INSULIN RESISTANCE IN PATIENTS WITH TYPE 1 DIABETES: RELATIONSHIP WITH METABOLIC AND INFLAMMATORY PARAMETERS

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SUMMARY – Although insulin resistance is usually associated with the development of type 2 diabetes, it can also be a feature of patients with type 1 diabetes. Insulin resistance has been documented in type 1 diabetes and may contribute to the high risk of cardiovascular disease in this population. To investigate the relationship of insulin resistance with metabolic and inflammatory parameters we divided 304 patients according to median estimated glucose disposal rate (eGDR=9.72 $mgkg^{-1}min^{-1}$) into lower (n=153) and higher (n=151) insulin sensitivity groups. Patients with lower insulin sensitivity had higher levels of serum lipids (except for HDL cholesterol), duration of diabetes, daily insulin dose, white blood cell count, C-reactive protein, homocysteine and ferritin. Spearman correlation analysis showed significant associations between individual components of insulin resistance and various metabolic and inflammatory parameters. Multiple logistic regression models found significant association of age, sex, duration of diabetes, serum lipids, daily insulin dose, white blood cell count and ferritin with progression to insulin resistance. The presence of insulin resistance indicates a greater risk of micro- and macrovascular disease and health care professionals need to be alerted that this subset of individuals with type 1 diabetes will require stringent control of hypertension, glycemia and serum lipids.

Key words: *Type 1 diabetes; Insulin resistance; Metabolic syndrome*

Introduction

Insulin resistance could be defined as the metabolic state in which the measured tissue response to insulin is less than that expected for the apparently available insulin. It could be caused by various genetic and acquired conditions, including insulin receptor gene, glucose transporters and signaling protein mutations, insulin receptor antibodies, inactivity, age, glucotoxicity and lipotoxicity[1]. Insulin resistance is the central pathophysiological phenomenon of metabolic syndrome, characterized by clustering of independent cardiovascular risk factors including impaired glucose regulation, central obesity, dyslipidemia, and hypertension[2-4]. Insulin resistance has been shown to confer an increased risk of cardiovascular disease both in the general population and in diabetic patients[5].

Although insulin resistance is usually associated with the development of type 2 diabetes, it can also be a feature of patients with type 1 diabetes[6,7]. Insulin resistance is an independent risk factor for development of type 1 diabetes and contributes to the prediction of disease alongside other risk factors, such as islet antibody number and titer, and HLA haplotypes[8,9]. Newly diagnosed patients with type 1 diabetes and insulin resistance have also a lower frequency of entering the "honeymoon phase"[10]. Type 1 diabetic sub-

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jects with insulin resistance show lower tissue levels of insulin receptor[11], GLUT-4 glucose transporter[12], and lower circulating levels of insulin-like growth factor 1 (IGF-1)[13].

Insulin resistance is an independent risk factor for micro- (nephropathy, neuropathy and retinopathy) and macro- (coronary artery disease and peripheral vascular disease) vascular complications in patients with type 1 diabetes[7,9,14]. Various factors may contribute to the high risk of cardiovascular disease in this population. The relation between insulin resistance and hypertension is well established[15]. Insulin is a vasodilator when given intravenously, with secondary effects on sodium reabsorption in the kidney[16]. In insulin resistance state, the vasodilatory effect of insulin can be lost[17], but the renal effect on sodium reabsorption is preserved[18]. Increases in angiotensinogen, resistin, and leptin secretion from adipose tissue have also all been implicated in the pathophysiology of hypertension[19]. Increases in prothrombotic factors, serum viscosity, uric acid, homocysteine, white blood cell count, C-reactive protein (CRP), albuminuria, non-alcoholic fatty liver disease and decreased circulating concentrations of adiponectin are all associated with insulin resistance[2]. Elevated levels of free fatty acids associated with insulin resistance cause endothelial dysfunction characterized by reduced production of nitric oxide, and the resultant decrease in nitric oxide bioactivity is important in the initiation and progression of atherosclerosis[20]. Cross-talk between inflammatory-signaling pathways and insulin-signaling pathways causes both metabolic insulin resistance and endothelial dysfunction that synergize to predispose to cardiovascular disorders[21]. The prevalence of insulin resistance in type 1 diabetes is currently around 20%, and it is continuing to rise reflecting the increasing rates of obesity[22,23].

Clinically, insulin resistance in type 1 diabetic patients is often recognized by their larger requirements for insulin, but more recently a validated method for estimated glucose disposal rate (eGDR), which has been previously validated by euglycemic-hyperinsulinemic clamp studies, has been developed[24]. This clinical score, based on hypertension, waist to hip ratio (WHR) and hemoglobin A1c (HbA1c), has recently been used in a number of large epidemiological studies for noninvasive assessment of insulin sensitivity in patients with type 1 diabetes[22,25-28].

The aim of this study was to determine the relationship between insulin resistance and metabolic and inflammatory parameters as well as associations between these parameters and progression to insulin resistance in type 1 diabetic patients.

Subjects, Materials and Methods

The study included 304 euthyroid type 1 diabetic patients. Type 1 diabetes was defined as the onset of diabetes before age 35 years, positive autoantibodies (ICA, GAD, or IA-2) and permanent insulin treatment initiated within 1 year of diagnosis. The study included patients with the following characteristics: age 18-65 years, minimum duration of type 1 diabetes of 1 year, no medical history of disorders of thyroid and adrenal glands, no medical history of liver, renal and cardiovascular diseases or electrocardiogram (ECG) evidence of ischemic heart disease, absence of any systemic disease, and absence of any infections in the previous month. Patients were excluded from the study if they took any of the following: lipid-lowering therapy, thyroid hormone therapy, medications that might affect glucose metabolism and insulin sensitivity such as glucocorticoids, oral contraceptives as well as patients taking oral glucose-lowering medication. To avoid influence of hypo- or hyperthyroidism on serum lipids, all patients had strictly normal thyroid function (TSH 1.9±0.9 mIU/L (0.4-4.0), FT3 5.4±0.9 pmol/L (2.8-8.2), and FT4 13.5±2.4 pmol/L (8.4-22.0)).

Basic anthropometric measurements were performed on all study subjects; WHR was calculated from the waist circumference (measured on bare skin as the narrowest circumference between the 10th rib and the iliac crest with tailor meter) and hip circumference (at the widest point of the gluteal muscles) and expressed in centimeters; weight was measured by the physician using a balanced-beam scale with light clothing without shoes and expressed in kilograms (kg); height was measured using a wall mounted stadiometer and expressed in centimeters (cm); and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). After a resting period of 30 minutes, blood pressure was measured twice in sitting position with

a mercury sphygmomanometer. Fasting venous blood samples were collected in the morning between 08:00 and 09:30 a.m. after overnight fast for determination of HbA1c (%), total cholesterol (mmol/L), high density lipoprotein (HDL) cholesterol (mmol/L), low density (LDL) cholesterol (mmol/L), very low density (VLDL) cholesterol (mmol/L), triglycerides (mmol/L), fasting glucose (mmol/L), homocysteine (μmol/L), C-reactive protein (CRP) (mg/L), ferritin (μg/L), and white blood cell count (WBC) ($x10^9$).

CRP and HbA1c were measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Results of HbA1c (%) are expressed in the DCCT-equivalent. Glucose, cholesterol and triglycerides in serum were measured with an enzymatic colorimetric method. Complete blood cell count was determined on an automatic blood counter (Advia 120, Siemens Diagnostic Solutions, USA). eGDR (estimated glucose disposal rate) as a measure of insulin sensitivity is calculated using the equation: 24.31-12.2x(WHR)-3.29x(AHT)-0.57 x(HbA1c), where the units are $mgkg^{-1}min^{-1}$; WHR indicates the waist to hip ratio, AHT indicates blood pressure, and is expressed as: 0-no or 1-yes. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication. This equation was derived from a substudy of 24 EDC (Epidemiology of Diabetes Complications) participants (12 men and 12 women drawn from low, middle and high age-specific tertiles of insulin resistance risk factors in order to represent the spectrum of insulin resistance) who underwent euglycemic-hyperinsulinemic clamp studies[25].

The study protocol complied with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethics committees.

All statistical analyses were performed with the SAS statistical program, version 9.1.3 (SAS Institute, Cary, NC, USA). Data were expressed as mean ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Differences between groups were examined, depending on the nature of data, by parametric (t-test) or nonparametric tests (Mann-Whitney). Correlations between individual components of insulin resistance and inflammatory and metabolic variables were determined using Spearman rho test. A multiple logistic regression analysis was performed to determine independent predictors of insulin resistance. A p value of less than 0.05 ($p<0.05$) was considered statistically significant.

Results

The main clinical and laboratory features of the study subjects are listed in Table 1. The mean age of our patients was 38±11 years, and 54.5% were males. Median of BMI, waist circumference, systolic and diastolic blood pressure was in the reference range for subjects with diabetes. Median of eGDR was 9.72 $mgkg^{-1}min^{-1}$ (interquartile range 3.9-12.7). There were

Table 1. Clinical and metabolic characteristics of study patients

Variable	Value
Age (yrs)	38±11
Duration of diabetes (yrs)	15±10
BMI (kg/m^2)	24 (15-37)
Waist circumference (cm)	81 (61-111)
WHR	0.82±0.07
HbA1c (%)	7.08 (4.4-14.2)
SBP (mmHg)	122 (90-180)
DBP (mmHg)	80 (50-110)
Heart rate (beats/min)	75±13
e-GDR ($mg/kg^{-1}min^{-1}$)	9.72 (3.9-12.7)
Total cholesterol (mmol/L)	5.0±0.8
LDL-cholesterol (mmol/L)	2.8±0.7
HDL-cholesterol (mmol/L)	1.66 (0.7-3.6)
VLDL-cholesterol (mmol/L)	0.41 (0.1-1.9)
Triglycerides (mmol/L)	0.91 (0.3-5.0)
Fasting glucose (mmol/L)	6.2±2.3
Daily insulin dose (units/day)	43±14
Homocysteine (μmol/L)	9.7 (4.8-127)
C-reactive protein (mg/L)	0.9 (0.1-33.7)
Ferritin (μg/L)	76 (7-448)
Creatinine (μmol/L)	92±15
RBC ($x10^{12}/L$)	4.6±0.4
Hemoglobin (g/L)	140±15.8
WBC ($x10^9/L$)	6.7±2.1

BMI = body mass index; WHR = waist to hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; eGDR = estimated glucose disposal rate; RBC = red blood cells; WBC = white blood cells

Table 2. Clinical and metabolic characteristics of patients depending on the level of insulin sensitivity

	eGDR <9.72	eGDR ≥9.72	*P*
Sex (m/f)	99/52	67/86	<0.001
Age (yrs)	40±12	35±9	<0.001
Duration of diabetes (yrs)	17±10	14±9	0.01
BMI (kg/m^2)	25 (17-37)	23 (15-33)	<0.001
Total cholesterol (mmol/L)	5.2±0.9	4.8±0.7	<0.001
LDL-cholesterol (mmol/L)	2.9±0.7	2.6±0.6	<0.001
HDL-cholesterol (mmol/L)	1.58 (0.7-3.6)	1.76 (0.7-3.6)	<0.001
VLDL-cholesterol (mmol/L)	0.50 (0.2-1.9)	0.35 (0.1-1.0)	<0.001
Triglycerides (mmol/L)	1.10 (0.4-5.0)	0.76 (0.3-3.6)	<0.001
Fasting glucose (mmol/L)	6.9±2.5	5.6±2.0	<0.001
Daily insulin dose (units/day)	47±14	38±12	<0.001
Homocysteine (μmol/L)	10 (4-127)	9 (4-41)	0.007
C-reactive protein (mg/L)	1.1 (0.1-33)	0.8 (0.1-21)	0.03
Ferritin (μg/L)	94 (9-448)	45 (7-404)	<0.001
WBC (x10^9/L)	7.1±2.0	6.3±2.1	<0.001

BMI = body mass index; eGDR = estimated glucose disposal rate; WBC = white blood cells

153 patients with lower insulin sensitivity (eGDR <9.72 mgkg^{-1}min^{-1}) and 151 with higher insulin sensitivity (eGDR ≥9.72 mgkg^{-1}min^{-1}). Patients with lower insulin sensitivity were older and had a longer duration of diabetes. BMI, heart rate, total, LDL and VLDL-cholesterol, triglycerides, daily insulin dose, homocysteine, CRP, ferritin, and WBC were significantly higher in patients with lower insulin sensitivity (Table 2). Conversely, HDL cholesterol was significantly lower in patients with lower insulin sensitivity.

Table 3. Spearman correlation analysis of associations between individual components of insulin resistance with metabolic and inflammatory variables

	Waist to hip ratio	HbA1c	Hypertension
Age	0.13*	– 0.10	0.29*
Duration of diabetes	0.10	– 0.08	0.20*
BMI	0.34*	– 0.08	0.25*
Total cholesterol	0.06	0.14*	0.21*
LDL-cholesterol	0.17*	0.14*	0.15*
HDL-cholesterol	– 0.28*	– 0.13*	0.06
VLDL-cholesterol	0.17*	0.33*	0.15*
Triglycerides	0.18*	0.31*	0.15*
Fasting glucose	0.07	0.16*	0.06
Daily insulin dose	0.14*	– 0.17*	0.08
Homocysteine	0.07	– 0.14*	0.08
C-reactive protein	– 0.03	0.13*	– 0.01
Ferritin	0.44*	– 0.02	0.13*
WBC	0.16*	0.18*	– 0.02

BMI = body mass index; WBC = white blood cells; *<0.05

Associations of individual components of insulin resistance with anthropometric, metabolic and inflammatory parameters are presented in Table 3. Age, LDL, HDL, VLDL-cholesterol, triglycerides, insulin dose, ferritin and WBC were significantly associated with WHR, with ferritin showing the strongest correlation (r=0.44, p<0.001). In addition, HbA1c correlated significantly with even 11 parameters (heart rate, total, LDL, HDL and VLDL-cholesterol, triglycerides, fasting glucose, daily insulin dose, homocysteine, CRP and WBC). The magnitude of these associations was strongest for VLDL-cholesterol and triglycerides (r=0.33 and 0.31, respectively, p<0.001). Finally, blood pressure significantly correlated with 8 parameters (age, duration of diabetes, BMI, total, LDL and VLDL-cholesterol, triglycerides and ferritin). The magnitude of these associations was strongest for age and BMI (r=0.29 and 0.25, respectively, p<0.001).

From multivariate analysis results (Table 4), progression to insulin resistance in type 1 diabetes was associated with sex, age, duration of diabetes, BMI, total, LDL, HDL and VLDL-cholesterol, triglycerides, fasting glucose, daily insulin dose, ferritin and

Table 4. Multiple logistic regression analysis of risk predictors of insulin resistance in patients with type 1 diabetes

	OR	95% CI	*P*
Sex (M)	2.44	1.53-3.88	<0.001
Age (yrs)	1.03	1.01-1.05	0.001
Duration of diabetes (yrs)	1.03	1.00-1.05	0.01
BMI (kg/m^2)	1.18	1.09-1.28	<0.001
Total cholesterol (mmol/L)	1.68	1.28-2.21	<0.001
LDL-cholesterol (mmol/L)	1.93	1.38-2.70	<0.001
HDL-cholesterol (mmol/L)	0.49	0.30-0.81	0.006
VLDL-cholesterol (mmol/L)	35.2	10.3-120.3	<0.001
Triglycerides (mmol/L)	4.96	2.83-8.69	<0.001
Fasting glucose (mmol/L)	1.26	1.13-1.41	<0.001
Daily insulin dose (units/day)	1.05	1.03-1.07	<0.001
Homocysteine (μmol/L)	1.08	0.99-1.17	0.05
C-reactive protein (mg/L)	1.05	0.97-1.13	0.17
Ferritin (μg/L)	1.00	1.00-1.00	0.001
WBC (x10^9/L)	1.20	1.07-1.34	0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; eGDR = estimated glucose disposal rate; WBC = white blood cells

WBC. CRP was not associated with progression to insulin resistance, and there was a tendency to statistically significant associations of homocysteine with progression to insulin resistance.

Discussion

Insulin resistance is the central pathophysiological phenomenon of metabolic syndrome[2], characterized by clustering of independent cardiovascular risk factors including impaired glucose regulation, central obesity, dyslipidemia, and hypertension[3]. In both type 1 and type 2 diabetes, the role of insulin resistance seems to be equally important as a cardiovascular risk factor[25,29]. In subjects with type 1 diabetes, insulin resistance is an independent risk factor for the micro- (nephropathy, neuropathy and retinopathy)[27,30] and macro- (coronary artery disease and peripheral vascular disease)[25,31] vascular complications, and liver disease[32]. In this study we documented significant associations of insulin resistance with various metabolic and inflammatory parameters in euthyroid subjects with type 1 diabetes without medical history of liver, renal and cardiovascular diseases and without lipid-lowering therapy.

It was shown that men and women with type 1 diabetes had a similarly increased risk of premature cardiovascular disease, although risk factors varied in both sexes[25]. However, in our study, the mean eGDR was lower in men than women, and on multivariate regression analysis sex, age and duration of diabetes were significantly associated with the risk of insulin resistance. Duration of diabetes was found to be a stronger predictor of metabolic syndrome in patients with type 1 diabetes[23]. The prevalence of metabolic syndrome increased from 7% in patients with diabetes for less than 7 years to 30% in patients with diabetes type 1 for more than 20 years[23]. In contrast, it was shown that duration of diabetes was not associated with insulin resistance in patients with type 2 diabetes[33].

When insulin resistance develops, the increased amount of lipolysis of stored triacylglycerol molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin. With increases in free fatty acid flux to the liver, increased production of triglyceride-rich VLDL, the precursor particles of LDL cholesterol, occurs[34,35]. Despite the increased production of LDL particles, LDL concentrations remain essentially unchanged in subjects with insulin resistance because of a decrease in cholesterol content of LDL particle, resulting in higher concentrations of more atherogenic small dense LDL particles[2,36]. Another major lipoprotein

disturbance in the insulin resistant state is change in HDL composition and metabolism resulting in an increased clearance of HDL from circulation[37,38]. Cardioprotective functions of HDL particles include direct inhibition of proatherogenic processes, prevention of monocyte adhesion and chemotaxis, and inhibition of endothelial dysfunction and apoptosis[38]. We found that patients with lower insulin sensitivity had significantly higher levels of total, LDL and VLDL cholesterol and triglycerides, and significantly lower levels of HDL cholesterol. Moreover, all lipid parameters were associated with individual components of insulin resistance as well as with progression to insulin resistance in our subjects.

Increased concentrations of prothrombotic factors, WBC, CRP and homocysteine are associated with decreased insulin sensitivity in patients with diabetes[2]. WBC, a potential marker for both the inflammatory and infective components of atherosclerosis, was significantly higher in our patients with lower insulin sensitivity. Moreover, it was shown that WBC was an important risk factor in the pathogenesis of nephropathy in type 1 diabetes[39], and an independent predictor of cardiovascular mortality[40]. More than 20 prospective epidemiologic studies have demonstrated that CRP is an independent predictor of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even in apparently healthy individuals[41]. However, 46.4% of our patients with lower insulin sensitivity had plasma CRP level less than 1 mg/L, which represents low risk of subsequent cardiovascular diseases[42]. In our study, patients with lower insulin sensitivity had significantly higher levels of CRP and WBC, but multivariate logistic regression analysis found only WBC to be a risk predictor of progression to insulin resistance.

A meta-analysis of 27 studies relating homocysteine, an intermediate in the catabolism of methionine, to coronary, cerebrovascular and peripheral arterial vascular diseases showed a very strong relationship between these diseases and homocysteine[43]. Despite the increase in cardiovascular risk found in diabetic patients compared with their nondiabetic counterparts, a clear relationship between homocysteine levels and diabetes has not been established. There are reports on positive, negative, as well as no relationship between insulin resistance and plasma homocysteine levels[44]. In our study, patients with lower insulin sensitivity had a significantly higher level of homocysteine, but logistic regression models found no significant association between serum homocysteine and progression to insulin resistance.

Patients with lower insulin sensitivity required a significantly higher dosage of insulin for glucoregulation. It was shown that total daily insulin dose correlated with insulin resistance[24], but it was a poor predictor of future complications in type 1 diabetes compared to insulin resistance assessed by eGDR[23]. It was shown that, although the excess weight gain with intensive insulin therapy was associated with increases in visceral adiposity[45], intensive treatment greatly reduced the long-term risk of cardiovascular disease by 42%[46]. In our study, multivariate logistic regression models found significant association between daily insulin dose and progression to insulin resistance.

Several studies have reported an association between serum ferritin, one of the key proteins regulating iron homeostasis, and insulin resistance[47], and it was found that ferritin had strong associations with obesity, inflammation, risk of type 2 diabetes, hyperglycemia, and metabolic syndrome[48]. Moreover, an insulin resistance phenotype has been associated with liver iron overload, and it is characterized by normal transferrin saturation and high ferritin in patients without genetic hemochromatosis[49]. It has been hypothesized that the formation of hydroxyl radicals catalyzed by iron, which are powerful prooxidants that attack cellular membrane lipids, proteins, and nucleic acids, contributes initially to insulin resistance[50]. In our study, patients with lower insulin sensitivity had higher levels of ferritin, and ferritin was a risk predictor of progression to insulin resistance.

In conclusion, we documented significant associations between insulin resistance and various metabolic and inflammatory parameters in type 1 diabetic patients. All these parameters could contribute to the propensity to develop micro- and macrovascular diseases. Health care professionals need to be alerted that this subset of individuals with type 1 diabetes will require stringent control of hypertension, glycemia and serum lipids. Interventions such as exercise, weight loss, improved glycemic control, and insulin-sensitizing medications can be considered to improve insulin resistance.

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Sažetak

INZULINSKA REZISTENCIJA U TIPU 1 ŠEĆERNE BOLESTI: POVEZANOST S METABOLIČKIM I UPALNIM PARAMETRIMA

T. Bulum i *L. Duvnjak*

Inzulinska rezistencija u tipu 1 šećerne bolesti dokazano doprinosi povećanom riziku razvoja kardiovaskularne bolesti. U ovoj studiji istraživana je razina inzulinske osjetljivosti koristeći kliničke parametre (eGDR) u bolesnika sa šećernom bolešću tipa 1 i istraživan je odnos razine inzulinske osjetljivosti s metaboličkim i upalnim parametrima. Od 304 bolesnika uključena u studiju njih 153 imalo je nižu inzulinsku osjetljivost (eGDR<9.72 $mgkg^{-1}min^{-1}$), a 151 bolesnik imao je višu inzulinsku osjetljivost (eGDR≥9.72 $mgkg^{-1}min^{-1}$). Bolesnici s nižom razinom inzulinske osjetljivosti imali su značajno više vrijednosti lipida u serumu (osim HDL kolesterola), indeks tjelesne težine, trajanje šećerne bolesti te upalne parametre, a svi navedeni čimbenici zajedno i pojedinačno doprinose razvoju mikro- i makrovaskularnih komplikacija u osoba oboljelih od šećerne bolesti tipa 1. Multiplom logističkom regresijom dokazano je da na razvoj inzulinske rezistencije u šećernoj bolesti tipa 1 utječu spol, godine života, trajanje šećerne bolesti, serumski lipidi, glikemija natašte, dnevna doza apliciranog inzulina i leukociti. Inzulinska rezistencija u tipu 1 šećerne bolesti doprinosi povećanom riziku razvoja mikro- i makrovaskularnih komplikacija, a ti pojedinci unutar skupine bolesnika sa šećernom bolešću tipa 1 zahtijevaju strožu kontrolu povišenog krvnog tlaka, glikemije i serumskih lipida.

Key words: *Šećerna bolest tip 1; Inzulinska rezistencija; Metabolički sindrom*