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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Apelin-13 and Omentin-1 as biomarkers for estimation of severity of diabetic nephropathy in type-2 diabetes mellitus

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ABSTRACT

Background & objective: Chronic diabetes affects millions of the people globally, leading to complications like micro-, and macro-vascular problems like neuropathy, and nephropathy. The adipokines Apelin-13 and Omentin-1 play beneficial functions in the early detection of diabetic nephropathy. We aimed to study and investigate the correlation between Apelin-13 and Omentin-1 levels and disease severity in diabetic nephropathy patients and evaluate their potential as biomarkers for early diagnosis.

Methodology: A case-control study at Al-Sadar Teaching Hospital/Al-Najaf Center assessed 180 individuals, including 60 type 2 diabetics with nephropathy (T2DM+Neph group), 60 without nephropathy (T2DM group), and 60 healthy individuals as controls, to provide insights into managing type 2 diabetes.

Results: The research found a notable decline in Omentin-1 ($P < 0.001$) in the T2DM+Neph group, followed by T2DM, and the highest value in the control group. There was a significant increase ($P < 0.001$) in the serum Apelin-13 in the patients' groups T2DM+Neph group and T2DM compared with the control group. There was no significant difference in the serum Apelin-13 between T2DM and T2DM+Neph groups

Conclusion: Our study found a decline in Omentin-1 levels in diabetics with nephropathy patients compared to healthy controls, suggesting using serum Omentin-1 level measurement for early diagnosis and treatment of diabetic nephropathy.

Keywords: ELISA, Nephropathy, Apelin-13, Omentin-1

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1. INTRODUCTION

Chronic diabetes mellitus (DM) affects millions worldwide, causing obesity and related conditions like type II diabetes mellitus (T2DM). Undiagnosed cases can lead to complications, including retinal, micro-, and macroangiopathies, neuropathy, and nephropathy. People with diabetes are more susceptible to non-infectious and infectious illnesses.[1]

DM, affecting 439 million, often leads to microvascular issues, including diabetic nephropathy (DN). Early detection and monitoring of microalbuminuria are crucial for better management.[2]

DN is the primary factor that leads to chronic kidney failure, with proteinuria being the gold standard for assessing renal function. However, one-third of patients experience deterioration before proteinuria onset, necessitating the search for lab biomarkers.[3]

1.1. Definition and clinical course of DN

DN is a clinical condition characterized by albuminuria, a decrease in glomerular filtration rate, hypertension, and the absence of other kidney or urinary tract infections. It can be influenced by factors like comorbidities, aging populations, and medication use.[4]

DN starts with a decline in GFR, is linked to structural glomerular damage, peripheral vascular disease, neuropathy, retinopathy, and lipid abnormalities. It is a strong predictor of cardiovascular disease death. The middle stage macroalbuminuria occurs as the disease progresses, with larger amounts of albumin excreted in the urine. Kidney function declines, and symptoms like ankle swelling, fatigue, and increased blood pressure may appear. The latter stage is called end-stage renal disease (ESRD), characterized inability by the kidney to eliminate waste products and extra fluid. Persistent albuminuria, indicative of overt diabetic nephropathy, is associated with cardiovascular issues and renal failure.[5]

1.2. Adipokines (adipocytokine)

White fat (subcutaneous and visceral fat) and brown fat are the two forms of fat that make up body fat in mammals, and their distribution varies.[6]

The word "adiposopathy" refers to the increased incidence of unfavorable metabolic and cardiovascular outcomes resulting from the belief that visceral adipose tissue (VAT) is ectopic fat.[7] Adipocytes are present in the VAT along with a wide range of other cells, including fibroblasts, mast cells, macrophages, and stromal vascular cells.[6]

Apart from its functions in energy storage and lipid metabolism, the VAT is an important endocrine organ that secretes around 600 bioactive cytokines, often known as adipocytokines or adipokines.[8]

Adipocytokines affect both locally through autocrine and paracrine pathways and endocrine functions. Important functions of adipocytokines include controlling insulin sensitivity, inflammatory responses, food and water consumption, bone metabolism, metabolic balance, and neuroendocrine activity. [6, 8]

1.2.1. Omentin-1:

The human omental white adipose tissue cDNA library produced the new peptide adipocytokine Omentin-1, released by various tissues. This secretory adipokine influences insulin sensitivity, lowers inflammation, and supports glucose uptake in human adipocytes via protein kinase B (PKB).[9]

1.2.2. Apelin-13

Apelin-13, a peptide binds to the G-protein-coupled receptor APJ; its variations are found in the hypothalamus and peripheral organs. According to research, apelin decreases insulin secretion and glucose metabolism while also controlling angiogenesis, food intake, cardiovascular health, and fluid balance. Adipocytes generate and secrete apelin, making it an adipokine. A connection between apelin and metabolic problems like obesity and T2DM has been established. Elevated plasma apelin concentrations in models of metabolic disorders suggest apelin's importance in lipid and glucose metabolism signaling pathways.[10]

Apelin-13 contributes to pathological glomerular angiogenesis by controlling the permeability of diabetic glomeruli and the growth of glomerular endothelial cells. Thus, apelin might have a role in the pathophysiology of DN.

2. METHODOLOGY

This case-control study aimed to assess 180 individuals diagnosed with T2DM at AL-Sadar Teaching Hospital/Al-Najaf Center. The study included patients with diabetic nephropathy, those without nephropathy, and healthy people. Most participants were treated by oral hypoglycemia agents and/or insulin. With each patient's written consent, clinical data, and anthropometric measurements were gathered.

The study used a comprehensive assessment of the patient's medical history, including their age, gender, diabetes duration, mode of treatment, renal stone history, hypertension, heart failure, leg edema, itching, and drug use. Blood pressure, height, and weight were recorded to calculate BMI, a measure of obesity. The study also conducted blood assays to determine omentin-1 and apelin -13 levels.

The fasting blood sugar was measured using an enzymatic technique by the CECIL lab instrument. Blood urea and creatinine levels were determined using a spectrophotometer, and the BA200. The HbA1c Testing System was used. The goal glycated hemoglobin (HbA1c) level was less than 7%.

A general urine examination was performed under a microscope to rule out renal diseases other than diabetic nephropathy. The ratio of albumin to creatinine (ACR) was calculated. using a semi-automated analyzer (DCA Vantage). The study aimed to provide valuable insights into the management of patients' type 2 diabetes with nephropathy.

Statistical analysis

The Lilliefors-corrected Kolmogorov-Smirnov test was utilized to analyze the data distribution. This test distinguished the variables into normally and non-normally distributed categories. The groups were compared using ANOVA and LSD tests, and the correlations between the variables were examined using $\chi 2$- and Kruskal-Wallis tests. Correlations were estimated using Spearman's coefficients and Pearson's product-moment correlation coefficients. Confounding variables were examined for their impact on biomarker levels using the multivariate general linear model

(GLM). Biomarkers were evaluated for their diagnostic potential in nephropathy diagnosis Among type 2 diabetic patients employing receiver operating characteristic (ROC) curves.

3. RESULTS

3.1. Comparison in sociodemographic parameters

Table 1 displays the sociodemographic characteristics.

3.2. Comparison of omentin-1 levels of patients and controls

Results for patients' and control groups' serum omentin-1 levels are shown in Figure 1.

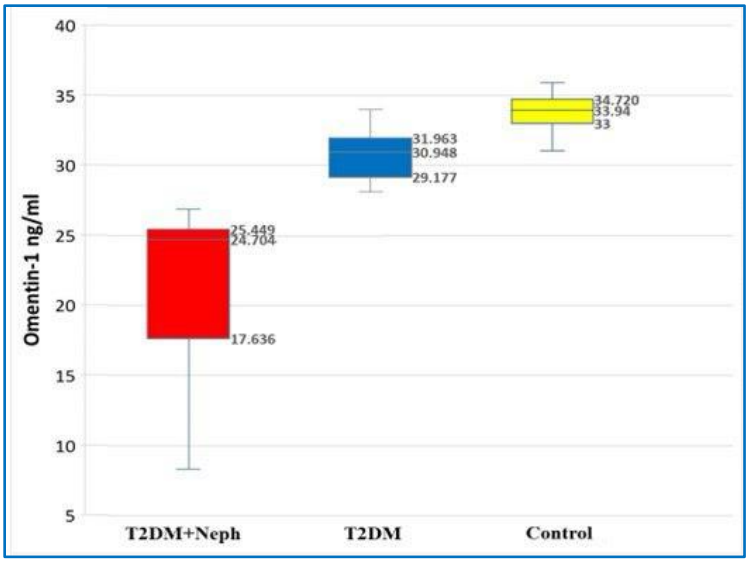

Figure 1: Serum levels of Omentin-1.

The results showed in Figure 1 a significant decrease (P < 0.001) in Omentin-1 in the study groups with the lowest value in the T2DM+Neph group (24.704(17.636-25.449) ng/ml), followed by T2DM (30.948(29.177-

Table 1: Comparison in sociodemographic parameters

Parameter	Control [A]	T2DM [B]	T2DM+Neph [C]	F/χ^2	P
Age (Yr)	49.068 ± 11.87	51.308 ± 8.633	51.583 ± 7.977	1.134	0.324
Duration of DM (Yr)	-	4.364 ± 2.4 [C]	10.333 ± 6.044 [B]	104.368	< 0.001
SBP (mmHg)	119.124 ± 4.477 [B,C]	121.808 ± 6.875 [A,C]	124.593 ± 7.022 [A,B]	11.751	< 0.001
DBP (mmHg)	78.456 ± 3.797 [B,C]	80.108 ± 4.171 [A,C]	82.315 ± 4.033 [A, B]	14.055	< 0.001
Height (cm)	168.051 ± 5.188	167.179 ± 8.482	169.5 ± 6.369	1.598	0.206
Weight (Kg)	75 ± 9.322	76.564 ± 11.306	79.117 ± 12.27	2.112	0.124
BMI(Kg/m$^{2)}$	26.583 ± 3.276	27.384 ± 3.435	27.493 ± 3.689	1.161	0.316
Gender: Female/Male	28/32	20/19	34/26	1.203	0.548
Insulin treatment No/Yes	-	36/3	25/35	25.630	< 0.001
FBG (mM)	5.31 ± 0.505 [B, C]	9.976 ± 2.609 [A, C]	11.402 ± 3.369 [A, B]	96.841	< 0.001
Hypoglycemic drugs No/Yes	-	4/35	35/25	22.883	< 0.001
TG	1.259 ± 0.323 [B, C]	1.646 ± 0.598 [A, C]	1.853 ± 0.384 [A, B]	29.356	< 0.001
T.Chol	4.728 ± 0.689 [B, C]	5.408 ± 1.089 [A, C]	5.631 ± 1.466 [A, B]	10.002	< 0.001
HDLc	1.088(0.948-1.291)[B,C]	1.01(0.858-1.091)[A]	1.044(0.888-1.19)[A]	KWT	0.014
LDLc	3.006(2.506-3.404)[B,C]	3.496(2.906-4.264)[A]	3.556(2.772-4.607)[A]	KWT	0.001
ACR (mg/g)	17(14.5-19.3) [C]	15.5(11-19.35) [C]	48(38.6-89.1) [A, B]	KWT	< 0.001
S. creatinine (mg/dl)	0.684 ± 0.169 [B, C]	0.817 ± 0.13 [A, C]	1.128 ± 0.327 [A, B]	55.061	< 0.001
S. Urea (mg/dl)	31.636 ± 5.337 [B, C]	34.667 ± 5.328 [A, C]	39.593 ± 8.756 [A, B]	20.426	< 0.001

Pairwise comparisons for A, B, and C Results for normally distributed data are expressed as mean ± standard deviation. Ratio-based binomial data were analyzed using the Chi-squared test. P is for probability; F/χ2 is for continuous variables; chi-square is for binominal variables; and so on. FBG - fasting blood glucose; ACR - albumin/creatinine ratio; TG - triglycerides; T.chol - Total cholesterol; HDLc - Lipoprotein with a high density; LDL: Lipoprotein with low density. Kruskal-Wallis test (KWT)

31.963) ng/ml), to the highest value in the control group (33.94(33-34.720) ng/ml).

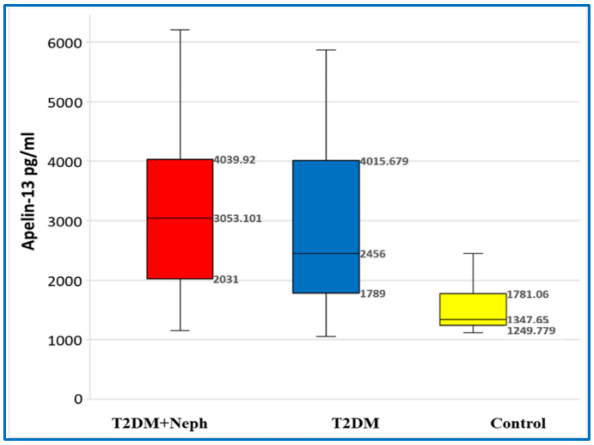

Figure 2: Serum levels of Apelin-13

3.3. Comparison of Apelin-13 between patients and controls

The results of serum Apelin-13 in patients and control groups are presented in Figure 2.

The results showed in Figure 2 a considerable increase ($P < 0.001$). in Apelin-13 serum in the patients' groups T2DM+Neph group (3053.102(2031-4001.456) pg/ml) and T2DM (2456(1833.93-4013.832) pg/ml) compared with the control group (1347.8(1251.62-1772.14) pg/ml).

There was no significant difference in the serum Apelin-13 between the T2DM and T2DM+Neph groups.

3.4. Comparison of Omentin-1/Apelin-13 between patients and controls

The results of serum Omentin-1/Apelin-13 in patients and control groups are presented in Figure 3.

The results showed in Figure 3 a significant decrease ($P < 0.001$) in Omentin-1/Apelin-13 in the study groups with the lowest value in the T2DM+Neph group (6.785(4.86-12.112), followed by T2DM (10.69(7.380-16.930)), to the highest value in the control group (24.790(18.700-27.307)).

4. Correlation studies

4.1. Correlation between demographic parameters with Omentin-1, Apelin-13, and Omentin-1/Apelin-3

Correlation between demographic parameters with Omentin-1, Apelin-13, and Omentin-1/Apelin-3 has been demonstrated in Table 2.

Table 2: Correlation between demographic parameters with Omentin-1, Apelin-13, and Omentin-1/Apelin-3

Parameter	Omentin-1	Apelin-13	Omentin/ Apelin
Age	-0.012	0.133	-0.070
Sex	0.082	0.075	-0.019
Duration of DM	-0.774**	0.549**	-0.687**
SBP	-0.379**	0.233**	-0.312**
DBP	-0.447**	0.249**	-0.353**
Height	-0.136	0.121	-0.167*
Weight	-0.108	0.136	-0.161*
BMI	-0.039	0.076	-0.084
FBG	-0.718**	0.480**	-0.626**
TG	-0.521**	0.328**	-0.430**
T0.Chol	-0.251**	0.195*	-0.246**
HDLc	0.133	-0.101	0.123
LDLc	-0.198*	0.139	-0.185*
Creatinine	-0.566**	0.454**	-0.551**
Urea	-0.414**	0.331**	-0.423**

**: Significant correlation ($P < 0.05$), **: Significant correlation ($P < 0.01$)*

4.2. Correlation among Omentin-1, Apelin-13, and Omentin-1/Apelin-3

Correlation among Omentin-1, Apelin-13, and Omentin-1/Apelin-3 has been depicted in Figure 3 and Table 3.

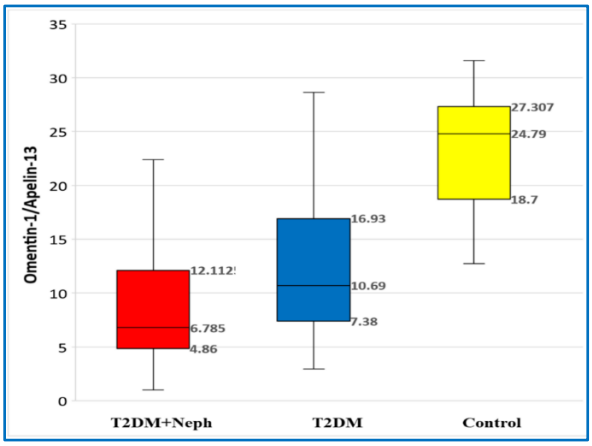

Figure 3: Omentin-1/Apelin-13 ratio

4.3. Study of diagnostic ability of the measured biomarkers for prediction of nephropathy in T2DM patients

Table 3: Correlation among Omentin-1, Apelin-13, and Omentin-1/Apelin-3

	Omentin-1	Apelin-13	Omentin/Apelin
Omentin-1	1.000	-0.564**	0.795**
APELIN-13	-0.564**	1.000	-0.927**
Omentin/Apelin	0.795**	-0.927**	1.000

**: Significant correlation (P < 0.05), **: Significant correlation (P < 0.01)*

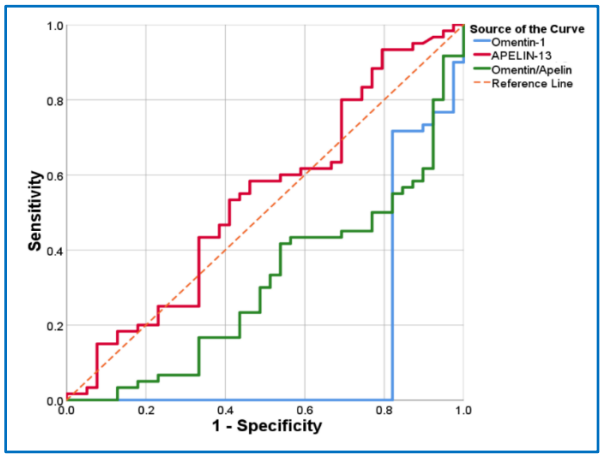

Figure 4: Receiver operating characteristic curves of the omentin-1, apelin-13, and their ratio in prediction of nephropathy in T2DM patients.

To evaluate the diagnostic potential of the detected biomarkers for the diagnosis of nephropathy in individuals with type 2 diabetes, a receiver operating characteristics (ROC) study was carried out. The sensitivity and specificity at each concentration were examined in the study. The plotted ROC curves for the measured parameters are displayed in Figure 4. Nonetheless, the results of the analysis are shown in Table 4.

Table 4 findings show that a drop in Omentin-1 levels below the threshold for detection (25.7 ng/ml) suggests a considerable possibility of nephropathy in the participants, with 83.3% specificity and 82.1% sensitivity. Apelin-13 lacks statistical significance in predicting nephropathy (P = 0.531). Table 4 shows that a decrease in Omentin/Apelin below the 7.869% the threshold value suggests that the participants may be suffering from nephropathy, with a 59.0% sensitivity and a 56.7% specificity.

4. DISCUSSION

Omentin-1, a secretory adipokine, is linked to obesity, insulin resistance, and diabetes. Apelin-13, a peptide, regulates angiogenesis, dietary intake, cardiovascular health, fluid homeostasis, and cellular proliferation. Adipocytes secrete apelin, which is an adipokine and ubiquitous peptide. It also influences diabetic glomeruli, potentially affecting glomerular angiogenesis and DN pathogens.[11]

Diabetes mellitus, characterized by hyperglycemia due to insufficient insulin secretion, affects 439 million people globally. Diabetic nephropathy, the most common adverse outcome, is mostly responsible for end-stage renal disease. linked to long-term diabetes. A study reveals omentin-1 and there is a negative link levels with diabetic nephropathy, regardless of other risk factors. Patients with macroalbuminuria or microalbuminuria experience higher declines in omentin-1 levels. Early detection of diabetes-related microvascular complications is beneficial. Diabetes-related consequences do not affect Apelin-13 serum levels.

The study analyzed the sociodemographic features of individuals suffering from type 2 diabetes (T2DM) and nephropathy. The control group did not differ significantly from the T2DM+Neph group in terms of BMI, age, and gender. However, there was a significant difference in the duration of diabetes mellitus (DM), blood pressure levels, and the use of insulin treatment and hypoglycemic drugs, particularly between the T2DM and T2DM+Neph groups.

The study found that nephropathy in addition to T2DM is associated with a longer duration of diabetes and higher blood pressure levels, necessitating more aggressive treatment approaches such as insulin and hypoglycemic drugs. The renal function tests showed

that T2DM+Neph patients exhibited notably elevated albumin creatinine ratio (ACR) values, serum creatinine

Table 4: Omentin-1, apelin-13, and their ratio: receiver operating characteristic-area under curve (AUC) analysis in the prediction of nephropathy in individuals with type 2 diabetes. Confidence interval, or CI

Test	Cut-off	Sensitivity %	Specificity %	Youden's J statistic	AUC (95% CI)	P-value
Omentin-1* ng/ml	25.700	82.1	83.3	0.654	0.864(0.770-0.957)	< 0.001
Apelin-13 pg/ml	2985.084	55.0	53.7	0.087	0.537(0.418-0.656)	0.531
Omentin/Apelin*	7.869	59.0	56.7	0.157	0.69(0.584-0.796)	0.001

**: The decrease in these biomarkers is a predictor of nephropathy.*

levels, and the highest urea levels, which may help evaluate kidney function in type 2 diabetic nephropathy. These results corroborated research that found diabetic nephropathy patients had greater blood urea levels than healthy controls.[11]

Another study that supported the current data revealed that persons with diabetic nephropathy had considerably higher serum creatinine levels than healthy people. [12,13]

The T2DM group had higher levels of TG and T.Chol, suggesting both T2DM and nephropathy may cause dyslipidemia. The nephropathy group had lower HDL cholesterol levels, suggesting T2DM+Nph may have a greater impact on reducing HDLc levels. Both groups showed elevated levels of VLDL and LDL cholesterol. These results agree with the earlier studies. [14-18]

The study compared the levels between Apelin-13, Omentin-1, and Omentin--1/Apelin-13 in individuals with type 2 diabetes (T2DM), T2DM+Nph, and control groups. Results showed a significant decline in Omentin-1 levels, peaking at 24.704 ng/ml in the T2DM+Neph group, followed by T2DM (30.948 ng/ml), and the control group (33.94 ng/ml). This decline is consistent with previous studies. [17-21]

Also, Nanda B, et al. and El-Mesallamy HO, et al. demonstrate that the Omentin-1 level exhibits a notable negative association with T2DM patients than control. [23-24] Insulin and glucose have been reported to reduce omentin mRNA expression and protein production, suggesting that insulin and glucose are involved in regulating omentin-1 synthesis.[25] Apelin-13 levels considerably elevated in the T2DM+Neph group and T2DM compared to the control group, which is believed to control glomerular filtration rate and renal blood flow. But there was little variation in serum Apelin-13 between T2DM and T2DM+Neph groups and this disagrees with studies.[16]

The Omentin-1/Apelin-13 ratio ranged from the lowest in the T2DM+Neph group to the highest in the control group, with T2DM coming in second.

The multivariate general linear model study reveals that Omentin/Apelin, and are effective biomarkers for separating T2DM, T2DM with nephropathy, and healthy controls. Other biomarkers, such as Apelin-13, VLDLc, and TG, show smaller effect sizes. Understanding these biomarker profiles can help identify, evaluate, and treat conditions, leading to more targeted interventions.

The study found that omentin-1 is the most promising biomarker for predicting nephropathy in type 2 diabetes patients, with the highest AUC, sensitivity, and specificity. Apelin-13, with decreased sensitivity, specificity, and AUC, has limited diagnostic performance. The Omentin/Apelin ratio shows moderate discriminative ability, suggesting potential as a composite biomarker.

5. CONCLUSION

The results of this study suggest that serum Omentin-1 level measurement could be crucial for early identification and treatment of type 2 diabetes with diabetic nephropathy.

6. Ethical considerations

All participants were fully informed about the conduct of the study and written informed consent obtained.

7. Acknowledgments

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8. Authors contribution

NNA: Writing the manuscript

NHA: Conducted the study; manuscript editing

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