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Source / Izvornik: **Collegium Antropologicum, 2012, 36, 1373 - 1378**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:100433

Coll. Antropol. **36** (2012) 4: 1373–1378
Original scientific paper

The Metabolic Syndrome is Associated With High-normal Urinary Albumin Excretion and Retinopathy in Normoalbuminuric Type 1 Diabetic Patients

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A B S T R A C T

Although metabolic syndrome was not extensively studied in type 1 diabetes, higher insulin resistance, the core feature of the syndrome was found to be associated with increased risk of developing microvascular complications. As diabetic nephropathy may progress to advanced lesion before microalbuminuria appears, we investigated the association of the metabolic syndrome and estimated glucose disposal rate (eGDR) with urinary albumin excretion (UAE), retinopathy and neuropathy in normoalbuminuric type 1 diabetic patients. Two hundred and 98 patients (UAE <30 mg / 24 h at three occasions) were divided according to the IDF metabolic syndrome; eGDR (mg kg^{-1} min^{-1}) was calculated: 24.31–(12.22 × WHR) – (3.29 × HT) – (0.57 × HbA1c), (WHR=waist-to-hip ratio, HT=hypertension). Patients with (n=99) compared to those without metabolic syndrome (N=199) showed higher UAE (15.96±9.10; 13.48±8.36 mg / 24 h), C-reactive protein (2.39±4.09;1.12±2.03 mg/L), prevalence of retinopathy (70.7;55.27%) and polyneuropathy (80.8; 68.3%), and lower eGDR (5.75±1.74; 8.96±1.9), (p>0.05). In patients with high-normal UAE, retinopathy and polyneuropathy eGDR was significantly lower compared with patients with low-normal UAE, and without retinopathy and polyneuropathy. In multiple regression analysis UAE and retinopathy were associated with diabetes duration (β= –0.20, β= –0.62), eGDR (β= – 0.106; β= –0.041), metabolic syndrome (β=0.49, β=0.28), (p>0.05). In type 1 diabetic patients insulin resistance and IDF defined metabolic syndrome are associated with high-normal UAE, retinopathy and polyneuropathy. The predictive value of the metabolic syndrome for development of microalbuminuria and retinopathy needs to be assessed in further follow-up studies.

***Key words**: metabolic syndrome, diabetes type 1, microvascular complications, urinary albumin excretion, retinopathy*

Introduction

In spite of medical controversies surrounding its pathogenesis and clinical presentation, the metabolic syndrome has been widely accepted as an important risk factor for the development of type 2 diabetes and cardiovascular disease[1,2]. It is characterized by central obesity, dyslipidemia, impaired glucose metabolism and hypertension with insulin resistance representing a key part of the syndrome[3]. During the last decades other disturbances such as NASH, PCO, microalbuminuria, abnormalities in fibrinolysis and coagulation have been linked to the syndrome[1]. Although a number of these components can be found in type 1 diabetic patients, the prevalence and significance of the metabolic syndrome in type 1 diabetes has been less extensively studied[4,5].

Few studies have investigated the impact of the metabolic syndrome on the development of microvascular complications in type 1 diabetes[6–8].

Received for publication August 15, 2012

A recent introduction of a validated method for estimated glucose disposal rate (eGDR) has allowed easier assessment of insulin resistance by calculating a score based on clinical factors of the patient[9].

Higher insulin resistance calculated by eGDR was found to be associated with increased risk of developing both micro and macrovascular complications in type 1 diabetic patients[8]. Insulin resistance has been suggested to be implicated in the development of diabetic nephropathy.

Increased insulin resistance has been documented in type 1 diabetic patients with microalbuminuria and the metabolic syndrome has been more frequent in patients with advanced diabetic nephropathy. Insulin sensitivity has been shown to be more strongly associated with AER than creatinine clearance, confirming that the change in insulin sensitivity preceded the decline in creatinine clearance[10].

Emerging data indicate that the complex interrelations between insulin resistance and low-grade inflammatory markers contribute to the development of microalbuminuria as a manifestation of endothelial dysfunction[7,11,12].

On the other hand, the degree of albuminuria, as a hallmark of diabetic renal disease, is closely related to the progression of diabetic nephropathy. In type 1 diabetic patients high normal urinary albumin excretion UAE represents a significant predictive factor of progression to microalbuminuria[13,14].

In view of the fact that glomerular and arteriolar abnormalities have already been developed in microalbuminuric subjects, it would be of special clinical interest to investigate insulin resistance, inflammatory markers and the presence of the metabolic syndrome at the normoalbuminuric stage[11,15].

The present study was undertaken to characterise a large group of normoalbuminuric type 1 diabetic patients according to the presence of the metabolic syndrome and determine a possible association of the metabolic syndrome, eGDR and inflammatory markers with UAE, retinopathy and neuropathy.

Patients and Methods

Two hundred and 98 patients with type 1 diabetes (146 men, 152 women) hospitalized at the Inpatient Department of the »Vuk Vrhovac« University Clinic in the period between January 2008 and September 2010, were included in the study.

Type 1 diabetes was diagnosed according to the presence of either ICA or GAD antibodies. ICA (islet cell antibodies) were determined using indirect immuofluorescence technique (IIF) on human pancreatic frozen tissue (0 negative blood group). The determination was done in human serum of patients and visualization using fluorescence microscope.

GAD (glutamic acid decarboxylase) antibodies determination was performed using commercial ELISA kit (Euroimmun, Lubeck, Deutschland). Our laboratory that was performing the test has successfully participated in DASP – Diabetes Antibody Standardization Program, 2010[16].

The following inclusion criteria were used: diabetes duration >1 year, patient age >18 years, UAE <30 mg/24h measured on three occasions, and absence of acute or chronic inflammatory and renal disease. All patients were treated by intensive insulin therapy, and 94 among them were taking ACE inhibitors.

Patients were diagnosed with the metabolic syndrome according to the IDF definition when their waist circumference was ≥94 in men and ≥80 in women, and at least one of the following three criteria was met: 1) triglycerides ≥1.7 mmol/L or specific hypolipemic treatment; 2) HDL <1.03 mmol/L in men and <1.29 mmol/L in women, or specific hypolipemic treatment and 3) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or specific antihypertensive treatment. All patients were considered to fulfil the criterion of high blood glucose as defined by the IDF.

Estimated glucose disposal rate – eGDR was calculated using the equation: $eGDR = 24.31 - (12.22 \times WHR) - (3.29 \times HT) - (0.57 \times HbA1c)$. The units were mg kg^{-1} min^{-1}, WHR=waist-to-hip ratio, HT=hypertension.

This equation was derived from a substudy of 24 participants in the EDC Study who underwent euglycemic-hyperinsulinemic clamp studies[9]. Direct ophtalmoscopy was performed with dilated pupils by an experienced ophthalmologist especially trained in screening for and treatment of diabetic retinopathy. Retinopathy was classified according to the European Protocol[17].

Urinary albumin concentration and C-reactive protein were determined by an immunoturbidimetric assay (Olympus diagnostics, Lismeehan, Ireland)., as was glycosylated haemoglobin (HbA1c) (Bayer, Terrytown, USA).

Homocysteine was measured by chemiluminiscence on an ACS+189 analyzer (Bayer diagnostic, Tarrytown, USA).

The results are expressed as X±SD. Statistical analysis was performed by Student's t test (differences between the two groups), Pearson test (correlation) and multiple regression analysis (stepwise linear regression, beta indicating the regression coefficient), with $p<0.05$ considered to be statistically significant. The study protocol was reviewed and approved by the Clinic's Ethics Committee. All participants signed an informed consent on entry to the study.

Results

Clinical data of normoalbuminuric type 1 diabetic patients divided according to the presence of the metabolic syndrome are given in table 1. The prevalence of the metabolic syndrome as defined according to IDF criteria was 32.88%, amounting to 34.24% in men and 30.92% in women. Patients with the metabolic syndrome were ol-

TABLE 1
CLINICAL CHARACTERISTICS OF NORMOALBUMINURIC TYPE 1 DIABETIC PATIENTS DIVIDED ACCORDING TO THE PRESENCE OF THE METABOLIC SYNDROME

	Metabolic syndrome absent (N=199)	Metabolic syndrome present (N=99)	p
Age (years)	41±11.63	46±11.95	0.004
Gender M/F	96/146 (65.8%) – male 105/152 (69.1%) – female	50/146 (34.2%) – male 47/152 (30.9%) – female	NS
Duration of the disease (years)	17±10.23	20±9.68	0.05
BMI (kg/m^2)	23.32±2.62	27.26±3.56	0.0001
Waist (cm)	79.04±8.12	92. 89±10.49	
Men	85.33±8.22	97.17±8.56	0.0001
Women	82.1±6.2	87.77±10.19	
UAE (mg / 24h)	13.48±8.36	15.96±9.10	0.02
A1C (%)	7.71±1.5	7.8±1.43	NS
eGDR (mg kg^{-1} min^{-1})	8.96±1.9	5.75±1.74	0.0001
LDL cholesterol (mmol/L)	2.9±0.7	3.36±0.95	0.0001
HDL cholesterol (mmol/L)	1.61±0.45	1.47±0.47	0.02
Triglycerides (mmol/L)	1.0±0.52	1.55±1.14	0.0001
C-reactive protein	1.12±2.03	2.39±4.09	0.0001
Homocysteine	9.01±2.92	10.36±6.91	0.03
Systolic blood pressure (mmHg)	125.29±14.73	135.47±17.54	0.0001
Diastolic blood pressure (mmHg)	79.53±8.01	85.98±7.21	0.0001
Retinopathy	110/199 (55.3%)	70/99 (70.7%)	0.04
Polineuropathy	136/199 (68.3%)	80/99 (80.8%)	NS

Data are expressed as $\overline{X}$±SD, except for gender, retinopathy and polineuropathy

der, had a longer duration of the disease and showed lower eGDR, higher UAE, CRP and homocysteine value (Table 1). Prevalence of retinopathy in patients with the metabolic syndrome was significantly higher compared to those without the syndrome, while the prevalence of neuropathy did not reach the statistical significance (Figure 1).

Among patients with the metabolic syndrome, the most frequent combination of diagnostic criteria was waist circumference (as required by definition) hypertension and triglycerides, which was shown in 26.26% of patients. Waist circumference, hypertension and low HDL were seen in 21.21% of patients (Figure 2). In the study population a significant correlation between UAE and eGDR was found (Figure 3). In multiple regression analysis with age, duration of diabetes, eGDR, LDL level, CRP and homocysteine as independent variables, the presence of the metabolic syndrome was associated with age, duration of the disease, eGDR, CRP and LDL cholesterol.

In multiple regression analysis with age, duration of the disease, IDF metabolic syndrome, eGDR, LDL, CRP,

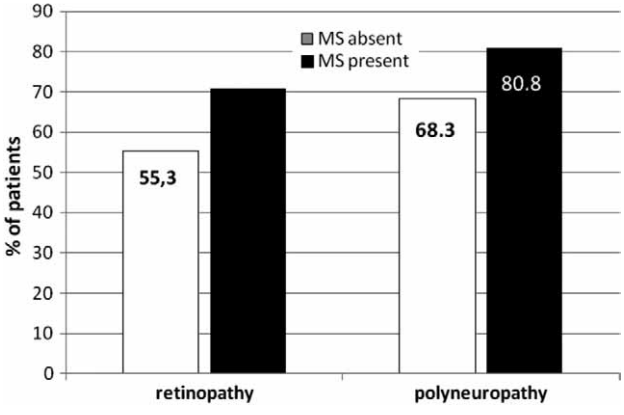

Fig. 1. Prevalence of retinopathy and polineuropathy in type 1 diabetic patients with and without metabolic syndrome.

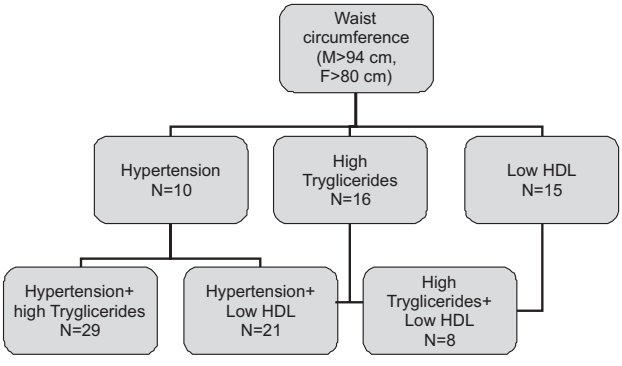

Fig. 2. Distribution of IDF criteria of the metabolic syndrome in 99 normoalbuminuric type 1 diabetic patients.

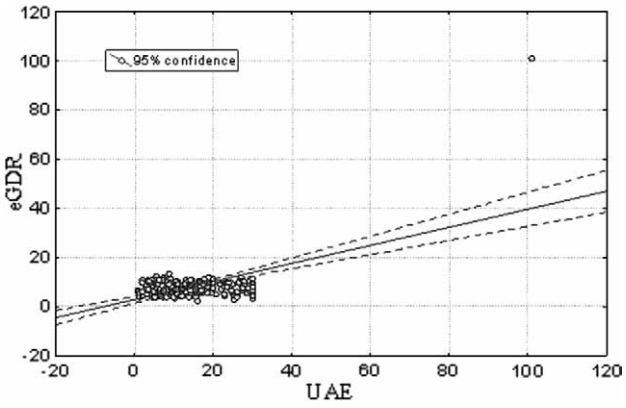

Fig. 3. Correlation between UAE and eGDR in normoalbuminuric Type 1 diabetic patients.

homocysteine, systolic and diastolic blood pressure and HbA1c as independent variables, UAE was associated with the duration of diabetes, eGDR, IDF metabolic syndrome and HbA1c.

In multiple regression analysis with age, duration of the disease, IDF metabolic syndrome, eGDR, LDL, CRP, homocysteine, systolic and diastolic blood pressure, UAE and HbA1c as independent variables, retinopathy was associated with the duration of diabetes, eGDR, IDF metabolic syndrome and HbA1c. In multiple regression analysis with age, duration of the disease, IDF defined metabolic syndrome, eGDR, LDL, CRP, homocysteine,systolic and diastolic blood pressure, UAE and HbA1c as independent variables, polineuropathy was associated with age, duration of diabetes, eGDR, IDF metabolic syndrome, LDL and HbA1c (Table 2).

Discussion

The results of the present study show that the metabolic syndrome is a frequent finding in type 1 diabetic patients. Although similar prevalence has previously been reported, this is the first study documenting the presence of the metabolic syndrome in a large number of strictly normoalbuminuric subjects with type 1 diabetes[7].

Patients with the metabolic syndrome were more likely to show increased insulin resistance, evidence of low-grade inflammation and high normal UAE compared to those without the syndrome.

The relationship between insulin resistance, inflammation and endothelial dysfunction in diabetes is complex[18–23].

As originally proposed by Steno investigators, microalbuminuria is a marker of vascular damage and is associated with the development of renal complications in diabetic patients[18]. Increased insulin resistance and inflammatory activity in type 1 diabetic patients with microalbuminuria have been previously demonstrated[11,12,18–23].

An analysis of the cross-sectional FinnDiane study showed lower eGDR and increased prevalence of the metabolic syndrome (defined according to NCEP criteria) in type 1 diabetic patients with microalbuminuria[7].

Increased CRP concentrations have been documented in type 1 diabetic patients with macro-and microalbuminuria[11,20].

The structural injury in diabetic nephropathy develops in silence over years and may have progressed to advanced lesion before a clinically detectable abnormality like microalbuminuria appears[23]. Thus, the temporal link between endothelial dysfunction, linked to insulin resistance and low-grade inflammation, and the appearance of microalbuminuria should be considered. Strategies to prevent diabetic nephropathy should focus on early factors that could influence the development of microalbuminuria.

According to the results of longitudinal studies high normal UAE, besides high blood pressure and poor glycaemic control, has been established as a significant predictive factor of progression to microalbuminuria[13,14]. The results of our study suggest a possible role of insulin resistance and CRP, the acute phase reactant and a very sensitive marker of acute inflammatory reaction in predicting the progression of high-normoalbuminuric stage to microalbuminuria.

It has been previously suggested that endothelial dysfunction might precede microalbuminuria by two or three years[25].

TABLE 2
RESULTS OF MULTIPLE REGRESSION ANALYSIS IN NORMOALBUMINURIC TYPE 1 DIABETIC PATIENTS

	Independent variables						
Dependent variables	Age	Duration of diabetes	eGDR	CRP	LDL	HbA1c	Metabolic syndrome
UAE		β= –0.20 (p=0.0001)	β= –0.106 (p=0.01)			β=0.107 (p=0.001)	β=0.49 (p=0.0001)
Retinopathy		β= –0.62 (p=0.0001	β= –0.041 (p=0.002)			β=0.049 (p=0.02)	β=0.28 (p=0.0001)
Polineuropathy	β= –0.24 (p=0.0001)	β= –0.34 (p=0.0001)	β= –0.049 (p=0.0001)		β=0.088 (p=0.025)	β=0.055 (p=0.004)	β=0.218 (p=0.0001)

* β – regression coefficient

A small study on 16 patients has demonstrated increased insulin resistance before the development of microalbuminuria[26].

We gave evidence in a large number of normoalbuminuric type 1 diabetic patients of the presence of increased insulin resistance already at the normoalbuminuric stage. Our data demonstrate a close link between chronic glucose exposure, insulin resistance and inflammation.

The results of multiple regression analysis showed an independent relation of diabetes duration, CRP and eGDR with the presence of the metabolic syndrome, suggesting that chronic exposure to glucose may stimulate the increase in insulin resistance and induce inflammatory activity. Insulin resistance, as a core of the metabolic syndrome, generates visceral adiposity, dyslipidemia and hypertension, the well known clinical manifestations of the condition[3,4]. Insulin resistance, inflammation and endothelial dysfunction are interrelated. As they progress with time, it is not possible to determine which factor precedes the others[28–30].

However, our results suggest that insulin resistance and low grade inflammation might induce endothelial dysfunction, manifested by the elevation of UAE within the normoalbuminuric range.

As the metabolic syndrome, eGDR and CRP represent potentially modifiable risk factors, their detection in patients with high-normal UAE can be of clinical significance. The results of the presents study suggest that strategies to decrease insulin resistance and inflammatory activity, and improve endothelial function should be introduced early in the course of the disease. Introducing appropriate therapy at this stage, beside the one aimed at treating conventional risk factors, could stop or delay the progression to microalbuminuria.

We have also noticed that normoalbuminuric type 1 diabetic subjects with the metabolic syndrome showed increased prevalence of retinopathy and neuropathy in comparison to those without the syndrome. These findings are consistent with those from the Metascreen, a multicenter diabetes clinic-based survey. This cross-sectional study found the metabolic syndrome, defined according to IDF or AHA/NHLBI criteria, to be an independent indicator of the presence of nephropathy and neuropathy in type 1 diabetes[6]. A strong association between the waist-to-hip ratio and triglyceride level, both components of the metabolic syndrome, and retinopathy has also been previously reported[30]. In this study, insulin resistance has been suggested as a unifying feature of these factors to account for their relationship with retinopathy[28].

A direct impact of insulin resistance on the pathogenesis of microangiopathy has been suggested[27–29]. Pathway-selective insulin resistance in the phosphatidylinositol-3-kinase signaling pathway with uneffected extracellular signal-regulated kinase-dependent pathway tips the balance of insulin action in favour of abnormal vasoreactivity and angiogenesis leading to microangiopathy[27].

Kilpatrick also found lower eGDR to be associated with increased risk of both micro- and macrovascular complications[8].

In contrast to other studies, this analysis of the DCCT found the IDF definition of the metabolic syndrome to be of little clinical utility in distinguishing type 1 diabetic patients prone to developing micro- or macrovascular complications[8]. Poor predictive outcome was attributed to the fact that the metabolic syndrome was primarily intended for type 2 diabetic patients. The lack of specificy of the IDF definition in identifying type 1 diabetic patients at an increased risk of developing complications was linked to the lower waist circumference tresholds used.

However, our results have shown that beside eGDR, metabolic syndrome itself might be an indicator of microvascular complications.

The metabolic syndrome may represent a simple tool to stratify type 1 diabetic patients according to the expected development of microalbuminuria and retinopathy. Considering the high morbidity rate of diabetic microvascular complications, the focus of therapeutic interventions needs to shift from the treatment of late-stage disease to the prevention[31–32].

Although it is obvious that the complex pathogenesis of diabetic microvascular complications will remain unclarified in clinical trials, our data may help clinicians in approaching type 1 diabetic patients with the metabolic syndrome.

The presence of the metabolic syndrome at the normoalbuminuric stage might point to patients at an increased risk of developing microalbuminuria and retinopathy, which needs to be clarified in future follow-up studies of normoalbuminuric patients.

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METABOLIČKI SINDROM JE POVEZAN S VISOKO NORMALNIM IZLUČIVANJEM ALBUMINA U MOKRAĆI TE RETINOPATIJOM U NORMOALBUMINURIČNIH BOLESNIKA SA ŠEĆERNOM BOLEŠĆU TIPA 1

S A Ž E T A K

Iako metabolički sindrom nije široko proučavan u šećernoj bolesti tipa 1, utvrđena je povezanost povećane inzulinske rezistencije, glavne odrednice sindroma, s povišenim rizikom razvijanja mikrovaskularnih komplikacija. Kako se dijabetička nefropatija može razviti do uznapredovalog oštećenja prije nego se pojavi mikroalbuminurija, istražili smo povezanost metaboličkog sindroma i procijenjene stope razdiobe glukoze (eGDR) s urinarnim izlučivanjem albumina (UAE), retinopatijom i neuropatijom u normalbuminuričnih bolesnika sa šećernom bolešću tipa 1. 298 bolesnika (UAE <30 mg / 24 h u tri mjerenja) podijeljeni su prema IDF (International Diabetes Federation) kriteriju na one s i one bez metaboličkog sindroma; eGDR (mg kg^{-1} min^{-1}) je izračunata: 24,31 – (12,22 × WHR) – (3,29 × HT) – (0,57 × HbA1c), (WHR=waist-to-hip ratio – omjer struk:bok, HT=hipertenzija). Bolesnici s (N=99) u usporedbi s onima bez metaboličkog sindroma (n=199) pokazali su povišene UAE (15,96±9.10; 13,48±8.36 mg / 24 h), C-reaktivni protein (2,39±4,09; 1,12±2,03 mg/L), prevalenciju retinopatije (70,7; 55,27%) i polineuropatiju (80,8; 68,3%), a nižu eGDR (5,75±1,74; 8,96±1,9), (p>0,05). Kod bolesnika s visoko-normalnim UAE, retinopatijom i polineuropatijom, eGDR je bila značajno niža u usporedbi s bolesnicima s nisko-normalnom UAE te bez retinopatije i polineuropatije. UAE i retinopatija su u multiploj regresijskoj analizi bili povezani s trajanjem dijabetesa (β= –0,20, β= –0,62), eGDR (β= –0,106; β= –0,041), metaboličkim sindromom (β=0,49, β=0,28), (p>0,05). U bolesnika sa šećernom bolešću tipa 1 inzulinska rezistencija i metabolički sindrom definiran po IDF-u bili su povezani s visoko-normalnom UAE, retinopatijom i polineuropatijom. Prediktivnu vrijednost metaboličkog sindroma za razvoj mikroalbuminurije i retinopatije treba procijeniti daljnjim istraživanjima.