

# Serum Adipocytokines, Metabolic and Immunological Correlations in Type 1 Diabetes mellitus (T1DM) Children

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**Abstract:** The prevalence of childhood type 1 diabetes mellitus (T1DM) is high among Saudi Arabian population. A viable solution is imperative for combating dreadful endocrine based diseases using adipocytokines functional characters. A relation between, adipocytokines, metabolism and immunological indices of healthy and T1DM insulin treated Saudi children is evaluated. The target group was Saudi children healthy and insulin treated T1DM aged between 3 to 14 years. A total of 28 Saudi pediatric volunteers consist of 13 diabetic and 15 healthy have participated from King Fahad Teaching Hospital in Alkhobar city. Inclusion criteria of insulin treated T1DM participants should be free from hypertension, obesity, history of cardiac, kidney or liver disease and endocrine dysfunction except diabetes. Healthy children free from all these problems were included. Serum adipocytokines (leptin, adiponectin, apelin, visfatin, resistin), metabolic parameters (insulin, fasting glucose, HbA1c,) immunological indices (IgG, IgA, IgM, and IgE) and complement factors (C3, C4) were assayed. Serum levels of leptin, apelin and visfatin were significantly elevated in T1DM treated with insulin group compared to healthy group. There is a positive correlation between adipocytokines and metabolic parameters but there is not with immunological indices. There was a significant positive correlation exists between HbA1c, glucose, leptin, apelin and insulin. Some elevated adipocytokines (leptin, visfatin and apelin) in serum may be attributed to the higher levels of HbA1c, glucose and insulin. Exogenous insulin treatment on T1DM children failed to control serum levels of adipocytokines (leptin, visfatin, apelin) and metabolic parameters (HbA1c, fasting glucose). The results revealed that leptin, visfatin and apelin may have a promising role as biomarkers in T1DM.

**Keywords:** Adiponectin, apelin, complement factors, glucose, HbA1c, immunoglobulins, leptin, resistin, visfatin.

## INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is the most common chronic metabolic autoimmune disease [1]. It is characterized by hyperglycemia due to the infiltration of lymphocytes in the pancreas causing destruction of insulin-producing beta-cells [2, 3]. The incidence of T1DM is reported to be increasing by 3-5% per year, and the number of people with diabetes is estimated to reach 380 million by 2025 [4]. The incidence rate of childhood T1DM is increasing dramatically in many countries over the past 20 years [5]. A community based survey in Kingdom of Saudi Arabia (KSA) reported that the prevalence of T1DM below the age of 19 year to be 109 per 100 000 [6]. The major cause of T1DM is attributed to changes in their habitual lifestyle represents a major clinical and public health problem [7, 8].

To date there is no definitively proven therapies that can stop the progressive beta-cell defect and the progression of the metabolic disorder. Diabetes reduces the average life span with expensive treatment that is projected to cost USD 490 billion in 2030. More prevention efforts are needed to reduce the expenditure burden to provide basic diabetes care [9].

Since 1994, after the Diabetes Control and Complication Trial (DCCT), the use of insulin analogues in intensive regimen i.e. multiple daily doses or insulin pump therapy had improved the metabolic control and reduce the chronic complication of T1DM significantly [10]. However, current insulin treatments are far from satisfactory levels of metabolic control and protection from the long-standing complication of T1DM [11].

Several studies have shown that T1DM is associated with metabolic abnormalities, and alteration of adipose tissue hormones (adipocytokines or adipokines) and immunoglobulins [12-14]. T1DM in children is characterized by progressive loss of glucose homeostasis due to defects in insulin secretion resulting in impaired metabolism of glucose

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and other energy yielding fuels [15]. Glucose concentrations rise due to lack of insulin-stimulated glucose disappearance, and suppression of glucose utilization in skeletal muscle and adipose tissue [2]. The excess glucose present in the blood reacts with hemoglobin to form glycated hemoglobin (HbA1c) in a non-enzymatic glycation pathway [16]. Recently, HbA1c as introduced was an additional diagnostic criteria for diabetes and pre-diabetes [17]. Although insulin is a hormone that plays a key role in the homeostasis of circulatory glucose [18], adipocytokines (soluble factors) which are secreted from adipose tissue, such as adiponectin, leptin, resistin, visfatin and apelin [12] have been implicated in the development of insulin resistance.

Leptin and adiponectin altered secretion or sensitivity have been extensively studied with T1DM. Leptin plays a major role in regulating energy metabolism in humans [19]. A significant relationship between leptin and insulin has been reported by Szalecki *et al.* [20]. Adiponectin possesses an effective insulin-sensitizing with anti-diabetic effect [21]. The elevated level of circulating adiponectin appears to be linked with long diabetes duration, irrespective of the metabolic control in T1DM [22]. Apelin is a novel adipocytokine that binds the APJ receptor. The synthesis and secretion of apelin tends to be regulated by insulin [23, 24]. However, so far the relation between apelin and T1DM has been scarcely reported. Resistin, a secretory protein is detected in human plasma. High level of resistin leads to impaired glucose tolerance and insulin action. Immunoneutralization of resistin was found to enhance insulin sensitivity in T1DM patients [25, 26]. Visfatin is a recently described adipokine that mimics insulin properties [27]. Visfatin gene mutation in mice results glucose intolerance primarily due to insulin secretion deficiency [28]. Erik *et al.* [29] found that blood visfatin may not be a useful clinical biomarker of metabolic traits. But Pfützner *et al.* [30] reported that visfatin is an assumed biomarker for metabolic disorders, also the pancreatic  $\beta$ -cell may be exposed to elevated visfatin levels, which can be used as specific markers for insulin sensitivity [31]. Recently, visfatin as a biomarker can be correlated with maternal factors to facilitate the early screening for Gestational diabetes mellitus (GDM)[32].

## AIM OF THE STUDY

The aim of this study is to measure the adipocytokines serum levels and evaluate their relation to metabolic and immune parameters in treated T1DM Saudi children compared to healthy age and sex matching children.

## MATERIALS AND METHODS

### Study Design and Target Patients

The target groups were Saudi children healthy and diabetic treated with insulin. They have been followed at King Fahad Hospital of the University of Dammam (KFHU) in Alkhobar city, Saudi Arabia. A consent from all participant or/and their parents was obtained before the study. The research was approved by Ethics Committee of Biological and Medical Research for University of Dammam. No (HAP-05-D-003).

## Medical History

A total of 28 Saudi pediatric subjects (3-14 years) were divided into two groups consisting of T1DM treated with insulin for at least 2 years (n=13) and healthy participants (n=15). The two groups were matched for both age and sex. This study has several limitations because of the narrow selection criteria, the sample size was small. Hence, our data may not be representative for all subjects with T1DM.

The inclusion criteria include kids having no hypertension, cardiac, renal, nor hepatic disease and no other endocrine dysfunction except diabetes. All of them were not obese; Body Mass Index (BMI) values were (15.4 - 20.2) kg/m<sup>2</sup> with normal height. Weight ranged (19 - 47.5 kg)

## Blood Sample and Biochemical Assessment

Fasting blood samples were collected in hospital lab. It was ensured that the participants were fasting for at least 12 hours. The last dose of insulin was 12 hours back. All patients receive regular insulin and (normal pressure hydrocephalus (NPH)) with average total dose of 0.8 u/kg/day range of (0.6-1.0). The study tools included blood biochemical tests collected in non-heparinized test tubes, then centrifuged to separate the serum and saved at -18 °C in deep freezer for the following assay:

Fasting serum glucose and Blood HbA1c were measured, using SIEMENS stream lab - Dimension clinical chemistry system-RXL max (USA), kits from SIEMENS. Leptin, adiponectin, apelin, visfatin and resistin were measured using the sandwich enzyme-linked immunosorbent assay (ELISA) by PHOENIX PHARMACEUTICALS, USA. Insulin was measured in serum using the ABBOT AxSYM SYSTEM produced by Axis-Shield Diagnostics, Ltd., Dundee, UK for Abbot Diagnostic Division 2009. The (0.016% at 10<sup>6</sup>pg/ml). Immunoparameters were measured in serum using BN proSpec System Produced by SIEMENS

## Statistical Analysis

Data were analyzed using SPSS software version 19. A *t*-test was carried out to compare means of the healthy and T1DM treated children. Pearson correlation test was done to find the correlation between the assessed parameters. The result was expressed as mean  $\pm$  standard error of mean. Statistical significance was considered at the level of ( $p < 0.01$ ) and ( $p < 0.05$ ).

## RESULTS AND DISCUSSION

### Adipocytokines Relationship with Fasting Glucose, HbA1c and Insulin in Pediatric

Table 1 showed that the serum level of adipocytokines such as leptin was ( $p < 0.01$ ) significantly elevated (87.47 $\pm$ 14.10 ng/ml) in insulin treated T1DM when compared with healthy control group (24.85 $\pm$ 11.29 ng/ml). The observed result could be explained by Szalecki *et al.* [20]. Leptin plays an important role in maintaining body energy balance, while insulin plays a key role in leptin secretion and regulation [33]. In experimental study, insulin treatment acutely increased both secretion and production of leptin from adipose cells by a mechanism that is distinct

from the release of stored secretory vesicles [34]. These were corroborated in the present clinical study with an increased serum leptin levels in insulin treated T1DM children. A rapid elevation in leptin after 24 h of insulinization was noticed and there was a stimulatory effect of insulin on leptin production in T1DM [35]. The increased serum leptin level was positively correlated with insulin therapy [36]. As shown in Table 2, in the present study serum leptin level has a positive significant correlation ( $p < 0.05$ ) with serum fasting glucose concentration. It may be due to the inability of insulin and leptin to control serum fasting glucose level in T1DM treated with insulin children's. In addition, interestingly, it revealed that during insulin treatment leptin correlated positively with highly significant ( $p < 0.01$ ) with, resistin, visfatin, apelin, and HbA1c.

Adiponectin is a unique adipokine that influences insulin-sensitizing action [37]. Several studies reported that T1DM

patients have significantly higher circulating adiponectin levels as compared to healthy individuals [38, 39]. It has also been suggested that insulin treatment negatively regulated the expression levels of adiponectin and insulin sensitivity in plasma and muscle [40, 41]. In comparison to earlier reports our result of serum adiponectin levels of T1DM children did not increase when compared with healthy children (Table 1). The unchanged level of adiponectin may be due to insulin treatment. Table 2 showed that adiponectin has a positive significant ( $p < 0.05$ ) correlation with resistin during T1DM treatment with insulin in children.

Resistin influences insulin resistance, fasting glucose homeostasis, diabetes, and inflammation. The role of resistin in glycemia, insulin resistance, obesity is still debated. Human resistin level is elevated in T1DM condition [25]. In the present study, no differences in serum resistin levels were found between healthy control and T1DM insulin

**Table 1. Serum Concentration of Adipocytokines, Metabolic Parameters, Immunoglobulins and Complement Factors in Healthy and T1DM Treated Children**

	Groups	
	Healthy Children	Insulin Treated T1DM Children
Leptin (ng/ml)	24.85±11.29	87.47±14.10**
Adiponectin (ng/ml)	12.11±1.97	7.67±0.87
Resistin (ng/ml)	4.27±1.04	5.55±0.59
Visfatin (ng/ml)	6.08±1.28	9.79±1.02*
Apelin (ng/ml)	1.28±0.12	1.89±0.10**
HbA1c (%)	5.54±0.11	11.05±0.56**
Glucose (mg/dl)	94.00±4.78	248.23±33.91**
Insulin (Uu/ml)	14.59±3.62	55.10±14.59*
IgM (mg/dl)	122.06±10.15	125.26±10.27
IgE (IU/ml)	191.94±56.92	77.23±19.15
IgA (mg/dl)	174.52±17.56	165.53±16.02
IgG (mg/dl)	1304.80±90.85	1219.69±37.05
C3 (mg/dl)	145.5067±8.80	148.2308±9.38
C4 (mg/dl)	28.3067±3.48	32.6231±3.42

Data indicate mean±SE.

\*\*Represent a significant difference with the healthy group at  $P < 0.01$ .

\*Represent a significant difference with the healthy group at  $P < 0.05$ .

**Table 2. Pearson Correlation Test of Studied Parameters in Children Serum**

	Leptin	Adiponectin	Resistin	Visfatin	Apelin	HbA1c	Glucose	Insulin
Leptin	-	-	** .487	** .861	** .785	.552**	* .461	-
Adiponectin	-	-	* .386	-	-	-	-	-
Resistin	** .487	* .386	-	-	** .567	-	-	-
Visfatin	** .861	-	** .567	-	** .798	-	-	-
Apelin	** .785	-	** .567	** .798	-	* .463	-	* .394

Data indicate mean±SE.

\*\* Correlation is significant at the  $P < 0.01$  level and \* at the  $P < 0.05$  level (2 - tailed).

treated kids (Table 1). Earlier literatures have shown the average concentration of resistin was in the range between 5-10 ng/ml [42-44]. Our results commensurate with the normal range, which implied that it was not involved in metabolic changes in T1DM insulin treated children. It may be due to the restoration of resistin in T1DM condition due to insulin treatment. Table 2 showed that resistin positively correlates highly significant ( $p < 0.01$ ) with leptin, apelin and adiponectin ( $p < 0.05$ ).

The apelin synthesis and gene expression was reported to be upregulated by insulin [45]. Apelin tends to be related closely with insulin resistance and fasting glucose metabolism [46, 47]. Meral *et al.* [24] reported that plasma apelin was increased in children with T1DM. In this study (Table 1), we observed serum apelin levels were significantly ( $p < 0.01$ ) higher in the T1DM insulin treated group ( $1.89 \pm 0.10$ ) compared to healthy controls ( $1.28 \pm 0.12$ ). Such elevations have direct positive correlation between serum apelin and insulin levels which might be due to insulin treatment. Table 2 showed that apelin positively correlated highly significantly ( $p < 0.01$ ) with leptin, resistin, visfatin and significantly ( $p < 0.05$ ) with HbA1c and insulin.

Visfatin is a recently discovered adipokine that has a primary role in regulation of insulin secretion in pancreatic  $\beta$ -cell. Toruner *et al.* [48] reported a lower level of visfatin in T1DM than controls with significant correlation between visfatin and HbA1c. On the contrary, in the present study, visfatin levels were significantly ( $p < 0.05$ ) elevated in T1DM insulin treated than healthy control. No correlation between HbA1c and visfatin levels was observed. The results coincided with a  $\beta$ -cell dysfunction mechanism linked between increased serum visfatin and T1DM [49,50]. It may be due to  $\beta$ -cell deterioration not restored by insulin treatment, which can be used as specific markers for insulin sensitivity [31]. It was reported that new insulin treatment mimics insulin secretion in the imperfection way [51]. Table 2 showed that visfatin positively correlated highly significantly ( $p < 0.05$ ) with leptin, resistin and apelin.

HbA1c determines the fasting glucose concentration in diabetic patients and therefore reflects detrimental diabetic complications [52]. HbA1c levels were elevated in T1DM treated with insulin due to poor glycemic control [53]. As shown in Table 1, HbA1c increased highly significantly ( $p < 0.01$ ) ( $11.05 \pm 0.56$ )% in diabetic children when compared with control level ( $5.54 \pm 0.11$ ). The present data showed inability of regulating blood fasting glucose level in T1DM treated with insulin children. The current results coincided with the result of Soliman *et al.* [54] who reported

a positive correlation between HbA1c level and leptin concentration. The higher serum levels of some adipocytokines in T1DM patients in present study may be attributed to associated high significant level of HbA1c (Tables 1 and 2). Insulin (exogenous) level may be the most important marker of leptin level. This can be partially explained with an increased appetite due to over substitution by insulin that contribute to increase leptin secretion and explained the higher leptin levels in diabetic children [55]. Table 3 revealed a highly significant positive correlation at the level ( $p < 0.01$ ) between HbA1c with fasting glucose and insulin. It may be due to the poor control of glycemic regulation by exogenous insulin treatment.

Insulin has many metabolic functions [56-58]. During dysfunction in T1DM patients, insulin secretion fails in pancreas beta cells leading to metabolic disturbances. In our study, the insulin level increased significantly ( $p < 0.05$ ) in T1DM insulin treated children ( $55.10 \pm 14.59$ ) ng/ml, when compared with healthy control ( $14.59 \pm 3.62$ )ng/ml. Table 3 represents a highly significant positive correlation at the ( $p < 0.01$ ) level of insulin with HbA1c. It may be attributed to elevated leptin, visfatin and apelin due to failure of exogenous insulin treatment in T1DM treated with insulin patients.

Table 1 showed a significant increase of fasting glucose, HbA1c ( $p < 0.01$ ) and insulin ( $p < 0.05$ ) in T1DM treated with insulin than healthy control. In addition, Table 2 showed that there was a positive significant correlation of leptin with fasting glucose and HbA1c ( $p < 0.05$  and  $p < 0.01$ ). Table 3 also revealed that HbA1c has a positive significant correlation with fasting glucose and insulin. This correlation indicated that leptin is the most important adipokine, which synchronized with high fasting glucose concentration in target Saudi patient who had high ratio of HbA1c and insulin. This is in agreement with Ashraf *et al.* [59] who reported that over substitution by insulin exerted many metabolic actions and contribute in elevation of leptin release. They attributed the higher leptin levels in uncontrolled childhood diabetic (higher circulating HbA1c concentrations) that they were treated with insulin.

### Metabolic and Immune Parameters Relationship in Pediatric

Immune parameters were assessed in T1DM treated with insulin and control healthy group. Complement C3 and C4 are the major plasma proteins of the immune system complement pathways. The synthesis of serum complement protein C3 increased in response to inflammation and metabolic disorders, diabetes C3 levels elevated in T1DM

**Table 3. Pearson Correlation test for Metabolic Parameters and Immunoglobulins and Complement Factors**

	HbA1C	Glucose	Insulin	IgM	IgE	IgA	IgG	C3	C4
HbA1C	-	** .663	** .518	-	-	-	-	-	-
Glucose	** .663	-		-	-	-	-	-	-
Insulin	** .518			-	-	-	-	-	-

\*\* Correlation is significant at the  $P < 0.01$  level (2 - tailed).

[60,61]. Zhain *et al.* [62] reported that serum C3 and C4 of T1DM patients is significantly lower than corresponding value of healthy subjects and the lowest value of C3 was observed in patients with HbA1c >11%. The C3 levels were tended to reduce after improving glycaemia. Insulin has potential anti-inflammatory effects [63]. Insulin closely related with C3 and plays a vital role in alteration of fasting glucose metabolism [64]. Plasma levels of C3 and C4 were normal during insulin treatment in type 1 diabetes, our results were in agreement with the report of Rego Filho *et al.* [65] where the levels of complement factors C3, C4 and immunoglobulins IgG, IgA, IgE, IgM in T1DM group didn't change compare with healthy control (Table 1).

T1DM patients have shown elevated plasma levels of IgM and IgA, and a reduced level of IgG compared to healthy controls [66]. Immunological complications have decreased significantly showing a prolonged restoration of  $\beta$ -cell function in T1DM insulin treated patient [67]. Earlier findings showed that T cells played adverse role in  $\beta$ -cell destruction in T1DM. Exogenous insulin treatment was used to stimulate activation of insulin-specific T-cell for subsequent restoration action in T1DM patients [68]. IgG and IgE are reported to be interrelated in T1DM condition [69]. In our data, IgE and IgG levels in T1DM patients were not change significantly compared with healthy children (Table 1). However, in between IgE and IgG, a highly significant ( $p < 0.01$ ) correlations was observed. No significant changes in IgA, C3 and C4 observed in T1DM treated with insulin and healthy children (Table 1). Notably, IgA was found to be positively correlated with C3 and C4 at the ( $P < 0.01$ ) level. Previous studies found a change with plasma levels of IgA, C3 and C4 which was reported to be associated with insulin treatment [70, 71]. Interestingly, Pearson test revealed that there was no correlation exists between adipocytokines with immunoglobulins and complement factor C3 and C4. It showed that insulin treatment in T1DM patients might regulate complement factors and immunoglobulins but not the disturbed adipocytokines (leptin, visfatin and apelin).

## CONCLUSION

- Leptin was the most important adipocytokine, where its high level was synchronized with high fasting glucose concentration in insulin treated T1DM patients who had high HbA1c and insulin level.
- Insulin treated T1DM children had significantly elevated serum level of leptin, apelin, visfatin, HbA1C, fasting glucose and insulin but showed near normal levels of adiponectin and resistin when compared with healthy children.
- Serum immunoglobulins and complement factors (C3, C4) levels of T1DM treated with insulin were found to near normal levels comparable to healthy children with no correlation with the adipocytokines.

Finally it could be suggested that serum leptin, visfatin and apelin appear to have a promising role as biomarkers in T1DM, the ability to regulate them in these patients was needed in further studies to help in managing this disorder.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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