Study of Circulating Adiponectin Level in Children with Type 1 Diabetes Mellitus in Najran-KSA

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Abstract

Background: Adiponectin is a polypeptide hormone produced exclusively by adipocytes and is believed to play a vital role in the pathophysiology of diabetes, especially Type 1 Diabetes. This study aimed to determine the relationship between total plasma adiponectin concentrations and body mass index (BMI), fasting glucose and glycated hemoglobin levels among Saudi children with type 1 diabetes mellitus in Najran city - Najran region Southern KSA.

Methods: Two hundred and four Saudi children were enrolled in the study, 132 with type 1 diabetes mellitus were selected as a test group compared with a control group which included 72 apparently healthy volunteers, ages and sex in both groups were matched.

Results: The adiponectin level was evaluated with special regard to the control of diabetes, gender, duration of disease, body mass index (BMI). Results showed that the plasma adiponectin concentrations were significantly higher in the diabetic group when compared to the controls, results also revealed a significant negative correlation between the serum levels of Adiponectin ng/ml and age/year, Duration/Year, FBG mg/dl & BMI Kg/m² in the diabetic group, while it revealed a significant positive correlation with HbA1c%.

Conclusion: Serum level of adiponectin in uncontrolled type 1 diabetic children was significantly higher than in healthy and good controlled type 1 DM children, it indicate that Adiponectin may play roles in diabetic control.

Keywords: Type 1 Diabetes mellitus; Adiponectin; Glycated hemoglobin

Abbreviations: T1 DM: Type 1 Diabetes Mellitus; BMI: Body Mass Index; HbA1c: Glycated Hemoglobin

Introduction

Diabetes mellitus is one of the most serious and widespread metabolic diseases today, affecting 10%-15% of the United States population. According to a report by the Saudi Arabian Ministry of Health, approximately 0.9 million people were diagnosed with diabetes in 1992, but this figure rose to 2.5 million people in 2010, representing a 2.7 time increase in the incidence rates in less than two decades [1]. Type 1 diabetes mellitus (T1DM) accounts for 5% of cases, affecting 11-22 million people worldwide, with 78000 new cases diagnosed each year, it is characterized by absolute deficiency of insulin resulting in severe hyperglycemia, and it is fatal if untreated [2-4].

Adiponectin is a 30kDa polypeptide hormone produced only by adipose tissues cells with anti-atherogenic, anti-inflammatory and insulin-sensitizing properties and glucose homeostasis [5] Low levels have been reliably connected with obesity and foresee the advancement of insulin resistance and type 2 diabetes mellitus (T2DM) [6,7]. The exact role of adiponectin in pathogenesis of type 1 diabetes is not fully clear. Some studies in children and most studies in adults have shown adiponectin to be higher in type 1 diabetes than in nondiabetic people and in those with type 2 diabetes [8-13]. Nonetheless, the low levels of adiponectin may likewise be identified with insulin resistance in type 1 diabetes [10,12,14-17]. Adiponectin has been shown

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to have anti-inflammatory and anti-thermogenic effects [18]
including upgraded secretion of nitric oxide and vasodilation
and inversion of the proinflammatory impacts of tumor
necrosis factor-alpha (TNF-α) on endothelial function [15].
It has been hypothesized that a compensatory system may lead
adiponectin levels to react to inflammation and oxidative stress
[11,14,16,19]. Other factors that may affect adiponectin include
peripheral hyperinsulinaemia accompanying subcutaneous
insulin administration or the chronic hyperglycemic state
of type 1 diabetes [5-7]. A reduced clearance of adiponectin may
contribute to higher levels found in individuals with advanced
kidney disease [6-8].

According to several studies, plasma concentration of
adiponectin is reduced in human obesity, particularly visceral,
and negatively correlated with insulin resistance (IR) [9,10].
Additionally, hypoadiponectinemia is independently associated
with the metabolic syndrome (MS), surrogate marker of IR,
and significantly related to T2DM development [10,11]. MS
represents an important risk factor for mortality and micro- and
macrovascular complications development both in patients with
type 1 diabetes mellitus (T1DM) and T2DM [12]. Adiponectin
was found to accumulate in damaged vascular walls and
beneficially modulate the endothelial inflammatory response
to vascular injury as it possesses anti-inflammatory and anti-
atherogenic properties [5]. Consequently normal adiponectin
concentrations or even induction of elevated concentrations
are considered to be beneficial. However, increased adiponectin
concentrations have been found to be associated with an
increased cardiovascular mortality in T1DM [5,13], but in cross
sectional data, the elevation in adiponectin levels has been
hypothesized as a compensatory response in T1DM patients
who have microvascular complications [5]. In addition, there
are a growing number of patients with T1DM and MS who
appear to be at increased risk of cardiovascular mortality and
development of diabetes related complications, a greater need
for higher insulin doses, and multifactorial intervention, thus,
more aggressive treatment [6,14]. Therefore, the purpose of this
study was to determine the relationship between total plasma
adiponectin concentrations and body mass index (BMI), waist
circumference, fasting glucose levels, and glycated hemoglobin.

Materials and Methods

This was an analytic, hospital based- case control study
that was conducted in Najran University Hospital & King
Khalid Hospital in Najran University- Southern Saudi Arabia from March 2015
to August 2017. The study samples comprised 132 Saudi children
(76 Male & 56 female) clinically diagnosed as type 1 diabetes mellitus as defined by The American Diabetes Association
[15]; in contrast, 72 healthy volunteers (40 males, 32 females)
were involved as a control group. Both groups were age and sex
matched and their ages ranged between 2 and 14 years.

Inclusion criteria

Those with other types of diabetes mellitus, thyroid disease,
renal disease, liver disease, anaemia and any medication that
may be affect the Parameters under study were excluded from
this study. An interview with a questionnaire to obtain the
clinical data was done for each participant in this study, clinical
history and examination of the test group and the controls were
done by physicians working in Najran University Hospital & King
Khalid Hospital. Weight was measured using electronic digital
scales. Height was measured using a wall-mounted stadiometer.
BMI was subsequently calculated as weight (kg) per height (m2).

In sterile condition and using a local antiseptic for skin
following an overnight fasting (8-12hrs), 5mls of venous blood
was collected from each participant and separated into 3mls as
serum and 2mls as plasma in EDTA tubes. For serum preparation
the blood samples were separated after complete clotting
by centrifugation at 4000rpm for 5 minutes and serum was
obtained. The sera were used to measure the concentrations of
adiponectin using ELISA (Enzyme-Linked Immunosorbent Assay)
from abcam-UK, FBG was measured using spectrophotometric
method., HbA1c was measured from sample of EDTA tubes using
chromatography technique (boronate affinity chromatography).
Results of this study were statistically analyzed using statistical
package for social science (SPSS) program. Independent
t-test, ANOVA and Persons correlation coefficients were used;
significance levels were set at (P<0.05).

Results

Table 1: Base Line Characteristics & Biochemical Measurements in the test group and the control group.

|                | Diabetic patients | Healthy control | P value  |
|----------------|-------------------|-----------------|----------|
| Age / year     | 10.5±3.9          | 10.7±2.3        | 0.674    |
| Duration / year| 7.1±3.9           | -               | -        |
| Adiponectin ng/ ml | 13.5±3.0       | 8.5±2.8         | 0.001    |
| FBG mg/dl      | 196.9±6.53        | 82.8±8.4        | 0.001    |
| HbA1c %        | 9.9±1.8           | 4.5±0.46        | 0.001    |
| BMI Kg/ m²     | 17.5±1.8          | 18.1±1.4        | 0.009    |

• The table shows the mean±SD.
• P value Less than 0.05 considered significant

One hundred and thirty two Type 1 diabetic patients (76
males and 56 females) and seventy two matched controls (40
males and 32 females) were participated in this study, their ages
ranged between 4 and 14 years (10.45±3.92 for diabetic group
and 10.53±3.43 for control group). There were no significant
differences between the two groups concerning ages & gender.
Adiponectin (ng/ml) was 13.5±3.0 (mean±S.D) for diabetic
children while it was 8.5±2.8 for control group (p=0.001), Fasting
plasma glucose, FPG (mg/dl) was 196.8±6.53 (mean±S.D.) for
diabetic children while it was 82.78±8.39 for control group (p =
0.001), HbA1c % was significantly higher in the diabetic group
than that of the healthy control group (9.90±1.79 vs. 4.53±0.46,
p=0.001) and BMI Kg/m² was significantly decreased in the
diabetic group than that of the healthy controls (17.5±1.8vs.
18.1±1.4, p=0.009), which were demonstrated by (Table 1).

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The study showed insignificant differences between male & female regarding the means of Duration of disease/Year, Adiponectin ng/ml & FBG mg/dl in the diabetic group when compared to the controls (p>0.05) while the means of HbA1c% and BMI Kg/m² shows significant increase in female compared to male in diabetic group (p<0.05) (Table 2).

Regarding Pearson correlation coefficients the results revealed a significant negative correlation between the serum levels of Adiponectin ng/ml and age/year, Duration/Year, FBG mg/dl & BMI Kg/m² in the diabetic group, while it revealed a significant positive correlation with HbA1c% (Table 3).

Concerning the age groups, results showed that the Adiponectin values were significantly different among the study groups (P=0.003) with the highest values were for Toddlers (16.5±2.92) while School–aged children were (13.52±3.13), and the lowest values were for Adolescent group (12.60±2.19) (Figure 3).

(Table 4) shows the mean and SD of Adiponectin among the four studied groups of children regarding to the duration of DM. The four groups differed significantly from each other.
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Discussion

Anti-inflammatory and anti-atherosclerotic effects of adiponectin have been suggested that had a role in protection against development of atherosclerosis [7]. Our study showed that, the mean adiponectin levels were considerably higher in the diabetic patients than the controls. The same results were obtained by Barnes et al. and Ljubicet et al. they found that adiponectin levels were considerably higher in diabetics than in controls [15,16]. Also Furuta et al. found that adiponectin levels exaggerated in conjunction with β-cells malfunction [17]. Researchers assumed that the increase in adiponectin levels is mediated by insulin, the accurate mechanism of insulin activate the gene of adiponectin expression, production and secretion is heretofore unknown [18]. In study that carried out in vitro showed that the adiponectin secretion was stimulated by insulin via phosphatidylinositol 3-kinase pathway [19] this signaling pathway stimulate both production and secretion of adiponectin hormone [20]. Several studies showed that higher serum adiponectin levels was reported in T1DM patients, specially patients surfing from diabetes complication like vascular complications or nephropathy [21]. The increased adiponectin concentration in patients with T1DM can interpreted as a response to posttranslational modifications (glycosylation) that exist in T1DM patients [22], decreased excretion due to renal failure [23], vascular injury [5], and impact of subcutaneous insulin therapy [24]. Also, possibly the fat distribution between diabetic patients and healthy control subjects and reduction of suppression effect by insulin [25]. Adiponectin perform a fundamental role in metabolism of carbohydrates and fats by its effect on insulin sensitivity by activating peroxisome proliferator-activated receptor-γ and the AMP-activated protein kinase [26].

The serum adiponectin level in poorly-controlled subgroup was much greater than in controlled diabetics subgroup and healthy control group, there was a significant difference regarding serum adiponectin level between controlled diabetics subgroup and healthy control children. Many previous studies found that the level of adiponectin was high in type 1 DM patients [27-29]. The collagenous domain of the adiponectin molecule has four conserved lysines. Glycosylation of these molecules is one of the major posttranslation modifications of adiponectin. In diabetic patients with constant hyperglycemia, the glycosylation process is altered, and this could lead to an altered adiponectin function. Consequently, a modified adiponectin molecule could lead to diminished negative feedback, and thus to increased adiponectin concentrations in diabetics [30].

Table 4: Adiponectin levels among different groups of children.

| Duration/years | Percent | Adiponectin ng/ml | p. value |
|---------------|---------|-------------------|----------|
| Less than 2 Years | 22.7 | 14.7±3.4 | 0.001 |
| 2 and less than 5 Years | 16.7 | 14.7±2.7 |
| 5 and less than 10 Years | 34.8 | 12.4±2.9 |
| more than 10 years | 25.8 | 13.1±2.4 |

There were no significant differences between male & female in diabetic group and healthy controls regarding adiponectin level and fasting blood glucose, this results was in harmonization with Diwan et al. which found that there was no significant difference between the two groups with respect to gender, but the level of serum adiponectin in males was lower compared diabetic females [31], this slight differences could be interpreted by the action of testosterone hormone [32]. Saltevo et al. found that the level of adiponectin in females was low compared to males in prediabetics and type 2 diabetic patients [33]. HbA1c% and BMI Kg/m² were significantly higher in females than in males in diabetic group, while there were no differences between male and female in healthy control group.

Our results showed negative correlation between the serum levels of Adiponectin ng/ml and duration of disease/year; this finding disagrees with the finding of Lindström et al. who reported that the increase in circulating adiponectin concentrations in patients with type 1 diabetes appears to be strongly associated with long diabetes duration [34], however, in our study group the majorities of patients with long duration of diabetes are well- controlled patients. Our data showed that there was an inverse correlation between the level of serum adiponectin and BMI in type 1 diabetic children, many studies showed the same finding [31,35,36]. Decreased adiponectin levels was linked to Obesity after gender; age and diabetes were adjusted when compared to none obese patients [31,37], serum adiponectin level increases with weight reduction in both diabetic and healthy control individuals [38]. Researchers found that conversion relation between the number of positive islet cell autoantibodies and body mass index, which explain that the obesity associated with insulin resistance lead to speed up the clinical presentation of TDM at an early phase of β-cell destruction [39].

Conclusion

The serum level of adiponectin in uncontrolled type 1 diabetic children was significantly higher than in healthy and good controlled type 1 DM children, indicates that the serum level of adiponectin hormone has a direct association with HbA1c in children with type 1 diabetes.

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Conflict of interest

The authors declare no conflicts of interest.
Category of study
Basic science.

Ethical approval
All patients were assured that all their obtained information will be handled in a confidential atmosphere and will not adversely affect their lives after taking verbal and written consents. All the human studies were carried out according to the guidelines of the Animal and Human Ethical Committee of Najran University, Kingdom of Saudi Arabia.

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