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Leptin and Resistin Levels in Iranian Children With Type 1 Diabetes Mellitus

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Abstract

Objectives: Diabetes mellitus (DM), as a metabolic disorder, affects life quality through insulin insufficiency. Leptin and resistin are two adipokines that are mainly produced as internal secretory proteins by the adipose tissue. Considering that adipokines are strongly associated with insulin sensitivity and inflammatory markers, any modification in their serum levels is probably assumed to contribute to the pathogenesis of type 1 diabetes mellitus (T1DM) as well.

Materials and Methods: The study was conducted on a population of diabetic children who were followed up during 2015 at the Pediatric Endocrinology and Metabolism Unit of Tabriz University, Faculty of Medicine. In general, 50 children with T1DM and 50 healthy control were selected in this regard. The exclusion criteria included hypertension, hyperlipidemia, anemia, or infection. Resistin and leptin levels were measured in the serums of children over a one-year period. Then the serum levels of leptin and resistin were measured and matched for gender, age, and body mass index (BMI), followed by measuring the correlations (adjusted for age and gender) between the serum levels of adipokines and either BMI or glycemic control (hemoglobin A1c, HbA1c).

Results: The distribution of age, sex, pubertal status, or BMI showed no significance between diabetic and control groups. On the other hand, resistin increased significantly in diabetic children compared to the control ones (24.75±10.56 ng/mL vs. 3.48±1.47 ng/mL, $P<0.001$). Although resistin demonstrated no significant correlation with age, sex, and BMI, it indicated a significant relationship with the level of HbA1c. The increased level of leptin did not represent a significant criterion between the 2 groups of children.

Conclusions: In general, resistin could associate with the pathophysiology of T1DM through the inflammatory pathway at the molecular level.

Keywords: Leptin, Resistin, Diabetes mellitus

Introduction

Diabetes mellitus (DM) is an endocrine-related metabolic disorder and the prevalence of type 1 diabetes mellitus (T1DM) dramatically increases approximately 3% per year among the world population (1). Regardless of its obscure etiology, T1DM is characterized by hyperglycemia. Insufficient secretion or action of endogenous insulin results from pancreatic B cell deficiency. The autoimmune process or idiopathic destruction plays a role in the impairment of B cells. Therefore, DM is closely linked to the adipose tissue and immunologic processes (2). It is well defined that the activity of other organs such as the brain, kidney, liver, and the like can be affected by the adverse effects of T1DM (3).

The adipose tissue, as an endocrine organ with prominent visceral and subcutaneous localization (4,5), is characterized by releasing some adipokines which are effective in the lipid and glucose metabolisms, homeostasis, and blood pressure (6). Furthermore, they have prominent metabolic functions by controlling energy metabolism (7). Leptin and resistin are 2 eminent adipokines with a role in T1DM and T2DM (8-10). The altered expression of leptin at the gene level has a consequence on body weight regulation, body fat content, and body mass index (11,12). Actually, it can increase energy expenditure by decreasing appetite. In addition, leptin can regulate insulin concentration by targeting insulin synthesis (12). More precisely, it can result in increased insulin sensitivity by inhibiting insulin secretion (13). Hence, altered leptin secretion seems to be involved in the T1DM and T2DM processes by disturbing the physiological balance. Further, leptin regulates the blood sugar through appetite control and fat storage, as well as liver function and the storage of glucose (14). Previously, the positive interaction between insulin and leptin was addressed, and resistin is detected in different tissues such as thymus, stomach, thyroid gland, placenta, and skeletal muscles (15). Resistin, as a cysteine-rich secretory protein with 144 amino acids, is also associated with insulin resistance and T2DM and can cause resistance to insulin and thus increase obesity (16). It also has an important role in inflammation and inflammation-related diseases (17).

It was indicated that leptin and resistin are related to pancreatic beta-cell function in T1DM. According to a previous study, leptin and resistin are both positively associated with fasting and stimulating beta-cell function

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in patients with T1DM (18). In the study by Ocłoń et al, resistin was recommended as an important marker in the regulation of glucose and insulin sensitivity among different adipokines (19). Given the above-mentioned explanations, the present study was conducted to determine leptin and resistin levels in Iranian children with T1DM. Moreover, the aim of this study was to obtain knowledge about the relationships between two adipokines and the pathogenesis of T1DM. Only a few studies have addressed leptin and resistin levels in relation to diabetes among Iranian children living in Tabriz.

Materials and Methods

Fifty children with T1DM (23 boys and 27 girls with a mean age of 10.43 ± 3.25 years) and 50 healthy control subjects (24 boys and 26 girls with a mean age of 9.70 ± 4.39 years) were selected according to certain inclusion and exclusion criteria in the study. All T1DM children were followed up in the Pediatric Endocrinology and Metabolism Unit of Tabriz University, Faculty of Medicine. General inclusion criteria were pre-puberty (age <12 years), and the absence of chronic diseases such as cardiac diseases, hypertension, hyperlipidemia, anemia, and acute infection. In diabetic children, the diagnosis of diabetes for more than 1 year was considered as well. All data including height, body weight, and body mass index (BMI) were measured, and the National Center for Health Statistics standard curve was used for adjusting the weight and height to the standard deviation score. Additionally, blood samples were obtained after 12 hours of fasting, and then the samples were centrifuged for serum separation. Immediately, the serum was stored at −70°C for further assessment by a sandwich ELISA kit, followed by examining leptin (Catalog Number RD191001100, RD194002100; Czech Company, Bio Vendor) and resistin (Catalog Number DRSN00, SRSN00, and PDRSN00). The intra- and inter-assay coefficients of the variation of the ELISA kit were below 5% and 4%, respectively. A monoclonal antibody specific for leptin and resistin was covered to a microplate. Eventually, the correlation between the resistin level and age, sex, and BMI were assessed further.

Statistical Analysis

The data were analyzed using the statistical software SPSS, version 25, and presented as the mean ± standard deviation (SD) and evaluated medians (25th; 75th percentile) for parametric and non-parametric variables. Finally, the *t* test and the Man-Whitney test were used for parametric and non-parametric data in order to determine the differences between the two groups, and differences at $P<0.05$ were regarded as statistically significant.

Results

Resistin and leptin serum level were examined to investigate the relation between T1DM and two adipokines. The male/female ratio of the diabetic group was 24/26 with a mean age of 8.97 ± 1.60 years. In addition, the mean duration of diabetes was 2.80 ± 0.73 years. The clinical characteristics of diabetic and nondiabetic children are shown in Table 1. Further, the ratio of male/female in the control group was 23/27 with a mean age of 8.74 ± 1.39 years and no significant differences were detected in the age, sex, or pubertal status between the diabetic and control groups. Similarly, the BMI distribution revealed no difference across diabetic and control groups ($P>0.05$). On the other hand, there was a substantial increase in the resistin level in the diabetic group compared to the control group (24.75 ± 10.56 ng/mL vs. 3.48 ± 1.47 ng/mL, $P<0.001$). Conversely, no significant difference was detected in the leptin levels between the two groups (30.50 ± 2.21 ng/mL vs. 30.35 ± 2.15) and a positive relationship was found between HbA1c and resistin levels (r=0.997, $P<0.001$). Eventually, there was no significant relation between leptin levels and other variables. The correlation between resistin and age (r= -0.22, $P=0.117$), BMI (r= -0.25, $P=0.085$), and sex (SD= 11.08, $P=0.861$) were not significant (Figure 2).

Discussion

Type 1 diabetes mellitus (T1DM), as childish diabetes or insulin-dependent, is a chronic situation in which the pancreas is unable to produce insulin (20). Several proinflammatory markers have a critical role in the pathogenesis of T1DM (21). It is emphasized that the autoimmune process in the pancreatic beta cells of T1DM patients results in the alteration of systemic cytokines (22). The adipose tissue, as an endocrine organ which is involved in energy expenditure, can synthesize and secrete some biologically active molecules (23). Adipocytokines, released hormones from the adipocytes, are associated with lipid and glucose metabolisms and adipocytokines dysfunction onsets inflammatory processes (24). To further describe the association between diabetes and inflammatory agents in children, in this study, resistin and leptin were considered as effective proteins derived from adipocyte.

Leptin is a protein hormone which is secreted by the white adipose tissue. Moreover, it regulates food intake,

Table 1. Characteristics of the Diabetic and Control Groups

	Diabetic Group	Control Group
N	50	50
Age (y)	8.971.60±	8.741.39±
Sex (M/F)	24/26	23/27
BMI (kg/m^2)	17.52±3.52 16.85 (16.55-17.84)	16.971.18± 16.93 (16.34-17.57)
HbA1C	10.88±3.67	-
Diabetic duration (y)	2.80±0.73	-
Leptin (ng/mL)	30.50± 2.21 30.07 (28.72-31.90)	30.35±2.15 29.95(28.68- 31.45)
Resistin (ng/mL)	24.75± 10.56 23.79 (10.79-35.39)	3.48 ±1.47* 3.15 (2.54- 4.20)

Note. M: Male; F: Female; BMI: Body mass index; HbA1c: Glycosylated hemoglobin; Data are expressed as means ± SD or medians (interquartile range) and are *statistically significant at $P<0.05$.

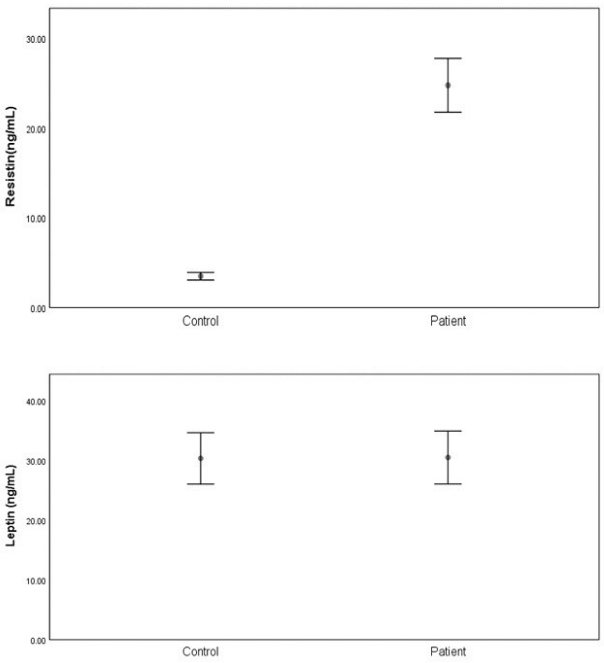

Figure 1. Mean (SD) Values of, Resistin and Median (25th; 75th percentile) Value of Leptin Levels in Children With Type 1 Diabetes Mellitus.

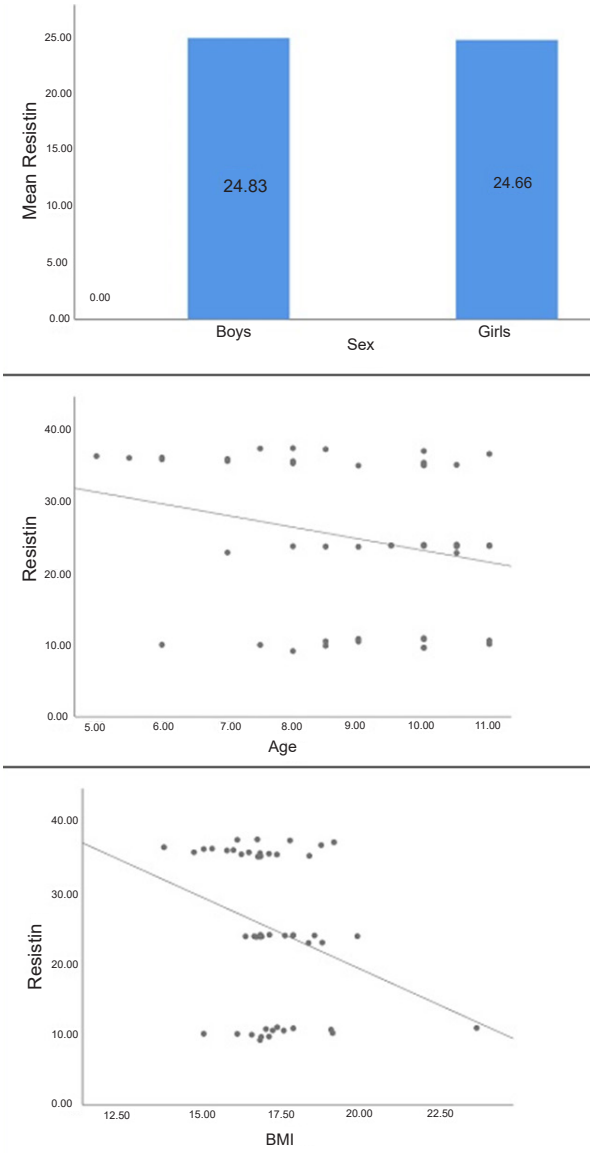

Figure 2. The Negative Correlation of Resistin With Age (r= -0.22, *P*=0.117), BMI (r= -0.25, *P*=0.085),

metabolism, and energy utilization through its receptor in the hypothalamus (25). A model of leptin deficiency in the rodent is associated with insulin resistance and diabetes. Leptin administration to deficient rodents had beneficial effects on blood glucose and insulin levels. In parallel, the leptin level as an adipokine was negatively correlated with diabetes in humans. Hence, leptin can reduce insulin resistance, control glycaemic conditions, and energy balance in both humans and rodents as laboratory models or in the clinical setting (26). Notably, leptin plays a permissive role in the puberty, especially in females. Thus, it is needed for puberty onset by balancing energy expenditure and metabolism pathways at the hypothalamic level (27). La Cava showed that leptin influences T1DM beginning and improves diabetes in non-obese mice by inducing the autoimmune damage of β-cells and increasing the level of interferon gamma (28). Although the increased leptin level in this study was in association with T1DM, it displayed significant negative differences in pediatric diabetic patients.

In the present study, the resistin level increased significantly in the diabetic group as compared to the control group. In addition, the high level of HbA1c was found in diabetic patients with high levels of resistin. Resistin is secreted as a peptide from white adipose tissues. As a novel cytokine, it is also involved in inflammation and is associated with insulin resistance and obesity (29). Consequently, the increased level of resistin in T1DM can be attributed to the autoimmunity and inflammatory background of the disease. Previously, resistin has been introduced as an inflammation cytokine in humans. For instance, Tofighi et al reported that resistin has a proinflammatory role in obesity-independent mechanisms (30). Similarly, Azab et al showed that the circulating level of resistin increases in obese diabetic patients compared to the non-obese ones. Significantly, resistin revealed a potential positive relationship with C-reactive protein as an inflammatory factor in the retinopathy of T2 diabetes (31). In a study by Wijetunge et al, subcutaneous white adipose tissue and visceral adipose tissue characterized the correlation between adipocytokines; and obesity, insulin resistance, and dysglycemia were measured in female patients. Their results demonstrated that the level of systemic and adipose tissue resistin depends on dysglycemia and may be assumed as an important biomarker in the diabetic population (32). It has been reported that resistin could create insulin resistance and

play a role in the pathogenesis of obesity and diabetes in animal models. Furthermore, the structure and biology of resistin are different between the species. Contrary to mice, the levels of human resistin show a reduction in adipocytes while an increase in the circulating blood (33). The cytokines, as the mediators of the inflammatory processes, are generated by macrophages and apoptotic cells in diabetes. Moreover, resistin could start the expression of TNF-α, interleukin-6, and other associated inflammatory markers in several pathophysiological conditions (34). Finally, resistin could deteriorate diabetic conditions through inflammatory pathways and the metabolic cascade signal (35). Accordingly, the effective treatment of T1DM patients can only be achieved by recognizing the pathophysiology of inflammation markers in diabetes. Thus, more studies are needed to illuminate the effect of adipokines like resistin in diabetes.

Conclusions

In general, it was determined that there is an increase in the resistin level of children with T1DM. The changes in the resistin level are not related to body mass index, age, and sex. Therefore, other factors such as the oxidative stress condition and antioxidant diet should be considered for further investigation. Given that resistin is not the main factor of diabetes-related disorders, it probably has a synergistic role with inflammation in the onset and progression of diabetes at the molecular level.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

This study was approved by the ethical committee of Tabriz University of Medical Sciences (TBZMED.REC.1394.60).

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