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Apelin and Its Relation with Glucose Metabolism in Adolescents with Type 1 Diabetes Mellitus: Comparative Study

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الأبلين وعلاقته بايض الكلوكوز لدى المراهقين المصابين بمرض السكري من النوع الأول: دراسة مقارنة

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ABSTRACT

Background: Type 1 diabetes mellitus, also known as insulin-dependent diabetes, characterized by elevated levels of blood glucose (hyperglycemia), which produced by the autoimmune destruction of pancreatic islet β-cells insulin-producing.

Objective: This study aimed to examine the alterations in Apelin, Lipid profiles, fasting blood glucose, HbA1C, calcium, parathyroid hormone and vitamin D in adolescents with type 1 diabetic and healthy adolescents.

Methods: This study was done in the Maternity and Children Teaching Hospital and Al-Ramadi Teaching Hospital in Ramadi city in Iraq, between January 2024 to July 2024. One hundred adolescents were selected: 60 patients with diabetes and 40 healthy as a control group. Biochemical tests for blood samples were performed.

Results: The results showed there was a significantly increase in concentrations of Apelin, lipid profile (except high-density lipoprotein cholesterol), fasting blood glucose, HbA1C and calcium in patients with diabetes than control group. Whereas, there was a significantly reduction in concentration of the high-density lipoprotein cholesterol, parathyroid hormone and vitamin D in patients with diabetes than control group. The results showed a significant positive correlation among glucose concentrations and Apelin concentrations, while there was a significant inverse relationship between blood parathyroid hormone and blood glucose concentrations, and also, there was a significant inverse relationship between vitamin D concentration and HbA1c.

Conclusion: The high serum concentrations of Apelin in diabetic patients supports the function of Apelin in diabetes mellitus development and highlight the utilize of Apelin as a medical sign in diabetes.

Keywords: Apelin, Lipid profile, Calcium, Parathyroid hormone, Vitamin D.

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INTRODUCTION

Type 1 diabetes mellitus is a chronic condition that happens when the immune system hits and ruins the cells that producing insulin in pancreas (β-cells). Its most common of childhood and adolescence, which characterized by hyperglycemia (high blood glucose level) due to a deficiency of insulin secretion [1].

Insulin hormone is a protein hormone secreted via beta cells in islets of Langerhans in the pancreas, that permits glucose (sugar) to enter cells to be utilized as energy (Figure 1). Diabetes impacts metabolism, so individuals with type 1 diabetes possess issues converting the food into metabolites [2]. After a meal consume, carbohydrates molder into glucose, which is carry to each of cells of the our body in order use it for producing energy. Since diabetics suffer from low levels of insulin, which works to bring sugar into the cells, some of this sugar remains in the blood, while cells stay hunger to energy [3].

Type 1 diabetes mellitus occurs by an interaction between risk-conferring genes and environmental agents evolving in the immune-mediated, selective demolition of the islet β-cell mass. In addition to the effect of insulin deficiency on carbohydrate metabolism [4], it also causes metabolic disorders of both proteins and fats, and thus needs great lifestyle modifications to decrease the risk of both short and long term problems. Lifestyle modifications involving: insulin and blood glucose levels monitoring, consume healthy diet, regular physical activity and aerobic exercise [5].

The symptoms of type 1 diabetes mellitus include: thirst sensation, increase in urine urination, increase eating food, decrease in weight, severe fatigue, poor in healing of wounds, increase the patient's blood glucose, blurred vision, irritability or mood swings [6].

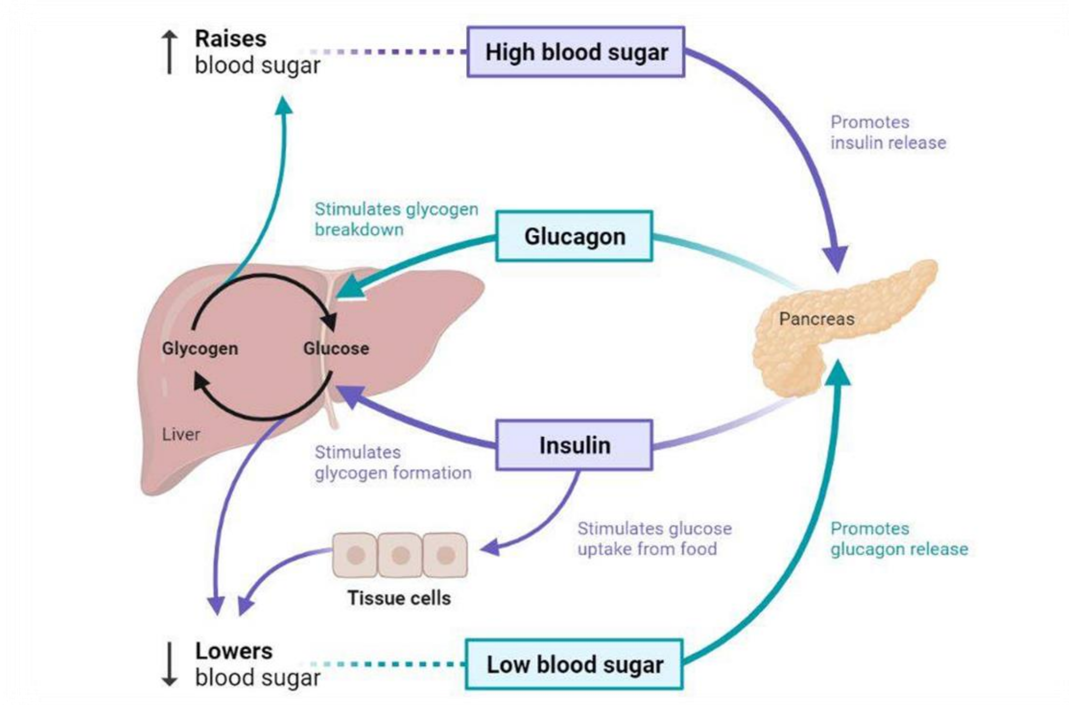

Figure 1: Shown the balance of glucose regulatory mechanisms. Lower levels of blood promote the pancreas to release glucagon for increasing glycogen breakdown in the liver to rise blood glucose levels. While high levels of blood glucose promotes release insulin from the pancreas foe promoting glycogen production in the liver for lowering levels of blood glucose [7].

Apelin is an adipocytokine known as the ligand of the G-protein-coupled receptor called APJ. It and its receptor are expressed in central nervous system (CNS), especially in the hypothalamus, numerous peripheral tissues, placenta, brain, kidney, lung, adipocytes and in variant organs [8]

Apelin has been revealed to be complicated in the regulation of a diversity of physiological activities such as: blood pressure, energy and fluid homeostasis, food consume, glucose and lipid metabolism, cardiovascular function, cell proliferation, immunity and angiogenesis. Also, it is an important bioactive peptide possess anti-obesity and anti-diabetic characteristics [9].

MATERIALS AND METHODS

- **Subjects**

The subject of the study were from two hospitals are: Maternity and Children Teaching Hospital and Al-Ramadi Teaching Hospital/Ramadi city/Anbar governorate/ Iraq. Subjects were chosen from the patients attending the Diabetic Consultation section at hospital through the period from January 2024 to the end of July 2024 with age ranged between (11-16) years (boys and girls).

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A total of 100 subjects, 60 (30 boys and 30 girls) diabetic patients and 40 (20 boys and 20 girls) control group of adolescents apparently healthy. Anbar Health Directorate was given the Ethical approval was for the study. Also, informed consent was take hold of all individuals.

- **Methods**

Venous blood was drawn from each study participant (patients and control groups) using a medical syringe. The blood was placed in the gel tube, after clotting, blood was centrifuged for 10 minutes at 3000 rpm at room temperature, and then separated the serum for using to biochemical tests.

- **Biochemical tests**

Concentrations of Apelin in blood serum was estimated by the enzyme-linked immunoassay (ELISA), utilizing the kit given via My BioSource - U.S.A. The standard curve of apelin determination was showed in the figure below (Figure 2). Triacylglycerol (TAG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and very-low-density lipoprotein (VLDL) cholesterol , low-density lipoprotein cholesterol (LDL-C) were assessed via utilizing the Randox Diagnostic kit. Fasting blood sugar (FBS) concentration in blood serum was estimated by Biolabo kit France. HbA1c in the blood serum was measured via high-performance liquid chromatography using the (HLC 723GX) Tosoh analyzer, the serum concentration of calcium was estimated by atomic absorption method. While, parathyroid hormone (PTH) concentration in blood serum was estimated by ELISA kit. The concentration of Vitamin D in blood serum was measure by kits prepared from Germany Immunodiagnostic systems (ids) company by used ELISA technique.

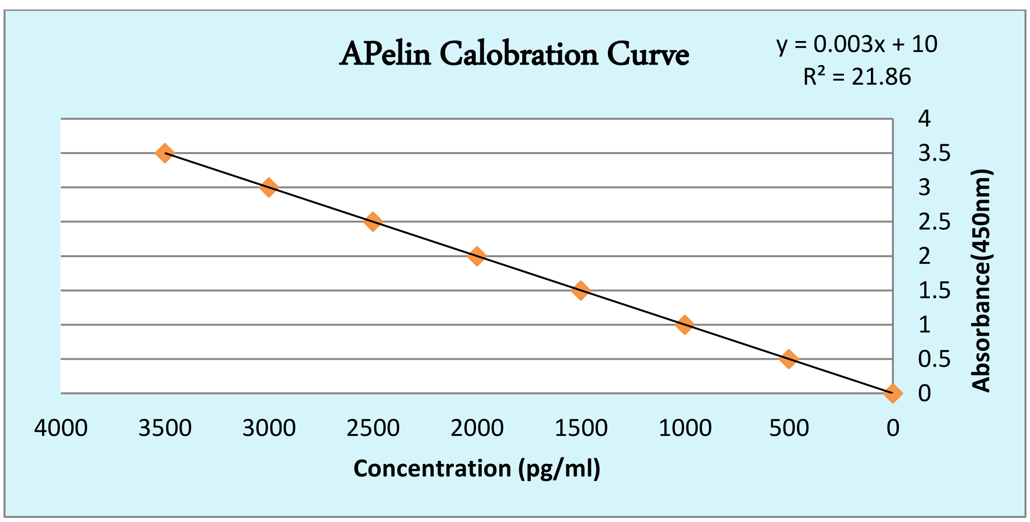

Fig 2: Illustration Standard curve of Apelin

- **Statistical Analysis**

All data were analyzed by the statistical packages for social sciences (SPSS) version 26. To determine the difference between independent variables was used ANOVA. The T- test was utilized to compare mean values of all variables between the comparison groups. Correlation

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coefficient (r) to utilized was describe association between the variables. P-value ($p \leq 0.05$) was considered statistically significant [10].

RESULTS AND DISCUSSION

The results in Table 1 showed the lipid profile levels of the diabetic patient and control groups. There was that the triacylglycerol (TAG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein (VLDL) were significantly ($P \leq 0.05$) increased in adolescents with diabetes than the healthy adolescents. while, the low-density lipoprotein cholesterol (LDL-C) were significantly ($P \leq 0.05$) decreased in adolescents with diabetes than to the healthy adolescents.

There were no significant ($P \leq 0.05$) differences between boys and girls (healthy and unhealthy) for all the explained characteristics, as showed in table 1. As well, there was no significant ($P \leq 0.05$) differences between adolescents (boy and girls) with type 1 diabetes for all explained characteristics as showed in the table 1 Likewise, for healthy adolescents, there were no significant ($P \leq 0.05$) differences between boys and girls for all explained characteristics as showed in the table 1.

Table 1. Comparison of lipid profile levels in patients with diabetes mellitus and control groups.

Variables	Diabetic Patients No.(60)		Control Group No. (40)		P-value
	Boy	Girl	Boy	Girl	
TAG (mg/dl)	144.76±0.32	142.01±0.14	120.87±0.45	121.97±1.01	**0.004**
TC (mg/dl)	130.10± 1.09	131.09±1.00	101.87±098	100.98±1.09	**0.001**
HDL-C (mg/dl)	44.08 ± 0.36	44.98 ± 0.18	52.76 ± 1.04	53.12 ± 0.34	**0.0001**
LDL-C (mg/dl)	98.42 ± 0.32	99.06 ± 0.58	71.12 ± 0.26	69.22 ± 0.11	**0.0002**
VLDL-C (mg/dL)	32.09 ± 1.06	33.16 ± 0.35	20.01 ± 0.76	21.09 ± 1.12	**0.007**

***Significant difference between means (mean ± standard error) using ANOVA -test at 0.05 level. *SE: Standard Error. *N.S: Not–Significant. *TAG: Triacylglycerol. * TC: total cholesterol. *HDL-C: High-density lipoprotein cholesterol. *LDL-C: Low-density lipoprotein cholesterol. *VLDL-C: Very-low- density lipoprotein.**

The results in Table 2 showed the Apelin, HbA1C percentage and fasing blood glucose of the diabetic patient and control groups. There were apelin, fasting blood glucose (FBG), and HbA1c were significantly ($P \leq 0.05$) increased in adolescents with diabetes than the healthy adolescents, there were no significant ($P \leq 0.05$) differences between boys and girls (healthy and unhealthy) for all the explained characteristics, as showed in table 2.

As well, there was no significant (P≤0.05) differences between adolescents (boy and girls) with type 1 diabetes for all explained characteristics as showed in the table 2 Likewise, for healthy adolescents, there were no significant (P≤0.05) differences between boys and girls for all explained characteristics as showed in the table 2.

Table 2. Comparison of biochemical variables in patients with diabetes mellitus and control groups.

Variables	Diabetic Patients No.(60)		Control Group No. (40)		P-value
	Boy	Girl	Boy	Girl	
Age (year)	14.02 ± 0.12	13.65 ± 0.24	13.16 ± 0.31	13.27 ± 0.43	**N. S**
Apelin (pg/ml)	238.12±0.13	239.61±1.00	117.06±0.24	115.98±0.16	**0.0001**
FBG (mg/dl)	178.01± 0.32	180.26±0.32	90.56 ± 1.03	92.02 ± 1.20	**0.0001**
HbA1C %	9.87 ± 0.27	9.45 ± 0.43	4.92 ±0.68	5.06 ± 0.42	**0.002**

***Significant difference between means (mean ± standard error) using ANOVA -test at 0.05 level. *SE: Standard Error. *N.S: Not–Significant. *TAG: Triacylglycerol. *FBG: Fasting blood sugar.**

The results in Table 3 showed the Calcium, PTH and Vitamin D levels of the diabetic patient and control groups. There were levels of calcium significantly (P≤0.05) increased in adolescents with diabetes than the healthy adolescents. while, the parathyroid hormone (PTH) and Vit. D were significantly (P≤0.05) decreased in adolescents with diabetes than to the healthy adolescents, there were no significant (P≤0.05) differences between boys and girls (healthy and unhealthy) for all the explained characteristics, as showed in table 3.

As well, there was no significant (P≤0.05) differences between adolescents (boy and girls) with type 1 diabetes for all explained characteristics as showed in the table 3 Likewise, for healthy adolescents, there were no significant (P≤0.05) differences between boys and girls for all explained characteristics as showed in the table 3.

Table 3. Comparison of biochemical variables in patients with diabetes mellitus and control groups.

Variables	Diabetic Patients No.(60)		Control Group No. (40)		P-value
	Boy	Girl	Boy	Girl	
Calcium (mg/dl)	16.92 ± 1.03	18.07 ± 0.11	8.97 ± 0.47	9.81 ± 0.16	**0.001**
PTH (pg/ml)	23.09 ± 0.16	24.76 ± 0.91	47.01 ± 0.18	45.98 ± 0.01	**0.0001**
Vit.D (ng/ml)	16.12 ± 0.36	13.12 ± 0.58	35.98 ± 1.10	34.22 ± 0.37	**0.0002**

***Significant difference between means (mean ± standard error) using ANOVA -test at 0.05 level. *SE: Standard Error. *N.S: Not–Significant. *PTH: Parathyroid hormone. * Vit.D: Vitamin D.**

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In a previous study conducted by Gregory and his colleauges [11], it was indicated that most of the patients with type 1 diabetes are children and adolescents, and this was interpreted that the rate of type 1 diabetes mellitus is dependent on age with a domain of less than one person per 1000 person at 5 years old to about three person per 1000 person at 16 years old. Infected with type I diabetes millitus increases with age and the disease peaks at the early to middle puberty.

Findings of the study showed that the adolescents with type I diabetes mellitus have increased in concentrations of serum apelin to healthy adolescents. The correlation between diabetes millitus and high levels of apelin concentrations is dependent on the existence of changes in glucose balance [12].

The results of the study showed a positive correlation between glucose concentrations and apelin concentrations. These results are consistent with the results of a study conducted by Helmy and his colleauges [13] , this is because of the concentration of apelin hormone in the serum prevents the secretion of insulin by binding to the apelin receptor APJ in the beta cells (β-cells) of the islets of Langerhans.

In another study, it was shown that the apelin works to inhibit the pancreatic β-cells that produce insulin by activating the enzyme Phosphodiesterase Kinase PDE3 (PDE3B) and thus reduces levels of cyclic Adenosine monophosphate (cAMP) [14].

The results in the table 1 showed there were increase in concentrations of Total cholesterol (TC), triglyceride (TG), low-density protein (LDL), and very low-density lipoprotein (VLDL) in patients to compared with healthy control, whereas there was a decrease in concentration of high-density lipoprotein (HDL) in patients groups to compared with healthy controls.

The findings are consistent with study done by Kumar and his group [15,16], which pointed that the increse of LDL concentrations is one of the lineament of the diabetic dyslipidemia, as well, is connected with risk of cardiovascular disease.

The high concentration of fasting blood glucose and HbA1C are all stimulators of synthesis very-low-density lipoprotein (VLDL-C) in the liver, and thus, the result is an increase in VLDL-C synthesis, as shown by the findings of this study and decrease in concentrations of HDL-C [17].

The results in this study showed there was increase in calcium cocentration in the blood serum in patients with diabetes millitus compared to the healthy control. Rupees and his group uggested that the regulation of the homeostasis calcium is crucial in a secratory function of islets pancreas and that weaked response to high levels of glucose in blood diabetes mellitus patients is the result of the deficient cellular calcium metabolism, and thus calcium is necessary in normalizing the glucose intolerance [18].

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The results of this study showed an inverse relationship between blood parathyroid hormone and blood glucose concentrations, this inverse correlation pointed that the hyperglycaemia (high levels of blood glucose) might possess an inhibitory activity on the production and secretion of parathyroid hormone (PTH), as well Williams mentioned that the hyperglycaemia with an insulin deficiency can lead to a hypoparathyriod condition and a downregulation receptors of PTH [19].

The results in this study revealed dificiency in vitamin D concentration in adolescents with type 1 diabetes than healthy adolescents, this results in agreement with [20].

Diabetes mellitus reasons main metabolic impacts in numerous tissues as: muscles , liver and adipose tissue, therefore, these alterations impact the balance of another endocrine system and the metabolic maintaining systems which include cholesterol, lipids and vitamin D metabolism [21].

Several previous studies have found that there is a deficiency in vitamin D concentration in adolescents with diabetes, although Iraq is a sunshine rich region during the year [22].

The results of this study did not consist with other previous study [23] which presented that concentration of vitamin D is equal in patients with diabetes mellitus and healthy controls. The diferences in concentrations of vitamin D between races and nations is due to skin color, geographical habitat, dietary consume, genetic factor and social impacts.

There was an inverse correlation between vitamin D concentration and HbA1c percentage, so, the receptors of vitamin D that present on pancreatic β-cells might play significant role in production of insulin and it secretion which may impact glycemic control in adilescents [24, 25].

CONCLUSION

The results indicate that high concentrations of apelin in the serum of diabetic patients support its pivotal role in disease progression. Apelin exhibits biological effects that may contribute to pathological processes associated with diabetes, such as regulation of energy metabolism, insulin sensitivity, and inflammation. These results highlight the importance of apelin as a biological agent that may help understand the mechanisms underlying diabetes. Furthermore, apelin could serve as a valuable biomarker for use as a diagnostic marker or as a potential target for therapeutic intervention in diabetes management.

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Conflict of interests.

Non conflict of interest

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الخلاصة

المقدمة:

داء السكري من النوع الأول، المعروف أيضًا باسم داء السكري المعتمد على الأنسولين، والذي يتميز بارتفاع مستويات الجلوكوز في الدم (فرط سكر الدم)، والذي ينتج عن التدمير المناعي الذاتي لخلايا بيتا في جزر البنكرياس المنتجة للأنسولين.

الهدف:

دراسة التغيرات في الأبلين، ومستويات الدهون، ونسبة السكر في الدم الصائم، والهيموجلوبين السكري، والكالسيوم، وهرمون الغدة جار الدرقية، (وفيتامين د) لدى المراهقين المصابين بداء السكري من النوع الأول والمراهقين الأصحاء.

طريقة العمل:

أجريت هذه الدراسة في مستشفى الولادة والاطفال ومستشفى الرمادي التعليمي في مدينة الرمادي في العراق، في الفترة من يناير 2024 إلى يوليو 2024. تم اختيار مائة مراهق: 60 مريضًا بالسكري و 40 سليمًا كمجموعة تحكم. وتم إجراء الاختبارات الكيميائية الحيوية لعينات الدم.

النتائج:

أظهرت النتائج وجود زيادة معنوية في تركيزات الأبلين ومستوى الدهون (باستثناء كوليسترول البروتين الدهني عالي الكثافة) وسكر الدم الصائم وهيموجلوبين السكري والكالسيوم لدى مرضى السكري مقارنة بالمجموعة الضابطة. بينما كان هناك انخفاض معنوي في تركيز كوليسترول البروتين الدهني عالي الكثافة وهرمون الغدة جار الدرقية (وفيتامين د) لدى مرضى السكري مقارنة بالمجموعة الضابطة. وأظهرت النتائج وجود علاقة طردية معنوية بين تركيزات الجلوكوز وتركيزات الأبلين، بينما كانت هناك علاقة عكسية معنوية بين هرمون الغدة جار الدرقية في الدم وتركيزات سكر الدم، كما كانت هناك علاقة عكسية معنوية بين تركيز (فيتامين د) وهيموجلوبين السكري.

الاستنتاج:

إن التركيزات العالية من الأبلين في مصل المرضى المصابين بالسكري تدعم وظيفة الأبلين في تطور مرض السكري وتسلط الضوء على استخدام الأبلين كعلامة طبية في مرض السكري.

الكلمات المفتاحية

الأبلين، ملف الدهون، الكالسيوم، هرمون الغدة جار الدرقية، فيتامين د.

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