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# Estimated Glucose Disposal Rate in Assessment of Renal Function in Patients with Type 1 Diabetes

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**A B S T R A C T**

*Insulin resistance has been documented in type 1 diabetes and may contribute to the high risk for cardiovascular disease in this population and progression of nephropathy. We investigated associations of renal parameters, including urinary albumin excretion rate (UAE), serum creatinine and creatinine clearance, with surrogate measure of insulin sensitivity calculated using a formula derived from euglycemic-hyperinsulinemic clamp studies (estimated glucose disposal rate, eGDR). Study included 353 patients with type 1 diabetes, none showed signs of adrenal, thyroid, renal, or cardiovascular diseases. Insulin sensitivity was measured with eGDR calculated with the equation: 24.31–(12.22×WHR)–(3.29×HT)–(0.57×HbA1c). The units were mgkg$^{-1}$min$^{-1}$; WHR=waist to hip ratio; HT=hypertension. Correlations and logistic regression analysis were performed to identify relationships between renal parameters and eGDR, individual components of insulin resistance and risk of insulin resistance. UAE and serum creatinine significantly correlated with insulin resistance measured by eGDR (r=–0.13, and –0.17, all p<0.05), and its components disorders, WHR and HbA1c. After stratifying patients in quartiles of eGDR, those in the upper quartile of the eGDR had significantly reduced levels of UAE and serum creatinine, compared to subjects in lowest quartile. In a logistic regression analysis risk for development of insulin resistance in our subjects were independently predicted only by UAE (odds ratio=1.01, p<0.01). Our results provide evidence of associations between insulin resistance and its components disorders with renal parameters, such as UAE and serum creatinine. Insulin resistance, measured with eGDR, predicts the increment in UAE in subjects with type 1 diabetes. Since progression to microalbuminuria is likely to occur in majority of diabetic patients, there is a need to further explore the role of risk factors such as insulin resistance.*

***Key words:*** *diabetes mellitus type 1, estimated glucose disposal rate, urinary albumin excretion, insulin resistance*

## Introduction

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[1,2]. Insulin resistance in subjects with type 1 diabetes may contribute to the high risk for cardiovascular disease and progression of nephropathy[2,3], because those subjects have elevated blood pressure, hyperglycemia, dyslipidemia, lowgrade inflammation, endothelial dysfunction, abnormalities in fibrinolysis and coagulation[4–7]. Three large prospective studies (Pittsburgh Epidemiology of Diabetes Complications, EURODIAB Prospective Complications Study and Diabetes Control and Complications Trial) have shown that insulin resistance is an independent risk factor for the micro- (nephropathy, neuropathy and retinopathy) and macro- (coronary artery disease and peripheral vascular disease) vascular complications in patients with type 1 diabetes[8,9]. Prevalence of insulin resistance in type 1 diabetes is currently around 20%, and it is continuing to rise reflecting the rising rates of obesity[10–12].

Clinically, insulin resistance in type 1 diabetic patients is often recognized by their larger requirements for insulin. However, more recently a validated method for estimated glucose disposal rate (eGDR), which has

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been previously validated by euglycemic-hyperinsulinemic clamp studies, has been developed[13]. 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 the non-invasive assessment of insulin sensitivity in patients with type 1 diabetes[10,14–17].

Identification of the determinants of the onset of early diabetic nephropathy is essential for reducing the morbidity and mortality associated with diabetes. Many studies have identified poor glycemic control as the most important risk factor for progression of diabetic kidney disease[18–20]. In addition, blood pressure was also higher in patients with higher albumin excretion rate compared to normoalbuminuric patients[21]. Prior studies have shown WHR to be a stronger predictor than overall adiposity of cardiovascular risk factors and complications in type 1 diabetes[22,23]. All this parameters are included in eGDR, because the physiological basis of insulin resistance being related to WHR, hypertension, and glucose intolerance is well founded and described[24]. Moreover, it was shown that higher insulin resistance at baseline, estimated by lower level of eGDR, was associated with increased subsequent risk of microvascular complications. In contrast, insulin dose and the presence of IDF-defined metabolic syndrome were poor predictors[10,17]. Based on this data, it appears that measurement of insulin sensitivity by eGDR can add to the prognostic value of albumin excretion in the prediction of subjects at risk of diabetic nephropathy.

Insulin resistance precedes and probably contributes to the development of microalbuminuria and progression of diabetic kidney disease in type 1 diabetic patients. The aim of this study, therefore, was to determine the level of insulin sensitivity in patients with type 1 diabetes using a surrogate measure of insulin resistance (eGDR), and to evaluate the associations of renal parameters, including urinary albumin excretion rate (UAE), serum creatinine and creatinine clearance with eGDR. We also explored relationship between renal parameters and individual components of insulin resistance, and whether disturbances of renal parameters were associated with progression to insulin resistance in subjects with type 1 diabetes.

## Subjects, Materials and Methods

This study included 353 euthyroid patients with diabetes mellitus type 1. Type 1 diabetes was defined as an onset of diabetes before the age of 35 years and permanent insulin treatment initiated within 1 year of diagnosis. Subjects with insulin-treated diabetes secondary to other pathologies were excluded. The study included patients following characteristics: age of 18–65 years, minimum duration of type 1 diabetes of 1 year, no medical history of disorders of thyroid and adrenal gland function, 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 with chronic renal disease or other chronic diseases likely to affect renal function were excluded. Patients were excluded from the study if they had taken 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. Acute and chronic inflammation was excluded on the basis of medical history, physical examination, and routine laboratory tests, including measurement of temperature and urinalysis.

All subjects were studied in the morning after an overnight fast. 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). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters ($kg/m^2$). Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 minutes and expressed in mmHg. UAE was measured from at least two 24-h urine samples and determined as the mean of 24-h urine collections. Patients performed collections on two consecutive days to minimize variability. Normoalbuminuria was defined as a UAE<30 mg/24h, and microalbuminuria as a UAE≥30<300 mg/24h. Those with macroalbuminuria (UAE≥300 mg/24h) were excluded from the study. To measure creatinine clearance, serum and 24-h urine samples were collected. Creatinine clearance was calculated from serum and urine creatinine concentrations and urine volume.

Fasting venous blood samples were collected in the morning between 08:00 and 09:30 hours after an overnight fast for the determination of HbA1c (%, reference range 3.5 to 5.7), high density lipoprotein (HDL) cholesterol (mmol/L, reference range >1.0 for men, >1.3 for women), low density (LDL) cholesterol (mmol/L, reference range <3.0), triglycerides (mmol/L, reference range <1.7), fasting glucose (mmol/L, reference range 3.0–6.1), serum creatinine (μmol/L, reference range 79–125), red blood cell count (RBC) ($\times 10^{12}$, reference range 4.34–5.72), hemoglobin (g/L, reference range 138–175), white blood cell count (WBC) ($\times 10^9$, reference range 3.4–9.7), and platelet ($\times 10^9$, reference range 158–424).

Microalbumin 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 by an enzymatic colorimetric method. Complete blood count was determined on an automatic blood counter (Advia 120, Siemens Diagnostic Solutions, USA). Measure of insulin sensitivity (eGDR) is calculated using the equation:

24.31–12.2×(WHR)–3.29×(AHT)–0.57×(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, 1-yes. Those on blood pressure medications or with blood pressure >140/90 mmHg were considered to have hypertension. 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[13]. It should be emphasized that lower eGDR levels indicate greater insulin resistance.

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

Differences between groups were examined, depending on the nature of the data, parametric (t-test) or nonparametric tests (Mann-Whitney). Correlations between parameters of renal function with anthropometric and metabolic variables were determined using Spearman rho test. To investigate the relation between renal parameters with insulin resistance data were also stratified in quartiles of eGDR. Kruskal-Wallis test was used for calculating the significance of the trend for each variable among the different quartiles. Logistic regression analysis was used to assess associations of renal parameters with risk of insulin resistance. Level of statistical significance was chosen to $\alpha=0.05$. Statistical analysis was performed by statistical package STATA/IC ver.11.1.

## Results

The characteristics of the study subjects are listed in Table 1. The average age was approximately 38 years, most were not overweight and 53% of subjects were male. Mean/median values of BMI, WHR, LDL, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, serum creatinine, UAE, and creatinine clearance were within the normal range for patients with diabetes. 83% of all patients had normoalbuminuria, 17% had microalbuminuria, and none had macroalbuminuria. Median of eGDR was 9.68 $mgkg^{-1}min^{-1}$ (interquartile range 3.9–12.7). There were 178 patients with lower (<9.68 $mgkg^{-1}min^{-1}$) and 175 with higher (≥9.68 $mgkg^{-1}min^{-1}$) insulin sensitivity. Those with lower insulin sensitivity were older, had a longer duration of diabetes, as well as metabolic parameters, except HDL cholesterol concentrations that were significantly lower (Table 2). Subjects with lower insulin sensitivity had significantly elevated concentrations of serum creatinine and UAE (all $p<0.05$), but creatinine clearance concentrations did not differ between two groups.

Associations of renal parameters with anthropometric and metabolic variables are presented in Table 3. Serum creatinine and UAE were significantly associated with insulin resistance measured by clinical parameters (eGDR), with serum creatinine showing the strongest correlation. In addition, serum creatinine and UAE were significantly associated with one individual component of eGDR (WHR and HbA1c). However, as eGDR is a function of WHR, HbA1c and hypertension, although creatinine clearance was in significant correlation with two individual components of eGDR (WHR and HbA1c), it was not significantly associated with measure of insulin sensitivity (eGDR). Serum creatinine was also positively correlated with duration of diabetes and BMI. Creatinine clearance significantly correlated with even 6 parameters (age, duration of diabetes, BMI, WHR, HbA1c, and triglycerides). The magnitude of these associations were strongest for serum creatinine with WHR ($r=0.39$, $p<0.001$), and creatinine clearance with age ($r=-0.26$, $p<0.001$). UAE significantly correlated only with eGDR and HbA1c ($r=0.13$, and 0.13, respectively, all $p\leq0.01$). Renal parameters were more modestly associated with serum lipids and blood pressure, and only creatinine clearance was significantly correlated with triglycerides. Intercorrelations among the renal parameters were low and not significant, for UAE with serum creatinine and creatinine clearance ($r=0.03$, and $-0.06$, respectively), and for serum creatinine with creatinine clearance ($r=-0.04$).

Relationship between renal parameters among those in the 2nd, 3rd and 4th quartiles of eGDR compared to

**TABLE 1**
CLINICAL AND METABOLIC CHARACTERISTICS OF ALL PATIENTS

| Variable | $\overline{X}$±SD | Interquartile range |
|---|---|---|
| Age (years) | 38±11 | 18–65 |
| Duration of diabetes (years) | 16±10 | 1–48 |
| BMI ($kg/m^2$) | 24±3 | 15–37 |
| WHR | 0.82±0.07 | 0.66–1.07 |
| HbA1c (%) | 7.29±1.68 | 4.4–12.2 |
| SBP (mmHg) | 126±15 | 79–180 |
| DBP (mmHg) | 79±9 | 50–110 |
| Heart rate (beats/min) | 74±13 | 44–111 |
| eGDR ($mg/kg^{-1}min^{-1}$) | 9.31±2.02 | 3.9–12.7 |
| LDL-cholesterol (mmol/L) | 2.8±0.8 | 0.6–6.2 |
| HDL-cholesterol (mmol/L) | 1.7±0.4 | 0.7–3.6 |
| Triglycerides (mmol/L) | 1.1±0.6 | 0.3–4.0 |
| Serum creatinine (μmol/L) | 92±14 | 52–154 |
| Creatinine clearance (ml/sec) | 1.88±0.52 | 0.93–3.71 |
| UAE (mg/24h) | 24.2±32.9 | 0.9–243.3 |
| RBC ($\times10^{12}$/L) | 4.6±0.4 | 3.2–5.9 |
| Hemoglobin (g/L) | 140±15.8 | 75–179 |
| WBC ($\times10^{9}$/L) | 6.7±2.1 | 2.4–13.7 |
| Platelet ($\times10^{9}$/L) | 259±72 | 22–549 |
| Smokers/non-smokers | 122/231 | |

BMI – body mass index, WHR – waist to hip ratio, SPB – systolic blood pressure, DBP – diastolic blood pressure, eGDR – estimated glucose disposal rate, UAE – urinary albumin excretion, RBC – red blood cell count, WBC – white blood cell count

**TABLE 2**
CLINICAL AND METABOLIC CHARACTERISTICS OF PATIENTS DEPENDING ON LEVEL OF INSULIN SENSITIVITY

| | eGDR<9.68 | eGDR≥9.68 | p |
|---|---|---|---|
| Sex (m/f) | 115/63 | 72/103 | <0.001 |
| Age (years) | 40±11 | 36±10 | <0.001 |
| Duration of diabetes (years) | 17±10 | 14±9 | 0.01 |
| BMI (kg/m$^2$) | 25 (17–37) | 24 (15–33) | <0.001 |
| Waist circumference (cm) | 86 (66–111) | 76 (61–102) | <0.001 |
| LDL-cholesterol (mmol/L) | 3.1±0.9 | 2.6±0.6 | <0.001 |
| HDL-cholesterol (mmol/L) | 1.59 (0.8–3.6) | 1.76 (0.7–3.6) | <0.001 |
| Triglycerides (mmol/L) | 1.13 (0.4–5.0) | 0.78 (0.3–2.3) | <0.001 |
| Fasting glucose (mmol/L) | 6.7±2.5 | 5.8±2.1 | 0.001 |
| Smokers/non-smokers | 72/106 | 50/125 | 0.02 |
| Serum creatinine (μmol/L) | 93±15 | 90±12 | 0.02 |
| UAE (mg/24h) | 16.2 (0.9–241) | 13.5 (1.4–243) | 0.002 |
| Creatinine clearance (ml/sec) | 1.88±0.56 | 1.88±0.48 | 0.9 |

BMI – body mass index, eGDR – estimated glucose disposal rate, UAE – urinary albumin excretion

those in quartile 1 are presented in Table 4. Stratifying renal parameters for degree of insulin sensitivity, determined according to percentiles of eGDR, trends across quartiles for serum creatinine and UAE were statistically significant (all p<0.05). Subjects in the 1$^{st}$ quartile of eGDR were at significantly elevated UAE and serum creatinine levels compared to subjects in 2$^{nd}$, 3$^{rd}$ and 4$^{th}$ quartiles. The magnitude of these associations were strongest for UAE (p=0.01). Among the different groups no significant changes in creatinine clearance was found.

In logistic regression analysis, after adjustment for age, only UAE was significantly associated with risk of insulin resistance in our subjects (OR=1.01, p=0.009). Although serum creatinine had strongest correlation with eGDR (r=–0.17) and especially with individual component of eGDR, WHR (r=0.39), these parameter was not significantly associated with risk of insulin resistance in our subjects, as well as creatinine clearance.

## Discussion

Insulin resistance is the central pathophysiological phenomenon of metabolic syndrome[25], characterized by a clustering of independent cardiovascular risk factors including impaired glucose regulation, central obesity, dyslipidemia, and hypertension[24]. In both, type 1 and type 2 diabetes, the role of insulin resistance seems to be equ-

**TABLE 3**
SPEARMAN CORRELATION ANALYSIS OF ASSOCIATIONS OF RENAL PARAMETERS WITH METABOLIC AND ANTHROPOMETRIC VARIABLES

| Variable | UAE | Serum creatinine | Creatinine clearance |
|---|---|---|---|
| Age | –0.07 | 0.08 | –0.26* |
| Duration of diabetes | 0.07 | 0.12* | –0.15* |
| BMI | 0.00 | 0.12* | 0.15* |
| WHR | 0.04 | 0.39* | 0.18* |
| eGDR | –0.13* | –0.17* | 0.01 |
| HbA1c | 0.13* | –0.08 | –0.14* |
| Fasting glucose | –0.02 | 0.02 | –0.07 |
| LDL cholesterol | –0.00 | 0.04 | –0.05 |
| HDL cholesterol | –0.04 | –0.10 | –0.09 |
| Triglycerides | 0.09 | 0.01 | –0.14* |
| Systolic blood pressure | 0.06 | 0.10 | 0.05 |
| Diastolic blood pressure | 0.06 | 0.08 | 0.08 |

*p<0.05, BMI – body mass index, WHR – waist to hip ratio, eGDR – estimated glucose disposal rate, UAE – urinary albumin excretion

**TABLE 4**
QUARTILES OF INSULIN RESISTANCE (EGDR)

| Variable | 1$^{st}$ quartile eGDR<7.82 | 2$^{nd}$ quartile 7.82–9.67 | 3$^{rd}$ quartile 9.68–10.8 | 4$^{th}$ quartile eGDR>10.8 | p for trend |
|---|---|---|---|---|---|
| Urinary albumin excretion (mg/24h) | 16.4 (1–241) | 15.8 (2–220) | 14.5 (1–243) | 12.6 (2–225) | 0.01 |
| Serum creatinine (μmol/L) | 93.5±17.1 | 94.2±13.1 | 92.5±12.1 | 87.8±12.7 | 0.02 |
| Creatinine clearance (ml/sec) | 1.82±0.53 | 1.96±0.58 | 1.89±0.51 | 1.86±0.46 | 0.5 |

eGDR – estimated glucose disposal rate

**TABLE 5**
AGE ADJUSTED LOGISTIC REGRESSION ANALYSIS OF RENAL PARAMETERS WITH DEVELOPMENT OF INSULIN RESISTANCE IN TYPE 1 DIABETES

| Independent variable | Odds ratio | p | 95% Con. Int. |
|---|---|---|---|
| UAE | 1.011 | 0.009 | 1.002–1.019 |
| Serum creatinine | 1.006 | 0.412 | 0.991–1.021 |
| Creatinine clearance | 0.977 | 0.924 | 0.617–1.549 |

UAE – urinary albumin excretion

ally important as a cardiovascular risk factor[2,14]. Previous studies in type 1 diabetes reported that patients with lower insulin sensitivity have a higher subsequent risk of developing the microvascular and macrovascular complications[4,10,15,26–29]. Moreover, insulin resistance was found to be predominant predictor of overt nephropathy in contrast to blood pressure and lipids in type 1 diabetes[4].

In the present study we documented, among subjects with type 1 diabetes, significant associations of renal parameters, including UAE and serum creatinine, with insulin resistance measured by eGDR as well as with individual components of insulin resistance. Furthermore, we demonstrated that concentrations of UAE and serum creatinine worsened in parallel with decreased in quartiles of eGDR. A major change in insulin sensitivity had already occurred in those with higher UAE and serum creatinine before the decline in creatinine clearance associated with the late-stage disease. Furthermore, most patients with microalbuminuria were in the lowest eGDR quartile, thereby showing a clear relationship between increased insulin resistance and microangiopathy. Finally, in logistic regression analysis only UAE was significantly associated with the development of insulin resistance in our subjects. Sample size, stable metabolic control (HbA1c 7.2 %), the relatively short duration of diabetes (16 years) and satisfactory serum lipid concentrations could probably explain the low prevalence of microalbuminuria in our study (17%). Moreover, frequency rates of microalbuminuria in our study were similar to the overall frequency in 1100 type 1 diabetic patients in the North Wales Study (17%)[30], and 15% in 4097 type 1 diabetic patients from National Diabetes Register in Sweden[31].

There are few possible mechanisms to explain relationship between insulin resistance measured with eGDR and worsening of renal function in type 1 diabetic patients. One of the main factors accounting for risk of progression to microalbuminuria is glycemic control[32]. Strict blood glucose control reduces the risk of developing microalbuminuria and nephropathy in type 1 and 2 diabetic patients[18,20,33]. This was also confirmed in our study were HbA1c positively correlated with UAE, and negatively with creatinine clearance. However, there is no glycemic threshold for risk of microalbuminuria, and efforts to reduce HbA1c should therefore be continued at all levels[32,34]. Apart from well-known risk factors such as HbA1c, independent associations with microalbuminuria were also observed with WHR. Moreover, EURODIAB Prospective Complications Study (PCS) showed that elevated WHR was risk factor for development of microalbuminuria, independently of diabetes duration and HbA1c[32]. Higher WHR seems to indicate the existence of other causative mechanisms than glycemic control only. Renal damage by obesity may be also related to low-grade inflammation or to hormonal changes of the renin-angiotensin and sympathetic nervous system[35]. In our study serum creatinine and creatinine clearance significantly correlated with WHR, but this was not confirmed with UAE. Data from previous cross-sectional studies showed that lipids are abnormal in patients with higher UAE[36,37]. However, lipids appear to predict risk of overt nephropathy in type 1 diabetes only in the short term[4]. That suggests that lipids mainly act as late-stage accelerators or precipitators rather than underlying etiologic factor. In our patients UAE and serum creatinine were not significantly correlated with serum lipids.

Duration of diabetes has an impact on the risk of microalbuminuria[38]. Most long-term epidemiologic studies have shown that 20 years duration of diabetes is a time at which the annual incidence of new development of microalbuminuria has already decreased markedly, and those who do not have microalbuminuria by that point are unlikely to ever develop it[39,40]. The mean disease duration of over 16 years in our study suggests that our patients have a rather low risk of developing nephropathy. The prospective studies also showed that elevated blood pressure was an independent baseline risk factor for the development of microalbuminuria[21], although it was not found to be either in the EURODIAB PCS on 1134 type 1 diabetic patients[32], or in the study at Steno Diabetes Center with over 400 type 1 diabetic patients[41]. In our study systolic and diastolic blood pressure was not significantly correlated with any renal parameter. However, impact of high blood pressure on renal function can not be irrelevant, because blood pressure is one of the component disorders of insulin resistance measured by eGDR. In addition, it is known that strict blood pressure control reduce UAE and deterioration of renal function in type 1 diabetic patients[21,41]. Current smoking was significantly associated with the risk of onset of microalbuminuria[42]. In our study higher incident of smokers were in group of patients with lower insulin sensitivity, so it seems that current smoking and insulin sensitivity may impact the risk of microalbuminuria through different pathophysiological mechanisms.

In insulin resistant state, plasma insulin may rise to supranormal concentrations that may sustain glomerular hyperfiltration[43], endothelial dysfunction[44], and increased vascular permeability[45], which can result in increased UAE. Endothelium-dependent vasodilatation is impaired in people with type 1 diabetes, especially in those with higher UAE[46]. In addition, a link between nephropathy and insulin resistance is consistent with the Steno hypothesis that microalbuminuria reflects ge-

neralized endothelial dysfunction[47], which is known to correlate with insulin resistance[48]. Moreover, impaired insulin sensitivity is associated with altered renal cellular metabolism and electrolyte composition, mesangial hyperplasia, renal hypertrophy and increased endothelial cell proliferation, effects that may directly contribute to progressive kidney damage[49]. Central actions of insulin stimulating the sympathetic nervous system activity and renal effects enhancing renal sodium reabsorption may contribute to the etiology of arterial hypertension that may further contribute to renal damage. Insulin resistance might also contribute to nephropathy via low--grade inflammation and increased oxidative stress. It was shown that increased concentrations of interleukin--6 and C-reactive protein are associated with decreased insulin sensitivity, which worsened in parallel with the severity of the renal disease[6].

We did not have access to direct, detailed measures of insulin resistance using euglycemic-hyperinsulinemic clamp test, which can be potential limitation of this study. It can be argued that, as eGDR is based on three risk factors, all we are doing is statistical manipulation. However, this computation is strongly related to measured GDR ($r=0.76$)[13], and those scoring high on eGDR clearly have better insulin sensitivity and reduced risk for nephropathy.

In summary, insulin resistance measured by eGDR has a negative impact on renal parameters in type 1 diabetes, most notably UAE. Thus, an easy formula based on clinical and laboratory parameters such as WHR, blood pressure, and HbA1c, can provide a reliable assessment of renal function as a chronic diabetes complication. Whether their total impact is greater than the sum of the individual components is a matter of debate. The close relationship between UAE and insulin resistance has important implications for treatment. Microalbuminuria is one of several risk factors for end-stage renal disease in diabetic patients and it is also an indicator of organ dysfunction and a marker of greatly increased cardiovascular morbidity and mortality in patients with type 1 diabetes. Since progression to microalbuminuria is likely to occur in majority of diabetic patients, there is a need to further explore the role of risk factors such as insulin resistance.

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## UTJECAJ INZULINSKE REZISTENCIJE NA PARAMETRE BUBREŽNE FUNKCIJE U ŠEĆERNOJ BOLESTI TIPA 1

### S A Ž E T A K

Pojam inzulinske rezistencije uglavnom se povezuje s razvojem šećerne bolesti tipa 2, ali je pokazano da i osobe sa šećernom bolešću tipa 1 također mogu imati značajke inzulinske rezistencije. Inzulinska rezistencija u tipu 1 šećerne bolesti dokazano pridonosi razvoju mikro i makrovaskularnih komplikacija. Istraživali smo utjecaj inzulinske rezistencije mjerene kliničkim parametrima na parametre bubrežne funkcije: razinu albumina u urinu, serumski kreatinin i klirens kreatinina. U istraživanje je uključeno 353 bolesnika sa šećernom bolešću tipa 1, bez anamneze bubrežne ili kardiovaskularne bolesti. Inzulinska osjetljivost mjerena je eGDR-om (estimated glucose disposal rate) koji se računa prema formuli: 24,31–(12,22×opseg struk/bokovi)–(3,29×povišeni krvni tlak)–(0,57×HbA1c). Korelacijom i logističkom regresijom analizirao se odnos između parametara bubrežne funkcije i eGDR-a, komponenti inzulinske rezistencije te s rizikom razvoja inzulinske rezistencije. Razina albumina u urinu i serumski kreatinin značajno su korelirali s eGDR-om ($r=-0,13$, i $-0,17$, $p<0,05$), kao i s pojedinim komponentama inzulinske rezistencije (opseg struk/bokovi, HbA1c). Podijelivši razinu inzulinske osjetljivosti u kvartile, bolesnici u 1. kvartili eGDR-a imali su značajno više vrijednosti albumina u urinu i serumskog kreatinina u odnosu na one u 4. kvartili. Logističkom regresijom dokazano je da samo razina albumina u urinu utječe na rizik razvoja inzulinske rezistencije (odds ratio=1,01, $p<0,01$). Rezultati istraživanja pokazali su da razina inzulinske osjetljivosti mjerena eGDR-om značajno utječe na parametre bubrežne funkcije, i to albumine u urinu i serumski kreatinin. Mikroalbuminurija je parametar povećanog kardiovaskularnog rizika i smrtnosti, a budući da će većina bolesnika sa šećernom bolešću tipa 1 tijekom vremena razviti mikroalbuminuriju, potrebno je istražiti ulogu faktora rizika kao što je inzulinska rezistencija.