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Apelin as a Potential Marker in Iraqi Children with Type 1 Diabetes Mellitus

Noor Thair Tahir[1,2,3*], Israa Qusay Falih[2], Mithal R. Alkubaisi[3], Abdilya Riyadh Alabdaly[4]

[1]National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.
[2]Department of Chemistry, College of Sciences, University of Misan, Mayssan, Iraq.
[3]College of Medicine, University of Anbar, Ramadi, Iraq.
[4]College of Medicine, University of Jordan, Amman, Jordan.
*Correspondence to: Noor Thair Tahir (E-mail: dr.noorthair.ndc@uomustansiriyah.edu.iq)
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Abstract
Objective: This study aims to evaluate apelin levels and their correlation with key metabolic parameters in pre-pubertal and pubertal individuals with type 1 diabetes in Iraq, providing insights into apelin's role in diabetes pathogenesis and its potential as an early diagnostic marker for cardiovascular disease.
Methods: Ninety children, divided into pre-pubertal T1DM, pubertal T1DM, and healthy subjects, underwent measurements of various biochemical parameters, including apelin, fasting blood glucose, lipid profile, and thyroid hormones.
Results: Positive correlations ($P < 0.01$) were found between apelin levels and FSB, TG, BMI, HbA1c, TC, TSH, and a negative correlation with HDL-C in pubertal and pre-pubertal groups, revealing potential links between apelin, glucose, and insulin sensitivity.
Conclusion: The study suggests apelin's involvement in diabetes pathogenesis, highlighting its rise in adulthood as an indicator of diabetes complications and its potential use as a diagnostic marker for early detection of cardiovascular disease in individuals with T1DM.
Keywords: T1DM, apelin, lipid profile, children, glycosylated hemoglobin (HbA1c), kidney function test

Introduction

Most cells need insulin for glucose phosphorylation, direct it to the cytomembrane, obtain energy as ATP and sustain cells.[1] Insulin also introduces excess glucose into adipose tissue or stimulates liver enzymes to store glucose as glycogen.[2] When the beta cells of the pancreas are unable to produce insulin, an autoimmune reaction causes their demise, it is one of hyperglycemia kinds called type 1 diabetes. It appears that 10% of people with type 1 diabetes have a genetic predisposition to make autoantibodies that destroy beta cells. Health centers attempt to lower and normalize the elevated glucose level in these individuals by subcutaneous insulin injection to avoid ketoacidosis, diabetic coma, then death.[3]

Studies and activities have been heading for about a decade to uncovering of endocrine problems solution and the serious complications that follow them, such as metabolic disorders, diabetes, kidney disease, as well as high immune proinflammatory cytokines which are the most prominent features of problems facing health systems around the world. Studies aim to highlight the functional properties of adipocytokines.[4]

Symptoms of insulin resistance and insulin deficiency are very clear in children with type 1 diabetes.[5] Adipose tissue produces many adipocytes that equal insulin sensitivity and play an effective role in causing diabetes.[6] Apelin is a multifunctional neuropeptide hormone that exerts its effect by binding to the Angiotensin (II) Protein J receptor (APJ), which is secreted in various locations and appears in white adipose tissue, renal tissue, and endothelial tissue. It has played a role in metabolic regulation. Cardiovascular and fluid homeostasis, and cell proliferation.[7]

Insulin is the main regulator of apelin, it stimulates its synthesis and release,[8] in addition to the fact that insulin binds apelin to its receptors in adipocytes and enhances its presence in them. Symptom in the large vessels is an important aspect of complications related to diabetes.[9] The weakness of the contraction and expansion of vessels is the highlight feature of endothelial dysfunction, it is responsible for the vascular pathophysiology of diabetic patients. Giant cell myocarditis and microvascular dysfunction are the main factors in the development of diabetic cardiomyopathy.[10] Apelin was expressed as the most powerful inotropic agent in the heart muscle.

In type 1 diabetic children, the level of apelin has a positive association with the thickness of the inner layer of the carotid artery,[11] as it reduces vasodilation and increases vasoconstriction in disorders related to insulin resistance, indicating the possibility of its use as a predictor of atherosclerosis. In type II diabetes, apelin plays a role in maintaining vessels and neutralizing the action of vasoconstriction[12] by preventing cell proliferation resulting from elevated glucose, migration, and invasion of aortic smooth muscle cells. Apelin relieves calcification caused by raising glucose,[13] thus significantly preventing DNA damage which causes high glucose activating fomes reactive oxygen species. Moreover, studies confirm that an existence metabolic pathway linking thyroid disruption (hypothyroidism or hyperthyroidism) with T1DM. Hence, it could been mentioned that there is a direct relationship between thyroid hormones and the regulation of glucose metabolism, as its hormones affect by creating an energy balance in cases of starvation and fasting through the lipolysis by gluconeogenesis, increasing glucose uptake from the intestine, and, affecting on adiponectin. Thus, due to the complications and complications of diabetes increase in the case of impaired thyroid function.[14]

Glomerulosclerosis interstitial, which is brought on by hyperglycemia, is a feature of diabetic nephropathy (DN).[15] The glomerular basement membrane becomes significantly enlarged and thickened in the early stages of DN. High glomerular filtration rates cause proteinuria as this illness

progresses, and end-stage Rehal disease is the result.[16] Elevated apelin encourages angiogenesis, glomerular capillary growth, and fast DN formation.

An effective, an innovative treatment recommendation is needed to reduce diabetes mellitus and mortality from metabolic diseases. Aim of this study: This study was aimed to evaluate apelin levels and other biochemical parameters in Iraqi prepubertal and pubertal T1DM.

Materials and Methods

Sixty patients with T1DM divided to two groups (G1 = (30) prepubertal T1DM and G2 = (30) pubertal T1DM), compared with G3 = (30) healthy control were collected from national diabetes center , Mustansiriyah University during of the years 2022. All subjects had to go through clinical examination to determine existence of other disease, Demographic characters such as sex, age, height, weight and BMI of all participants were noted. Blood samples were taken for laboratory investigation which included: FBS, RBS, TC, TG, HDL, LDL, B.urea and S.creatinen were measured by using automated analyzer (cobas c 111). Apelin level was estimated by ELISA (sunlong cataloge (SL0277Hu)).

Mean ± SD were expressed for all data. Statistical analysis was performed using LSD, considering $P < 0.05$ as the lowest limit of significance. It's used SPSS programs, version 22 (SPSS, Chicago, IL, USA).

Results

The anthropometric data were presented in Table 1, which aims to compare between type 1 diabetes patients and the control. There was a significant difference at ($P < 0.05$) for each of the weight, height and body mass index (BMI) between the competing groups. A highly significant difference at ($P < 0.001$) for each of the healthy weight, Overweight and obese in patients with type 1 diabetes compared to the healthy group.

Including the clinical data obtained in a Table 2 that shows the significant differences among groups of patients in pubertal G_1, pre-pubertal G_2 and healthy G_3 subjects. The statistics view that there is no significant in groups for each of the HDL-C, B.urea, and S.creatinine. A highly significant different increase at ($P < 0.001$) was recorded between G_1 vs G_3 and G_2 vs G_3 for each of FBS, RBS, HbA1c, and TC, while a significantly different increase ($P < 0.05$) for TG and LDL-C. Also, the statistical values had been indicated, there is no significant difference between the groups with TT3, while a highly significant difference ($P < 0.01$, $P < 0.001$) are recorded for each of TT4 and TSH. Although the children

Table 1. **Anthropometric measurements between T1DM patients and control**

	T1DM patients	Control	*P*-value
	Mean ± SD	Mean ± SD	
	N (60)	*N* (30)	
Sex (male/female)	(33/28)	(16/14)	/
Age (years)	11.73 ± 1.00	10.80 ± 2.00	**NS**
Weight (kg)	39.66 ± 14.78	30.16 ± 2.98	**0.05**
High (cm)	135.13 ± 18.08	126.76	**0.05**
BMI (kg/m^2)	25.90 ± 0.70	20.61 ± 1.32	**0.05**
Healthy weight *N*, %	*N* = 33 58%	*N* = 25 90%	
Over weight *N*, %	*N* = 20 28%	*N* = 5 10%	
Obese *N*, %	*N* = 7 14%	*N* = 0 0%	**0.001**

n: number; Data are presented as mean ± SD; NS is no significant; *P*-value is significantly $P<0.05$, and high significant $P < 0.01$ and $P < 0.001$.

Table 2. **Clinical parameters among groups of study (prepubertal T1DM, pubertal T1DM and control)**

Parameter	Prepubertal T1DM (G_1)	Pubertal T1DM (G_2)	Control (G_3)	G_1 vs G_2	G_1 vs G_3	G_2 vs G_3
	Mean ± SD	Mean ± SD	Mean ± SD			
	N (30)	*N* (30)	*N* (30)			
FBS (mg/dl)	207.26 ± 3.80	208.9 ± 1.74	79.93 ± 0.48	NS	0.001	**0.001**
RBS (mg/dl)	247.7 ± 49.09	251.2 ± 57.38	99.83 ± 6.38	NS	0.001	**0.001**
HbA1c %	11.44 ± 1.38	11.90 ± 4.46	5.14 ± 2.31	NS	0.001	**0.001**
TC (mg/dl)	146.46 ± 61.51	160.63 ± 63.10	126.96 ± 16.20	0.05	0.001	**0.001**
TG (mg/dl)	98.16 ± 14.28	125.03 ± 27.03	83.66 ± 13.58	0.05	0.05	**0.05**
HDL-C (mg/dl)	52.26 ± 7.57	53.06 ± 11.12	55.2 ± 7.59	NS	NS	**NS**
LDL-C (mg/dl)	87.16 ± 4.91	88.04 ± 5.34	68.5 ± 3.49	NS	0.05	**0.05**
TT_3 (ng/dl)	1.893 ± 0.485	1.706 ± 1.26	1.94 ± 6.46	NS	NS	**NS**
TT_4 (ng/dl)	61.33 ± 0.53	88.93 ± 0.59	101.4 ± 0.43	NS	0.05	**0.05**
TSH (ng/dl)	13.25 ± 3.093	5.22 ± 0.03	1.74 ± 0.02	NS	0.001	**0.01**
B.Urea (mg/dl)	27.33± 16.57	25.93 ± 26.68	27.13 ± 15.25	NS	NS	**NS**
S.Creatinine (mg/dl)	0.7 ± 0.04	0.70 ± 0.40	0.67 ± 0.11	NS	NS	**NS**

n: number; Data are presented as mean ± SD; NS is no significant; *P*-value is significantly $P<0.05$, and high significant $P < 0.01$ and $P < 0.001$. Pre-pubertal T1DM (G_1) vs pubertal T1DM (G_2), pre-pubertal T1DM (G_1) vs Control (G_3), pubertal T1DM (G_2) vs Control (G_3).

Table 3. **Apelin levels among groups of study (prepubertal T1DM, pubertal T1DM and control)**

Parameter	Prepubertal T1DM(G_1)	Pubertal T1DM(G_2)	Control (G_3)	G_1 vs G_2	G_1 vs G_3	G_2 vs G_3
	Mean ± SD	Mean ± SD	Mean ± SD			
	N (30)	*N* (30)	*N* (30)			
Apelin levels (ng/ml)	337.64 ± 12.36	696.36 ± 13.30	222.23 ± 11.25	0.001	0.0001	**0.0001**

n: number; Data are presented as mean ± SD; NS is no significant; *P*-value is significantly $P < 0.05$, and high significant $P < 0.01$ and $P < 0.001$. Pre-pubertal T1DM (G_1) vs pubertal T1DM (G_2), prepubertal T1DM (G_1) vs Control (G_3), pubertal T1DM (G_2) vs Control (G_3).

Table 4. **Correlation coefficient of apelin levels between (prepubertal T1DM and pubertal T1DM)**

	Apelin levels (ng/ml)	
	Prepubertal T1DM	Pubertal T1DM
	r	r
Age (years)	0.02	**0.015**
Weight (kg)	0.026	**0.019**
High (cm)	–0.020	**0.271**
BMI (kg/m^2)	0.357*	**0.371***
FBS (mg/dl)	0.502**	**0.586****
RBS (mg/dl)	0.037	**0.119**
HbA1c %	0.359*	**0.339***
TC (mg/dl)	0.308*	**0.388***
TG (mg/dl)	0.369*	**0.363***
HDL-C (mg/dl)	0.029	**–0.148**
LDL-C (mg/dl)	0.508**	**0.563****
TT_3 (ng/dl)	0.102	**0.136**
TT_4 (ng/dl)	0.221	**0.169**
TSH (ng/dl)	0.344*	**0.363***
B.Urea (mg/dl)	0.078	**0.180**
S.creatinen (mg/dl)	–0.082	**0.132**

*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

in the pre-pubertal stage have hypothyroidism, it has been recorded that this condition decreases in the puberty group, indicating that they are taking drugs to improve their condition.

The values of apelin were expressed in Table 3 with a highly increase significant at ($P < 0.001$) among the groups G_1, G_2, and G_3.

Statistical analysis data in Table 4 shown that the apelin has a positive correlation coefficient with BMI, HbA1c, TC, TG and TSH at ($P < 0.05$) for pre-pubertal T1DM and pubertal T1DM groups. In addition, a positive correlation at ($P < 0.01$) to apelin with FBS and LDL-C. A negative correlation coefficient for apelin with HDL-C in pubertal T1DM group.

Discussion

Diabetic mellitus treating and avoiding diseases that occur as a result of its affliction is the most prominent goal for generally biochemical research. The vast majority of research papers are seeking to find a solution to this chronic autoimmune disease. Showing the possessed features of some adipocytokines as well as its roles that play for rapid diabetes symptoms development besides the complications become an important source to spy the nature or the adapting possibility of these hormones for early diagnosis, treatment before worsens the condition to deteriorating stages.

Research indicates that children with type 1 diabetes have a high level of apelin in the serum, and a positive correlation with the inner layer thickness of the carotid artery. Apelin systems depend on its receptors presence sites in both of the endothelial and smooth muscle cells, when it binds with its receptor located in endothelial cells, apelin enhances the secretion of relaxation factors derived from the endothelium such as nitric oxide (NO) and prostacyclin,[17] leading to vasodilatation. Whereas, if it binds with its receptor in smooth muscle cells, it causes vasoconstriction.[18] With considering the apelin as a strong factor for angiogenesis, especially in the lining of the retina (for the human eye with proliferative diabetic retinopathy), so that the rise of Apelin in endothelial progenitor cells with areas of ischemia lead to contributes to the formation of vessels.[19] Thus, apelin is a promising therapeutic target for diseases related to angiogenesis.

(Jiang, Y et al., 2021) considered the first study to show evidence that apelin inhibits insulin secretion, and this reference agrees with recent reports that apelin works to reduce insulin secretion by decreasing the production of (cAMP) the secondary messenger compound, which receives insulin signals by ordering the cells with introduce glucose as fat stored form.[20] Apelin contributes to decreasing insulin sensitivity to high glucose.[21] Therefore, an increase in the fasting blood sugar level was observed for children with type 1 diabetes, despite taking insulin injections in daily doses.

Insulin resistance appears in obese people when their free fatty acids levels secreted from adipocytes were raised. Adipose tissue produces many cells that modulate insulin sensitivity such as apelin, Visfatin, tumor necrosis factor TNF, adiponectin and interleukin IL-27 etc., that were played the greatest role in causing diabetes, insulin resistance, atherosclerosis, inflammation, angiogenesis, and immune function.[22] Apelin is associated with diabetes and obesity participates in multiple physiological processes due to the presence of its receptors in a wide site of the body.

Some clinical references moreover in vivo experiments which agree with our papers about the direct relationship between elevated apelin concentration and increased indices of obesity (TG, TC, and LDL).[23–25] Consequently, the present study indicates that children with type 1 diabetes who are

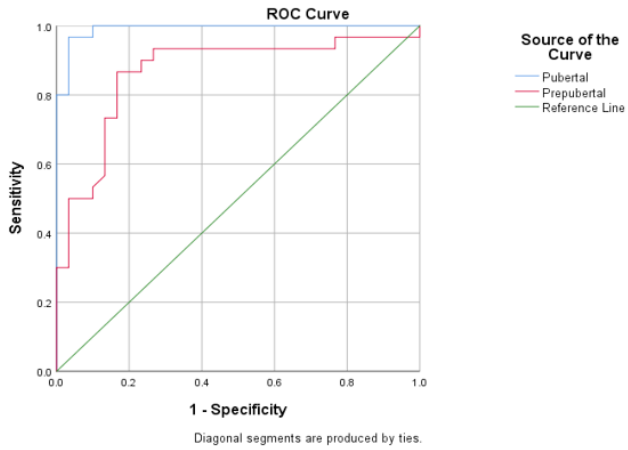

Fig. 1 **The receiver operating characteristic curve for diagnostic accuracy of serum apelin level between prepubertal and pubertal in early discrimination of cardiovascular disease.**

Table 5. **Area under ROC curve and performance criteria of apelin levels for discrimination among prepubertal, pubertal and control groups**

	Pubertal	Prepubertal
AUC	0.991	0.866
Cut off	1299	1014
Sensitivity (%)	100	68
Specificity (%)	100	67
PPV (%)	100	86.5
NPV (%)	97	76
Accuracy (%)	95	95

treated with insulin show insulin resistance with a positive correlation with apelin, as it has an effect related to fasting glucose level.[26]

Thyroid gland secretions appear to have a significant role in regulating metabolic reactions and the effectiveness of the insulin hormone, so when there is a deficiency in thyroid hormones (hypothyroidism), it a depression in the action of cells which are contributed to metabolism and insulin action. In addition, the thyroid gland is controlling over the releases of the islet cell (pancreas) and glucose transporter, so there is a dyspancreatism lead to a high level of cumulative glycated haemoglobin (HbA1c) in patients with hypothyroidism.[27]

At pubertal for children with type 1 diabetes, the rise is more severe for apelin in the serum. Diabetes is usually accompanied during this period by changes in lipid metabolism, increased growth, hormonal changes, oxidative stress enhanced by hyperglycemia, endothelial dysfunction, and programmed cell death.[28] The relationship among apelin levels, glucose concentrations, and insulin sensitivity shows the participation of apelin in the pathogenesis of diabetes and that its rise during adolescence is an indicator of the first serious diabetes complications. Children and adolescents with diabetes type 1 suffer from ischemic heart disease. The American Heart Association states that the greatest disorder occurs when atherosclerosis was done. Cardiovascular disease was paired to the action that regulates metabolism during diabetes while controlling the secretions of adipocytokines peptides released by cells, causing complications.[29]

Conclusion

Adipose tissue produces many peptides that increase insulin resistance. Apelin plays a major role in causing complications of diabetes such as inflammation, atherosclerosis, and cardiovascular diseases. The results show the patients who were gotten subcutaneous insulin injections had a highly positive correlation between apelin vs FBS (high insulin resistance) and LDL. Moreover, Apelin has a positive correlation with HbA1c, and THS in both groups (pubertal and prepubertal) withT1DM by being closely associated with diabetes complications. It can conclude that the relationship between apelin levels, glucose concentrations, and insulin sensitivity shows the participation of apelin in the pathogenesis of diabetes, and its rise in adulthood is an indicator of the beginning of diabetes deterioration, in addition to the possibility of using apelin as a diagnostic marker in early discrimination of cardiovascular disease Figure 1 and Table 5. We hope for more research establishing the role of apelin as a diagnostic marker or therapeutic agent in diabetes.

Author Contributions

Methodology, Noor Thair Tahir; validation, All Authors; formal analysis, All Authors; investigation, All Authors; resources, All Authors; data curation, All Authors; writing—original draft preparation, Noor Thair Tahir; writing—review and editing.

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Informed Consent

The individuals participating had been informed about the desired benefit for using their samples in this research paper, and the ethics of the approval could committee from the National Diabetes Center/Mustansiriyah University was obtained.

Data Availability Statement

The data that support the findings of this study are available from the cor-responding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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