Original Article

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Female Sex as a Risk Factor for Glycemic Control and Complications in Iranian Patients with Type One Diabetes Mellitus

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Abstract

Objective: The aim of this study was to evaluate the influence of sex on glycemic control, diabetes complications and associated abnormalities in patients with type one diabetes mellitus.

Methods: In a cross-sectional study in 309 patients (156 females and 153 males within the age range of 3-16 years) with type one diabetes mellitus referred to endocrinology clinic in Children's Medical Center in Tehran from March 2005 to March 2007 gender differences in diabetes control were analyzed.

Findings: Mean glycosylated hemoglobin (HbA1c), was significantly higher in females (9.25 vs. 8.01). Insulin dose per kilogram of body weight was significantly more in girls (0.91±0.31 vs. 0.74±0.37, *P*<0.001) self monitoring of blood glucose was performed significantly more in boys. Frequency of Diabetic ketoacidosis, height growth problems and dyslipidemia were significantly higher in girls. 1.20±0.86 vs. 0.93±0.55, *P*=0.004), (-0.05±1.20 vs. -0.41±1.17, *P*=0.015), (134.60±44.43 vs. 110.56±20.72, *P*=<0.001) respectively.

Conclusion: Female sex is a risk factor in glycemic control and complications of diabetes type I and females should be managed more seriously regarding self monitoring of blood glucose, nutritional and psychological factors and puberty issues.

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Key Words: Diabetes Mellitus; Risk Factor; Blood Glucose; Female; Glycemic Control

Introduction

Type one diabetes mellitus (T1DM), one of the most common chronic diseases in childhood, affects 15 million children in the world and is rapidly increasing in specific regions [1,2] so that an annual increase of 2 to 5 percent in Europe, the Middle East, and Australia is reported [3].

In addition, wide range of serious complications and associated diseases makes T1DM a very serious medical problem so that the average life

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span of individuals with diabetes is about 10 years shorter than that of the non-diabetic population[1].

These complications could be acute, subacute or chronic. And poor adherence resulting in poor control can predispose children at risk up these complications. Therefore to decrease burden of this disease, the medical team should attempt to ensure a normal growth and development with minimal effect on lifestyle for the patient[1]. In fact, intensive control dramatically reduces the risk of long-term vascular complications (such as retinopathy, nephropathy and neuropathy) by 46-76%, growth retardation and puberty delay and also reduces abnormalities in plasma lipid levels [1,4-7]. Thus it is important to maintain a balance between tight glucose control and avoiding hypoglycemia [1]. Also issues like nutrition, exercise, and psychosocial factors that have an impact on glycemic control should be addressed in the management of children and adolescents with type 1 diabetes.

A reliable index of long-term glycemic control is measurement of the fraction of glycosylated hemoglobin (HbA1c). Therefore to obtain a profile of long-term glycemic control, it is recommended that HbA1c measurments be obtained 3 to 4 times per year.

Beside checking HbA1c, optimal glycemic and metabolic control is dependent upon frequent self-monitoring of blood glucose (SMBG). Adherence to this treatment regimen is difficult especially for adolescents. Poor adherence can result in poor metabolic control especially in females.

Hence being female has been an independent risk factor of poor glycemic control in previous studies.

Springer in his study on 455 patients with type one diabetes found that mean $HbA1_C$ level was higher in girls than in boys [8]. In another study in 2180 Swedish children (1033 girls and 1147 boys) mean $HbA1_C$ was higher in girls at ages 14-18 [9]. Gerstl et al in study on 27035 patients with type 1 diabetes in Germany and Austria reported that gender has a significant influence on $HbA1_C$ [10]. In a study in 2270 Californian children with insulin-dependent diabetes mellitus (IDDM), females had more diabetes hospitalization than did males. These occurred primarily in adolescents (for females ages 10-14 years 50 vs. 38/100000) and for ages 15-18 (68 vs. 29/100000) [11]. In another study by Knerr et al, on 26687 children and adolescents in Germany and Austria' female gender was one of the factors associated with higher prandial insulin doses.

Also mean $HbA1_C$ was higher in females and girls reported higher insulin doses per CHO units for 3 meals [12]. In another study by Habib in Saudi Arabia, females had more ketoacidosis at the onset of their illness (58.7% vs. 41.3%) [13]. In a study by Ahmed et al on 46 children with IDDM (23 girls and 23 boys) he showed that final height in girls was shorter than in boys and at final height, they were significantly shorter with respect to mid parental height [14].

Because effect of gender on glycemic control has not been evaluated in Iran, we have studied the T1DM patients referring to our outpatient clinic to evaluate the effect of gender on glycemic control, diabetes complications and associated abnormalities.

Subjects and Methods

In a cross-sectional study on, patients with type one diabetes mellitus referred to endocrinology clinic in Children's Medical Center in Tehran, Iran from March 2005 to March 2007 were enrolled. All subjects provided informed consent and the study was approved by ethical committee affiliated with Tehran University of Medical Sciences.

Patients within the age range of 3 to 16 years with type one diabetes mellitus who were diagnosed at least one year before our evaluation were included. The diagnosis of diabetes mellitus was based upon the guidelines of the American Diabetes Association (ADA)[23]. During the evaluation patients with following criteria were excluded: 1) type 2 diabetes mellitus as any secondary diabetes (such as thalassemia, chronic active hepatitis, cystic fibrosis, mitochondrial disease), 2) in adequate clinic visits (less than four visits per year).

Regarding these conditions 309 patients (156 females and 153 males) were enrolled in the study. By using medical records of patients, a questionnaire was filled for every patient. As boys and girls are different in their start of puberty, it

Table 1: Descriptive statistics of studied patients

variable	Male mean (SD)	Female mean (SD)	P-value
Age (year)	9.27 (4.02)	9.80 (3.35)	0.2
Disease duration (month)	26.22 (28.72)	25.06 (24.23)	0.7
Age at diagnosis (year)	7.19 (4.22)	7.88 (2.87)	0.1

SD: Standard Deviation

can affect the comparison between boys and girls, Therefore patients were categorized with respect to puberty stages. 1) prepubertal group (younger than 11 years for boys and younger than 8 years for girls), 2) pubertal start group (11 to 13 years for boys and 8 to 10 years for girls), 3) mid puberty group (older than 13 years for boys and older than 10 years for girls). $HbA1_C$ levels according to ADA levels was used as a reference as follows, for children 0-6 years, 7.5-8.5%, children 6-12 years <8%, and for older children <7%.

To eliminate effect of puberty, HbA1c was compared between sexes in the three puberty groups.

Variables included sex, age, age at onset of diabetes, height, height standard deviation score (SDS), weight, BMI (body mass index), duration of diabetes mellitus (DM), mean HbA1c of the last measured ones, daily insulin dose, number of blood glucose measurement in a day, lipid profile, thyroid function tests and puberty indexes (based on Tanner criteria).

Using SPSS software, genders differences were analyzed by using chi-square or Fisher's exact test for nominal variables and t-test or Mann-Whitney U-test for quantitative variables.

Findings

Our data collected from 309 (156 femeals and 153 males with age range of 3-16 years) type 1 diabetes. Descriptive and demographic data of all variables are summarized in Table 1.

Age at onset of disease, disease duration and BMI and sexual maturity rating (SMR) are considered as baseline characteristics.

HbA1c as a measurement of glycemic control was significantly higher in females when evaluated quantitatively (P<0.001) or qualitatively (P<0.001) (Table 2).

Insulin dose per kilogram of body weight (insulin/kg) was significantly different between females and males both when compared quantitatively and when compared between puberty groups (Table3). Also self monitoring of blood glucose (SMBG) was performed significantly more in boys compared to girls (Table 3).

Finally complications, co-morbidities and associated diseases of DM were compared between boys and girls. As shown in Table 4 height SDS was significantly lower in females than in males, BMI was not significantly different in females and males, total cholesterol, low density

Table 2: Comparison of glycemic control in different genders

Variable		Male mean (SD)	Female mean (SD)	*P*-value
Quantitative HbA1c		8.01 (1.7)	9.25 (1.9)	<0.001
qualitative HbA1c	**appropriate**	63.9 (98.0)	30.3 (42.0)	<0.001
	intermediate	19.7 (30.0)	39.4 (72.0)	
	poor	16.4 (25.0)	30.3 (42.0)	
HbA1c based on puberty	**Pre pubertal**	7.2 (1.2)	8.6 (1.4)	<0.001
	Pubertal start	7.4 (0.7)	9.1 (2.1)	
	Mid puberty	9.8 (1.5)	9.5 (1.9)	

SD: Standard Deviation / HbA1c: Glycosylated Hemoglobin

Table 3: Comparison of insulin dose in both genders

Variable		Male mean (SD)	Female mean (SD)	*P*-value
Insulin dose		2369.0 (14.8)	26.8 (14.4)	0.06
Insulin dose/kg		0.7 (0.4)	0.9 (0.3)	<0.001
Insulin dose/kg based on puberty	**Pre pubertal**	0.7 (0.3)	0.9 (0.3)	<0.04
	Pubertal start	0.6 (0.2)	0.9 (0.2)	
	Mid puberty	0.9 (0.6)	0.8 (0.3)	
Self monitoring of blood glucose		59.2 (74.0)	45.3 (63.0)	0.02

SD: Standard Deviation

lipoprotein (LDL), and triglyceride levels were significantly higher in females than in males respectively. HDL was not significantly different..

In terms of thyroid function tests, hormones thyroxine (T4) levels were significantly higher in girls than in boys though in the normal renege. The thyrotrophin-stimulating hormone (TSH) levels were not significantly different among the both sexes. Diabetic ketoacidosis (DKA) times were significantly higher in girls than in boys, also DKA times based on the stage of puberty were higher in girls at all puberty stages (Table 4).

Discussion

Our findings demonstrates that there are gender differences in diabetes control. Means HbA1c was 8.01 in boys and 9.25 in girls. Apart from gender differences, mean HbA1c is higher than ADA recommendation, this maybe indicative of our urgent need to improve glucose monitoring and patient education. It is worth to mention that our treatment policy has changed in the recent years from conventional therapy with two times insulin therapy a day towards much intensified treatment with 3 times a day insulin regimen.

Therefore we are waiting for better results in the next years. Other studies have shown significant association between metabolic control and gender. In Gerstl et al study on 27035 patients from different centers in Austria and Germany in all age groups, girls had higher HbA1c levels than boys (mean difference 0.1%) [10]. In another study by Springer et al, girls had HbA1c levels higher than boys that has been attributed to greater

Table 4: Complications and associated comorbidities of diabetes in both genders

Variable		Male mean (SD)	Female mean (SD)	*P*-value
Height SDS		-0.41 (1.17)	-0.05 (1.20)	0.01
Body Mass Index		32.27 (13.86)	30.66 (12.33)	0.3
Triglyceride (gr/dl)		99.72 (29.32)	109.72 (62.33)	0.01
Total cholesterol (gr/dl)		110.56 (20.72)	134.60 (44.43)	<0.001
LDL(gr/dl)		93.03 (14.58)	106.93 (34.28)	<0.001
HDL(gr/dl)		44.77 (7.10)	45.38 (3.80)	0.5
TSH		2.36 (2.02)	2.74 (1.85)	0.1
T4		7.45 (1.62)	7.94 (1.91)	0.01
DKA times		0.93 (0.55)	1.20 (0.86)	0.004
DKA times based on puberty	**Pre pubertal**	1.07	1.0	0.01
	Pubertal start	0.8	0.9	
	Mid puberty	0.7	1.5	

SDS: Standard Deviation Score / LDL: low density lipoprotein / HDL: High density lipoprotein / TSH: Thyrotrophin-Stimulating Hormone / T4: Hormones Thyroxine / DKA: Diabetic Ketoacidosis

than boys that has been attributed to greater depression and psychological problems in girls [8]. In our study HbA1c was categorized due to puberty stages in both girls and boys and there was significant different within both sexes (Table 2). There are known differences in glucose metabolism in women and men. It has been shown that healthy females are less insulin sensitive than healthy males, and this decreased sensitivity is compensated by increased insulin secretion [15]. In another study higher insulin concentration during oral glucose tolerance test in non diabetic females than in males was shown [16]. In our study insulin dose/Kg was significantly higher in girls than in boys.

This is consistent with other studies that girls have less sensitivity to insulin. These may be due to non compliance in the pubertal age group, these places adolescents at risk of poor glycemic control. Kaufman showed in her study that adolescents have increased levels of HbA1c and also decreased number of clinic visits.

In terms of complications of type 1 diabetes there was significant difference between the genders. As shown in Table 4 for height, SDS was significantly different between girls and boys and girls were shorter than boys.

These differences have been shown in previous studies. In a study by Ahmed et al on 46 children with diabetes, final height was shorter in girls than in boys, and at final height girls were significantly shorter with respect to mid parental height SDS. He concluded that advanced bone age in girls at the onset of puberty may explain blunted pubertal growth spurt, hence their shorter final height [14].

There was no significant difference in BMI between the genders these has been shown in the study by Vanelli et al in Italy [17].

In terms of lipid control in type 1 diabetes, there was significant difference in total cholesterol, LDL, and triglyceride levels between sexes. Girls had higher cholesterol, LDL, and triglyceride levels than boys. These may be attributed to poorer diabetes control in girls than in boys and this may endanger them for cardiovascular diseases in adulthood. Therefore the protectiveness of cardiovascular disease in premenopausal women maybe endangered in type 1 diabetes. HDL levels were not significantly different in both sexes.

In contrast to several studies, we did not find any significant difference in thyroid function tests between the two genders [18,19], though T4 levels were higher in girls but they were in the normal range.

Another significant finding in our study was more DKA times in girls than boys. Similar findings were shown in a study in Germany [20] and Saudi Arabia where a female to male ratio of 1.4 to 1 was found [13].

The mechanism by which gender might affect these differences is unclear. One of the reasons may be that girls used SMBG less than boys. In fact because children and their parents show poor ability to detect high or low blood glucose levels based on symptoms alone, frequent monitoring improves glycemic control and decreases prevalence of DKA in children and decrease the frequency of severe hypoglycemic episodes [21]. Thus optimal glycemic control can only be achieved if SMBG is used frequently [1].

Thus lower rate of using SMBG in girls could cause the worse glycemic control in them.

Regarding effect of nutritional and psychological factors on glycemic control, higher rate of nutritional and psychological problems in female patients could be another reason of worse glycemic control in girls. While available data suggests normal eating attitudes in most male patients, eating disorders and sub-threshold eating disorders are almost twice as common in adolescent females with T1DM as in their non-diabetic peers [1,22]. Also adolescent girls are at greater risk than adolescent boys for recurrent episodes of depression.

Conclusion

because of worse glycemic control in female patients with T1DM compared to males as well as higher incidence of DKA, dyslipidemia and height growth retardation in female patients, it is needed to focus on girls in local guidelines of managing T1DM regarding SMBG, nutritional and psychological factors and puberty issues.

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Conflict of Interest: None

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