

ORIGINAL ARTICLE

Insulin resistance in young, lean male subjects with essential hypertension

A Penesova¹, E Cizmarova², V Belan³, P Blazicek⁴, R Imrich¹, M Vlcek¹, M Vigas¹, D Selko⁵, J Koska¹ and Z Radikova¹

¹Laboratory of Human Endocrinology, Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia; ²Department of Cardiology, Out-patient Clinic Karlova Ves, Bratislava, Slovakia; ³Department of Radiology, Derer's Faculty Hospital, Bratislava, Slovakia; ⁴Alpha Medical, Institute of Laboratory Diagnostics, Bratislava, Slovakia and ⁵The National Institute of Cardiovascular Diseases, Bratislava, Slovakia

Impaired insulin action, frequently found in essential hypertension (HT), is modified by other factors, such as higher age, accumulation of body fat, dyslipidaemia, impaired glucose metabolism and endothelial dysfunction. In addition, antihypertensive and insulin-sensitizing medication itself may significantly affect cardiovascular and metabolic milieu. The aim of this study was to assess insulin sensitivity, acute insulin response, lipidaemic status and the adipokines' concentrations with regard to abdominal fat distribution in young, lean male subjects with treatment-naïve essential HT and in matched healthy normotensive (NT) subjects. We studied 27 HT patients (age: 19.9 ± 0.6 years; body mass index (BMI): $22.9 \pm 0.5 \text{ kg m}^{-2}$) and 15 NT controls (age: 22.3 ± 1.0 years; BMI: $23.7 \pm 0.6 \text{ kg m}^{-2}$). The subjects underwent an oral and an intravenous glucose tolerance test (OGTT, IVGTT) on separate days in random order. Higher fasting insulin ($P < 0.001$), non-esterified fatty acids ($P < 0.05$) and plasminogen activator inhibitor factor 1 concentrations

($P < 0.05$) were found in HT patients when compared with NT patients. Despite comparable anthropometric parameters and body fat distribution assessed by magnetic resonance imaging in both groups, newly diagnosed untreated young hypertensive male subjects showed decreased insulin sensitivity, augmented insulin response to both oral and intravenous glucose load ($P < 0.01$; $P < 0.05$ respectively) and 'higher still normal' 2-h plasma glucose levels during OGTT. Untreated, young, lean hypertensive male subjects, with distribution of abdominal adipose tissue and lipid profile comparable with their healthy NT matched counterparts, showed considerable signs of insulin resistance and hyperinsulinaemia. We hypothesize that insulin resistance is the initial feature, which is influenced by several environmental factors, and HT is one of their common consequences.

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Introduction

Interest in the youth hypertension (HT) has increased over the past decade owing to increasing prevalence of the individual risk factors in childhood.^{1,2} It is known that similar to older individuals, HT in young age coexists with features of metabolic syndrome, such as overweight/obesity, hyperinsulinaemia/insulin resistance and dyslipidaemia.^{3–5} It is even suggested that the pathophysiologic precursors of adult HT originate earlier in life.^{6,7} The general focus of the research of HT in youth has been studies on overweight/obese children and adolescents because of the long-recognized association of the

features of metabolic syndrome with obesity and the ongoing high prevalence of obesity in this age group.⁵ However, an overall worsening of insulin sensitivity, lipid levels and blood pressure in adolescent male subjects may occur despite a minimal alteration in total body fat.¹ No studies have been carried out on these lean individuals on whether the presence of these risk factors, including HT, is owing to the preferential visceral deposition of adipose tissue, as documented by studies in overweight/obese subjects.^{8–10}

Despite fatness being associated with insulin resistance and HT, it is clear that obesity *per se* cannot fully explain the development of insulin resistance.⁴ Many studies have provided evidence for a body size-independent association between insulin resistance and/or hyperinsulinaemia and elevated blood pressure, within the context of the cardiometabolic syndrome.^{11,12} However, most of these studies were performed on individuals above the normal range of body weight. Therefore, to avoid

Correspondence: Dr Z Radikova, Laboratory of Human Endocrinology, Institute of Experimental Endocrinology, Slovak Academy of Sciences, Vlarska 3, Bratislava SK 833 06, Slovakia.

E-mail: zofia.radikova@savba.sk

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the confounding influence of obesity, age factor, therapy, physical fitness, and so on, we recruited young, lean male hypertensive yet untreated subjects and healthy controls, who were matched for gender, age, body mass index (BMI), physical fitness and family history of HT.

The aim of this study was to compare the lipid status, insulin sensitivity, insulin secretion, systemic concentrations of adipokines and plasminogen activator inhibitor factor 1 (PAI-1), and abdominal adipose tissue distribution in young, lean male adults with newly diagnosed yet untreated essential HT and healthy young, male adults with similar BMI.

Subjects and methods

Twenty-seven young male subjects with recently diagnosed yet untreated grade 1 essential HT¹³ were recruited from the registry of the Department of Cardiology, Out-patient Clinic Karlova Ves, Bratislava, Slovakia. The diagnosis of HT was confirmed by 24-h blood pressure monitoring. Secondary HT was excluded by clinical examination, routine blood and urine analysis and hormonal measurements before the study.¹⁴ Only individuals with confirmed diagnosis of essential HT were enrolled. Fifteen young healthy male subjects with similar BMI and normal blood pressure served as controls. Furthermore, all subjects (patients and controls) had to fulfil the following inclusion criteria: (a) BMI <25 kg m⁻²; (b) no history of impaired glucose tolerance, diabetes mellitus, dyslipidaemia and any endocrine disorders; (c) non-smokers; and (d) without any current medication. Each participant completed a questionnaire that included questions with regard to alcohol intake, usual pattern of physical activity, family history of HT, use of drugs and other lifestyle factors. Clinical characteristics of the groups are provided in Table 1. The study was approved by the Ethics Committee of

the Institute of Experimental Endocrinology, SAS, Bratislava, Slovakia and the informed written consent was obtained from all subjects.

Protocol of the study

The subjects were asked to fast and restrain from the use of strong physical activity for 12 h before the examination. Upon arrival in the laboratory at 0800 hours, antecubital vein of one or both arms (depending on the test performed) was cannulated and the subjects were asked to rest in a comfortable armchair. Blood pressure was measured (Dinamap Vital Signs Monitor model 845 XT; Critikon Inc., Tampa, FL, USA) and the baseline blood sample was taken at least 30 min after the intravenous catheter insertion, to avoid the effect of acute stress of venipuncture on the variables of interest. After obtaining the fasting samples, the subjects underwent the frequently sampled oral and intravenous glucose tolerance tests (OGTT, IVGTT), each at separate visit at least 3 days apart, in a random order.

During OGTT, the subjects were asked to ingest over 3 min a solution containing 75 g glucose diluted in 250 ml water. Blood samples were collected just before (0 min) and 15, 30, 45, 60, 90 and 120 min after ingestion.

During IVGTT, a bolus of 0.3 g per kg glucose solution (40% (w v⁻¹) glucose injection; BBraun, Melsungen, Germany) was administered intravenously over 3 min. Blood samples from the contralateral arm were obtained just before (0 min) and 3, 5, 7, 9, 11, 13, 15, 30, 60 and 90 min after starting the infusion.

Twenty-three HT patients underwent the IVGTT and 19 HT patients underwent the OGTT. All 15 NT controls underwent both tests.

Anthropometrics

Anthropometric measurements (body height, weight and waist circumference) were performed by a

Table 1 Clinical characteristics of study subjects

	NT	HT		
	IVGTT/OGTT	All	IVGTT	OGTT
<i>n</i>	15	27	23	19
Age (years)	22.3 ± 1.0	19.9 ± 0.6*	20.1 ± 0.6	19.9 ± 0.7
BMI (kg m ⁻²)	23.7 ± 0.6	22.9 ± 0.5	23.1 ± 0.5	22.2 ± 0.6
Waist (cm)	84.4 ± 2.2	82.4 ± 1.5	82.2 ± 1.6	81.8 ± 1.6
BP systolic (mm Hg)	119 ± 3	141 ± 2***	142 ± 2	141 ± 2
BP diastolic (mm Hg)	66 ± 2	72 ± 1*	73 ± 2	72 ± 2
HR (beats per min)	62 ± 2	73 ± 2***	73 ± 3	75 ± 3
Mean physical activity (h per week)	6.6 ± 0.9	5.9 ± 0.8	5.7 ± 0.9	5.9 ± 1.0
Family history of HT (%)	40.0	40.7	43.5	36.8
Body fat (%)	17.4 ± 0.8	15.8 ± 0.6	16.2 ± 0.6	15.0 ± 0.8
Total AT (mm ²)	17 085 ± 1368	16 609 ± 1800	16 647 ± 1943	14 459 ± 1558
SAT (mm ²)	11 022 ± 1045	11 668 ± 1339	11 719 ± 1445	10 324 ± 1300
VAT (mm ²)	6063 ± 734	4942 ± 721	4928 ± 779	4135 ± 611

Abbreviations: AT, adipose tissue; BMI, body mass index; BP, blood pressure; HR, heart rate; HT, hypertension; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

trained examiner using a standardized protocol. Body fat content (BF%) was calculated using the formula of Deurenberg *et al.*¹⁵ $BF\% = 1.2 \times BMI + (0.23 \times \text{age}) - (10.8 \times \text{sex}) - 5.4$, where sex equals 1 for male subjects (and 0 for female subjects, if applicable).

Abdominal adipose tissue distribution

Abdominal body fat distribution was evaluated by magnetic resonance imaging using gradient sequence, repetition time of 34 ms and echo time of 2.38/5.24 ms (Symphony 1.5T spin echo; Siemens, Munich, Germany). Total abdominal as well as visceral and subcutaneous abdominal adipose tissue areas were evaluated from a single-slice scan at the level between the L4 and L5 vertebral body using image analysis freeware (ImageJ; NIH, Bethesda, MD, USA). A histogram of pixel intensity in the region of interest was displayed and the intensity corresponding to the nadir between the lean and fat peaks was used as a cut-point. Abdominal adipose tissue compartments were defined as follows: (1) visceral adipose tissue, as the sum of the pixels in the area defined by internal boundaries of the abdominal muscle wall; and (2) subcutaneous adipose tissue (SAT), as the sum of the pixels located outside the outermost boundaries of the muscle wall.

Biochemical assays

After centrifugation at 4 °C, the aliquots of plasma and serum were stored at -20 °C until assayed. Fasting serum total cholesterol, high-density lipoprotein-cholesterol and triglyceride (TG) levels were measured with enzymatic kits (Roche Diagnostics, Lewes, UK) using an autoanalyzer Hitachi 911 (Roche Diagnostics). Low-density lipoprotein-cholesterol concentration was calculated using the Friedewald formula. Fasting serum levels of non-esterified fatty acids were measured spectrophotometrically by commercial kit (Randox Laboratories Ltd, Crumlin Co., Antrim, UK). Enzyme-linked immunosorbent assay sandwich assay was used for the measurement of fasting plasma PAI-1 concentration (Diagnostica Stago, Asnieres, France). Fasting plasma leptin and adiponectin concentrations were measured by radioimmunoassay (Linco Research, St Charles, MO, USA). Plasma glucose concentrations in both tests were measured by commercial kits (Roche Diagnostics) using an automatic biochemical analyzer Hitachi 911 (Roche Diagnostics). Plasma insulin and C-peptide levels in both tests were measured by commercial IRMA kits (Immunotech SA, Marseille, France).

Calculation of indices of insulin sensitivity and insulin secretion

The insulinogenic index was calculated as the ratio of incremental insulin to incremental glucose concentrations 30 min after glucose ingestion.¹⁶ The updated HOMA2 (homeostasis model assessment) model was used to estimate the insulin resistance

(HOMA2-IR) and β -cell function (HOMA2-%B) from fasting plasma glucose and insulin levels.¹⁷ Fasting insulin and TG concentrations were used to calculate insulin sensitivity index proposed by McAuley *et al.*¹⁸ (ISI_{McAU}). Glucose and insulin concentrations from the OGTTs were used to calculate the following indices of insulin sensitivity: index of peripheral insulin sensitivity as proposed by Cederholm and Wibell¹⁹ (ISI_{CED}); and composite whole-body insulin sensitivity index as proposed by Matsuda and DeFronzo²⁰ (ISI_{MAT}).

During the OGTT and IVGTT, areas under the curves (AUC) of insulin and C-peptide levels were calculated by means of the trapezoidal rule. Insulin secretion was defined as total ($AUC(Ins)_{0-90 \text{ min}}$), first phase ($0-11 \text{ min}$, $AUC(Ins)_{0-11 \text{ min}}$) and late phase ($11-90 \text{ min}$, $AUC(Ins)_{11-90 \text{ min}}$). Glucose-stimulated insulin secretion was assessed as the acute insulin response to glucose (AIR_g), determined as the mean insulin concentration increment above the fasting value from 0 to 7 min after intravenous bolus glucose injection.¹⁶

Statistical analysis

The results are expressed as the mean \pm s.e.m. Statistical evaluation was completed using the Sigma Stat 2.0 program (Jandel Scientific, San Rafael, CA, USA) and SPSS 11.5 program (SPSS Inc., Chicago, IL, USA). Comparisons of single variables were performed using the Mann-Whitney *U*-test. Two-way (time \times group) analysis of variance for repeated measures with Student-Newman-Keuls *post hoc* test was used to determine the differences in glucose, insulin and C-peptide responses during OGTT and IVGTT between HT and NT subjects. Differences were considered significant at $P < 0.05$.

Results

Clinical characteristics of study subjects are given in Table 1. The hypertensive subjects were slightly younger ($P = 0.027$), but there were no other significant differences in BMI, waist circumference, family history of HT and physical activity between HT and NT subjects. Patients with HT had higher systolic blood pressure ($P < 0.001$), diastolic blood pressure ($P = 0.02$) and heart rate ($P < 0.001$). The size of the subcutaneous and visceral abdominal adipose tissue compartments was similar in the two groups. Fasting serum concentrations of non-esterified fatty acids ($P = 0.016$) and baseline plasma concentrations of PAI-1 ($P = 0.021$) were higher in HT patients compared with NT. There were no differences between study groups in fasting serum concentrations of TG, and total, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol, and in fasting plasma levels of leptin and adiponectin (Table 2). Fasting plasma

Table 2 Parameters of lipid and glucose metabolism, PAI-1 and adipokines measured in fasting state in NT and HT subjects

	NT	HT
<i>n</i>	15	27
Total cholesterol (mmol ⁻¹)	4.02 ± 0.18	4.23 ± 0.13
HDL-cholesterol (mmol ⁻¹)	1.23 ± 0.08	1.07 ± 0.04
LDL-cholesterol (mmol ⁻¹)	2.58 ± 0.20	2.62 ± 0.18
Triglycerides (mmol ⁻¹)	0.77 ± 0.08	1.16 ± 0.17
NEFA (mmol ⁻¹)	0.81 ± 0.07	1.09 ± 0.07*
PAI-1 (ng ml ⁻¹)	12.9 ± 1.9	34.0 ± 8.4*
Leptin (ng ml ⁻¹)	3.8 ± 0.6	3.8 ± 0.5
Adiponectin (ng ml ⁻¹)	1.41 ± 0.26	1.57 ± 0.32
Fasting plasma glucose (mmol ⁻¹)	4.94 ± 0.10	5.10 ± 0.08
Fasting plasma insulin (mU l ⁻¹)	5.11 ± 0.40	10.07 ± 1.21***
Fasting plasma C-peptide (pmol l ⁻¹)	545 ± 37	704 ± 57
HOMA2-%B	74.4 ± 4.4	105.9 ± 6.7**
HOMA2-%S	163.2 ± 12.3	97.5 ± 8.9***
HOMA2-IR	0.66 ± 0.05	1.31 ± 0.16***
ISI _{McAU}	10.1 ± 0.5	8.0 ± 0.4**

Abbreviations: HDL, high-density lipoprotein; HOMA2-%B, homeostasis model assessment to estimate β -cell function; HOMA2-%S, HOMA indexes of insulin sensitivity; HOMA2-IR, HOMA to estimate insulin resistance; HT, hypertensive; ISI_{McAU}, insulin sensitivity index proposed by McAuley *et al.*; NEFA, non-esterified fatty acids; NT, normotensive; PAI-1, plasminogen activator inhibitor factor 1.

glucose and C-peptide concentrations were not significantly different between the two groups, whereas HT patients had higher fasting plasma insulin concentrations ($P < 0.001$) than NT patients (Table 2).

Plasma glucose concentrations increased during OGTT in both groups with interactive differences between HT and NT subjects (effect of diagnosis \times time $P < 0.001$, $F = 4.6$). Oral glucose administration resulted in a significantly higher response of insulin in HT subjects compared with NT controls (effect of diagnosis $P = 0.008$, $F = 7.9$). The response of C-peptide to oral glucose administration was comparable in both groups (Figure 1). In spite of normal glucose tolerance, HT patients had elevated 2-h plasma levels of glucose ($P = 0.039$), insulin ($P = 0.004$) and C-peptide ($P = 0.020$) compared with controls (Table 3).

Parameters of insulin sensitivity/resistance are given in Tables 2 and 3. Both HOMA2-IR ($P < 0.001$) index of insulin resistance and HOMA2-%B ($P = 0.002$) index of insulin secretion, based on fasting glucose and insulin concentrations, were higher in HT compared with NT. Decreased peripheral and whole-body insulin sensitivity in HT subjects was confirmed by ISI_{CEd} ($P = 0.008$) and ISI_{MAT} ($P < 0.001$) indices, using both fasting and OGTT glucose and insulin values. Insulinogenic index did not significantly differ between the groups.

Intravenous glucose administration resulted in a comparable increase in plasma glucose levels in HT and in NT subjects. The insulin response was significantly higher in HT than in NT subjects (effect of diagnosis $P = 0.04$, $F = 4.5$; effect of diagnosis \times time $P = 0.048$; $F = 1.9$). A significant increase

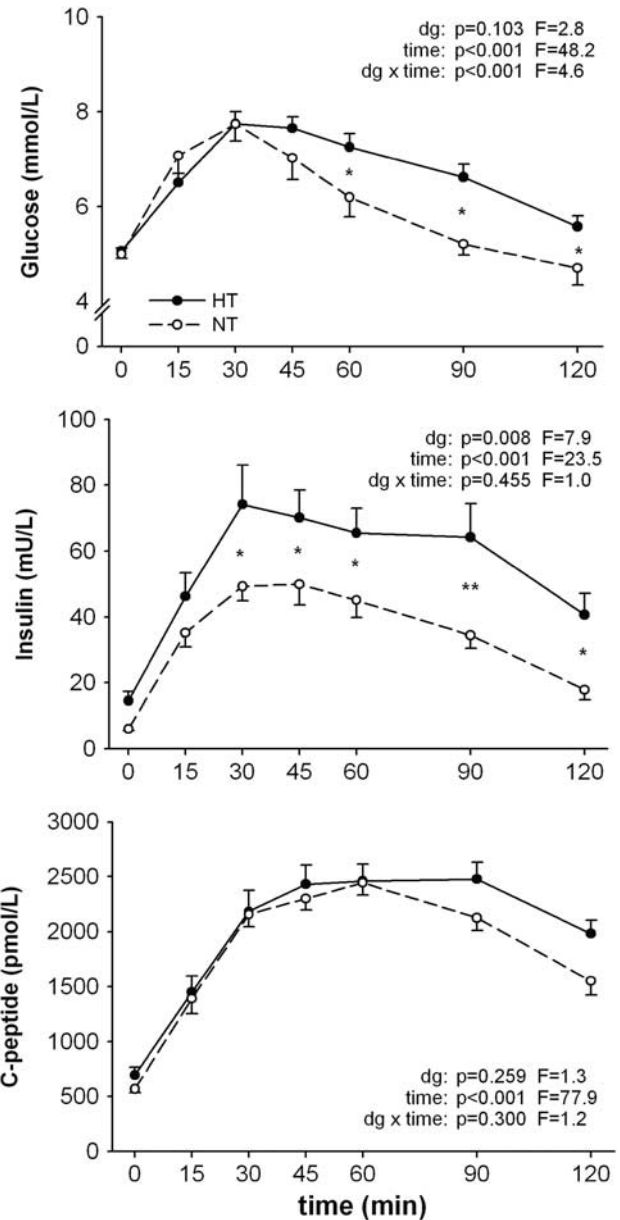


Figure 1 The course of glucose, insulin and C-peptide concentrations during oral glucose tolerance test, *post hoc* test. * $P < 0.05$; ** $P < 0.01$. HT vs NT in respective times; HT subjects—full circles, solid line; NT controls—empty circles, dashed line. HT, hypertension; NT, normotensive

in C-peptide levels was observed in both groups after intravenous glucose bolus (effect of time $P < 0.001$, $F = 70.9$). The response of C-peptide during IVGTT was significantly higher in HT subjects when compared with NT controls (effect of diagnosis $P = 0.012$, $F = 7.0$) (Figure 2).

During the IVGTT, total and late, but not early phase of insulin secretions were significantly higher in HT patients than in controls ($P = 0.018$, 0.025 and 0.068 , respectively). Acute insulin secretion response of β -cells during IVGTT (AIR₀) tended to be higher in HT patients; however, it did not reach statistical significance ($P = 0.092$).

Table 3 Parameters of glucose metabolism measured or calculated during OGTT and IVGTT in NT and HT subjects

	NT	HT	
	IVGTT/OGTT	IVGTT	OGTT
<i>n</i>	15	23	19
<i>OGTT</i>			
Insulinogenic index (mU mmol ⁻¹)	20.2 ± 3.3	—	22.3 ± 3.8
Two-hour plasma glucose (mmol l ⁻¹)	4.70 ± 0.35	—	5.58 ± 0.23*
Two-hour plasma insulin (mU l ⁻¹)	17.88 ± 3.00	—	40.67 ± 6.57**
Two-hour plasma C-peptide (pmol l ⁻¹)	1551 ± 129	—	1983 ± 120*
AUC glucose (mmol min l ⁻¹)	6.1 ± 0.3	—	6.8 ± 0.2
AUC insulin (mU min l ⁻¹)	37.8 ± 2.9	—	58.1 ± 6.5**
AUC C-peptide (pmol min l ⁻¹)	1953 ± 56	—	2130 ± 125
ISI _{MAT}	12.2 ± 1.4	—	6.0 ± 0.8***
ISI _{CED}	71.9 ± 4.6	—	57.2 ± 2.9**
<i>IVGTT</i>			
Δmax Glucose (mmol l ⁻¹)	8.51 ± 0.22	9.15 ± 0.51	—
Δmax Insulin (mU l ⁻¹)	41.3 ± 6.7	57.3 ± 6.7	—
Δmax C-peptide (pmol l ⁻¹)	1164 ± 112	1349 ± 95	—
AIR _g (mU l ⁻¹)	31.7 ± 5.9	45.7 ± 5.3	—
AUC(Ins) _{0–90 min} (mU min l ⁻¹)	17.7 ± 1.6	24.7 ± 2.0*	—
AUC(Ins) _{0–11 min} (mU min l ⁻¹)	33.7 ± 4.4	46.7 ± 4.8	—
AUC(Ins) _{11–90 min} (mU min l ⁻¹)	15.5 ± 1.6	21.7 ± 1.8*	—
AUC(C-pep) _{0–90 min} (pmol min l ⁻¹)	1128 ± 65	1423 ± 66**	—
AUC(C-pep) _{0–11 min} (pmol min l ⁻¹)	1358 ± 113	1677 ± 97*	—
AUC(C-pep) _{11–90 min} (pmol min l ⁻¹)	1096 ± 66	1388 ± 66**	—

Abbreviations: AIR_g, acute insulin response to glucose; AUC, area under the curve; C-pep, C-peptide; HT, hypertension; Ins, insulin; IVGTT, intravenous glucose tolerance test; NT, normotensive; OGTT, oral glucose tolerance test; ISI_{CED}, index of peripheral insulin sensitivity as proposed by Cederholm and Wibell; ISI_{MAT}, composite whole-body insulin sensitivity index as proposed by Matsuda and DeFronzo.

Systolic blood pressure in all subjects (HT + NT) correlated positively with plasma levels of non-esterified fatty acids and PAI-1 ($r = 0.361$, $P = 0.024$; $r = 0.372$, $P = 0.024$, respectively) and negatively with insulin sensitivity indices (Table 4). The amounts of total adipose tissue and SAT correlated positively with serum TG concentrations ($r = 0.441$, $P = 0.035$; $r = 0.417$, $P = 0.048$, respectively), plasma leptin concentrations ($r = 0.679$, $P < 0.001$; $r = 0.761$, $P < 0.001$, respectively) and negatively with serum high-density lipoprotein concentrations ($r = -0.476$, $P = 0.022$; $r = -0.482$, $P = 0.020$, respectively). SAT also correlated with plasma adiponectin concentrations ($r = 0.485$, $P = 0.019$). Interestingly, with regard to insulin sensitivity, only indices calculated from fasting concentrations correlated negatively with the amounts of total adipose tissue and SAT (Table 4). The amount of visceral adipose tissue predicted fasting plasma levels of only glucose ($r = 0.461$, $P = 0.023$), whereas no significant correlations were found between visceral adipose tissue and measures of insulin sensitivity/resistance.

Discussion

The main finding of this study is that young, lean male patients with recently diagnosed yet untreated HT show a substantial impairment of insulin sensitivity compensated by hyperinsulinaemia.

It has been speculated for a long time about the possible role of insulin resistance and hyperinsuli-

naemia in essential HT.^{21,22} The common occurrence of insulin resistance and HT is frequent owing to the overlapping prevalence of overweight/obesity, diabetes, HT and dyslipidaemia in Western civilization.^{11,23} Although HT is more frequent in obese than in normal-weight children,² investigation of the mechanisms involved in the onset and development of HT in youth has to be carried out in lean and otherwise healthy hypertensive individuals to exclude as many confounding factors as possible. Our patients were only young, lean men, carefully selected with newly diagnosed HT, who were not pharmacologically treated for any condition and had no history of diabetes; thus, avoiding the most common confounding factors.

Several mechanisms have been suggested to link hyperinsulinaemia with increased blood pressure, including dysbalance in sympathetic activity,^{24,25} vascular smooth muscle cells abnormalities,²⁶ increased kidney renin output²⁷ and sodium retention.²⁸ It is also known that sympathetic stimulation activates lipolysis.²⁹ In fact, in our previous study,³⁰ we found higher levels of norepinephrine in young hypertensive patients, reflecting the overactivity of sympathetic nervous system, which may lead to elevated free fatty acid (FFA) levels found in our hypertensive patients. Besides decreased insulin sensitivity in the liver and muscle,³¹ elevated levels of FFAs lead to the increase in insulin secretion.^{32,33} This might be the compensatory reaction to the peripheral insulin resistance,³³ the result of diminished hepatic insulin extraction³⁴ or the response to

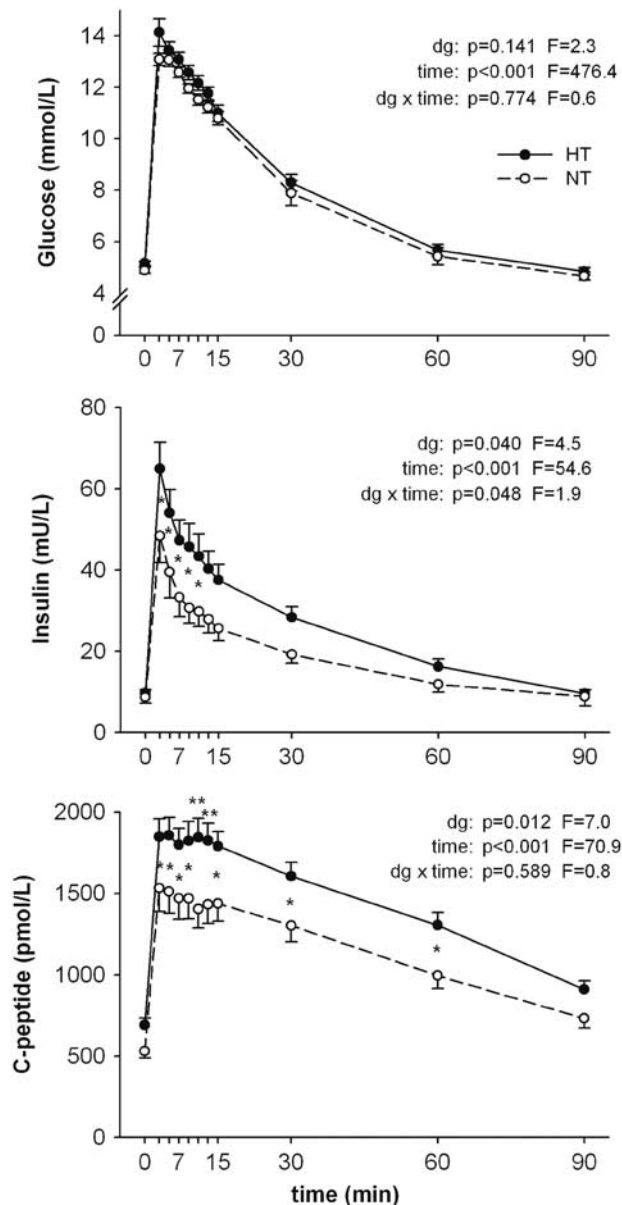


Figure 2 The course of glucose, insulin and C-peptide concentrations during intravenous glucose tolerance test, *post hoc* test. * $P < 0.05$; ** $P < 0.01$. HT vs NT in respective times; HT subjects—full circles, solid line; NT controls—empty circles, dashed line. HT, hypertension; NT, normotensive

the enhanced hepatic glucose production caused by reduced inhibitory effect of insulin owing to the elevated FFAs from the visceral fat.³² On the other hand, hyperinsulinaemia itself increases the activity of sympathetic nervous system,²⁴ closing this part of the 'vicious circle'. The fact that our patients showed clinical signs of sympathicotonic circulation (increased carotic pulsation, eretic heart action, tachycardia, positive red dermographism) supports this hypothesis on early development of insulin resistance in young hypertensive patients.

Enhanced hepatic gluconeogenesis caused by increased FFAs in the liver may significantly

contribute to increased plasma glucose levels after oral glucose load. More than half of our HT patients (58%), but only 27% of controls had 'higher still normal' value of 2-h plasma glucose concentration (5.6–7.7 mmol⁻¹). This is considered as an independent cardiovascular risk factor³⁵ and higher 2-h plasma levels of glucose is strongly associated with the risk of development of HT over 5 years after adjustment for confounding factors.³⁶

It is evident that obesity and furthermore body fat distribution are risk factors for the conditions of metabolic syndrome and associated with type 2 diabetes and cardiovascular disease.³⁷ As insulin resistance also occurs in lean individuals, such as in our lean hypertensive patients, it has been suggested that these 'metabolically obese, normal-weight individuals'³⁸ are predisposed to insulin resistance owing to a higher percentage of body fat, a unfavourable central fat distribution with higher amount of visceral fat,³⁷ and inactivity. Toft *et al.*³⁹ hypothesized that central obesity and body fat distribution are involved in the pathogenesis of insulin resistance, which is independent of blood pressure and occurs only parallel to HT owing to the increased FFAs turnover. Our findings do not support these suggestions; our hypertensive patients had comparable %BF, BMI and waist circumference, similar adipose tissue distribution and equivalent mean physical activity when compared with our control group. Our data showed that hypertensive men are insulin resistant despite their young age, lean body constitution, good physical fitness and distribution of abdominal adipose tissue comparable with normotensive (NT) subjects. Interestingly, our data indicate that in this 'lean range', the amount of SAT may be an important determinant of several metabolic cardiovascular risk factors, such as higher TG and lower high-density lipoprotein -cholesterol concentrations.

Adiponectin, as a marker of metabolic syndrome,⁴⁰ and leptin, as an indicator of the amount of adipose tissue mass,⁴¹ have been associated with insulin resistance and HT.⁴² Patel *et al.*⁴³ found inverse association of adiponectin with insulin resistance, visceral adiposity, and positive family history of coronary heart disease, HT and type 2 diabetes in young adults. However, we did not find any significant differences in adiponectin and leptin levels between the groups nor association of those two markers with elevated blood pressure or insulin resistance. It seems that changed adiponectin and leptin levels are rather a later consequence of a cluster of aforementioned features than their cause.

Insulin resistance and hyperinsulinaemia have been associated with increased activity of PAI-1,^{44,45} seen also in our hypertensive patients. Furthermore, baseline levels of PAI-1 correlated positively with the systolic blood pressure. PAI-1 is an inhibitor of fibrinolysis and a possible marker of endothelial dysfunction⁴⁶ that is associated with increased cardiovascular risk, especially the risk of myocardial

Table 4 Correlation coefficients (*r*) of parameters expressing insulin resistance with blood pressure, abdominal fat distribution and lipid profile

	<i>HOMA2-%B</i>	<i>HOMA2-%S</i>	<i>HOMA-IR</i>	<i>ISI_{MAT}</i>	<i>ISI_{CED}</i>	<i>ISI_{McAu}</i>	Fasting insulin
BPsys	0.288 <i>P</i> = 0.065	-0.398 <i>P</i> = 0.009	0.269 <i>P</i> = 0.084	-0.551 <i>P</i> < 0.001	-0.484 <i>P</i> = 0.004	-0.335 <i>P</i> = 0.037	0.266 <i>P</i> = 0.089
BPdias	0.279 <i>P</i> = 0.074	NS	NS	-0.326 <i>P</i> = 0.060	-0.308 <i>P</i> = 0.076	NS	NS
HR	0.491 <i>P</i> < 0.001	-0.475 <i>P</i> < 0.001	0.491 <i>P</i> < 0.001	-0.466 <i>P</i> = 0.005	-0.399 <i>P</i> = 0.019	-0.340 <i>P</i> = 0.034	0.490 <i>P</i> < 0.001
Total AT	NS	-0.474 <i>P</i> = 0.019	0.510 <i>P</i> = 0.011	NS	NS	-0.500 <i>P</i> = 0.015	0.492 <i>P</i> = 0.015
SAT	0.367 <i>P</i> = 0.077	-0.531 <i>P</i> = 0.008	0.555 <i>P</i> = 0.005	NS	NS	-0.496 <i>P</i> = 0.016	0.546 <i>P</i> = 0.006
VAT	NS	NS	NS	NS	NS	NS	NS
Cholesterol	NS	NS	NS	0.380 <i>P</i> = 0.032	0.348 <i>P</i> = 0.051	NS	NS
HDL	NS	0.346 <i>P</i> = 0.031	-0.294 <i>P</i> = 0.070	0.345 <i>P</i> = 0.053	0.329 <i>P</i> = 0.066	0.503 <i>P</i> < 0.001	-0.290 <i>P</i> = 0.073
LDL	-0.312 <i>P</i> = 0.053	NS	NS	0.402 <i>P</i> = 0.023	0.320 <i>P</i> = 0.074	NS	NS
TG	0.350 <i>P</i> = 0.029	-0.380 <i>P</i> = 0.017	0.472 <i>P</i> = 0.002	-0.355 <i>P</i> = 0.046	-0.318 <i>P</i> = 0.076	-0.788 <i>P</i> < 0.001	0.469 <i>P</i> = 0.003

Abbreviations: AT, adipose tissue; BPdias, diastolic blood pressure; BPsys, systolic blood pressure; HDL, high-density lipoprotein; HOMA2-%B, homeostasis model assessment to estimate β -cell function; HOMA2-%S, HOMA indexes of insulin sensitivity; HOMA2-IR, HOMA to estimate insulin resistance; HR, heart rate; *ISI_{MAT}*, composite whole-body insulin sensitivity index as proposed by Matsuda and DeFronzo; *ISI_{McAu}*, insulin sensitivity index proposed by McAuley *et al.*; *ISI_{CED}*, index of peripheral insulin sensitivity as proposed by Cederholm and Wibell; LDL, low-density lipoprotein; NS, nonsignificant; SAT, subcutaneous adipose tissue; TG, triglyceride; VAT, visceral adipose tissue.

infarction in the presence of insulin resistance,⁴⁷ and belongs to the non-standard features of the metabolic syndrome.⁴⁵

Recently, several studies reported that incretin mimetics had wide range of additional protective effects on the cardiovascular system. Animal studies showed their antihypertensive and natriuretic effects.^{48–50} In humans, treatment of type 2 diabetic patients with these drugs was associated with improvement of systolic blood pressure,⁵¹ and improvement of endothelial function, independent of the improvement of insulin sensitivity.⁵² The precise mechanisms underlying the reported effects of incretin mimetics on cardiovascular system are not fully clear as yet. Cabou *et al.*⁵³ hypothesized the involvement of incretins in brain regulation of arterial blood flow, heart rate and insulin sensitivity.

In support of the paradigm that insulin resistance and compensatory hyperinsulinaemia have a primary role in the pathogenesis of essential HT,^{21,54} young, lean healthy offsprings of hypertensive parents are more insulin resistant and have increased blood pressure, heart rate and plasma insulin levels compared with matched healthy individuals with negative family history of HT.^{55–60}

In this study, however, family history of HT among first-degree relatives was comparable in both groups.

One of the few limitations of this study is that we did not quantify insulin sensitivity by hyperinsulinaemic euglycaemic clamp, which is considered the ‘gold standard’.⁶¹ However, all the surrogate indirect measures of insulin sensitivity used in this study have been extensively validated in the non-diabetic population previously.⁶² The small number of patients in this study is counterbalanced by the careful diagnosis and selection of patients and their matched controls.

We can conclude that untreated normal-weight adolescents in early stage of HT, with distribution of abdominal adipose tissue and lipid profile comparable with their healthy NT gender-, age- and BMI-matched counterparts, showed considerable signs of insulin resistance and hyperinsulinaemia. On the basis of our results, we hypothesize that insulin resistance is the initial feature that is influenced by several environmental factors and HT is one of their common consequences. Therefore, young, lean hypertensive patients represent another target group in which the identification of insulin resistance and levels of PAI-1 is necessary for lifestyle management

What is known about topic

- Insulin resistance in essential hypertension is often confoundingly influenced by obesity, body fat distribution, age, antihypertensive therapy, physical fitness, comorbidity, and so on.

What this study adds

- Young, normal weight, male patients with recently diagnosed yet untreated essential hypertension show a substantial impairment of insulin sensitivity compensated by hyperinsulinaemia.
 - Insulin resistance is the initial feature that is influenced by several environmental factors and hypertension is one of their common consequences.
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and for the selection of adequate antihypertensive medication.

Conflict of interest

The authors declare no conflict of interest.

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