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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Comparative analysis of apelin levels in type 2 diabetes mellitus among the obese and non-obese population of Karachi, Pakistan

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ABSTRACT

Background & objective: Recent research has identified various biomarkers in metabolic diseases, which can indicate the severity and the outcome of the disease. This study aimed to compare serum Apelin levels between obese and non-obese patients with type 2 diabetes mellitus (T2DM) and investigate their relationship with obesity and cardio-metabolic indicators. By analyzing these connections, the study attempted to clarify Apelin's role in obesity-related cardio-metabolic risks and its potential as a biomarker for better T2DM management.

Methodology: This cross-sectional study included a total of 200 patients, divided into two groups: 100 obese and 100 non-obese T2DM patients, and their anthropometric and clinical data, including weight, body mass index (BMI), waist and hip circumferences (WC and HC), and blood pressure, were collected. We measured serum Apelin, fasting blood sugar (FBS), hemoglobin A1C (HbA1c), and lipid profile, and analyzed correlations between Apelin levels with the study parameters.

Results: Serum Apelin levels were significantly higher in obese T2DM patients compared to non-obese T2DM patients ($P < 0.000$). Apelin levels exhibited a positive but weak correlation with weight ($r = 0.150$), BMI ($r = 0.384$), WC ($r = 0.331$), and HC ($r = 0.422$). Diastolic blood pressure showed an average positive correlation with Apelin ($r = 0.224$). FBS levels were negatively correlated with Apelin ($r = -0.214$, $P < 0.0001$) while HbA1c and serum Apelin had a weak and statistically insignificant correlation ($r = 0.064$). Serum total cholesterol TC ($r = 0.194$) and triglycerides TG ($r = 0.146$) had weak positive correlations with Apelin, while High-Density Lipoproteins (HDL) exhibited a significant, negative correlation ($r = -0.253$).

Conclusion: Elevated serum Apelin levels observed in obese T2DM patients indicate a potential compensatory mechanism in response to obesity-related complications. Further studies are warranted to elucidate the exact role of Apelin in the pathophysiology of T2DM, particularly in the context of obesity.

Abbreviations: BMI: Body Mass Index, T2DM: type 2 diabetes mellitus, FBS: fasting blood sugar, HDL: High-Density Lipoproteins, HC: hip circumference, WC: waist circumference

Keywords: Apelin; Diabetes Mellitus; Obesity; Cardiometabolic risks; Pakistan

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1. INTRODUCTION

Diabetes mellitus and its complications have become a global epidemic, whereas type 2 diabetes mellitus (T2DM) constitutes over 90% of all diabetic cases, imposing a significant global financial burden of around $850 billion.[1] T2DM is a chronic metabolic disorder characterized by hyperglycaemia, insulin resistance (IR), and impaired insulin secretion. Globally, more than 537 million people are affected by T2DM and are estimated to reach beyond 783 million by the year 2045. Moreover, T2DM-mediated IR is significantly linked with obesity, which acts as an independent risk factor for the development and progression of T2DM. Body mass index (BMI) of ≥25kg/m^2 and ≥30 kg/m^2 is categorized as overweight and obese, respectively. [2]

T2DM and obesity are now well-known and prevalent health-threatening metabolic disorders. In recent years, the global prevalence of metabolic disorders has increased at an alarming rate. It is reported that overweight and obese females are at higher risk of T2DM compared to males, while childhood obesity significantly increases the risk of T2DM in young males and females.[3] The interplay between T2DM and obesity involves complex pathophysiological mechanisms, including chronic inflammation, adipokine dysregulation, and altered lipid metabolism.[4]

Adipokines are bioactive peptides secreted by adipose tissue and local immune cells. Adipokines play pivotal roles in the regulation of insulin sensitivity, energy balance, body weight, inflammation, and autoimmunity.[5] Apelin is a peptide cytokine and endogenous ligand for angiotensin-II protein-J (APJ) G-protein coupled receptor. Apelin is found to be a significant regulator of glucose homeostasis and exerts various physiological effects, such as promoting angiogenesis, vasodilation, cardiac contractility, and modulating insulin sensitivity. Apelin synthesis and secretion is primarily regulated by insulin.[6] At present, Apelin role in obesity and T2DM has gained increasing attention owing to its link with glucose metabolism, IR, and vascular function. In this regard, several research studies have also reported elevated levels of Apelin among obese individuals, suggesting adiposity-mediated upregulation of Apelin.[7] However, the association between Apelin levels and T2DM remains unclear, specifically in relation to varying degrees of obesity. Some studies found a reduction in plasma Apelin levels in newly diagnosed and untreated T2DM patients, demonstrating Apelin dysregulation might be a significant contributor to the onset of overt diabetes,[8] while on the contrary, studies found higher serum Apelin levels in type 2 diabetic obese patients, suggesting a compensatory increase in Apelin levels against obesity and IR-mediated metabolic disturbances.[9]

Hence, the present study aimed to compare serum Apelin levels between obese and non-obese T2DM patients and to investigate the correlation of Apelin levels with obesity and metabolic status indicators, including BMI, waist-to-hip ratio (WHR), fasting blood sugar (FBS), glycated haemoglobin (HbA1c), blood pressure, and lipid profile.

2. METHODOLOGY

The study protocol was approved by the institutional ethics committee (Ref. No. BMU-EC/05-2022). Participants were briefed about the study protocol, and written informed consent was obtained from all participants beforehand.

This cross-sectional study was conducted from February 23 to November 23 over a period of 10 months at the Department of Physiology, Baqai Medical University (Karachi, Pakistan).

The study sample size was calculated via the OpenEpi software.[10] A total of 200 T2DM patients were enrolled in this study and divided into two groups based on their BMI, as follows:

i. Group-I, Obese Diabetic Group: including 100 obese T2DM subjects (BMI ≥ 30 kg/m²)

ii. Group-II, Non-Obese Diabetic Group: including 100 non-obese T2DM subjects (BMI < 30 kg/m²)

The inclusion criteria were as follows:

- Diagnosed cases of T2DM - (FBS ≥ 126 mg/dL with $HbA1_C$ ≥ 6.5%), based on the American Diabetes Association (ADA) criteria of diabetes.
- Both genders male and female, age between 20 to 65 years were included.

The exclusion criteria were as follows:

- Patients with type 1 diabetes mellitus.
- Participants with a history of gestational diabetes mellitus.
- Participants with a history of renal insufficiency, cardiovascular disease, or liver disease.
- Participants with autoimmune conditions.

Demographic and clinical data, including age, gender, weight, height, BMI, waist circumference (WC), and hip circumference (HC), WHR, diastolic blood pressure (DBP), and systolic blood pressure (SBP), were recorded as per standard established protocols.[11]

From all study participants, overnight fasting blood samples were obtained under aseptic conditions via standard venepuncture technique. All samples were collected in appropriate anticoagulant tubes, and serum was immediately separated by centrifugation (3500 rpm for 10 min), then aliquoted and stored at 2ºC for up to 24 hours. Or freeze at -20°C for longer storage, as per analyses of serum Apelin, FBS, HbA1c, lipid profile parameters including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL).[12]

Serum Apelin concentration was measured using a commercially available Sandwich enzyme-linked immunosorbent assay (ELISA) kit specific for human-Apelin (E2014Hu, BT Lab, China). All reagents and samples were brought to room temperature prior to analysis. As per the manufacturer's protocol, 40 µl serum sample was added to each well, followed by 10 µl of biotinylated human-Apelin antibody and 50 µl of Streptavidin-HRP. The plate was incubated at 37°C for 60 min and then washed five times with wash buffer. Next, 50 µl of substrate solutions A and B were added to each well, and the plate was again incubated for 10 min at 37°C in the dark. The reaction was stopped with 50 µl of stop solution, and the optical density (OD) was measured immediately at 450 nm wavelength using a microplate reader (DR-200Bs Diatek, USA). A standard curve was constructed for quantification. The assay sensitivity was 3.47 ng/L, with intra-assay and inter-assay CVs of <10%, ensuring precise and accurate measurements.[12]

Serum FBS was estimated by the glucose oxidase 4-amino-antipyrine (GOD-PAP) enzymatic oxidation method via commercially available glucose assay reagents using Indiko Analyser (Thermo Scientific™). Serum samples were run as per the manufacturer's instructions, and all calibrations and quality control were performed before testing.[12]

Blood HbA1c levels were quantified via high-performance liquid chromatography (HPLC) technique using H-8 HbA1c Analyser (Lifotronic, Shenzhen, China). Whole blood samples were diluted and then separated on an analytical cartridge through ionic interactions. The separated haemoglobins were measured at 415 nm using a photometer to determine HbA1c levels.[13]

Analytical grade, commercially available assay reagents were utilized and analysed as per the manufacturer's instructions.

Serum TC was determined by the cholesterol oxidase 4-amino-antipyrine (CHOD-PAP) method, which involves enzymatic hydrolysis followed by oxidation. Absorbance was recorded at 500-550 nm using the Indiko Analyser (Thermo Scientific™).

Serum TG levels were measured by the glycerol 3-phosphate oxidase 4-amino-antipyrine (GPO-PAP) method. Absorbance of the formed colour was measured at 510 nm wavelength using Indiko Analyser (Thermo Scientific™).

Serum HDL cholesterol and LDL cholesterol concentrations was estimated by a direct, homogeneous enzymatic colorimetric method using cholesterol oxidase. The Indiko Analyser (Thermo Scientific™) was used for this analysis.

Study data were managed and analyzed using statistical software SPSS (Version 23.0 for Windows; SPSS, Chicago, IL, USA). Results for continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as percentages and frequencies. Comparison between study group variables was calculated by Student's independent t-test and Chi-Square test, while Pearson's correlation coefficients were applied to assess the relationships between variables. $P < 0.05$ was considered statistically significant.

3. RESULTS

The study included two groups of type 2 diabetic subjects: obese and non-obese, with an equal distribution of 50% in each group. The obese diabetic group consisted of 38 males and 62 females, while the non-obese diabetic group had 43 males and 57 females.

Table 1: Comparative demographic and anthropometric profiles if the study groups

Parameters	Obese Diabetic Group (n = 100)	Non-obese Diabetic Group (n = 100)	P-value
Age (Years)	51.23 ± 11.02	49.04 ±10.87	0.576
Weight (Kg)	90.25 ± 7.51	64.22 ± 6.75	0.000**
Height (cm)	160.45 ± 9.09	161.47 ± 6.67	0.288
BMI (kg/m^2)	35.38 ± 4.93	22.81 ± 2.05	0.000**
Waist Circumference (cm)	109.67 ± 10.67	85.060 ± 23.34	0.003**
Hip Circumference (cm)	112.45 ± 10.12	95.77 ± 7.00	0.001**
Waist / Hip Ratio (cm)	0.97 ± 0.06	0.89 ± 0.24	0.000**
SBP (mm/Hg)	139.19 ± 23.59	122.81 ± 20.64	0.000**
DBP (mm/Hg)	97.40 ± 12.21	81.14 ± 13.29	0.025*
Positive family history of diabetes (%)	74	67	0.278

*Values presented as mean ± SD (*P < 0.05 and **P < 0.01 indicate statistical significance)*
[BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, SD: standard deviation]

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Table 1 summarizes the baseline characteristics of our studied groups. According to the Independent t-test analysis obese diabetic group exhibited higher BMI, WC, HC, WHR, SBP, and DBP when compared with the non-obese group (Table 1).

Serum biochemical parameters of both study groups are summarized in Table 2. The obese diabetic group had significantly higher levels of serum Apelin, TC, and TG when compared to the non-obese diabetic group. While serum LDL levels were similar between the two groups, with no significant differences observed. FBS and HDL levels were found to be significantly higher among the non-obese diabetic group than the obese diabetic group (Table 2).

Pearson's correlation analyses exhibited a significant ($P < 0.05$) positive correlation of serum Apelin with weight, BMI, WC, HC, and DBP (Table 3). Whereas, no significant ($P > 0.05$) correlations were found between serum Apelin and age, height, WHR, or SBP among the studied groups (Table 3).

Table 3: Correlation of serum Apelin with demographic, anthropometric, and biochemical parameters

Demographic & anthropometric parameters	Correlation Coefficient (r)	P-value
Age (years)	-0.019	0.788
Weight (kg)	0.15	0.033*
Height (cm)	0.02	0.777
BMI (kg/m2)	0.384	0.000**
Waist Circumference (cm)	0.331	0.000**
Hip Circumference (cm)	0.422	0.000**
Waist / Hip Ratio (cm)	0.133	0.061
SBP (mm/Hg)	0.03	0.677
DBP (mm/Hg)	0.244	0.001**
Biochemical Parameters		
FBS (mg/dL)	-0.214	0.002**
HbA1c (%)	0.064	0.366
Total Cholesterol (mg/dL)	0.194	0.006**
Triglyceride (mg/dL)	0.146	0.039*
LDL (mg/dL)	0.045	0.53
HDL (mg/dL)	-0.253	0.000**

*Pearson's correlation test considered significant at *P < 0.05 and **P < 0.01; BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood glucose, HbA1c: glycated haemoglobin A, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SD: standard deviation]*

Serum Apelin levels were found to be negatively correlated with FBS and HDL. A weak positive correlation was observed between serum Apelin and TC, as well as TG levels. HbA1c and LDL cholesterol showed a positive but statistically insignificant correlation with serum Apelin (Table 3).

4. DISCUSSION

T2DM is a multi-factorial endocrine disorder characterized by alterations in insulin secretion, the Presence of IR, and a compensatory increase in hepatic gluconeogenesis. Obesity is one of the most important risk factors for the development of T2DM. The WHO declares diabetes and obesity as a global epidemic.[12] Several studies have documented that Pakistan exhibits an increasing prevalence of T2DM and prediabetes, with obesity rates rising in parallel, highlighting significant public health concerns.[14,15] Obesity is strongly linked with adipokine dysregulation, which plays a major role in obesity-related co-morbidities and complications.[2]

Apelin is a peptide hormone that acts as an adipokine, cardiokine, and myokine. Apelin plays a crucial role in the regulation of endocrine signalling pathways, insulin sensitivity, glucose and lipid metabolism, and thus highlights the significant molecular link between T2DM and obesity.[16] In-depth analysis of these associations provides an understanding of Apelin's role in the pathophysiology of T2DM and its potential as a biomarker and therapeutic target. The present study aimed to evaluate the association between serum Apelin levels with T2DM and obesity and its relationship with cardiometabolic parameters, by comparing obese and non-obese type-2 diabetic patients from Karachi, Pakistan.

Our findings demonstrated significantly higher serum Apelin levels in group-I obese T2DM patients compared to group-II non-obese diabetic individuals (mean Apelin: 646.78 ± 439.46 vs. 271.04 ± 278.73, P = 0.000). Our study observation is consistent with a previous study, which also found elevated serum Apelin in obese T2DM patients compared to the control group, signifying Apelin upregulation correlates with excess adiposity / clinical obesity.[12] Because Apelin is primarily secreted from adipose tissue, increased adiposity leads to higher Apelin secretion. This compensatory Apelin elevation counteracts the obesity-mediated IR, inflammation, and other metabolic disturbances.[5,9] On the other hand, a longitudinal study on 909 children found lower Apelin levels during pubertal development and observed no association between Apelin levels and body weight.[17] Another study finding also reported lower Apelin concentration in obese non-diabetic patients compared to diabetic patients with obesity, suggesting that Apelin is associated with diabetes but not with obesity.[18]

This study also examined the relationship between serum Apelin levels and various metabolic and cardiovascular parameters in obese and non-obese diabetic subjects. In the present study, group-I obese diabetic patients were found to have significantly higher BMI, WC & HC, WHR, SBP, and DBP compared to group-II non-obese diabetics, hence confirming the link between Apelin and adiposity. Moreover, higher BMI, WHR, and hypertension are well-established risk factors for cardiovascular diseases, which is one of the most prevalent complications of T2DM. Our study also found a significant positive correlation between serum Apelin and BMI, WC, HC, and DBP, which further highlights the role of apelin in obesity-related cardio-metabolic disturbances. The present study findings are consistent

with previous studies demonstrating that elevated Apelin levels among diabetics play an important role in obesity-related metabolic dysfunctions, inflammation, and hormonal dysregulation.[8,19]

On the contrary, other studies exhibit no difference in serum Apelin level among underweight, normal, overweight, and obese individuals, indicating no association between Apelin and BMI in the study population.[20]

IR is a major characteristic of T2DM and is often associated with obesity. In the present study, compared to group I obese diabetic group had higher FBS levels were observed in group II, non-obese diabetics; however, our study found a significant negative correlation between FBS and Apelin levels ($r = -0.214$, $P = 0.002$). Similarly, in our study, mean HbA1c levels were slightly higher in the obese diabetic group as compared to the non-obese diabetic group; however, this difference was not statistically significant ($P > 0.05$). Furthermore, the correlation between HbA1c levels and Apelin was weak ($r = 0.064$) and not statistically significant ($P > 0.05$). In line with the present study, one study reported higher Apelin concentration and low FBS level in obese diabetics when compared with non-obese diabetics.[21] An experimental study by Gao and colleagues (2021) demonstrated that treatment of apelin-13 significantly lowers the blood glucose levels in a rat model of diabetic nephropathy.[22] In contrast to our findings, a previous study concluded that Apelin directly inhibits insulin secretion from pancreatic beta-cells in a dose-dependent manner by activating PI3-kinase-dependent PDE3B signalling pathway, which subsequently reduces cAMP levels. This underscores a suppressive effect of apelin on insulin response in an attempt to mitigate hyperglycaemia.[23] However, the exact physiological significance of this correlation needs further investigation.

Under physiological conditions, Apelin efficiently modulates lipid metabolism; however, higher Apelin levels are reported to be associated with atherogenic dyslipidaemia. In parallel to this notion, the present study also found elevated TC, TG, and lower HDL in the obese diabetic group compared to the non-obese group. Likewise, significant positive correlation of serum Apelin with TC and TG, but a significant negative correlation with HDL, highlighting the lipid profile dysregulation in obese individuals and thereby contributing to higher cardiovascular risk. In this regard, previous studies also revealed a positive correlation of Apelin with lipid profile among T2DM and obese individuals.[24] On the flip side, a preclinical study reported that apelin-13 administration reduces plasma TC, TG, and LDL, while increasing HDL in a hyperlipidaemic animal model of T2DM compared to metformin and atorvastatin-treated groups.[25]

5. LIMITATIONS

The study has several limitations and restrictions that should be acknowledged. First, the sample size and demographic focus on T2DM patients from Karachi, Pakistan, may limit the generalizability of the findings to other populations or ethnic groups. A larger, more diverse sample would strengthen the applicability of the results. Additionally, the cross-sectional design restricts the ability to establish causal relationships or long-term trends between Apelin levels, T2DM, obesity, and cardiometabolic parameters. Potential confounding factors such as diet, physical activity, genetics, or comorbidities were not fully accounted for, which could influence the observed outcomes.

While the study highlights Apelin as a potential biomarker and therapeutic target, it does not explore its clinical applicability or the feasibility of targeting Apelin in therapeutic interventions. These limitations underscore the need for additional research to validate the findings and explore the underlying mechanisms.

6. CONCLUSION

In summary, the present study findings highlight the intricate relationship between obesity, Apelin levels, and metabolic parameters in diabetic patients. The significant associations between serum apelin and several obesity-related factors underscore the potential role of apelin as a biomarker for metabolic risk in diabetic populations and may suggest Apelin as a promising therapeutic agent for the treatment of type 2 diabetes and metabolic syndrome. However, further studies are needed to elucidate the underlying mechanisms and explore the therapeutic potential of targeting Apelin pathways in the management of obesity and diabetes-related complications.

7. Data availability

The numerical data regarding this study are available from the authors and can be provided on reasonable request.

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9. Disclaimer

This manuscript is part of a thesis project titled “Comparison of Apelin levels in Obese and Non-obese type 2 Diabetic patients”.

10. Conflicts of interest

The authors declare no conflict of interest in relation to this work.

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12. Authors' contribution

SR: Research initiative, Manuscript writing, Literature search, data collection, and final revision.

QA: Supervised the study, Critical revision, and editing of the manuscript, and approved the final version to be published.

IAA: Data collection, design of work, revision, and drafting.

RN: Selection of analytical tests, running and interpreting statistical analysis.

IA, AF: Drafting, Critical revision, and editing of the manuscript.

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