol. Metab. (Suppl. A) 1994; 1: 80.
16. O'Neal DN, Kalfas A, Dunning PL, Christofer MJ, Sawyer SD, Ward GM, Alford FP. The effect of 3 months of recombinant human growth hormone (GH) on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults: a minimal model analysis. J. Clin. Endocrinol. Metab. 1995; 79: 975–983.
17. Page R, Boolell M, Kalfas A, Sawyer S, Pestell R, Ward G, Alford F. Insulin secretion, insulin sensitivity and glucose-mediated glucose disposal in Cushing's disease: a minimal model analysis. Clin. Endocrinol. 1991; 35: 509–517.
18. Fowelin J, Attwall S, Lager I, Bengtsson BA. Effects of treatment with recombinant human growth hormone on insulin sensitivity and glucose metabolism in adults with growth hormone deficiency. Metabolism 1993; 42: 1443–1447.
19. Beshyah SA, Henderson A, Richmond W, Johnston D. Metabolic abormalities in growth hormone-deficient adults: II. carbohydrate tolerance and lipid metabolism. Endocrinol. Metabol. 1994; 1: 173–180.
20. Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J. Clin. Invest. 1987; 79: 790–800.
21. Welch S, Gebhart SSP, Bergman RN, Phillips LS. Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. J. Clin. Endocrinol. Metab. 1990; 71: 1508–1518.
22. Brun JF, Orsetti A, Boegner C, Bringer J. Hétérogénéité des paramètres de l'assimilation glucidique mesurée par le minimal model dans les situations cliniques évocatrices d'une insulinorésistance. (Abstract) Diabetes Metab. 1994; 20: 29A.
23. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward K, Beard JC, Palmer JP, Porte DJ, Jr. Quantification of the relationship between insulin sensitivity and b-cell function in human subjects. Diabetes 1993; 42: 1163–1672.
24. Rosén T, Bosaeus I, Tollis J, Lindstedt G, Bengtsson BA. Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency. Clin. Endocrinol. 1993; 38: 63–67.