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Insulin Sensitivity in Young Patients with Hypertension Devoid of Conventional Risk Factors

A. Penesová¹, Z. Radiková¹, E. Cizmarova³, M. Vlcek^{1,2}, R. Imrich^{1,2}

Abstract: *Objective:* The term “metabolic syndrome” denotes a constellation of factors that increase an individual's risk of cardiovascular morbidity and mortality. Insulin resistance and associated abnormalities are considered to be a link between obesity and cardiovascular diseases. The aim of our study was to investigate the association of insulin sensitivity markers in a group of young patients with hypertension free of other metabolic risk factors and in obese, otherwise healthy subjects in comparison to healthy normotensive subjects.

Methods: 20 males with hypertension (HT), 21 males with obesity (OB), and 23 healthy controls underwent the oral glucose tolerance test. The insulin sensitivity indices according to Matsuda (ISI_{MAT}), and Cederholm and Wibell (ISI_{CED}), and IR HOMA were calculated. Lipid profile was measured in baseline blood samples.

Results: All HT and control subjects had normal glucose tolerance (NGT), but 5 obese individuals had impaired glucose tolerance. Despite NGT, HT patients had lower ISI_{MAT} , ISI_{CED} and higher IR HOMA than controls and comparable to the OB group. 65 % of young lean HT patients and 70 % of OB otherwise healthy subjects exhibited ≥ 3 features of the metabolic syndrome.

Conclusions: Young lean patients with hypertension without other metabolic risk factors displayed signs of insulin resistance and metabolic

abnormalities typical of cardiometabolic syndrome comparable to obese subjects. Early lifestyle intervention might prevent or delay the development of complete metabolic syndrome in young hypertensive and obese subjects.

Key words: hypertension, insulin sensitivity, obesity, metabolic syndrome

Kurzfassung: Insulinsensitivität bei jungen Patienten mit Hypertonie frei von herkömmlichen Risikofaktoren.

Hintergrund und Ziele: Der Begriff Metabolisches Syndrom bezeichnet eine Konstellation von Faktoren, die das individuelle Risiko für kardiovaskuläre Morbidität und Mortalität erhöhen. Insulinresistenz und die damit verbundenen Veränderungen werden als eine Verbindung zwischen Übergewicht und Herz-Kreislauf-Erkrankungen betrachtet. Das Ziel unserer Studie war es, den Zusammenhang der Marker für Insulinsensitivität zu untersuchen und zwar in einer Gruppe von jungen Patienten mit Hypertonie frei von anderen metabolischen Risikofaktoren und bei fettleibigen, ansonsten gesunden Probanden im Vergleich zu gesunden Probanden mit normalem Blutdruck.

Methoden: 20 Männer mit Hypertonie (HT), 21 Männer mit Adipositas (OB) und 23 gesunde

Kontrollpersonen haben sich dem oralen Glukose-Toleranztest unterzogen. Die Insulinsensitivitätsindizes nach Matsuda (ISI_{MAT}) und nach Cederholm und Wibell (ISI_{CED}) sowie auch IR-HOMA wurden berechnet. Das Lipidprofil wurde in den basalen Blutproben gemessen.

Ergebnisse: Alle HT und Kontrollpersonen zeigten eine normale Glukosetoleranz, aber 5 fettleibige Personen hatten eine gestörte Glukosetoleranz. Trotz normaler Glukosetoleranz hatten HT-Patienten niedrigere ISI_{MAT} , ISI_{CED} und höhere IR-HOMA-Werte als die Kontrollen, waren aber vergleichbar mit der OB-Gruppe. 65 % der jungen schlanken HT-Patienten und 70 % der OB, aber ansonsten gesunden Probanden zeigten ≥ 3 Merkmale des Metabolischen Syndroms.

Schlussfolgerungen: Junge schlanke Patienten mit Bluthochdruck ohne andere metabolische Risikofaktoren zeigten Anzeichen von Insulinresistenz und metabolische Abnormalitäten typisch für das Kardiometabolische Syndrom, vergleichbar mit fettleibigen Probanden. Mit früher Lebensstiländerung könnte die Entwicklung des vollständig ausgeprägten Metabolischen Syndroms bei jungen Hypertonikern und übergewichtigen Probanden verhindert oder verzögert werden. **J Hypertonie 2013; 17 (1): 15–9.**

Schlüsselwörter: Hypertonie, Insulinsensitivität, Fettleibigkeit, Metabolisches Syndrom

■ Introduction

The metabolic syndrome (MS) comprises a cluster of cardiovascular risk factors including abdominal obesity, diabetes or prediabetes, hypertension (HT), and dyslipidemia, and is linked to an increased risk of type-2 diabetes, cardiovascular diseases, and overall morbidity and mortality. Obesity can be regarded as an underlying risk factor for cardiovascular disease (CVD) [1] because it raises the risk for CVD through other risk factors (hypercholesterolemia, hypertension, hyperglycemia) and emerging risk factors (atherogenic dyslipidemia, insulin resistance, proinflammatory state, prothrombotic state). The relationship of obesity to major and emerging risk factors varies, depending on the genetic and acquired characteristics of individuals.

It is argued that resistance to insulin action and associated abnormalities are the link between obesity and CVD. Hypertension is often associated with insulin resistance as well as with increased amounts of body fat [2–6].

The question remains if insulin resistance precedes hypertension or if cardiovascular risk factors contribute to impaired insulin action. Many studies have been performed in subjects with higher age, with other confounding factors, and co-morbidities.

Therefore, the aim of our study was to compare insulin sensitivity, lipidemia, and lifestyle factors in young lean subjects with newly diagnosed hypertension grade I, normotensive obese subjects, and lean healthy controls. The study was performed in non-diabetic young subjects without other co-morbidities to avoid possible confounding effects by preexisting metabolic syndrome risk factors.

■ Subjects and Methods

20 male, lean ($BMI < 25 \text{ kg/m}^2$) hypertensive (HT) patients fulfilling the criteria for grade-I hypertension were studied. The patients were recruited from the registry of the Depart-

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Table 1. Clinical characteristics of study subjects.

	Controls	OB	HT
n	23	21	20
Age (yrs)	24.3 ± 1.0	29.0 ± 1.6 ^{#Δ}	20.7 ± 0.7
BMI (kg/m ²)	22.7 ± 0.4	33.9 ± 0.9 ^{###}	22.7 ± 0.5
Mean physical activity (hrs/wk)	6.5 ± 0.8	1.8 ± 2.4 ^{###ΔΔΔ}	6.0 ± 0.9
Waist circumference (cm)	84 ± 2	112 ± 3 ^{###}	82 ± 1
BP sys (mmHg)	116 ± 2	134 ± 4 [#]	142 ± 2 [*]
BP dia (mmHg)	68 ± 1	74 ± 3 [#]	71 ± 2
HR (1/min)	64 ± 1	74 ± 4 ^{###}	74 ± 3 ^{***}
Total cholesterol (mmol/l)	4.05 ± 0.13	4.66 ± 0.14 ^{###Δ}	4.15 ± 0.16
HDL cholesterol (mmol/l)	1.24 ± 0.06	0.95 ± 0.05 ^{###ΔΔ}	1.09 ± 0.04
TG (mmol/l)	0.78 ± 0.07	1.95 ± 0.22 ^{###ΔΔΔ}	0.88 ± 0.11
Fasting plasma glucose (mmol/l)	4.80 ± 0.07	5.22 ± 0.10 ^{##}	5.06 ± 0.09
Fasting plasma insulin (mIU/l)	5.09 ± 0.44	11.23 ± 1.24 ^{###}	9.82 ± 0.66 ^{***}
IR HOMA	1.09 ± 0.10	2.63 ± 0.30 ^{###}	2.22 ± 0.77 ^{***}
ISI _{MAT}	10.6 ± 0.8	4.71 ± 0.45 ^{###}	5.96 ± 0.68 ^{***}
ISI _{CED}	79.2 ± 4.6	49.1 ± 2.6 ^{###}	63.0 ± 3.6 ^{**}

Data are expressed as mean ± SE.

* p < 0.05; ** p < 0.01; *** p < 0.001 HT vs controls

p < 0.05; ## p < 0.01; ### p < 0.001 OB vs controls

Δ p < 0.05; ΔΔ p < 0.01; ΔΔΔ p < 0.001 OB vs HT

OB: obese group; HT: patients with hypertension; BMI: Body Mass Index; BP sys: systolic blood pressure; BP dia: diastolic blood pressure; HR: heart rate; HDL: high-density lipoprotein; TG: triglycerides; IR HOMA: insulin resistance index HOMA; ISI_{MAT}: insulin sensitivity index according to Matsuda; ISI_{CED}: insulin sensitivity index according to Cederholm and Wibell

ment of Cardiology Outpatient Clinic Karlova Ves, Slovakia. The diagnosis of hypertension was confirmed by 24-hour blood pressure monitoring. Secondary hypertension was excluded by clinical examination, routine blood and urine analysis, and hormonal measurements prior to enrolment and only individuals with confirmed diagnosis of essential hypertension were enrolled. All parameters were compared to 21 obese but otherwise healthy subjects with a Body Mass Index (BMI) ≥ 30 kg/m² (OB) and 23 healthy male subjects with a BMI < 25 kg/m² (C). Furthermore, all subjects (patients, obese subjects, and controls) had to fulfill the following inclusion criteria: (a) no history of diabetes mellitus, dyslipidemia, and any endocrine or renal disorders, (b) non-smokers, and (c) without any current medication. Each participant completed a questionnaire that included questions regarding alcohol intake, usual patterns of physical activity, family history of hypertension, use of drugs, and other lifestyle factors. Basic characteristics of all subjects enrolled in the study are summarized in Table 1. All subjects gave informed written consent and the study was approved by the Ethics Committee of the Institute of Experimental Endocrinology, Slovak Academy of Sciences, Slovakia, in agreement with the ethical guidelines of the Declaration of Helsinki as revised in 2000.

All subjects were asked to fast and restrain strong physical activity for 12 hours prior to examination. Upon arrival in the laboratory at 08:00 am, the cubital vein of one arm was cannulated. Blood pressure was measured (Dinamap Vital Sign Monitor, model 845 XT, Criticon X, Inc, Tampa, FL, USA) 3× after 10 minutes of rest in a comfortable chair. Baseline blood samples were taken at least 30 minutes after iv catheter insertion to avoid the effect of acute stress of venipuncture. Body weight, height, and waist circumference were measured using a standard protocol.

During the oral glucose tolerance test (oGTT), subjects were asked to ingest a solution containing 75 g glucose. Blood samples were collected before (0 min) and 15, 30, 45, 60, 75, 90, 105, and 120 minutes after glucose ingestion. After centrifugation at 4 °C, all plasma and serum aliquots were stored at –20 °C until assay. Plasma glucose concentrations and fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels were measured with enzymatic kits (Roche Diagnostics, Lewes, UK) using an autoanalyzer Hitachi 911 (Roche Diagnostics, Lewes, UK). Insulin levels were measured by IRMA kits (Immunotech SA, Marseille, France).

From fasting glucose and insulin concentrations index of insulin resistance IR HOMA was calculated [7]. Glucose and insulin concentrations from the oral glucose tolerance tests were used to calculate the composite whole-body insulin sensitivity index as proposed by Matsuda and DeFronzo (ISI_{MAT}) [8] and the index of peripheral insulin sensitivity proposed by Cederholm and Wibell (ISI_{CED}) [9].

The metabolic syndrome was identified according to the World Health Organization 1999 [10].

Statistics

ANOVA was used to determine differences in basal parameters and insulin sensitivity indices among study groups. The General Linear Model repeated measures (GLM-RM) procedure was used to determine the differences in glucose and insulin responses during oral glucose tolerance test between HT patients, OB, and controls. All calculated indices of insulin sensitivity were correlated with the measured blood pressure with Pearson's correlation. Statistical evaluation was per-

formed using the SPSS 11.5 program (SPSS, Inc, Chicago, IL, USA). The results are expressed as the mean $\pm$ SD. Differences were considered significant if $p < 0.05$.

Results

General and anthropometric characteristics of the study population are shown in Table 1.

Obese subjects and controls were slightly older than patients with HT ($p < 0.05$ and $p < 0.01$, respectively). There were no significant differences in BMI, waist circumference, and percentage of body fat (BF) between the HT and control groups. As expected, obese subjects had higher a BMI and waist circumferences than HT or controls ($p < 0.0001$). HT patients had higher systolic blood pressures than controls ($p = 0.01$). Systolic and diastolic blood pressures were also higher in the OB group but still within normal range in comparison to controls ($p < 0.05$). Heart rates were higher in both the HT and OB groups in comparison to controls ($p = 0.002$ and $p = 0.004$, respectively).

There were no differences in the mean fasting total and HDL cholesterol and triglycerides (TG) between HT and controls, but total cholesterol ($p = 0.003$) and TG ($p < 0.001$) were higher and HDL lower ($p = 0.001$) in OB subjects compared to controls and the HT group.

All controls and HT patients had normal glucose tolerance. We found 5 OB subjects with impaired glucose tolerance. Fasting plasma glucose concentrations were comparable in HT and controls, but higher in the OB group ($p < 0.01$). Normal glucose tolerance in HT patients was compensated by higher 2-h insulin concentrations ($p = 0.03$) compared to controls. Differences in 2-h plasma glucose and insulin concentrations were more pronounced between OB subjects and controls ($p < 0.001$).

During the oral glucose tolerance test, glucose and insulin increased significantly ($p < 0.001$; Figure 1). HT patients and OB subjects had higher fasting plasma insulin ($p < 0.001$), and insulin responses during oGTT were higher in both groups in comparison to controls ($p < 0.001$) as well.

Parameters of insulin sensitivity/resistance are given in Table 1. Patients with HT and OB subjects had a higher insulin resistance index IR HOMA ($p < 0.001$) and lower composite whole-body insulin sensitivity index ISI_{MAT} ($p < 0.001$) as well as ISI_{CED} ($p = 0.01$; Table 1). There were no differences in insulin sensitivity/resistance indices between HT patients and OB subjects, except ISI_{CED} , which was lower in OB subjects than in HT patients ($p = 0.005$).

Discussion

The main finding of our current study is lower insulin sensitivity in young lean patients with hypertension comparable to obese but otherwise healthy subjects. Our results are in good agreement with previous studies [11, 12] but most of the previous studies were done in older subjects or in subjects with higher BMI [5, 12]. Our study revealed the importance of

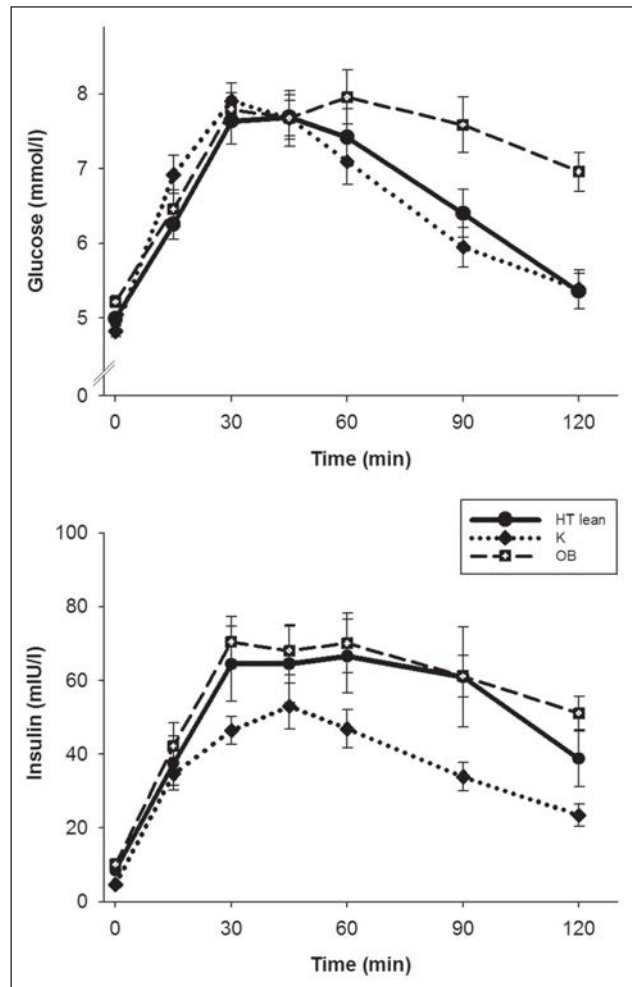


Figure 1. Plasma glucose, and insulin concentrations in HT patients (circles), in OB group (squares) and controls (diamonds) during oGTT.

early identification of impaired insulin action in young lean patients with grade-I hypertension, which represent high-risk subjects.

According to the results of our study, hyperinsulinemia in HT patients is more pronounced than hypertension and might potentiate a further increase of blood pressure.

The causality of insulin resistance in these patients is unknown. Development of insulin resistance depends on many factors including genetic predisposition, physical fitness, amount of body fat, liver fat content, etc.

Several mechanisms have been suggested to link insulin resistance and hypertension, including sympathetic nerve system overactivity [12–14], impaired renin-angiotensin-aldosterone function and sodium metabolism [15, 16], vascular mechanisms (eg, endothelial dysfunction), or smooth muscle cell hypertrophy [17, 18]. High blood pressure associated with overactivity of the sympathetic nerve system might contribute to impaired insulin action in peripheral tissues [12]. On the other hand, hyperinsulinemia is thought to promote hypertension through increased activity of the sympathetic nervous system [13], closing this part of the “vicious circle”. In our previous study [14], we found higher levels of norepinephrine

in young hypertensive patients, reflecting the overactivity of the sympathetic nervous system.

There is impaired insulin signaling in essential hypertension [19, 20]. For example, untreated patients with essential hypertension have higher fasting and postprandial insulin levels than age- and sex-matched normotensive persons regardless of body mass; a direct correlation between plasma insulin levels and blood pressure exists [21] as confirmed by our results.

Normally, there is a close relationship between insulin-mediated glucose disposal during euglycemic hyperinsulinemic clamp and incremental blood flow in response to insulin. This normal response is lost in insulin-resistant/obese persons, suggesting resistance to the action of insulin to induce vascular nitric oxide production [22]. Accumulating data suggest that insulin sensitivity in skeletal muscle, fat, and vascular tissue is impaired in persons predisposed to develop hypertension [22–24]. Another mechanism are impaired vascular relaxation effects of insulin/IGF-1, mediated in part, by endothelial cell production of vasodilatory factors [25, 26].

Abdominal obesity is associated with microvascular endothelial dysfunction through indirect mechanisms, such as insulin resistance and the association with risk factors (including diabetes mellitus, hypertension, and dyslipidemia), and directly, among others, by the production of adipokines and pro-inflammatory cytokines which in turn induce oxidative stress leading to reduced NO availability. Hyperinsulinemia in both HT and OB subjects has an adverse effect on lipid metabolism characterised by increased accumulation of abdominal fat and dyslipidemia, resulting in a vicious circle of events further promoting metabolic imbalance and potentiating proatherogenic effect of high blood pressure [27].

Surprisingly, almost $\frac{2}{3}$ of HT patients displayed ≥ 3 traits of the metabolic syndrome. Previously, these subjects were indicated as “metabolic obese normal weight” [28–30] and they are predisposed to insulin resistance owing to a higher amount of body fat or different body fat distribution. In our previous study, we examined abdominal fat distribution using magnetic resonance imaging (MRI) in young lean patients with hypertension and we did not find any differences in subcutaneous or visceral adipose tissue amount [31]. Further studies are warranted to elucidate if total body fat content or fat content in different organs such as liver or skeletal muscle can play a role in IR development in lean HT patients.

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Conflict of Interest

None.

Conclusion and Relevance to Practice

In conclusion, our results demonstrate that young lean patients with HT without other risk factors including obesity, higher age, or smoking display signs of insulin resistance. These parameters were similar to the obese but otherwise healthy individuals. Most young HT and OB subjects presented features of the metabolic syndrome. Our results indicate that evaluation of glucose tolerance and insulin concentrations at least in fasting state may represent an early step to identify high-risk subjects. These young individuals from the HT and OB groups represent another target group in which identification of impaired insulin action and incipient metabolic syndrome is necessary for early intervention, such as lifestyle changes and pharmacological treatment.

Zusammenfassung und Relevanz für die Praxis

Zusammenfassend zeigen unsere Ergebnisse, dass bei jungen schlanken Patienten mit HT ohne weitere Risikofaktoren wie Übergewicht, höheres Alter oder Rauchen Anzeichen von Insulinresistenz vorhanden sind. Diese Parameter waren ähnlich wie die der übergewichtigen, aber sonst gesunden Personen. Die meisten der jungen HT- und OB-Probanden zeigen Merkmale des Metabolischen Syndroms. Unsere Ergebnisse deuten darauf hin, dass die Auswertung der Glukosetoleranz und Insulinkonzentrationen zumindest in nüchternem Zustand einen frühzeitigen Schritt zur Identifikation der Probanden mit hohem Risiko darstellen kann. Diese jungen Menschen aus der HT- und OB-Gruppe repräsentieren eine weitere Zielgruppe, in der die Identifizierung der gestörten Insulinwirkung und des beginnenden Metabolischen Syndroms für ein frühzeitiges Eingreifen erforderlich ist, wie zum Beispiel die Lebensstiländerung oder medikamentöse Behandlung.

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