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ESTIMATED GLUCOSE DISPOSAL RATE (eGDR) – A MARKER FOR THE ASSESSMENT OF INSULIN RESISTANCE IN TYPE 1 DIABETES MELLITUS

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Abstract

Background and Aims: *Studies have shown an increased incidence of chronic complications in people with type 1 diabetes mellitus (T1DM) with insulin resistance (IR) compared to people with T1DM without IR. Estimated glucose disposal rate (eGDR) is an important indicator of IR in patients with T1DM, lower eGDR levels indicating greater IR. It was shown that T1DM patients with chronic complications (diabetic retinopathy - DR, diabetic peripheral neuropathy - DPN or diabetic kidney disease - DKD) exhibit higher IR compared to patients without chronic complications. The aim of our study was to evaluate eGDR as a marker for the assessment of IR in T1DM patients.* ***Materials and Methods:*** *The study was observational, cross-sectional and included 140 T1DM patients with diabetes duration>10 years. The collected data were analyzed using the Statistic Package for Social Sciences (SPSS) version 22 software (IBM Corporation, Armonk, NY, USA).* ***Results:*** *eGDR presented statistically significant correlations ($p<0.05$) with the presence of metabolic syndrome (MS), obesity, chronic complications of T1DM, cardiovascular risk (CVR) and smoking status in patients with T1DM duration >10 years.* ***Conclusions:*** *eGDR represents a reliable marker for assessing the IR in T1DM.*

key words: *estimated glucose disposal rate, insulin resistance, type 1 diabetes mellitus, chronic complications.*

Background and Aims

A number of clinical trials [1-5] have shown an increased incidence of chronic complications in people with type 1 diabetes mellitus (T1DM) with insulin resistance (IR) compared to T1DM subjects without IR. Estimated glucose disposal rate (eGDR) was shown to be an important indicator of IR in patients with T1DM, lower eGDR levels indicating greater IR [1-3]. eGDR validation as a marker of IR in patients with T1DM was made using euglycemic - hyperinsulinemic clamp studies performed on 24 non-hispanic whites adults, participants in the

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Epidemiology of Diabetes Complications (EDC) study [2,3]; eGDR was highly correlated with clamp-measured IR (r=0.79) [3].

It was also shown that T1DM patients with chronic complications (diabetic retinopathy - DR, diabetic peripheral neuropathy - DPN or diabetic kidney disease - DKD) exhibit significantly lower eGDR compared with patients without chronic complications [1,4].

The aim of our study was to evaluate eGDR as a marker for the assessment of IR in T1DM patients.

Material and Methods

The study was observational, cross-sectional and was conducted between 2010 and 2013. The study included (after signing informed consent) 140 unselected T1DM patients with diabetes duration > 10 years, 58 (41.43%) women and 82 (58.57%) men. All patients were registered in the Clinical Center of Diabetes, Nutrition and Metabolic Diseases - Clinical Emergency County Hospital, Craiova. We recorded both anamnesis data, anthropometric data: height, weight, Body Mass Index (BMI), waist circumference (WC), hip circumference (HC), Waist-to-Hip Ratio (WHR) and paraclinical data: glycemia, HbA1c, creatinine, urinary albumin/creatinine ratio (ACR), total Cholesterol (T-Chol), HDL-Chol, triglycerides (TG), C-peptide; LDL-Chol was calculated using Friedwald formula (if TG<400mg/dl) [6].

eGDR (mg x kg^{-1} x min^{-1}) was calculated according to the following equation: 24.31 - (12.22 x WHR) - (3.29 x HT) - (0.57 x HbA1c) [1,2], where HT - hypertension status (1=with HT, 0=without HT). The presence of *DKD* was established based on estimated glomerular filtration rate - eGFR (CKD-EPI) <60 ml/min/1.73m^2 and/or urinary ACR ≥ 30 mg/g [7,8]. *Cardiovascular risk (CVR) at 10 years* was determined with the Cardiovascular Risk Calculator, using Anderson's et al. equation, which includes age, systolic blood pressure (sBP), T-Chol (mmol/l), HDL-Chol (mmol/l), gender, smoking and the presence of DM [9]. *Metabolic syndrome (MS)* was defined according to the 2009 consensus of The International Diabetes Federation (IDF); National Heart, Lung, and Blood Institute (NHLBI); American Heart Association (AHA); World Heart Federation (WHF); International Atherosclerosis Society (IAS); and International Association for the Study of Obesity (IASO), including for diagnostic at least 3 from the following 5 criteria: abdominal obesity (AO) - in people with european origin, waist circumference (WC) values ≥ 80 cm in women and ≥ 94 cm in men, TG ≥150 mg/dl, HDL-Chol <40 mg/dl in men and <50 mg/dl in women, HT defined as sBP ≥130 mmHg and/or dyastolic BP (dBP) ≥85 mmHg or antihypertensive medication, fasting glycemia ≥100 mg/dl (or antidiabetic medication) [10]. Because all participants fulfilled the criteria for hyperglycemia, at least 2 of the remaining 4 criteria were required. Patients who smoked at least 5 cigarettes per day for a minimum of 12 months were considered smokers [11].

Statistical analysis

The collected data were analyzed using the Statistic Package for Social Sciences (SPSS) version 22 software (IBM Corporation, Armonk, NY, USA). Statistic tests used were: t-test, Mann-Whitney test, Kolmogorov-Smirnov test, Chi-square test, Kruskal-Wallis test, and ANOVA as appropriate. Interpretation of p values was: $p<0.05$ - the difference between the 2 means is significant (S); $p<0.01$ - the difference between the 2 means is highly significant (HS); $p<0.001$ - the difference between the 2 means is very highly significant (VHS); $p>0.05$ - the difference between the 2 means is not significant (NS).

Results

The characteristics of T1DM patients with diabetes duration > 10 years included in the study are reported in Table 1.

Analyzing the correlation between eGDR and gender in T1DM patients with DM duration >10 years, we observed that men had lower eGDR than women (5.82±2.22 vs. 7.18±2.25), indicating that men show higher IR than women, the difference being statistically highly significant (p=0.001).

Table 1. Characteristics of the study population.

Parameter analyzed	Average ± standard deviation
Age at time of the study (years)	42.67±11.29
Age at diagnosis of DM (years)	22.42±9.99
Duration of DM (years)	20.26±7.49
Creatinine (mg/dl)	1.11±1.18
Weight (W) (kg)	69.71±12.34
Height (H) (cm)	169.27±9.02
Body mass index (BMI) (kg/m^2)	24.25±3.58
WC (cm)	88.23±10.28
Hip circumference (HC) (cm)	96.47±7.58
C-peptide (nmol/l)	0.40±0.37
eGDR (mg x kg^{-1} x min^{-1})	6.38±2.32
Fasting glycemia (mg/dl)	194.83±71.45
HbA1c (%)	8.72±1.72
Daily insulin dose (IU/kg/day)	0.70±0.20
CVR at 10 years (%)	6.12±7.22
Average sBP (mmHg)	132.14±20.35
Average dBP (mmHg)	81.10±10.98
T-Chol (mg/dl)	163.62±39.61
LDL-Chol (mg/dl)	81.95±38.31
HDL-Chol (mg/dl)*	58.86±18.86
TG (mg/dl)	114.60±67.92

*HDL-Chol in women: 62.96±18.42mg/dl; HDL-Chol in men: 55.96±18.75 mg/dl.

Analyzing the correlation between eGDR and the presence of MS in the T1DM patients with DM duration >10 years (Figure 1), we observed that patients with MS have lower eGDR than patients without MS (5.82±2.22 vs. 7.18±2.25), the difference being statistically very highly significant (p=0.0001).

Analyzing the correlation between eGDR quartiles and the presence of MS, we observed that MS prevalence decreased from Q1 of eGDR (corresponding to a higher IR) by Q4 of eGDR (corresponding to a lower IR), so: 77.14% for Q1, 51.43% for Q2, 22.86% for Q3 and 5.71% for Q4, the difference being statistically very highly significant (p=0.0001).

The optimal cutt-off value of eGDR for diagnosis of MS was 5.806 mg x kg^{-1} x min^{-1}, having 88.9% sensitivity and 72.7% specificity as shown in Figure 2.

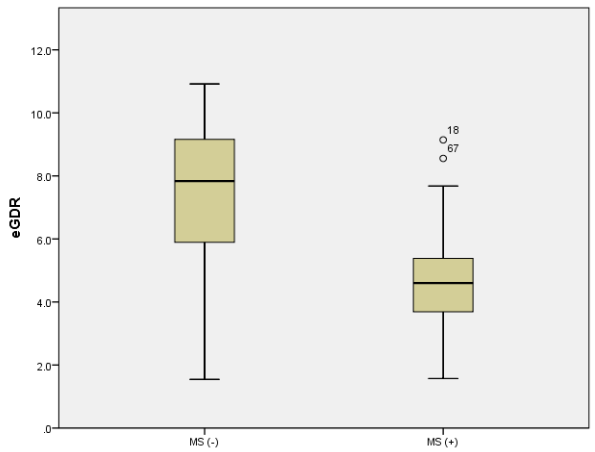

Figure 1. *The correlation between eGDR and MS presence.*

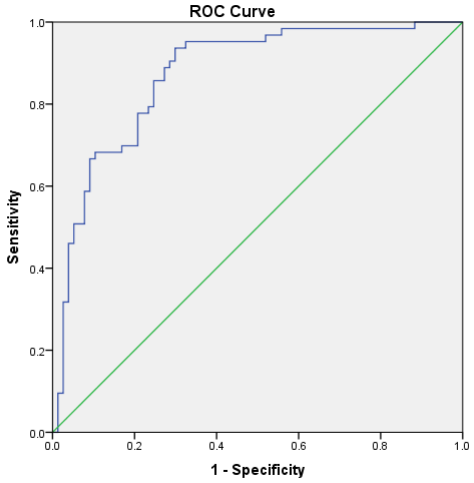

Figure 2. *Optimal cutt-off value of eGDR for the diagnosis of MS.*

Analyzing the correlation between eGDR and obesity in T1DM patients with DM duration >10 years, we observed that patients with BMI ≥ 30 kg/m^2 had lower eGDR than those with BMI <30 kg/m^2 (4.96 ± 2.18 vs. 6.53 ± 2.30), so the patients with obesity presented higher IR, the difference being statistically significant (p=0.020).

Analyzing the correlation between eGDR and smoking in T1DM patients with DM duration >10 years (Figure 3), we observed that smokers had lower eGDR than non-smokers (5.69±2.12 vs. 7.06±2.44), so smokers have higher IR than non-smokers, the difference being statistically highly significant (p=0.001).

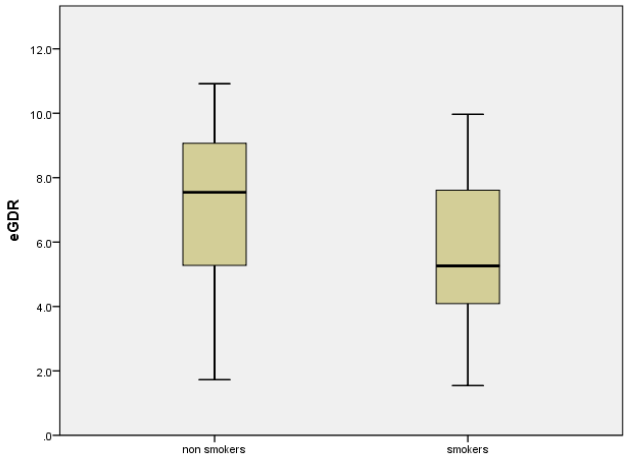

Figure 3. *The correlation between eGDR and smoking status.*

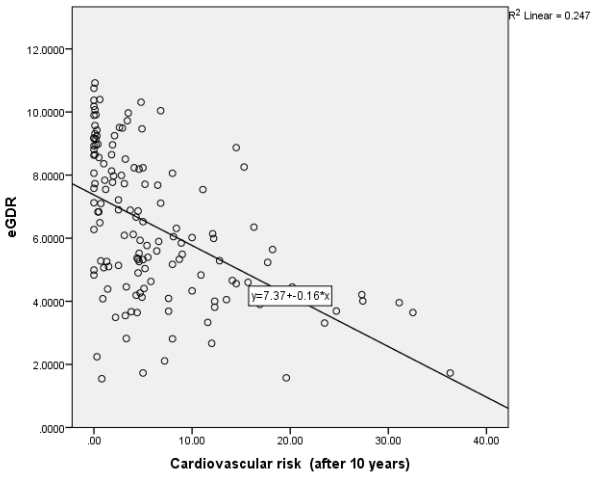

Figure 4. *The correlation between eGDR and CVR at 10 years.*

In addition, eGDR has shown statistically significant correlations with: age at diagnosis of DM (r= -0.383, p=0.0001), average age (r= -0.416, p=0.0001), BMI (r= -0.310, p=0.0001), T-Chol (r= -0.170, p=0.045), HDL-Chol (r= 0.209, p=0.016) and TG (r= -0.330, p=0.0001).

Analyzing the correlation between eGDR and CVR (the risk for cardiovascular events occurring in the next 10 years) in the T1DM patients with DM duration >10 years, we observed that eGDR negatively correlated with

CVR, the correlation being very highly significant (r= -0.547, p=0.0001) (Figure 4).

Analyzing the correlations between eGDR and chronic complications of T1DM, we observed that average eGDR in patients with chronic complications (DKD, DR, DPN, coronary heart disease - CHD and peripheral arterial disease - PAD) was lower than in patients without chronic complications, indicating higher IR in patients with chronic complications, the differences being highly or very highly significant (Table 2).

Table 2. Correlations between eGDR and chronic complications.

	Chronic complication	Average± standard deviation	p
eGDR	DKD (-) DKD (+)	7.16±2.24 5.84±2.24	0.001
	DR (-) DR (+)	7.59±1.76 6.00±2.36	0.0001
	DPN (-) DPN (+)	7.64±2.02 6.08±2.30	0.001
	CHD (-) CHD (+)	6.82±2.34 5.26±1.89	0.0001
	PAD (-) PAD (+)	6.97±2.24 5.36±2.13	0.0001

Table 3. Correlations between eGDR quartiles and chronic complications.

Chronic complication	eGDR Quartiles				p*
	Q1 (1.54-4.48)	Q2 (4.48-6.10)	Q3 (6.10-8.33)	Q4 (8.33-10.92)	
DKD	71.43%	71.43%	57.14%	34.29%	0.004
DR	97.14%	80%	65.71%	60%	0.001
DPN	91.43%	85.71%	82.86%	62.86%	0.015
CHD	45.71%	34.29%	22.86%	8.57%	0.004
PAD	62.86%	37.14%	22.86%	22.86%	0.001

**p* represents the difference between Q1 and Q4 of eGDR

Analyzing the correlations between eGDR quartiles and chronic complications of T1DM patients with DM duration > 10 years, we found that the percentage of patients with chronic complications decreased from Q1 to Q4 of eGDR (so prevalence of chronic complications is greater in lower value of eGDR, corresponding to a higher IR), the differences being statistically significant (Table 3).

Discussions

Similar to some literature data [1-3], in our study eGDR was an accurate indicator of IR in patients with T1DM. eGDR showed lower values in MS patients than in those without MS, similar to previously reported data [1]. In our study, the optimal cut-off value of eGDR for diagnosis of MS in T1DM patients with DM duration > 10 years was 5.806 mg x kg^{-1} x min^{-1}, having 88.9% sensitivity and 72.7% specificity. For comparison, in another study [1], an eGDR value < 8.77 mg x kg^{-1} x min^{-1} had 100% sensitivity and 85.2% specificity for the diagnosis of MS in T1DM patients. eGDR was lower in patients with chronic complications compared with those without, indicating higher IR in patients with chronic complications, similar to literature data reported by Chillaron et

al. [1]. According to their study in 91 T1DM patients, diabetes complications occurred in patients in their lowest eGDR tertile (<8.16 mg x kg^{-1} x min^{-1}) [1]. Chronic complications are found in higher percentage at eGDR lower values (corresponding to a higher IR), similar to literature data reported by Epstein et al. [12].

Our study has a limit represented by the relatively small number of patients with T1DM enrolled. Although insulin resistance is not a fundamental characteristic of T1DM, there are increasingly more data that support its important role in the appearance of chronic complications of T1DM, requiring further studies on large groups of patients with T1DM.

Conclusions

eGDR represent an accurate indicator of IR in patients with T1DM and increased the risk for chronic complications. It has the advantage of being easy to calculate using routine clinical and laboratory data.

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