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Original Article

The prevalence and the clinical profile of metabolic syndrome in children and adolescents with Type 1 diabetes

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1. Introduction

Diabetes is one of the commonest chronic metabolic diseases in the pediatric age group. Although it is not contagious, it is considered the first and only health problem regarded by the United Nations as an epidemic of the 21st century [1]. The WHO report in 2017 has mentioned that about 425 million people suffer from diabetes. It is believed that this range can increase to 642 million by 2040 [2].

Although insulin therapy has decreased the development of microvascular and macrovascular diabetic complications, it might cause increased weight gain and obesity-associated cardiovascular (CV) risk factors. A group of CV risk factors known as metabolic syndrome (MS) (central obesity, insulin resistance, hypertension and abnormal lipid profile) are also associated with increasing atherosclerosis in children and adolescents with T1DM [3,4].

Several mechanisms have been hypothesized for the underlying pathophysiology of MS, and the most widely accepted of them is insulin resistance (IR) with fatty acid flux. Other possible mechanisms include oxidative stress and low-grade chronic inflammation [5].

Insulin resistance (IR) in T1DM might be related to the route of administration of exogenous insulin therapy. Insulin absorbed from subcutaneous (SC) tissues results in relative peripheral hyperinsulinemia and hepatic hypoinsulinemia compared with normal physiology. Chronic adaptation to the present combination may decrease peripheral insulin-mediated glucose uptake and increase hepatic glucose production. Moreover, reduced hepatic insulin exposure could result in a reduced level of circulating insulin growth factor-1 (IGF-1), with a parallel increase in growth hormone and IGF-binding proteins, which may also contribute to increased peripheral insulin resistance [6–8].

The euglycemic-hyperinsulinemic clamp is the accepted standard for measurement of insulin sensitivity (IS); however, it is not practical for use in the clinical setting it is invasive, expensive and mainly used in research settings. Moreover, HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) or QUICKI (Quantitative Insulin Sensitivity Check Index) cannot be used in patients on insulin treatment. The estimated glucose disposal rate (eGDR) can be easily calculated using routine clinical measures: glycosylated hemoglobin (HbA1c), presence of hypertension and waist circumference. The eGDR shows good correlation with IR measured by the euglycemic-hyperinsulinemic clamp and has been validated for the estimation of IS in individuals with T1DM. Therefore, eGDR represent an accurate indicator of IR and increased risk of chronic complications in patients with T1DM [9–11].

This study aims to determine the prevalence of MS in Egyptian children and adolescents with T1DM, and to assess its relation with certain clinical parameters (anthropometric measures [weight, height, BMI, waist circumference], arterial blood pressure, and pubertal status) and laboratory parameters (glycosylated hemoglobin, urine albumin-to-creatinine ratio, fasting lipid profile and insulin resistance (IR) assessed by eGDR). Moreover, the relation of IR to these clinical and laboratory parameters will be assessed.

2. Subjects and methods

2.1. Patients

This cross-sectional study was conducted on 160 children and adolescents with T1DM. All were recruited from Diabetes, Endocrine& Metabolism Pediatric Unit (DEMPU); Cairo University during the period from July 2017 to June 2018. Patients were included if they have T1DM for 1 year or more and their age were below 18 years. Patients with associated endocrinal, systemic diseases or patients on long term medications apart from insulin were

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excluded from the study.

2.2. Methods

The study protocol was approved by the ethical committee of Cairo University Hospital Research Committee. The study and data collection were conformed to all local laws and were compliant with the principles of the Declaration of Helsinki. Written informed consent and assents were obtained from parent/guardian or patients after an explanation of the details of the study.

The entire study group was subjected to the following:

- Thorough history taking laying stress on age, gender, age of onset of diabetes, diabetes duration, diabetes complications, any long term medications other than insulin, in addition to family history of diabetes.
- Complete clinical examination stressing on:
  - Complete physical examination including: anthropometric measurements, including weight, weight SDS, height, height SDS, body mass index (BMI), BMI SDS and plotting of the anthropometric measure on standard deviation curve be analyzed by the software program Growth Vision 2 provided by Novo-Nordisk, Denmark.
  - Pubertal assessment according to the norms of Tanner staging for girls and boys [12,13].
  - Blood pressure (BP) measurements will be compared to age-specific percentiles for BP [14].
  - Waist circumference (WC) using a tape measure at just above the uppermost lateral border of the right ilium, at the end of a normal expiration, and was recorded at the nearest millimeter (mm), as recommended by the National Center of Health Statistics. Then, plotted on WC percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents [15].
- The most recent results of laboratory tests (glycosylated hemoglobin (HbA1c)), urine albumin-to-creatinine ratio (A/C ratio), fasting lipid profile including: serum Cholesterol (TC), Triglycerides (TG), High density lipoproteins (HDL) and Low-density lipoproteins (LDL) were obtained from the medical record.
- Insulin resistance was assessed by calculating estimated glucose disposal rate (eGDR) mg Kg $^{-1}$ min $^{-1}$ from the formula of " 21.158-[3.407 × hypertension status (yes = 1; no = 0) − [0.09 × waist circumference (cm) − [0.551 × HbA1c (%)] [16].
- Metabolic syndrome (MS) was defined in patients with diabetes as having three or more of these criteria: 1) abdominal obesity (waist circumference ≥ the age- and gender specific 90th percentile for this population); 2) high blood pressure (systolic and/or diastolic blood pressure ≥ age and gender and height specific 90th percentile), 3) decreased HDL level (≤40 mg/dL); 4) elevated serum TG (≥150 mg/dL) 5) elevated fasting blood glucose (FBS) (≥100 mg/dL). All our patients with diabetes had the fifth criterion (elevated FBS), thus having two or more of the above criteria was defined as metabolic syndrome in our patients [3].
- The study group was divided according to these criteria into 2 groups; Non MS group (patients with diabetes with no metabolic syndrome) and MS group (patients with diabetes and metabolic syndrome).

2.3. Statistical analysis

All data were tabulated and analyzed using the Statistical Package for Social Science (SPSS version 22). Mean and standard deviation were used for quantitative data, while frequency and percentage were done for qualitative data. Comparison of numerical variables was done using Mann Whitney *U* test for independent samples. Chi square ($\chi 2$) test was performed for comparing categorical data. P values < 0.05 was considered statistically significant.

3. Results

The study included 160 children and adolescents with T1DM, 77 males, 81 females, their mean age was 13.38 ± 2.17 years, the mean diabetes duration was 5.74 ± 3 (1–15) years, mean HbA1c was 9 ± 2.16 (6–14.9) gm%.

Using IDF based criteria, 21 (13.12%) of these children and adolescents with T1DM had MS. Non MS group included 139 patients; 68 females and 71 males, their mean age was 13.28 ± 2.17 years, while MS group included 21 patients; 15 females and 6 males, their mean age was 14.03 ± 2.08 years. MS group had significantly higher percentage of pubertal subjects. In addition, weight, weight SDS, BMI, diastolic blood pressure and WC were significantly higher in MS group (Table 1).

As regards the laboratory findings, lipid profile (TC, TG, LDL) were significantly higher in the MS group. However, eGDR was significantly lower in the MS group indicating significantly higher insulin resistance (Table 2).

Table 3 showed significant negative correlations between eGDR and age, diabetes duration, weight, BMI, systolic and diastolic BP, HbA1c, A/C ratio and fasting lipid profile (TC, TG, LDL) with no significant correlation with the required insulin dose.

4. Discussion

Using IDF based criteria, 13.12% of children and adolescents with T1DM in this sample were estimated to have MS. This is different from an Iranian study that showed a prevalence of 23.9% [3] and another one which found MS in 9.5% patients [17]. The different prevalence in MS in different studies may be due to ethnic and racial differences in addition to variations in the MS definition throughout different studies.

In our study, the percentage of the pubertal patients was significantly higher in MS group. This agreed with a recent study which found that most of the MS patients were pubertal and considered that time in puberty is a more important risk factor for adolescents than age [18].

In the present study, patients with MS had significantly higher body weight, BMI and WC. This is in agreement with *earlier studies* found that MS is more prevalent in obese and overweight patients and this can be explained by the current trend of increasing weight and obesity and its complications in the general population which is considered an important risk factor for the development of metabolic syndrome especially the central obesity [17,18].

However, HbA1c and the insulin dose (as an indirect measure of insulin resistance) showed no significant difference between the two groups and fail to differentiate between the patients with and without MS [19]. This is also in line with earlier studies which reported that there was no difference in insulin dose between groups [18,20]. While this is on the contrary to a previous study which demonstrated that T1DM patients with MS exhibited higher insulin requirement per body surface area and higher HbA1c than patients without MS [17].

We found also that MS group had significantly higher diastolic BP, fasting lipid profile (TC, TG and LDL), this agreed with another study which emphasized that those patients with T1DM are at particularly high risk of cardiovascular disease already, so there has been concern that this increase in body weight may only add to this likelihood [21].

Table 1
Demographic and clinical characteristics in the study groups.

	Non-MS group (n = 139)	MS group (n = 21)	P-value
Age (years)	13.28 ± 2.17	14.03 ± 2.08	0.069
Sex			
Females	68 (48.95%)	15 (71.4%)	0.054
Males	71 (51.1%)	6 (28.6%)	
Puberty			
Pubertal	74 (53.2%)	18 (85.7%)	0.005*
Pre-pubertal	65 (46.8)	3 (14.3%)	
Age of onset of diabetes (years)	7.5 ± 2.9	7.1 ± 2.34	0.28
Duration of diabetes (years)	5.6 ± 3	6.68 ± 2.68	0.063
Insulin dose (IU/Kg/d)	1.2 ± 0.4	1.36 ± 0.5	0.45
Weight (Kg)	44.7 ± 12.7	54.69 ± 16.7	<0.001*
Weight SDS	0 ± 1.1	2.33 ± 0.77	0.001*
Height (cm)	145.45 ± 13.48	149.2 ± 10.87	0.113
Height SDS	−1.08 ± 1.28	−1.2 ± 2	0.35
BMI (kg/m2)	20.58 ± 3.53	24.25 ± 6.26	<0.001*
BMI SDS	0.67 ± 1	1.25 ± 1.58	0.47
Systolic BP (mmHg)	112 ± 14.5	118.94 ± 15.27	0.056
Diastolic BP (mmHg)	74.57 ± 10.1	79.75 ± 10.44	0.032*
WC (cm)	75.3 ± 9.76	81.33 ± 11.47	0.005*

*P values < 0.05 was Significant, BMI: body mass index, SDS: standard deviation score, WC: waist circumference, BP: blood pressure.

Table 2
Laboratory data in the study groups.

	Non-MS group (n = 139)	MS group (n = 21)	P-value
HbA1c (%)	9 ± 2.03	9.44 ± 2.22	0.19
HDL (mg/dl)	50.67 ± 14	45.76 ± 7.45	0.59
LDL (mg/dl)	102.85 ± 31.4	129.71 ± 41.89	<0.001*
TG (mg/dl)	85 ± 40.25	145.48 ± 65.44	<0.001*
TC (mg/dl)	167.17 ± 35.78	201.29 ± 56.73	<0.001*
eGDR (mg Kg ' min ')	8.63 ± 2.29	7.36 ± 2.77	0.01*

*P values < 0.05 was Significant, AC: Albumin/Creatinine ratio, eGDR: estimated glucose disposal rate, HbA1c: glycosylated hemoglobin, HDL: High density lipoproteins, LDL: Low density lipoproteins, TC: Cholesterol, TG: Triglycerides.

Table 3
Correlations between eGDR and different variables in the study.

	Pearson correlation	P- value
Age	−0.27	0.001*
Age of onset of diabetes	−0.028	0.73
Duration of diabetes	−0.18	0.02*
Insulin dose (IU/Kg/d)	0.04	0.61
Weight	−0.35	<0.001*
BMI	−0.27	0.001*
Systolic BP	−0.48	<0.001*
Diastolic BP	−0.4	<0.001*
WC	−0.5	<0.001*
HbA1c	−0.69	<0.001*
A/C ratio	−0.18	0.02*
HDL	0.01	0.94
LDL	−0.18	0.02*
TG	−0.18	0.02*
Cholesterol	−0.16	0.04*

*P values < 0.05 was Significant, A/C ratio: Albumin/Creatinine ratio, BMI: Body mass index, eGDR: estimated glucose disposal rate, HbA1c: glycosylated hemoglobin, HDL: High density lipoproteins, LDL: Low density lipoproteins, TC: Cholesterol, TG: Triglycerides, WC: waist circumference, BP: blood pressure.

We found that MS group had significantly lower eGDR. This is in line with many previous studies which found that eGDR was an accurate indicator of IR in patients with T1DM and eGDR showed lower values in MS patients than in those without MS, like previously reported data [10,11,20,22].

In this study; eGDR had significant negative correlations with age, duration of diabetes, weight, BMI, WC, SBP, DBP, HbA1c, A/C ratio, fasting lipid profile (TC, TG and LDL). However, eGDR has no significant correlation with the insulin dose. This is in line with a previous study which found that 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 ($r = -0.310$, $p = 0.0001$), TC ($r = -0.170$, $p = 0.045$), HDL ($r = 0.209$, $p = 0.016$) and TG ($r = -0.330$, $p = 0.0001$). Also, he found that, eGDR was lower in patients with chronic complications compared with those without, indicating higher IR in patients with chronic complications [11]. Moreover, it was found that patients with the lowest eGDR compared with the highest eGDR had a significantly greater risk of any diabetes complication compared with the least IR patients [9].

5. Conclusion

Metabolic syndrome (MS) is more prevalent in pubertal patients with T1DM (13.12%). In addition, weight, weight SDS, BMI, diastolic blood pressure, WC and Lipid profile (TC, TG, and LDL) were significantly higher in patients with MS. However, eGDR was significantly lower in the MS group indicating significantly higher IR in patients with MS. Thus, MS is significantly correlated with cardiovascular (CV) risk factors in T1DM.

Declarations of interest

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