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THE ASSOCIATION BETWEEN INSULIN RESISTANCE AND ADVANCED RENAL DISEASE IN TYPE 1 DIABETES

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Abstract

Background and Aims. *Insulin resistance is documented in type 1 diabetes and it has been associated with chronic complications. Diabetic nephropathy is a major cause of morbidity and mortality. The purpose of this article is to quantify insulin resistance in type 1 diabetes subjects according to the presence or absence of advanced renal disease. A secondary objective was to study the possible association between insulin resistance and advanced renal disease.* ***Material and Methods.*** *This was a cross-sectional study that included 167 type 1 diabetes patients. Insulin resistance was determined using the eGDR (estimated glucose disposal rate) formula. The association between eGDR and diabetic nephropathy was assessed in uni and multivariate models using stepwise logistic regression analysis of variables. The contribution of individual predictors in the final regression model was examined using Wald statistic.* ***Results.*** *Significantly lower eGDR's values were observed in patients with nephropathy: 5 vs. 7.3 ($p<0.001$). In univariate analysis eGDR was significantly associated with diabetic nephropathy ($p<0.001$). eGDR variable was retained in the final model of stepwise logistic regression ($p<0.001$) and showed the strongest association with diabetic nephropathy (Wald = 30.4).* ***Conclusions.*** *In type 1 diabetes patients insulin resistance was the most important independent risk factor associated with advanced renal disease.*

key words: *Type 1 diabetes, insulin resistance, estimated glucose disposal rate, diabetic renal disease*

Background and Aims

Worldwide, diabetic renal disease is one of the leading causes of end stage renal disease (ESRD) [1]. Despite medical progresses in the field, mortality rate for patients on renal replacement programs is ~20% [2]. In this context identifying patients at risk of renal impairment is mandatory.

The occurrence of diabetic kidney disease is related to risk factors such as hyperglycemia, hypertension, dyslipidemia and abdominal obesity. This aggregation of risk factors known as metabolic syndrome predisposes to insulin resistance. The role of insulin resistance in type 2 diabetes mellitus pathogenesis is well established, but it also seems to be involved in type 1 diabetes. Thus, in type 1 diabetes insulin resistance appears to be associated with renal

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disease and with other chronic complications [3-7].

The aim of this article was to quantify insulin resistance in type 1 diabetes patients using the estimated glucose disposal rate (eGDR) with and without advanced renal impairment. A secondary objective was to assess the potential association between insulin resistance and advanced diabetic renal disease.

Material and Methods

Study design was cross-sectional. The analysis included 167 type 1 diabetes patients, enrolled from January to December 2012 from "N. C. Paulescu" Institute.

Inclusion criteria. Type 1 diabetes mellitus was defined as: diabetes onset before the age of 35 years with permanent insulin treatment initiated within the first year after diagnosis. The diagnosis was confirmed by determining serum C-peptide levels (<0.3 nmol/l).

According to the presence or absence of nephropathy, *patients with type 1 diabetes were divided into 2 groups: with advanced renal disease and without renal disease*. Mogensen classification (2000) was used to assess renal status [8]. In the advanced renal disease group we included all type 1 diabetes patients with stages 4 and 5 according to Mogensen classification. Thus, patients were considered as having advanced renal disease if any of proteinuria (urinary albumin excretion rate - AER > 300 mg/24h) or ESRD (predialysis/dialysis/renal transplant) were present. Those with at least 15 years duration of diabetes, eGFR (estimated glomerular filtration rate) between 90-130 ml/min/1.73 m^2 and AER < 30 mg/24h were considered free of renal impairment. Type 1 diabetes patients that met the inclusion criteria but had AER = 30-300 mg/24 h and any of the following conditions: severe hyperglycemia (fasting plasma glucose > 210 mg/dl and/or HbA1c > 9%), uncontrolled hypertension, heart failure or urinary tract infection, were re-examined within the next 3 months.

Exclusion criteria. Patients were excluded from the study in the case of any doubt about type 1 diabetes diagnosis or presence of chronic kidney disease of other cause than diabetes.

C*linical data*. Diabetes-related data (disease duration, age at onset), anthropometric data (weight, height, body mass index- BMI, waist to hip ratio- WHR), blood pressure (BP), level of physical activity, smoking status, family history, data on diabetes complications (retinopathy, neuropathy and cardiovascular disease) were recorded using standardized questionnaires. Supine systolic (SBP) and diastolic (DBP) blood pressure was measured in both arms after 10 minutes of rest. We used the arithmetic mean of the values obtained. Hypertension was defined as a BP > 140/90 mm Hg and/or use of anti-hypertensive treatment.

Laboratory data. Fasting blood samples were assessed for lipids, HbA1c (glycated hemoglobin) and serum creatinine. Lipids (total cholesterol, HDL cholesterol, triglycerides) were assessed using enzymatic methods. HbA1c level was measured by HPLC (high-performance liquid chromatography). C-peptide levels were measured using an ELISA technique. Renal status was assessed by determining the AER/24 h and serum creatinine level. The glomerular filtration rate was estimated using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration).

Assessment of insulin resistance. Insulin resistance was assessed using the eGDR equation. The formula was previously validated in clamp studies [9]. eGDR (ml/kg/min) is based on three clinical parameters and is calculated as follows: eGDR = 24.31 - (12.22 x WHR) - (3.29 X BP) - (0.57 X HbA1C), where WHR – waist to hip ratio, BP - history of hypertension (yes =

1, no = 0), HbA1c - glycated hemoglobin A1C. It was shown that eGDR is a statistical calculation closely correlated with measured GDR (r = 0.76) [9].

Ethical considerations. Patient enrollment was made according to the Declaration of Helsinki, obtaining their informed consent in advance. The study was approved by the local ethics committee.

Statistical analysis. Individual patient data were inputted into a statistics program (SPSS 20.0). Normally distributed variables are presented as mean ± SD. Non-normally distributed variables are presented as median and interquartile range. The Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to assess data normality. Categorical variables are presented as frequencies (%). Comparison between groups were made using the Student T test for normally distributed variables while for non-normally distributed variables, Mann-Whitney U test was used. Categorical variables were compared using $\chi 2$ test.

Initially, we analyzed the association between eGDR and diabetic nephropathy in univariate logistic regression models and then regression was adjusted for duration of diabetes and sex. Subsequently, in order to determine the most important risk factors for diabetic nephropathy, we performed analysis of variables using multiparametric stepwise logistic regression models. The following variables were considered in the model: sex, duration of diabetes, BMI, eGDR, HDL cholesterol, LDL cholesterol, triglycerides, smoking, presence of retinopathy, neuropathy and cardiovascular disease. HbA1c and BP, although the main risk factors for the occurrence and progression of chronic kidney disease, were not considered in the regression model (because included into eGDR's equation). We considered as significant a p value < 0.05. Variables that did not meet this criterion were removed from the model. The contribution of individual predictors in the final regression model was examined using Wald statistic.

Results

General characteristics of patients. The study included 167 patients with type 1 diabetes (108 men and 59 women). The mean age was 46 years, mean duration of diabetes was 24 years, mean HbA1c was 8.8% and the average eGDR was 6.7 mg/kg/min. The prevalence of hypertension was 58.7% and that of dyslipidemia was 61.7%. General characteristics of the subjects are listed in Table 1.

Table 1. Characteristics of the studied population.

Variable	Value
n	167
Age (years)	46.3±13.5
Men/Women	108/59
Duration of diabetes (years)	24.7±8
BMI (Kg/m^2)	24.6±3.9
Waist circumference (cm)	90.1±12.7
WHR	0.9±0.08
Smokers (%)	59.8
SBP (mm Hg)	130.3±21.7
DBP (mm Hg)	76±12.4
Hypertension (%)	58.7
Fasting plasma glucose (mg/dl)	198.1±106.7
HbA1c (%)	8.8±1.5
eGDR (mg/kg/min)	6.7±2.3
Family history of diabetes (%)	44.9
Total cholesterol (mg/dl)	191.5±48.7
LDL cholesterol (mg/dl)	117.2±44.9
HDL cholesterol (mg/dl)	56.7±16.2
Triglycerides (mg/dl) *	90.1±54
Dyslipidemia (%)	61.7
AER (mg/24h) *	300.1±348
Creatinine (mg/dl) *	0.8±0.4
eGFR (ml/min/1.73 m^2)	86.6±33.6
Renal disease (%)	52.1

Normally distributed variables: mean ± SD;
* Non-normally distributed variables: median ± interquartile range; Categorical variables: percent.

Patients characteristics according to the presence of advanced renal disease. A total of 47.9% (*n*=80) of patients from the targeted group were free from renal impairment; 28.7% (*n*=48) had macroalbuminuria and 23.4% (*n*=39)

had ESRD. The prevalence of hypertension was significantly higher in the group with renal impairment (73.5% vs. 26.5%; p <0.001).

Patients with *advanced renal disease* had significant different values for variables that assess renal function: AER (1080 vs. 5.6 mg/24h; p<0.001) and eGFR (46.9 vs. 101.5 ml/min/1.73 m^2; p<0.001). Mean eGFR in patients with ESRD was 13.9 ml/min/1.73 m^2 (data not shown).

BMI (p=0.049), total cholesterol (p<0.001) and HDL cholesterol (p=0.002) differed significantly between groups, but this was not the case for LDL cholesterol or triglycerides. Although blood pressure (p<0.001) and WHR (p=0.035) were significantly different between groups, we found no differences in HbA1c levels (p=0.44). Significantly lower eGDR's values were observed in patients with *advanced renal disease*: 5 vs. 7.3 ml/kg/min (p<0.001). Characteristics of patients with diabetic renal disease are presented in Table 2.

Table 2. Characteristics of patients according to diabetic renal disease status.

Variable	Without diabetic renal disease	With advanced diabetic renal disease	p
n	80	87	
Age (Years)	47.4±13.7	43.5±13	0.11
Men/Women	44/37	64/22	0.009
Duration of diabetes (years)	24.7±8.2	24.6±7.8	0.54
Weight (kg)	71.1±14.8	72.1±14.6	0.52
Height (cm)	169.6±9.1	170.3±8	0.07
BMI (Kg/m^2)	24.7±4.1	23.5±3.2	0.049
Waist circumference (cm)	90.2±11.9	90±15	0.75
WHR	0.9±0.07	0.92±0.11	0.035
SBP (mm Hg)	122.9±16.4	149.9±22.2	<0.001
DBP (mm Hg)	72.6±10.6	85.1±12.3	<0.001
Hypertension (%)	26.5	73.5	<0.001
Fasting plasma glucose (mg/dl)	201.6±109.8	188.9±100.2	0.98
HbA1c (%)	8.6±1.4	9.1±1.8	0.44
eGDR (mg/kg/ min)	7.3±2.1	5±1.9	<0.001
Total cholesterol (mg/dl)	192.5±39.1	168.1±48.8	<0.001
LDL cholesterol (mg/dl)	114.8±38.5	110.5±43.5	0.50
HDL cholesterol (mg/dl)	58.3±16.9	51±12.5	0.002
Triglycerides (mg/dl) *	91±55	106±61	0.07
AER (mg/24h) *	5.6±7	1080±1072	<0.001
Creatinin (mg/dl)	0.7±0.1	2.4±1.6	<0.001
eGFR (ml/min/1.73 m^2)	101.5±19.6	46.9±30.7	<0.001

Normally distributed variables: mean ± SD; * Non-normally distributed variables: median ± interquartile range; Categorical variables: percents.

eGDR: univariate and multivariate analysis. eGDR was significantly associated with advanced renal disease both in the univariate analysis (OR=0.62; p<0.001) and after adjustment for sex and duration of diabetes (OR=0.62; p<0.001).

eGDR was one of the variables retained in the final model of stepwise logistic regression (OR=0.55; p<0.001) and was the parameter most strongly associated with advanced renal disease (Wald=30.4).

Along with eGDR, the following variables were retained in the final regression model: BMI (OR=0.79; p<0.001) and Male sex (OR=0.45; p=0.047) as shown in Table 3.

Variables rejected from the model (p>0.05) were: duration of diabetes, LDL cholesterol, HDL cholesterol, triglycerides and smoking.

Table 3. Association between eGDR and advanced diabetic renal disease.

Variable	Wald	OR	95%CI	p
Unadjusted				
eGDR	27.1	0.62	0.52-0.74	<0.001
Adjusted				
eGDR	24.9	0.62	0.52-0.75	<0.001
Gender	3	0.52	0.25-1.08	0.08
Duration of diabetes 1		0.97	0.94-1.01	0.29
Final regression model**				
eGDR	30.4	0.55	0.44-0.68	<0.001
Male sex	3.9	0.45	0.20-0.98	0.047
BMI	13.9	0.79	0.71-0.89	<0.001

** Stepwise logistic regression analysis for eGDR and advanced diabetic renal disease. Variables rejected from the model were: duration of diabetes, serum triglycerides, LDL cholesterol, HDL cholesterol and smoking.

Discussion

The main finding of the study is that *insulin resistance*, assessed using eGDR, is a characteristic of patients with advanced diabetic renal disease. A low value of eGDR, suggestive of increased insulin resistance, was independently associated with advanced diabetic renal disease, representing the most important factor associated with this condition (Wald = 30.4).

The equation that estimates insulin-resistance is based on three well-known risk factors for diabetic renal disease: HbA1c [10-15], hypertensive status [16] and waist-to-hip ratio [17].

A possible link between insulin resistance and diabetic nephropathy was analyzed in previous studies. The Pittsburgh Epidemiology of Diabetes Complications Study showed that insulin resistance (eGDR) and white blood cells count are among the major risk factors for the occurrence of macroalbuminuria [3]. In the DCCT (Diabetes Control and Complications Trial) a low eGDR at baseline predicted the onset of diabetic nephropathy independent of glycemic control [6]. In a cross-sectional analysis of FinnDiane Study a decreased value of eGDR significantly associated with increased albuminuria and renal function decline [7]. These studies suggest that an elevated eGDR is associated with insulin sensitivity and with lower risk of renal impairment.

The results of our analysis are consistent with previous observations. In addition, another finding is that insulin resistance, measured using eGDR, would represent the most important risk factor for diabetic nephropathy.

BMI was one of the variables retained in the final regression model (Wald=13.9); OR= 0.79; p<0.001), but the association with diabetic kidney disease was negative – a lower BMI was associated with advanced renal disease. This suggests that in patients with macroalbuminuria and ESRD, renal cachexia would be associated with diabetic nephropathy, independently from analyzed risk factors. These observations are consistent with data from the literature [18,19].

Male sex is another variable retained in the final stepwise regression model (Wald=3.9; OR=0.45; p=0.047). We found that male gender is an independent risk factor for diabetic nephropathy. The literature also suggests that men are at higher risk of developing nephropathy and associate this higher risk with abdominal fat disposal (using WHR as a surrogate marker), but there are no data on sex hormones differences [20].

Variables such as *lipid profile* components, *duration of diabetes and smoking* were excluded from the final model after stepwise selection of the most important risk factors for advanced diabetic renal disease. A possible explanation for these observations could be the insufficient number of patients in the analyzed group in order to achieve statistical significance. Another possibility would be a favorable control of modifiable risk factors (lipid-lowering treatment and effective control of smoking) in the analyzed group. A third possibility is that insulin resistance (measured using eGDR) would be the most important risk factor, independent of lipid profile, duration of diabetes or smoking.

The main methods designed to increase insulin sensitivity are: diet, exercise and metformin or thiazolidindiones as add-on therapies to insulin. Except for a recent prospective analysis of FinnDiane study which showed that a moderate-intense physical activity significantly decreases the risk of nephropathy (both initiation and progression) [21], we found no data that examined the relationship between adjunctive therapy and diabetic nephropathy. It was implied, however, that metformin added to insulin, reduces HbA1c levels, insulin requirements [22] and weight [23].

Limitations of the study. A study limit is represented by the cross-sectional design. Therefore we can say that eGDR is associated with diabetic nephropathy without establishing the causality.

Another limit is represented by the method used for estimating insulin resistance. Although eGDR equation shows a strong correlation with measured GDR (r = 0.76) [9], it is though a statistical calculation that uses clinical parameters.

Other possible limitations of our study are related to renal status assessment. Kidney disease was classified using Mogensen criterion and not the current KDIGO / KDOQI guidelines. Although albumin to creatinine ratio is currently recommended for proteinuria assessment, we used AER / 24 h. This determination is related to patient compliance in completing urine collection.

The number of type 1 diabetes patients was limited. Future research is needed involving a larger sample size to establish the role of insulin resistance type 1 diabetes patients.

Conclusions

In type 1 diabetes insulin resistance was the most important risk factor associated with advanced diabetic renal disease. The practical use of this finding lies in the possibility to identify patients at risk of developing diabetic renal disease that can benefit from early and aggressive strategies.

Duality of interest: The authors declare that there is no duality of interests associated with this manuscript.

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