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Hemorheology of growth hormone-deficient adults

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Abstract. Growth hormone deficiency (GHD) in adults results in alterations of body composition and metabolism associated with a lowered insulin sensitivity and an increased cardiovascular risk. Since hemorheologic disturbances (putative factors of vascular risk) are found in the insulin-resistance syndrome, we investigated blood rheology in 9 adults GHDs (5 men, 4 women; age 37.9 ± 4.7 years; body mass index 30.23 ± 3.2 kg/m^2) compared with 23 lean controls and 37 controls matched for sex, age and body mass index. While this sample of GHDs exhibits the typical metabolic picture of this syndrome (upper body overweight with a waist-to-hip ratio at 0.91 ± 0.07; low HDL cholesterol at 1.07 ± 0.09 mmol.l^{-1}; low insulin sensitivity with the minimal model technique at 3.3 ± 1.29 min^{-1}/(μU/ml).10^{-4}) they have similar values of blood viscosity at either native or corrected hematocrit, similar hematocrit, similar red cell rigidity viscometric index, similar red cell aggregation parameters than overweight matched controls. There is only a nonsignificant tendency for plasma viscosity to be higher in GHDs: this tendency becomes significant when women are considered alone (GHDs: 1.44±0.04 mPa.s; controls: 1.31±0.04 mPa.s, $p < 0.05$) while it is no longer found in men. This study suggests that GHDs exhibit the classical hemorheological disturbances of non-GHD individuals with the same degree of obesity. There is no evidence for a further impairment of blood rheology associated with the specific metabolic and endocrine pattern of GHDs that may be involved in their increased vascular risk.

Keywords: Blood viscosity, hemorheology, erythrocyte aggregation, growth hormone deficiency, adults, insulin sensitivity

1. Introduction

The growth hormone deficiency (GHD) syndrome in adults has only recently been recognized as a specific disease [1,2]. This syndrome includes alterations in body composition (i.e., an increase in fat relatively to lean mass), a deterioration of lipid metabolism, and decreased psychosocial well-being [1]. This syndrome is responsible for a higher cardiovascular morbidity and mortality [1,2]. A possible explanation for the increased cardiovascular risk of this disease may be that GHD adults are insulin resistant [3–6], probably because of their modified body composition [5–7]. A large body of literature has been published on insulin resistance as a mechanism of cardiovascular disease [8–10], and, recently, this metabolic situation has been reported to be correlated with both increased blood viscosity [11–13] and increased fibrinogen [14]. Whether these rheologic disturbances are involved in the pathogenesis of vascular risk is not known, but the recent epidemiological literature on plasma viscosity and fibrinogen as strong predictors of cardiovascular disease [15–18] is consistent with this assumption. Interestingly, fibrinogen is high in GHD adults [19]. In addition, obesity, which is characterized by an insulin-resistance

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syndrome quite similar to that of adult GHD, is associated with increased blood viscosity [20,21]. However, there is no report, as far as we know, on blood rheology in GHD adults. Therefore, this study was undertaken in order to investigate blood rheology in adult GHDs, in comparison with individuals matched for sex, age and body mass index.

2. Patients and methods

2.1. Subjects

Nine GHD adult patients were compared with 37 controls matched for sex, age and body mass index. GH deficiency was defined according to a GH serum peak below 5 ng/ml on two provocative tests (levodopa, ornithine or glucagon-propranol). 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 6 took it in the morning 1 hr before the test (10 to 15 mg). Study subjects were 5 men and 4 women, age 37.9 $\pm$ 4.7 years; body mass index 30.23 $\pm$ 3.2 kg/m^2. They were compared with two control groups. The first control group included 37 healthy control subjects matched with GHDs for age, sex, weight and body mass index. The second control group was composed of 23 healthy control subjects matched for age and sex, but who had normal weight and body mass index. Subjects characteristics are shown in Table 1.

2.2. 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 fat mass and fat-free mass [22].

2.3. Intravenous glucose tolerance test (IVGTT)

Subjects were asked to fast for 12 hr before the test which began at 9:00 A.M. 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 administerd 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, i.e., 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 [23]. The other times were necessary for minimal model calculations [24,25].

2.4. Glucose assimilation coefficient 'Kg'

The least square slope of the log of the absolute glucose concentration between 4 and 19 minutes after the glucose bolus was used as an index of glucose tolerance Kg_{4-19}. This Kg value describes glucose assimilation by tissues and depends on three factors: insulin release, insulin sensitivity, and glucose effectiveness independent of insulin [26,27].

2.5. 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 [25,28–30] 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 [31]: the contribution of hyperglycaemia 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.

2.6. Assessment of beta cell function

First phase insulin secretion [23] was calculated by the sum of insulin concentration at the 1st and the 3rd minute 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.

2.7. Laboratory measurements

Blood samples for hemorheological measurements (7 ml) were drawn with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer). Viscometric measurements were done at high shear rate (1000 s^{-1}) with a falling ball viscometer (MT 90 Medicatest, F-86280 Saint Benoit) [32,33]. Accuracy of the measurements was regularly controlled with the Carrimed Rheometer 'CS' (purchased from Rhéo, 91120 Palaiseau, France) [34]. The coefficient of variation of this method ranged between 0.6 and 0.8% [35]. With this device we measured apparent viscosity of whole blood at native hematocrit, plasma viscosity, and blood viscosity at corrected hematocrit (0.45) according to the equation of Quemada [36]:

$$\eta_b = \eta_{pl}(1 - 1/2\, kh)^{-2}$$

where η_{pl} is plasma viscosity, h hematocrit, and k a structural parameter of blood viscosity which depends at high shear rate on RBC flexibility. This formula was used for correction of blood viscosity for hematocrit 0.45 from data at native hematocrit. Dintenfass' 'Tk' index of erythrocyte rigidity was calculated with the following formula:

$$\mathrm{Tk} = (\eta_r^{0.4} - 1)/(\eta_r^{0.4} h)$$

where η_r is relative blood viscosity (i.e., η_b/η_{pl}) [37]. RBC aggregation was assessed with the Myrenne aggregometer [38] which gives two indices of RBC aggregation: 'M' (aggregation during stasis after shearing at 600 s^{-1}) and 'M1' (facilitated aggregation at low shear rate after shearing at 600 s^{-1}). 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 analyzed for plasma insulin by a radioimmunoassay (kit SB-INSI-5 from the international CIS) and plasma glucose with a Beckman glucose

Table 1
Clinical characteristics of the 69 subjects of the study and comparison among the three groups

	Group		
	GHDs	Obese controls	Lean controls
Number of subjects	9	37	23
Age (yr)	37.9 ± 4.7	37.1 ± 1.9	37.9 ± 2.51
Weight (kg)	81.2 ± 10	83.5 ± 2.1	65.9 ± 2.1
Height (cm)	163.4 ± 2.7	168.6 ± 1.2	170.1 ± 2.1
Body mass index (kg/m^2)	30.2 ± 3.2	29.26 ± 6.32	22.8 ± 0.5
Waist/hip ratio	0.91 ± 0.07*	0.84 ± 0.01	0.76 ± 0.03
% of fat mass	38.4 ± 4.13	35.4 ± 2.7	31.8 ± 2.8

*$p < 0.05$ vs. lean controls.

analyzer. 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.

2.8. *Statistics*

Results are presented as mean ± the SE of the mean. A value of $p < 0.05$ was considered as significant. Comparisons between controls and GHDs were made with the two-tailed rank test of Mann–Whitney for unpaired data [39].

3. Results

As shown in Table 1 the three groups of subjects were matched for age and sex. GHDs and obese controls are matched for weight and BMI while these parameters are significantly lower in lean controls. Comparison of the waist-to hip ratio shows a tendency towards a higher value in GHDs but the difference is only significant between GHD and lean controls ($p < 0.05$). The percentage of fat is almost the same in GHDs and obese controls. This sample of GHDs exhibits the typical metabolic picture of this syndrome (upper body overweight with a waist-to-hip ratio at 0.91 ± 0.07; low HDL cholesterol at 1.07 ± 0.09 mmol.l^{-1}. The minimal model analysis (Table 2) shows that GHDs exhibit a low insulin sensitivity which does not however represent a profound insulin-resistance.

GHDs have similar values of blood viscosity at either native or corrected hematocrit, similar hematocrit, similar red cell rigidity viscometric index 'Tk'. Concerning red cell aggregation there is a tendency to a higher "M" index in GHDs, but the difference is only significant between GHDs and lean controls while it does not reach significance between obese and GHDs. Similarly, there is a nonsignificant tendency for plasma viscosity to be higher in GHDs: this tendency becomes significant when women are considered alone (GHDs: 1.44 ± 0.04 mPa.s; controls: 1.31 ± 0.04 mPa.s, $p < 0.05$) while it is no longer found in men.

4. Discussion

GHD adults investigated in this paper exhibit the typical metabolic picture of this syndrome [1]. They are characterized by an upper body overweight, a low HDL cholesterol, a low insulin sensitivity. The

Table 2

Parameters calculated from the IVGTT in study subjects and controls (mean ± SEM) Kg_{4-19} is the exponential slope of glucose decrease between 4 and 19 min during IVGTT; Sg is glucose effectiveness; SI is insulin sensitivity; I_{1+3} is the sum of insulinemia at 1 and 3 min after i.v. glucose; BIE is basal insulin effectiveness and GEZI is glucose effectiveness at zero insulin

	Group		
	GHDs	Obese controls	Lean controls
Number of subjects	9	37	23
I_{1+3} (μU/ml)	199.1 ± 62.9	85.7 ± 0.9	58.9 ± 9.3
Kg_{4-19} ($min^{-1} \cdot 10^{-2}$)	2.26 ± 0.3	1.78 ± 0.12	2.27 ± 0.22
Sg ($min^{-1} \cdot 10^{-2}$)	2.93 ± 0.2	2.63 ± 0.19	3.04 ± 0.25
SI ($min^{-1}/(\mu U/ml) \cdot 10^{-4}$)	3.26 ± 1.3*	7.82 ± 1.29	12.31 ± 2.45
BIE ($min^{-1} \cdot 10^{-2}$)	0.36 ± 0.11	0.71 ± 0.15	0.93 ± 0.23
GEZI ($min^{-1} \cdot 10^{-2}$)	2.89 ± 1.2	2.03 ± 0.19	2.29 ± 0.32

*$p < 0.05$ vs. obese controls.

Table 3

Comparison of hemorheologic parameters among the three groups

	Group		
	GHDs	Obese controls	Lean controls
Number of subjects	9	37	23
Sex ratio (M/F)	5/4	17/20	13/10
Hematocrit (%)	40.4 ± 1.6	40.7 ± 0.6	40.1 ± 0.8
Blood viscosity η_b (mPa.s)	2.98 ± 0.15	2.86 ± 0.06	2.79 ± 0.01
η_b at corrected hct 45%	3.11 ± 0.08	3.25 ± 0.08	3.11 ± 0.09
Plasma viscosity η_p (mPa.s)	1.39 ± 0.03	1.33 ± 0.01	1.32 ± 0.005
Erythrocyte rigidity 'Tk'	0.62 ± 0.01	0.63 ± 0.01	0.63 ± 0.02
Erythrocyte aggregation 'M'	6.6 ± 1.03***	5.51 ± 1.78	4.64 ± 0.4
Erythrocyte aggregation 'M1'	10.03 ± 2.25	9.11 ± 2.55	8 ± 0.75

***$p < 0.01$ vs. lean controls; ns vs. obese controls.

minimal model analysis (Table 2) shows that GHDs exhibit a low insulin sensitivity, but a value of 3.3 ± 1.3 ($min^{-1}/(\mu U/ml) \cdot 10^{-4}$) does not represent a profound insulin-resistance [26]. 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 [1,7], since lean mass is a determinant of glucose disposal and fat mass induces metabolic abnormalities which impair glucose tolerance [40]. It is now well known that GHD subjects have an increase in abdominal fat [5,7]. Consistent with these previous reports, we found in the patients of this study a higher percentage of body fat and a higher waist to hip ratio in GHD patients when compared to controls.

Concerning blood rheology, however, GHDs have similar values of blood viscosity at either native or corrected hematocrit, similar hematocrit, similar red cell rigidity viscometric index 'Tk', similar red cell aggregation parameters than matched controls. There is only a nonsignificant tendency for plasma viscosity to be higher in GHDs that is significant when women are considered alone. Red cell aggregation is moderately increased in GHDs, but this increase is not significant when subjects are matched for body mass index.

Our finding of a significantly higher value of plasma viscosity in female GHDs is not, in our opinion, related to a more pronounced effect of GH deficiency in females. Some experimental literature in

rodents shows that the anabolic effects of GH differ between males and females, with a stronger growth-promoting effect in males, while a gender-specific pattern is required in either sex for optimal anabolic actions [41]. This gender-related difference is likely to exist also in humans and to explain how men and women have not the same dose-effect responses to GH treatment. However, when looking closely to our individual results, it is clear that the tendency also exists in males, so that our findings are rather likely to indicate that, in a larger sample of GHD patients of both sexes, one could observe a significant, although moderate, increase in this hemorheologic parameter. Several reported metabolic disorders that are part of the GHD syndrome may explain this raised plasma viscosity: impaired fibrinolysis leading to increased blood fibrinogen [19], increased LDL cholesterol [1,2], insulin resistance [3–6]. However, neither fibrinogen nor lipid parameters appeared in our sample of subjects to be correlated with blood rheology. In fact, all these metabolic disturbances can be explained by the alterations in body composition [5–7], which could in turn be associated with increased blood viscosity [20,21]. The influence of adiposity on blood rheology can be observed not only in pathologic conditions (e.g., obesity [20,21]), but also in healthy lean people [42]. Thus, the total mass of adipose tissue appears to physiologically regulate blood rheology [42,43]. This situation is likely to occur also in GHDs, given the increase in fat percentage that is a prominent sign of this disease [1,2,5,7]. We think that our comparison with obese, non GHD patients leads to think that most of the hemorheologic profile of GHDs is rather related to increased fat mass, independent of the endocrine defect itself.

Actually, GH may be expected to exert specific hemorheologic actions, via its effects on hematopoiesis [44], immune and leukocyte functions [45], and body fluid homeostasis [46,47]. Data reported in this paper do not give any evidence of these actions, but other investigations are required to further elucidate this point.

In conclusion, this study suggests that there is no marked hemorheological difference between GHDs and non-GHD individuals with the same degree of obesity. Thus, although GHDs exhibit the classical hemorheological disturbances of overweight subjects, there is no further impairment of blood rheology associated with their specific metabolic and endocrine pattern. Accordingly, the increased vascular risk of GHDs is not likely to be related to blood rheology.

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