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Prevalence of Metabolic Syndrome in Children With Type 1 Diabetes in South of Iran

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Abstract

Objectives: The aim of this study was to investigate the prevalence of metabolic syndrome, in children with type one diabetes mellitus (T1DM) for the first time in a population in the Middle East, and assess the influence of type of insulin therapy, daily dosage of insulin, family history of type 2 diabetes, gender and level of HbA1c on the prevalence of metabolic syndrome.

Methods: This cross-sectional study was conducted on children with T1DM aged < 20 years, and duration of T1DM >2 years during years 2013 to 2014. Waist circumference, blood pressure, height and weight of children with diabetes, for calculation of body mass index (BMI), were measured by one physician. Fasting blood glucose and lipids were also measured. According to the age-modified standards of the ATPIII, metabolic syndrome was defined. All data were analyzed using the SPSS 18 software.

Results: In this study, 87 children with diabetes (48 females and 39 males) aged 12.38 ± 4.2 were enrolled. Overall, 40.9% of our patients had hypertension, 55.2% had hypertriglyceridemia, 36.8% had low high-density lipoprotein (HDL) and 6.9% of patients had abdominal obesity. Furthermore, 29.9% of these children had metabolic syndrome, which did not have a significant association with the type of insulin regimen (P = 0.97), nor the daily dosage of insulin (P = 0.234), however the serum concentration of HbA1c had a significant correlation with metabolic syndrome (P = 0.027).

Conclusions: This study provides evidence indicating high prevalence of metabolic syndrome in children with T1DM in southern Iran. Preventive programs aimed towards decreasing the risk factors of metabolic syndrome and interpretation of a healthier diet and physical activity for children with T1DM should be considered in our country.

Keywords: Hypertension, Hypertriglyceridemia, High Density Lipoprotein, Obesity, Metabolic Syndrome, Type 1 Diabetes Mellitus

1. Background

Type 1 diabetes mellitus (T1DM) is one of the most prevalent autoimmune diseases in children (1). Although insulin therapy has decreased the development of microvascular and macrovascular complications of diabetes (2), it could promote weight gain and obesity-associated cardiovascular risk factors (2-4). A group of cardiovascular risk factors known as metabolic syndrome (abdominal obesity, insulin resistance, abnormal lipid profile and hypertension) are also associated with increasing atherosclerosis in children with T1DM (5). It could increase the mortality of children with T1DM by four to eight folds compared to non-diabetic age-matched children (6). Up to now, four studies in Norway, Germany, Poland and the Netherlands were done to evaluate the prevalence of metabolic syndrome in children with T1DM (2, 7-9). They showed that metabolic syndrome was seen in 13 to 28% of children with T1DM in these European countries (2, 7-9).

2. Objectives

The present study investigated the prevalence of metabolic syndrome in children with T1DM for the first time in a population from the Middle East. We also studied metabolic syndrome, according to an adjusted pediatric definition, and assessed the influence of type insulin therapy, daily dosage of insulin, family history of type 2 diabetes, gender and level of HbA1c on the prevalence of metabolic syndrome.

3. Methods

3.1. Patients

This was a cross-sectional study on all children with T1DM, whom were referred to the pediatric diabetes clinic affiliated with the Shiraz University of Medical Sciences, between July 2013 and August 2014.

The inclusion criteria were, age of < 20 years, duration of T1DM more than two years, Fasting blood sugar (FBS)

> 125 mg/dL or random blood sugar ≥ 200 mg/dL along with the presence of diabetes symptoms (e.g. polyuria and polydipsia), and insulin dependency for controlling blood sugar in the normal range. Diagnosis of T1DM in children was confirmed by the frequent presence of auto-antibodies (10), glutamic acid decarboxylase, islet-cell-antibody and insulin auto anti body (10) in blood samples.

We excluded all children with diabetes who had a known chronic liver disease, congenital heart disease and chronic kidney diseases.

During the patients visits to the outpatient clinic, the waist circumference, and height and weight for calculation of body mass index (BMI) were measured by one physician with standard methods with a wall-mounted meter and a standard scale (Seca, Germany), respectively; the child standing in a light dress and without shoes. During this visit, a detailed history, including glycemic control, insulin regimen and family history of type-2 diabetes were recorded. Furthermore, three consecutive blood pressures were measured for all patients with at least five-minute intervals, in a seated position and through a standard method with an appropriate cuff using an ALPK2 sphygmomanometer (Zhejiang, China).

Fasting blood glucose and lipids were measured after overnight fasting. Fasting blood sugar (FBS) was measured by the enzymatic colorimetric method using glucose oxidase test. Serum total cholesterol and triglyceride (TG) concentrations were measured by enzymatic reagents (Pars Azmoon, Tehran, Iran) with a Selectra Autoanalyses. High-density lipoprotein-cholesterol (HDL-C) was measured after apolipoprotein B-containing lipoproteins precipitation with phosphotungstic acid.

There are some definitions for defining metabolic syndrome in adults, however in children there is limited data (5, 11, 12). We defined metabolic syndrome in our diabetic children according to age and gender-modified standards of the IDF (12). In this system, metabolic syndrome 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, except for those 18 - 20 years old, which has cut-off values of ≥130 and ≥85 mmHg for systolic and diastolic blood pressure, respectively) 3) reduced HDL-C level (≤ 40 mg/dL); 4) elevated serum TG (≥ 150 mg/dL) 5) elevated 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. Another definition for metabolic syndrome is ATPIII, which considers gender and age differences (5, 11) to avoid the confusion arose due to conflicting opinions on the value of each set of criteria.

All data were analyzed by the SPSS 18 software. Mean ± standard deviation (SD) and interquartile range (IQR) were measured for all the general characteristics and biochemical parameters. Prevalence of metabolic syndrome in both genders, type of insulin regime and family history of DM2 (yes or no) was also calculated. Comparison of the prevalence values in each group was done, using the chi-square test. $P < 0.05$ was defined as statistical significance.

4. Results

In this study, 87 children with diabetes (48 females and 39 males) aged 12.38 ± 4.2 were enrolled. Twenty-three children (26.4%) had family history of type 2 diabetes mellitus. Three boys (3.4%) were cigarette smokers. Eighty-three percent, 48.5% and 63% of patients had positive results for glutamic acid decarboxylase, islet-cell-antibody and insulin auto anti body, respectively. High blood sugar in 36 patients (41.4%) was controlled with insulin regime of NPH twice daily added to regular insulin. Others were controlled with once daily Glargin and three times Aspart insulin per meal. Other general characteristics and biochemical variables are summarized in Table 1.

According to the IDF definition, 14.9% of our patients had hypertension, 37% had hypertriglyceridemia, 36.8% had low HDL and 6% had abdominal obesity. There was no difference between genders regarding these parameters. Only one patient had diabetic nephropathy and hypertension that was excluded from this study. Data are summarized in Table 2. However, according to ATPIII criteria, 14.9%, 51.1%, 36.8%, and 6.9% of the patients had hypertension, hypertriglyceridemia, low HDL, and abdominal obesity, respectively.

According to IDF definition and irrespective of high blood sugar, 20 patients did not have any other criteria of metabolic syndrome; 35 patients had one criteria, 21 two criteria and one patient had three criteria of metabolic syndrome. There was no significant difference between the prevalence of obesity in different genders ($P = 0.528$). Among the 87 T1DM children, 23 patients had a family history of type 2 diabetes mellitus (T2DM), nine of whom had metabolic syndrome; family history of T2DM was not associated with the development of metabolic syndrome ($P = 0.193$). Also metabolic syndrome did not have a significant association with the type of insulin regimen ($P = 0.97$), nor the daily dosage of insulin ($P = 0.234$), however the serum concentration of HbA1c had a significant correlation with metabolic syndrome ($P = 0.027$).

Table 1. General Characteristics of the Patients

Variable	Female		Male		Total	
	Mean ± SD	IQR	Mean ± SD	IQR+	Mean ± SD	IQR+
Age	11.88 ± 4.03	9-15	13 ± 4.4	10-16	12.38 ± 4.2	9 - 15
Duration of DM	4.41 ± 3.36	3 - 4	4.35 ± 2.05	3 - 5	4.4 ± 2.8	3 - 4
Insulin/kg	0.72 ± 0.24	0.54 - 0.9	0.67 ± 0.29	0.46 - 0.88	0.69 ± 0.26	0.89 - 65
Weight	37.29 ± 13.87	25 - 47.7	42.6 ± 16.5	29 - 56	39.7 ± 15.3	27 - 50
Height	143.3 ± 17.6	130 - 158	150.6 ± 22.1	136 - 170	146.6 ± 19.9	131 - 161
Diastolic BP	65.7 ± 7.9	60 - 70	67.7 ± 8.7	60 - 70	66.6 ± 8.3	60 - 70
Systolic BP	107.19 ± 10.04	102.5 - 110	110.5 ± 13.7	110 - 120	108.7 ± 11.9	110 - 120
HbA1c	10.23 ± 2.28	10 - 11.6	10.1 ± 2.2	8.3 - 11.7	10.15 ± 2.23	8.4 - 11.7
Age - onset of DM	7.46 ± 3.65	4.25 - 10	8.6 ± 4.4	5 - 12	7.9 ± 4.1	5 - 11
Waist circumference	68.54 ± 9.33	59.2 - 75	72.2 ± 10.3	67 - 78.7	70.2 ± 9.9	61 - 77
HDL	45.99 ± 12.2	35.4 - 53.6	45.3 ± 11.7	35.9 - 56.2	45.7 ± 11.9	35.9 - 53.7
TG	118.68 ± 56.4	85 - 127.2	127.9 ± 42.2	94 - 161	122.8 ± 50.5	91 - 141
Total cholesterol	147.3 ± 31.7	128 - 156	157.4 ± 41.3	131 - 166	151.8 ± 36.4	128 - 166
LDL	77.6 ± 38.06	50.2 - 92.8	86.5 ± 42.4	59 - 106.5	81.6 ± 40.1	55.3 - 95.1
BMI	17.41 ± 2.82	15 - 28	17.3 ± 3.06	14.3 - 19.9	16.6 ± 2.97	14.24 - 18.29

Table 2. Criteria of Metabolic Syndrome in our Patients

Criteria	Female, n = 48, No. (%)	Male, n = 39, No. (%)	Total, n = 87, No. (%)	P Value
Hypertension	7 (14.6)	6 (15.4)	13 (14.9)	0.575
Hypertriglyceridemia	18 (37.5)	14 (31.5)	32 (37)	0.195
Low HDL	18 (37.5)	14 (35.9)	32 (36.8)	0.528
Abdominal obesity	1 (2.1)	5 (12.8)	6 (6)	0.061
High FBS	48 (100)	39 (100)	87 (100)	0.999
Metabolic syndrome	11 (23.2)	10 (24.8)	26 (23.9)	0.528

5. Discussion

This study was conducted on 87 children with T1DM in southern Iran, and showed that according to IDF based criteria, 23.9% of these children had metabolic syndrome. However, ATPIII showed a metabolic syndrome prevalence of 29.9% in our diabetic children. Most of the differences were due to the difference in definition of hypertriglyceridemia and minor ethnic variations in waist circumference (12). Hypertriglyceridemia was the most common criterion in children with T1DM, and abdominal obesity was the least common. Also, it was shown that metabolic syndrome in children with T1DM had no association with gender, family history of T2DM, type of insulin therapy, and daily dosage of insulin; however it was related to the level of HbA1c. This is the first study reporting the prevalence of metabolic syndrome among children with T1DM in the Middle East. Metabolic syndrome was previously reported in children with T1DM from Holland and Poland with a prevalence of 6.3%, and 5.5%, respectively (2, 4). The lack of a standard definition for the metabolic syndrome in diabetic children made some difficulty in the comparison of these studies, however ethnicity and diet were two important factors. Insulin resistance and metabolic syndrome had a different pathophysiological mechanism from T1DM; however hyperglycemic state (irrespective of cause, e.g. T1DM or metabolic syndrome) may result in development of cardiovascular disease. However, including T1DM in the metabolic syndrome criteria might reflect an overestimation. In normal Iranian children, metabolic syndrome was reported as 9 to 11% (13), that was less than that of children with T1DM in the present study. Reduction in physi-

cal activity in T1DM in the Iranian population (14) and also in T1DM children (15) could also explain, to some extent, such a high prevalence. Several investigations revealed some association between insulin resistance and the presence of chronic complication in T1DM (16, 17). One study showed that presence of metabolic syndrome components was high in T1DM and is associated with chronic complications and mortality (16).

In one study from the Netherlands, suboptimal HbA1c was associated with elevated LDL cholesterol and TG in overweight children with diabetes (2). Another recent study revealed that glycemic control and HbA1c were associated with serum lipid profile (18). However, further investigations should be done to find out the cause of the high prevalence of metabolic syndrome in children with T1DM and its association with HbA1c.

This study revealed that 14.9% of T1DM had hypertension and this prevalence was not associated with gender. This prevalence was higher than that reported by Schwab et al. (7.4%) (8), however similar to a population of T1DM in the Netherlands (13.1%) (2) and Holland (13.1%) (19). Basiratnia et al. showed that the prevalence of childhood hypertension in south of Iran was 11.8% (20). Our study revealed that the prevalence of hypertension in T1DM is much more than the normal population of children in southern of Iran. Many studies showed that hypertension and cardiovascular disease were one of the late complications of diabetes mellitus; however hypertension was reported in the early phase of T1DM, as well. Some previous animal studies revealed that both the innate and adaptive immune systems had a significant role in hypertension (21-23). Another study on mice lacking vascular macrophages, angiotensin-II and deoxycorticosterone acetate-salts could not raise blood pressure (24, 25). This emphasizes the role of the immune system in hypertension. Also, it highlights the role of pediatric endocrinologists and family physicians in the monitoring of blood pressure in children with T1DM, in order to prevent the future risk of cardiovascular morbidity and mortality.

This study revealed that prevalence of hypertriglyceridemia was 37%, which was not dependent to the child's gender. Previously, the prevalence of hypertriglyceridemia was reported in children with T1DM of the Netherlands (2), Spain (15) and Poland (4), which was 21.1%, 2.6% and 16.6%, respectively. Similar to our data, in an Indian population, the prevalence of hypertriglyceridemia was reported as 41.7% in patients with T1DM (26). Esmaillzadeh et al. showed that the prevalence of hypertriglyceridemia was 37.7% in normal Iranian adolescents, and 50.6% in overweight children (13). The definition of hypertriglyceridemia in our study, unlike Esmaillzadeh et al. (13), was that of IDF [12] (TG $\geq$ 150 mg/dL) similar to European studies (14, 23). Esmaillzadeh et al. (13) considered the ATPIII scoring system, which defined hypercholesterolemia as serum cholesterol more than 110 mg/dL. Therefore, differences in ethnicity and definition could be the cause of the variance in the reported prevalence of hypertriglyceridemia. Also, the role of glycemic control in decreasing serum triglycerides of children with T1DM in this and previous studies cannot be established. Moreover, the risk of microangiopathy was two to three folds in hypertriglyceridemic T1DM patients (27), even at young ages and without an excessively long duration of diabetes (27).

This study indicated a low HDL in 36.8% of children with T1DM. Studies from the Netherlands (2), Spain (15) and Poland (4) revealed the prevalence of low HDL in T1DM children as 23.5%, 4.34%, and 6.8%, respectively. Kumar et al. reported that 18.1% of T1DM children in India had low HDL (26). In Iran the prevalence of low HDL was reported as 41 to 44% in normal children (13). Interestingly, we found a higher prevalence of low HDL in T1DM in children. The difference in ethnicity and the definition of low HDL may be the cause of these dissimilarities. Another proposed mechanism contributing to low HDL cholesterol levels in T1DM is the reduction of Apolipoprotein A-1 (Apo A-1) synthesis in the liver (28). In one study, hypoalphalipoproteinemia was present in 17.2% of T1DM and was associated with macroalbuminuria and polyneuropathy (27).

The Prevalence of abdominal obesity was 6.9% in our children with T1DM. Previous research showed that 9% of normal Iranian children had abdominal obesity (13). In line with our study, 3.47%, 9.2% and 14% of Spanish, Dutch and Polish children with T1DM had abdominal obesity, respectively. It seems that obesity was not more prevalent in our cases compared to the normal population and therefore could not explain the higher prevalence of metabolic syndrome in children with T1DM, by itself.

Another finding of the present study was the poor glycemic control in our diabetic children in spite of using proper age and gender associated dose of insulin per kilogram of body weight. Overall, HbA1C was 10.15 $\pm$ 2.23, in spite of using 0.69 $\pm$ 0.26 U/kg insulin, and it was not significantly different in the two genders (P = 0.459). This may be due to the relatively high prevalence of depression, low socioeconomic status and poor quality of life in our studied population, which interferes with the use of a safe diabetic diet and insulin (29).

The findings of this study should be interpreted while considering some limitations. The major limitation was the definition of metabolic syndrome in children with diabetes. We used the IDF definition of metabolic syndrome, which was the most prevalent definition in studies that investigated metabolic syndrome in children and also patients with diabetes (2, 4, 12, 14). Another limitation was the

lack of detailed information regarding dietary habits and physical activity.

5.1. Conclusion

This study provides evidence showing poor glycemic control and high prevalence of metabolic syndrome in children with T1DM in southern Iran. More studies should be conducted in Asian countries. Also, further studies should be undertaken to show the pathophysiology of metabolic syndrome in T1DM. Also, preventive programs aimed toward decreasing the risk factors of metabolic syndrome and interpretation of a healthier diet and physical activity for children with T1DM should be considered in our country.

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