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RESEARCH ARTICLE

Estimated Glucose Disposal Rate in Egyptian Children and Adolescents with Type 1 Diabetes Mellitus in Relation to Their Renal Function

Jonair H. Labib[1], Azza M. Hassan [2]

1. Department of Pediatrics, Pediatric Diabetes Unit, Ain Shams University, Cairo, Egypt.
2. Department of Community, Environmental and Occupational Medicine, Ain Shams University, Cairo, Egypt.

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Corresponding Author

Jonair H. Labib

Abstract

The estimated glucose disposal rate (eGDR) is a clinical score used for indirect assessment of insulin resistance. It is based on waist to hip ratio (WHR), hemoglobin A1c (HbA1c), and the presence or absence of hypertension. The present study aimed to investigate the relationship between the insulin resistance, assessed by eGDR, in T1DM children & adolescents and their renal functions. The study included 82 Egyptian patients with T1DM who were followed up in the Pediatric Diabetes Clinic of Ain Shams University, Cairo, Egypt. Their demographic, anthropometric measures and clinical data were recorded. Assessments of HbA1c, serum creatinine, serum cystatin C, calculated GFR, creatinine clearance, twenty-four-hour urinary albumin excretion (UAE), and urinary albumin/creatinine ratio were done for all studied participants, and the eGDR was calculated. Microalbuminuria was detected in nearly one third of patients and macroalbuminuria was present in approximately one quarter of patients. The eGDR was inversely related to the diabetes duration, and the lower level of eGDR was associated with presence of diabetic nephropathy ($p=0.05$, $p=0.048$ respectively). The best cutoff value of eGDR for predicting microalbuminuria and increased urine albumin excretion was $\leq$ 8.9 mg/kg/min. Patients with lower eGDR had significantly higher microalbumin level, 24 hour UAE, serum cystatin c, serum creatinine, lower creatinine clearance, and longer duration of DM. In conclusion, low eGDR level was associated with the presence of diabetic nephropathy, and it could predict the presence of microalbuminuria and increased 24 hour UAE.

Introduction

Insulin resistance has been described in patients with type 1 diabetes mellitus (T1DM) (Teupe & Bergis, 1991), and it could place them at the high risk for development and progression of nephropathy (Orchard et al., 2002). Moreover, insulin resistance was found to be an independent risk factor for the occurrence of micro- and macro-vascular complications in T1DM patients (Pang & Narendran, 2008). In clinical practice, insulin resistance in T1DM patients is usually identified by their larger requirements for insulin (Bulum et al., 2012). A more recent method, for indirect assessment of insulin resistance, is the estimated glucose disposal rate (eGDR). The latter method has been validated by euglycemic-hyperinsulinemic clamp studies (Williams et al., 2000). The eGDR is a clinical score that is based on presence or absence of hypertension, waist to hip ratio (WHR) and hemoglobin A1c (HbA1c) (Orchard et al., 2003). The present study aimed to investigate the relationship between the presence of insulin resistance, as assessed by eGDR, in children and adolescents with T1DM and their renal function as assessed by level of microalbuminuria, 24 hour urine albumin excretion, serum creatinine, creatinine clearance, serum cystatin c and cystatin c based GFR.

Material and Methods

Patients

The study included 82 patients with T1DM who were regularly followed up in the Pediatric Diabetes Clinic of Ain Shams University Children Hospital, Cairo, Egypt. The study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. The Pediatric Department Board Committee approved upon the study protocol in January, 2013, and recruitment of patients started in February, 2013 till July, 2013. Eligibility criteria were a diagnosis of T1DM, diabetes duration ≥5 years, current age 8 to 18 years, residence in Cairo, and regular follow up at the former clinic. The exclusion criteria were end stage renal disease, end organ failure, hemodynamic instability, and major psychiatric troubles. Eligible patients who attended the clinic during the previously mentioned period were interviewed and were asked to take part in the study. Their consent and/or their guardian's consent were obtained after being fully informed about the study aims and procedures.

Study design

The study team recorded the patients' demographic data, diabetes duration, HbA1c values in the preceding year, and current insulin doses. Patients were physically examined to obtain their blood pressure, and their anthropometric measures (height in meters, weight in kg, waist and hip circumferences in centimeters). Then body mass index (BMI) and waist/hip ratio (WHR) were calculated (Katzmarzyk et al., 2004). The height, weight and BMI were all expressed in percentile values. Blood pressure was measured on 3 different occasions, and hypertension was diagnosed when the mean readings of systolic and/or diastolic values were above the 95th percentile (Raile et al., 2007)**.** In addition, neurological and fundus examination were done to detect peripheral neuropathy and retinopathy respectively.

Samples of blood and urine were obtained for assessment of serum creatinine, serum cystatin C, a calculated GFR using cystatin C-based formula, creatinine clearance, twenty-four-hour urinary albumin excretion (UAE), and urinary albumin/creatinine ratio. Blood samples were withdrawn under complete aseptic conditions and were sent rapidly to the laboratory. Urine samples were early morning samples and 24 hour urine collections that were delivered to the laboratory early in the morning. The values of WHR, mean readings of blood pressure, and mean HbA1c were used to determine the eGDR.

Measurement of waist/hip ratio

Waist and hip circumferences were measured in centimeters with an anthropometric tape while the patients were wearing light clothing. Waist circumference was measured midway between the lateral lower rib margin and the superior anterior iliac crest while the patient was standing. Hip circumference was measured at the level of bilateral greater trochanters. Then, the waist/hip ratio was calculated as waist circumference/ hip circumference (Katzmarzyk et al., 2004). There is no current consensus on the cut off value of waist circumferences and/or WHR that impose health risks among children and adolescents. However, a group of Dutch researchers documented age references for waist circumference (WC), hip circumference (HC), and waist/hip ratio (WHR) in Dutch children (Fredriks et al., 2005).

Calculation of the eGDR

It was measured in mg /kg/min and the following equation was used:

24.31 - (12.22 × *WHR*) - (3.29 × *hypertension*) - (0.57 × *HbA1C*). Hypertension was calculated as 0=no & 1=yes, and mean HbA1c level over the preceding year in percentage (DCCT units, Diabetes Control and Complications Trial units). The eGDR was reported to inversely correlate to IR; so that the lower the eGDR levels, the greater the IR (Williams et al., 2000).

Laboratory investigations

Glycosylated hemoglobin was determined by high performance liquid chromatography using the Bio-Rad hemoglobin testing system, D-10 Dual Program. The values of HbA1c of the preceding year were gathered from the patient medical records after patient and Clinic Head approval. Microalbuminuria (MA) was determined in a random spot collection using the immunoturbidimetric assay. Calculation of albumin/creatinine ratio was expressed in mg albumin/g creatinine. The diagnosis of microalbuminuria (MA) was determined when the level exceeded 30 mg/gm creatinine, while macroalbuminuria was present when the level exceeded 300 mg/gm creatinine. Serum cystatin C was assessed by ELISA technique; kits were product of Human cystatin C, Biovender Research and Diagnostic Products. The reference range for serum cystatin C was considered 0.81-1.38 mg/L (Filler et al., 2002).

Cystatin C based GFR (cGFR) was calculated in ml/min as the reciprocal of cystatin C in mg/L multiplied by 86.7 and then reduced by subtracting 4.2 (MacIsaac et al., 2006).
The twenty-four-hour urine was collected in a plain container and was taken to the hospital in the morning for evaluation of UAE, in addition to another morning sample for microalbumin testing. Girls with ongoing menstruation were asked to postpone urine sample collection. The presence of 24 hour urine albumin was assessed by photometric test, which was considered positive when the albumin was > 100mg/24 hours.

Statistical analysis

In order to describe the studied sample, quantitative data were presented as minimum, maximum, mean and standard deviation. Qualitative data e.g. sex, were presented as count and percentage. Student t test was used to compare quantitative data between two groups and one-way ANOVA was used when more than two groups were to be compared then Post Hoc test was used to detect the difference between individual groups. Chi-Square test was used to compare qualitative data between different groups, Pearson correlation test was used to compare correlation between different continuous variables, ROC curve was used to measure diagnostic validity and determine the best cut off value for some variables and logistic regression analysis was used to measure independent effect of different variables on some outcomes. Data were considered significant if a p value was ≤ 0.05 throughout the analysis. Statistical analysis was performed by version 12.0 of the Statistical Package for the Social Sciences (SPSS) computer program.

Results

Personal characteristics and demographic data of the studied patients are listed in Table 1. The mean age was approximately 15.34 years with average diabetes duration of 9.71 years; females were 56% of the studied subjects. Most of the patients' weights were below 90th percentile; most had BMI, weight, height, systolic and diastolic blood pressure percentiles within the normal range. The mean HbA1c was suboptimal (8.90 gm %), and only one third of patients had their blood glucose level optimally controlled with HbA1c < 7.5 gm% (n=28, 34.1%). Mean serum creatinine and creatinine clearance were within the normal range. Microalbuminuria was detected in nearly one third of patients (n=24, 29.3%), and macroalbuminuria was present in approximately one quarter of patients (n=18, 22%). Sixteen patients were hypertensive (19.51%), four patients had retinopathy and another four had peripheral neuropathy (4.9% each).

The eGDR

The Median value of eGDR was 8.1 mg/kg/min, but the mean eGDR was 7.96 mg/kg/min. Patients with lower insulin sensitivity (below the median eGDR value) had renal functions that were not statistically different from the renal functions of those having eGDR higher than the median value. The level of insulin sensitivity (eGDR) was inversely related to the diabetes duration, and the lower level of eGDR was associated with presence of diabetic nephropathy (p=0.05, p=0.048 respectively) as listed in Table 2. There was no significant relation between the eGDR level and the presence of diabetic retinopathy or neuropathy in the studied patient group. Neither WHR nor HbA1c was related to any of the renal function parameters (p>0.05). Serum cystatin, microalbumin level, UAE were all positively correlated with the duration of diabetes (p=0.002, p= 0.032, p=0.017 respectively), while cGFR was inversely correlated with the duration of diabetes (r= - 0.388, p=0.012). The systolic blood pressure percentiles were positively correlated with the serum cystatin c levels (p=0.037), but was not related to the rest of renal function parameters. On the other hand, diastolic blood pressure percentiles were not related to any of the renal function tests. Applying the receiver operating characteristic (ROC) curve, the best cutoff value of eGDR for predicting the presence of microalbuminuria was ≤ 8.9 mg/kg/min, with 81% sensitivity, 50 % specificity, and area under the curve of 0.652 (Fig.1). The same eGDR cut off value could predict the increased urine albumin excretion with 73.3% sensitivity , 54.4 % specificity, and area under the curve of 0.617 (Fig.2). Upon splitting of the patients into 2 groups according to the eGDR cut off value (Table 3), patients with lower eGDR and lower insulin sensitivity, had significantly higher microalbumin level, 24 hour UAE, serum cystatin c, serum creatinine, lower creatinine clearance, and longer duration of DM.

Table 1. Patients' demography, clinical and laboratory data (n=82)

Variable	Mean ± SD	Range
Age (years)	15.34±2.48	9.2-18.00
Duration of diabetes (years)	9.71±3.28	5.3-17.5

Body weight (Kg)	53.67±14.42	25.3-80.4
Body weight percentiles (n & %)		
5-90	70	85.37%
90-95	12	14.63%
>95	0	0%
Height (cm)	152.83±12.59	125.5-169
Height percentiles (n & %)		
<5	16	19.51%
5-90	62	75.61%
90-95	4	4.88%
>95	0	0%
BMI (kg/m^2)	22.59±3.79	13.50-30.40
BMI percentiles (n & %)		
5-90	62	75.61%
90-95	14	17.07%
>95	6	7.32%
SBP (mmHg)	114.27±9.32	100-140
SBP percentiles (n & %)		
>10-90	74	90.24%
90-95	2	2.44%
>95	6	7.32%
DBP (mmHg)	75.37±6.74	60-90
DBP percentiles (n & %)		
>25-90	68	82.92%
90-95	6	7.32%
>95	8	9.76%
Hb A1c in gm%	8.90±1.93	6-14
WHR	0.87±0.08	0.75-1.15
eGDR (mg/kg/min)	7.96±1.72	4.49-10.75
Micro-albumin (mg/gm)	54.95±60.47	3-280
24 hrs urinary proteins (mg/24hrs)	175.29±213.86	4-1000
Cystatin C in (ng/dl)	2469.51±1899.89	250-6500
cGFR (ml/min/1.73 m^2)	67.32±66.29	9.13-341.8
Serum creatinine (mg/dl)	0.70±0.20	0.5-1.4
Creatinine clearance (ml/min/1.73 m^2)	133.68±36.27	54.6-227.9

SBP, systolic blood pressure; **DBP,** diastolic blood pressure; **cGFR**, cystatin C-based GFR.

Table 2. Relation between eGDR and different studied variables

Variable		Mean	SD	Pearson correlation	P value
Age in years		15.34	2.48	-0.04	0.83
Body weight in Kg		53.67	14.42	-0.23	0.14
Height in cm		152.83	12.59	-0.12	0.47
BMI (kg/m^2)		22.59	3.79	-0.25	0.11
Duration of diabetes in years		9.71	3.28	-0.30	***0.05***
Micro-albumin in mg/gm		54.95	60.47	-0.05	0.75
24 hrs urinary proteins in mg/24hrs		175.29	213.86	-0.11	0.51
Cystatin C in ng/dl		2469.51	1899.89	-0.24	0.14
cGFR (ml/min/1.73 m^2)		67.32	66.29	0.10	0.55
Serum creatinine in mg/dl		0.70	0.20	-0.06	0.71
Creatinine clearance (ml/min/1.73 m^2)		133.68	36.27	0.02	0.92
		eGDR		**Student t**	**P value**
		Mean	**SD**		
Sex	**Male**	7.67	1.62	-0.68	0.50
	Female	8.08	1.78		
Nephropathy	**No**	7.60	2.05	1.71	***0.048***
	yes	7.40	1.58		

cGFR, cystatin C-based GFR

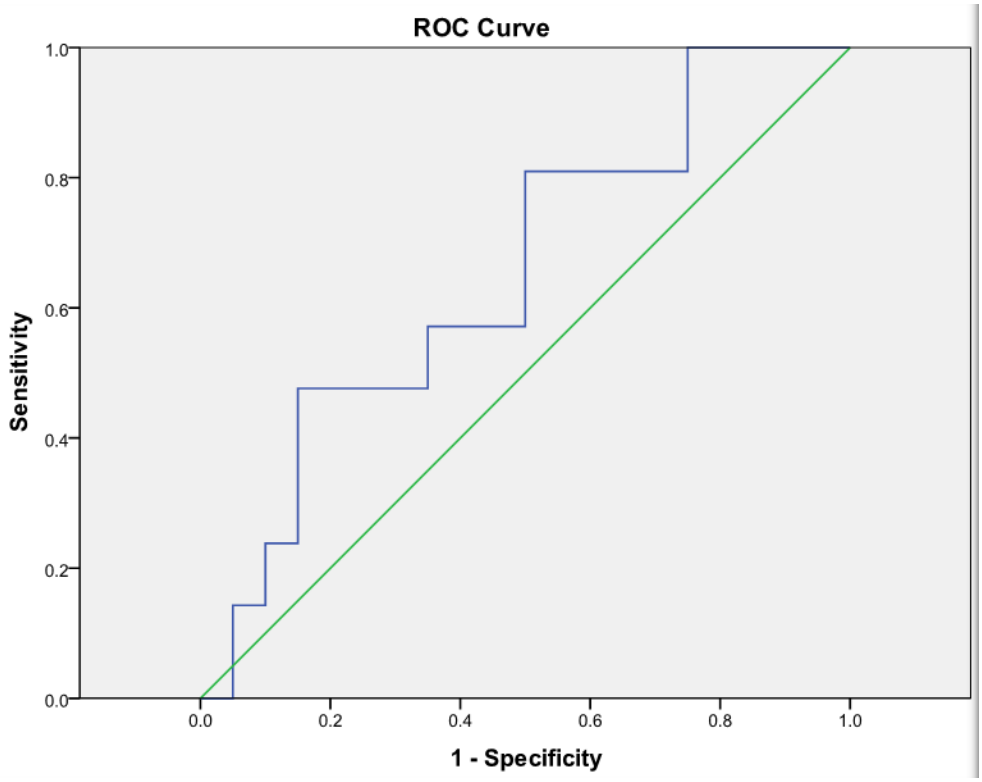
Table 3. Comparison between patients above and below cut off value of eGDR (8.90 mg/kg/min) regarding personal characteristics

Variable	(eGDR ≤ 8.90) (n=54)		(eGDR > 8.90) (n=28)		Student t test	P value
	Mean	**SD**	**Mean**	**SD**		
Age in years	15.67	2.27	14.71	2.81	1.17	0.25
Body weight in Kg	55.98	14.59	49.21	13.50	1.44	0.16
Height in cm	154.44	12.17	149.71	13.25	1.15	0.26
BMI (kg/m^2)	23.07	3.92	21.65	3.47	1.15	0.26
Duration of diabetes in years	10.70	3.00	7.79	3.02	2.95	***0.01***
Micro-albumin in mg/gm	68.55	67.70	28.74	30.99	2.58	***0.01***
24 hrs urinary albumin in mg/24hrs	215.85	240.49	97.07	122.70	1.73	0.09
Cystatin C in ng/dl	2985.19	2027.16	1475.00	1127.02	3.06	***0.004***
cGFR (ml/min/1.73 m^2)	60.09	75.55	81.25	42.28	-0.97	0.34
Serum creatinine in mg/dl	0.75	0.22	0.59	0.09	3.24	***0.002***
Creatinine clearance (ml/min/1.73 m^2)	125.30	39.09	149.83	23.78	-2.14	***0.04***
	N.	**%**	**N.**	**%**	**Chi square test**	**P value**

Variable		(eGDR ≤ 8.90) (n=54)		(eGDR > 8.90) (n=28)		Student t test	P value
		Mean	SD	Mean	SD		
Age in years		15.67	2.27	14.71	2.81	1.17	0.25
Body weight in Kg		55.98	14.59	49.21	13.50	1.44	0.16
Height in cm		154.44	12.17	149.71	13.25	1.15	0.26
BMI (kg/m^2)		23.07	3.92	21.65	3.47	1.15	0.26
Sex	**Male**	10	37.04%	2	14.29%	2.31	0.13
	Female	17	62.96%	12	85.71%		
Nephropathy	**No**	20	88.89%	20	92.86%	8.73	***0.003***
	Yes	34	11.11%	8	7.14%		

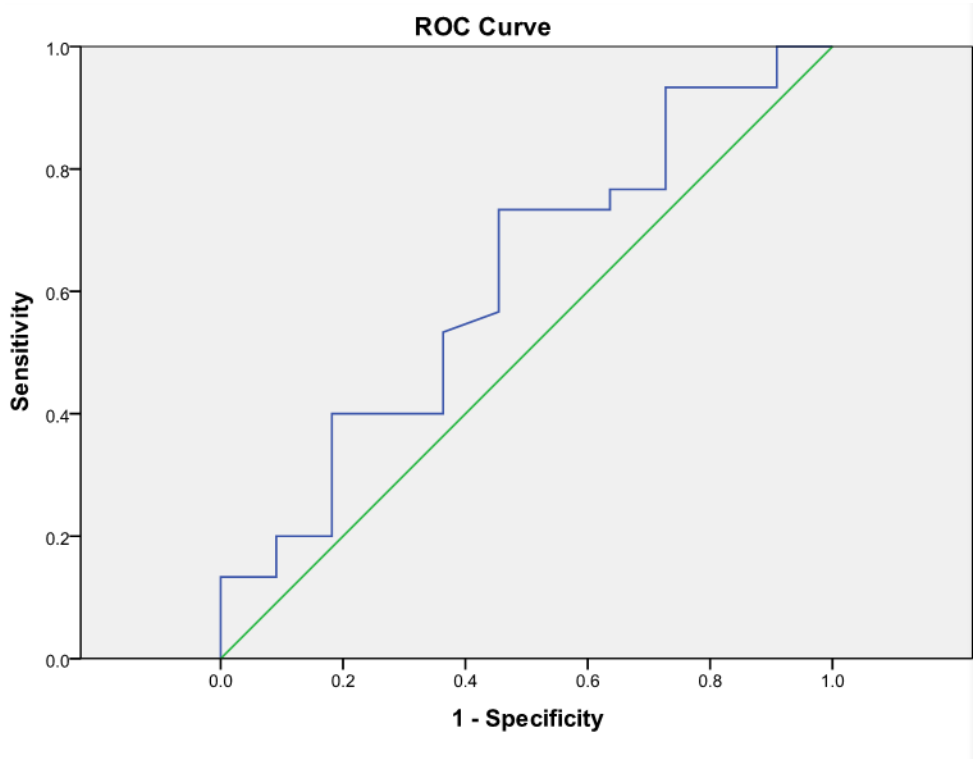
cGFR, cystatin C-based GFR

Fig 1. Cut off value for eGDR for diagnosis of microalbuminuria



Cut off value for eGDR with highest sensitivity and specificity to predict microalbuminuria is (< or =8.90 mg/kg/min) where sensitivity = 81% and specificity = 50% and area under the curve of 0.652.

Fig 2. Cut off value for eGDR for diagnosis of high 24 hourr urine albumin excretion



Cut off value for eGDR with highest sensitivity and specificity is (< or =8.90 mg/kg/min) where sensitivity = 73.3% and specificity = 54.4% and area under the curve of 0.617.

Fig 1. Cut off value for eGDR for diagnosis of microalbuminuria.

Fig 2. Cut off value for eGDR for diagnosis of high 24 hourr urine albumin excretion.

Discussion

Insulin resistance plays a central role in metabolic syndrome (Eckel et al., 2005), and seems to act as an independent cardiovascular risk factor in both T1DM and T2DM (Orchard et al., 2003). Several studies reported that lower insulin sensitivity in T1DM was associated with higher risk of micro- and macro-vascular complications (Orchard et al., 2002; Tesfaye et al., 2005; Thorn et al., 2005; Kilpatrick et al., 2007). Overt diabetic nephropathy was one of these microvascular complications associated with the presence of insulin resistance in T1DM (Orchard et al., 2002). The present study was a trial to uncover the relation between insulin resistance and the presence of diabetic nephropathy in T1DM pediatric sample.

Approximately two thirds of our diabetic patients had suboptimal or high levels of HbA1c, which partly explained the presence of micro- and macro-albuminuria in more than half of the studied patients (51.3%). Poor glycemic control is one of the main risk factors accounting for progression to microalbuminuria (Chaturvedi et al., 2001). Optimal glycemic control decreases the risk of developing microalbuminuria in both T1DM and T2DM patients (Krolewski et al., 1995; Gaede et al., 2003). There was no significant correlation between HbA1c and any parameter of renal functions, nevertheless efforts for optimal control of HbA1c should be continued at all times. Another study, in adult population with longer duration of diabetes, documented that HbA1c was positively correlated with UAE and negatively correlated with creatinine clearance. However, the authors did not identify a glycemic threshold for the development of microalbuminuria (Bulum et al., 2012).

In the present study, nearly one fifth of patients suffered from hypertension. The systolic blood pressure percentiles were positively correlated with serum cystatin c levels (p=0.037). The impact of increased blood pressure on renal function is substantial, and raised blood pressure was an independent risk factor for the development of microalbuminuria. In addition, blood pressure control could decrease UAE and delay kidney function deterioration in T1DM patients (Mogensen et al., 1995; Mogensen et al., 2003). However, the EURODIAB PCS study, which

included 1134 T1DM adult patients, did not confirm this association (Chaturvedi et al., 2001). Other components of the eGDR equation (WHR & HbA1c) were not related to any of the renal function parameters. However, Bulum and colleagues described that HbA1c was correlated positively with UAE, and negatively with creatinine clearance. They also stated that serum creatinine and creatinine clearance were significantly correlated with WHR in adult T1DM patients (Bulum et al., 2012).

The diabetes duration was positively correlated with serum cystatin, microalbumin level, UAE and inversely correlated with the cGFR. The level of insulin sensitivity (eGDR) was inversely related to the diabetes duration as well. Duration of diabetes is known to be associated with increased risk of hypertension and microalbuminuria (Warram et al., 1996; Chillarón et al., 2011). The decreased insulin sensitivity with longer duration of diabetes might be related to the progressive increase in weight of poorly controlled diabetic patients who have high WHR.

The presence of diabetic nephropathy in the form of micro- or macro-albuminuria was significantly associated with lower eGDR values. The ROC curve defined the best cutoff value of eGDR for predicting both the presence of microalbuminuria and increased UAE to be $\leq$ 8.9 mg/kg/min, with very close sensitivity and specificity. Patients with eGDR below this value had significantly higher microalbumin level, 24 hour UAE, serum cystatin c, serum creatinine, lower creatinine clearance, and longer duration of DM.

It is documented that in conditions with decreased insulin sensitivity, insulin level may rise to supranormal concentrations that may induce glomerular hyperfiltration, increased vascular permeability, and endothelial dysfunction (Catalano et al., 1997). Furthermore, reduced insulin sensitivity was associated with altered kidney metabolism at cellular level, mesangial hyperplasia, and endothelial proliferation. These effects may contribute to the progressive renal damage (Parvanova et al., 2006). Low-grade inflammation and increased oxidative stress, resulting from insulin resistance, might also contribute to nephropathy (Bulum et al., 2012). Increased levels of C-reactive protein and interleukin 6 were associated with decreased insulin sensitivity, and might worsen the severity of the renal disease (Saraheimo et al., 2003). The measurement of insulin resistance using euglycemic-hyperinsulinemic clamp test, was not done in the present study due to lack of accessibility. Instead, the study team implemented the eGDR equation which was a validated, non-invasive method that can be easily used in the pediatric population. This eGDR equation, based on WHR, blood pressure, and HbA1c, provided a reliable assessment of renal function in T1DM pediatric patients. The total impact of the three former parameters was more significant in predicting renal dysfunction than their individual impact. However, the EURODIAB Prospective Complications Study (PCS) stated that elevated WHR was a risk factor for development of microalbuminuria, independently of diabetes duration and HbA1c (Chaturvedi et al., 2001) Since the progressive renal damage occurs in the majority of T1DM patients, further studies of the role of insulin resistance in development of microvascular complications, particularly nephropathy, in T1DM may be needed.

Conclusion

Low eGDR level was associated with the presence of diabetic nephropathy. A cut off value of $\leq$ 8.9 mg/kg/min could predict the presence of microalbuminuria and increased 24 hour UAE. Diabetic patients below this cut off value had significantly impaired renal functions.

Conflict of interest statement

Authors have no conflict of interest to declare.

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