Insulin-like growth factor-1 levels in children and adolescents with type1 diabetes mellitus and its relationship with serum zinc

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Abstract

Background: Some studies have indicated impaired metabolism of Insulin-like growth factor-1 (IGF-1) and zinc in type-1 diabetic patients. However, no results have been reported to date on the relationship between IGF-1 and serum zinc levels in children and adolescents with type-1 diabetes mellitus. Therefore, the objectives of this cross-sectional study were to compare IGF-1 levels in type-1 diabetic children and adolescents with that of healthy controls, and also to determine whether there is a relationship between IGF-1 and serum zinc levels.

Methods: Thirty children and adolescents with type-1 diabetes mellitus and 30 age- and sex-matched healthy controls participated in the study. Serum IGF-1, serum zinc, fasting blood sugar, hemoglobin A_{1C} (HbA_{1C}) were measured by enzyme-linked immunosorbent assay, flame atomic absorption spectrophotometry, enzymatic colorimetry and ion-exchange chromatography methods, respectively.

Results: The mean level of serum IGF-1 (ng/l) in the diabetics was significantly lower than in the controls (208.2 ± 15.7 and 317.0 ± 33.2, respectively; p=0.001). No relationship was found between the IGF-1 levels and serum zinc or the amount of glycemic control.

Conclusion: IGF-1 levels of the diabetic children and adolescents were significantly lower compared to those of healthy controls and were independent of serum zinc levels and the amount of glycemic control.

Keywords: Insulin-like growth factor-1, Zinc, Type-1 diabetes mellitus, Children, Adolescents

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Introduction

Some studies have shown impaired growth and pubertal development in type-1 diabetic children and adolescents (1, 2). Impairment of linear growth and sexual development is one of the common complications in children and adolescents with type-1 diabetes mellitus (T1DM) in many parts of the world. However, the related factors are not fully understood (3, 4). One of the possible explanations could be the impairment of insulin-like growth factor (IGF) system which is responsible for linear growth. This system consists of insulin-like growth factor 1, 2 and their receptors as well as IGF-binding proteins and their proteases (5, 6). Insulin-like growth factor-1 (IGF-1) is an important growth factor which mediates most of the postnatal growth processes (7). It has indicated that insulin has a great role in the IGF system and its absence can lead to great hormonal disturbances (2). Some studies reported derangement and low levels of IGF-1 in children and adolescents with T1DM (8, 9). Therefore, it is important to pay more attention to this growth factor especially at this age range.

On the other hand, among minerals and trace elements, zinc seems to have the most influence on growth. It has been shown that impaired growth in rats induced by zinc deficiency is associated with lower levels of IGF-1 and growth hormone receptors (10). Some studies have indicated alterations in IGF-1 and zinc status and metabolism in type-1 diabetic patients (9, 11, 12). However, based on our knowledge no study has been done to date on the relationship between IGF-1 and serum zinc levels in children and adolescents with type-1 diabetes mellitus. Therefore, the objectives of this cross-sectional study were to compare IGF-1 levels in type-1 diabetic children and adolescents with that of healthy controls, and also to determine whether there is a relationship between IGF-1 and serum zinc levels.

Methods

Thirty children and adolescents with T1DM (diagnosed by a pediatric endocrinologist), 6 to 18 years old (patient group), including 13 girls and 17 boys and 30 age and sex-matched healthy subjects (control group) participated in this cross-sectional study. The patients were randomly selected among those with active files in Namazi Medical Teaching Center, one of the main teaching hospitals of Shiraz University of Medical Sciences in Shiraz, Iran. The controls were randomly selected among the diabetics' classmates. The patients had no other systemic disease and were taking no medication that would interact with zinc metabolism (except insulin). The controls were apparently healthy children taking no zinc supplement. None of the participants had taken vitamin and mineral supplements for at least 3 months before initiation of the study.

Fasting blood samples were taken from all participants at 7:30 A.M. and analyzed for serum IGF-1, serum zinc, fasting blood sugar (FBS), hemoglobin A_{1c} (HbA_{1c}), using enzyme-linked immunosorbent assay, flame atomic absorption spectrophotometry, enzymatic colorimetry and ion-exchange chromatography, respectively.

Informed consent was taken from the parents, and the protocol was approved by the Ethics Committee of the Nutrition and Biochemistry Department, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

Data are expressed as mean and Standard error of mean (SEM). After ascertaining that all variables were normally distributed, Paired t-test was used to detect differences between groups. The correlation test and Pearson coefficient as well as Linear regression were used to determine the association between IGF-1 levels and serum zinc concentration, FBS, HbA_{1c}, the duration of diabetes or the amount of injected insulin per kg. Statistical analyses were performed using SPSS 11.5. A value of $p<0.05$ was considered as significant in all statistical analyses.

Results

No significant difference was found between the patient and the control groups with respect to their age, weight, height and body mass index. The average duration of diabetes in patient group was 30.5 ± 4.7 months. As expected, the FBS and HbA_{1c} levels were noticeably higher in the diabetics (Table 1). Further analysis of the data showed that the serum IGF-1 concentration was significantly lower in children and adolescents with T1DM compared to that of healthy controls. This difference was statistically significant only among girls (Table 2).

No correlations were found between IGF1 levels and serum zinc, FBS or HbA_{1c} in both the patient and the control groups. The duration of diabetes and insulin dose/kg in the patient group was also not correlated with IGF-1 levels (Table 3). Analyzing the data by linear regression also indicated that the difference of IGF-1 levels between the patient and the control group was not related to the between-group differences of serum zinc and the amount of glycemic control (Table 4).

Table 1. HbA_1c and FBS concentrations in diabetic the patients and healthy controls

	Diabetic patients N=30	**Healthy controls N=30**	
	Mean ± SEM	Mean ± SEM	P-value
HbA_{1c} (%)	8.7 ± 0.4	6.5 ± 0.1	<0.001
FBS (mg/dl)	221.9 ± 20.9	82.6 ± 1.8	<0.001

HbA1c, HemoglobinA_{1c}
FBS, fasting blood sugar
SEM, Standard error of mean
N, number

Table 2. Serum IGF-1 concentrations in the diabetic patients and healthy controls

		Diabetic patients N=30	**Healthy controls N=30**	
		Mean ± SEM	**Mean ± SEM**	**P-value**
Serum IGF-1 (ng/l)	Male	186.7 ±15.7	227.7±31.6	0.19
	Female	236.3±28.7	433/9 ±49/0	0.002
	Total	208/2 ±15/7	317/0 ±33/2	0.001

SEM, Standard error of mean

Table 3. Pearson coefficients between IGF-1 levels and other variables in the diabetic and control group

	Diabetic patients N=30		**Healthy controls N=30**	
	r	**P-value**	**r**	**P-value**
Serum zinc (mg/dl)	0.26	0.17	-0.31	0.09
HbA_1c (%)	0.01	0.9	0.18	0.3
FBS (mg/dl)	0.07	0.7	0.13	0.4
Duration of the diabetes (months)	-0.13	0.4	-	-
Insulin (unit/kg)	0.05	0.7	-	-

SEM, Standard error of mean
HbA1c, HemoglobinA_{1c}
FBS, fasting blood sugar
r, Pearson correlation

Table 4. The results of linear regression analysis between the difference of serum IGF-1 levels and the difference of other independent variables between the diabetic patients and healthy controls

		B ± SEM	**P-value**
Serum zinc (mg/dl)	constant	115.05 ± 32.3	0.001
	coefficient	0.97 ± 1.07	0.37
HbA_1c (%)	constant	105.7 ± 42.2	0.19
	coefficient	2.22 ± 12.8	0.86
FBS (mg/dl)	constant	143.2 ± 48.2	0.006
	coefficient	-0.24 ± 0.26	0.36

SEM, Standard error of mean
HbA1c, HemoglobinA_{1c}
FBS, fasting blood sugar

Discussion

In this study, the mean IGF-1 level was significantly lower in children and adolescents with T1DM than in the healthy controls. Most of the researches which have been already done in this field are in tune with our experiment (6, 8, 9, 13).

Insulin is a major factor for regulating the IGF system. It has been shown that insulin deficiency in portal circulation led to decrease in hepatic growth hormone (GH) receptors and post-receptor defect and finally led to hepatic GH resistance (5). Studies in human diabetes showed that both basal and stimulated GH levels are usually high in type-1 diabetic patients who poorly controlled their blood sugar. However, high GH levels could not stimulate IGF-1 production effectively (14). This pattern of increased GH with low IGF-1 levels in type-1 diabetic patients can be explained by the lack of IGF-1 negative feedback because of the reduced IGF-1 levels (15). Li et al. showed that the influence of diabetic status on IGF-1 gene expression in liver tissues of diabetic rats starts from early diabetic stages, causing down regulation of IGF-1 expression. Therefore, serum IGF-1 level decreases (16).

Subdividing the data according to gender showed that the IGF-1 difference was only significant in girls. One of the possible explanations could be the difference of pubertal stages among participated boys and girls. Average age of diabetic girls was higher than that of boys (12.4 ± 0.76 and 10.9 ± 0.73, respectively; $p=0.16$). Therefore, according to Karamizadeh and Amir Hakimi study (17), girls were closer to puberty (9 girls out of 13 had reached puberty). Furthermore, according to Argente et al. (18) IGF-1 puberty peak occurs 2 years earlier in girls compared to the other sex. The puberty is associated with a reduction in insulin sensitivity, which is known to be more sever in patients with T1DM (19). It has been demonstrated that increased GH concentration is associated with insulin resistance in diabetic adolescents (4, 20). Therefore, partial resistance to GH accompanied with increased serum GH concentration and reduced levels of IGF-1 can explain this difference.

The reported results on the association between serum IGF-1 and the amount of glycemic control have been contradictory up to now. In our study no relationship was found between serum IGF-1 and glycemic control (based on HbA_{1c}) in diabetic patients, which was in tune with some studies done on this matter (9, 21, 22). In contrast, in Dills et al study a negative correlation has been found (23). Berecket et al. (5) in a study on children recently diagnosed with type-1 diabetes mellitus indicated that after one month insulin therapy improvement in HbA_{1c} was correlated with an increase in IGF-1 level. Certainly more research is required to shed more light on this subject.

Although, several studies have indicated impaired metabolism of IGF-1 and zinc in diabetic patients, no results have been reported to date on the relationship between IGF-1 and serum zinc in children and adolescents with T1DM. It has been demonstrated that zinc deficiency in rat's diet led to decrease in serum IGF-1 level and its hepatic mRNA (24). Moreover, Cesur et al. study (25) on zinc deficient and growth retarded children and adolescents whose IGF-1 levels were low, has shown that zinc supplementation enhance serum IGF-1 levels in 62% of children, which was statistically significant in 48% of them. Blostein-Fujii et al. (26) in a zinc supplementation study on women with insulin dependent diabetes mellitus whose plasma zinc was low showed that plasma IGF-1 concentrations increased with zinc supplementation if the initial IGF-1 concentrations were < 165 microg/l, but were unchanged if they were > 165 microg/l. Consequently, they concluded that zinc can lead to increase IGF-1 levels if initial IGF-1 concentrations are low. In our study no relationship was found between IGF-1 and serum zinc levels. One of the possible reasons is that participated children and adolescents had not been zinc-deficient (serum zinc < 70 mg/dl), while the participants in the two aforementioned studies were zinc deficient.

In conclusion, our results revealed that serum IGF-1 levels were significantly lower in type-1 diabetic children and adolescents and according to gender subdivision the difference was significant only to girls. Also, the difference of IGF-1 levels between the patient and control group was independent of serum zinc levels and the amount of glycemic control. Therefore, the common ground between our study and other studies is the lower levels of IGF-1 in type-1 diabetic children and adolescents which can lead to growth problems in this age range. Therefore, more attention should be devoted to this subject.

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