EMBJ.ORG FOR YOUNG DOCTORS

EuroMediterranean Biomedical Journal
2026, 21 (1)
(*Formerly: Capsula Eburnea*)

Original article

THE RELATIONSHIP BETWEEN SERUM OSTEOGLYCIN AND DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ARTICLE INFO

Article history:
Received 27 October 2025
Accepted 21 April 2026
Published 4 May 2026

Keywords:
osteoglycin; diabetic nephropathy; type 2 diabetes mellitus.

ABSTRACT

Osteoglycin (OGN) is a key modulator of the circuit among bone, pancreas, and hypothalamus, responsible for glucose homeostasis, bone formation, and energy balance. This study aimed to evaluate the association between serum OGN levels and diabetic nephropathy (DN), as well as to assess its potential as a biomarker for disease presence and severity. Additionally, it explored the utility of OGN as an early detection marker for DN in the Egyptian population. Four groups were enrolled in the study: Group I (control group) included 23 healthy subjects; Group II included 23 normoalbuminuric type 2 diabetic patients; Group III included 23 type 2 diabetic patients with microalbuminuria; and Group IV included 23 type 2 diabetic patients with macroalbuminuria. Laboratory investigations included fasting blood glucose (FBG), glycated hemoglobin (HbA1c), complete blood count (CBC), kidney function tests, liver function tests, and lipid profile. The estimated glomerular filtration rate (eGFR) was calculated. Serum C-peptide and OGN levels were determined using enzyme-linked immunosorbent assay (ELISA). Significantly lower OGN levels were detected in the control group and diabetic normoalbuminuric groups compared with micro- and macroalbuminuric diabetic patients ($p<0.001$ for each). Additionally, significantly higher OGN levels were detected among macroalbuminuric patients than diabetic patients with microalbuminuria ($p=0.04$). Moreover, there were statistically significant negative correlations between serum OGN and high-density lipoprotein-cholesterol (HDL-C), total protein, serum albumin, eGFR, and C-peptide. Furthermore, statistically significant positive correlations were detected between serum OGN and total cholestenol, triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), FBG, HbA1c, systolic blood pressure, creatinine, blood urea nitrogen (BUN), and albumin-creatinine ratio (ACR). HbA1c, LDL-C, ACR, BUN, and HDL independently correlated with serum OGN. Furthermore, serum OGN was a good predictor of macroalbuminuria with 87% sensitivity and specificity. It was also a good predictor of macroalbuminuria with 82.6% sensitivity and 78.3% specificity. In conclusion, serum OGN levels were significantly associated with markers of kidney function and protein levels in patients with type 2 diabetes mellitus (T2DM). Serum OGN served as a discriminatory biomarker for the early detection of DN with high sensitivity and specificity.

Introduction

Type 2 diabetes mellitus (T2DM) affects more than 536.6 million people worldwide. By 2045, 783.2 million people are expected to have diabetes mellitus (DM).[1] Diabetic nephropathy (DN) is a progressive complication of T2DM with persistent albuminuria (>300 mg/day) accompanied by a progressive decrease in glomerular filtration rate (GFR) and raised arterial blood pressure.[2] DN is the major cause of end-stage renal disease with subsequent disability and mortality.[3]

Osteoglycin (OGN) (osteoinductive factor or mimecan) is a glycoprotein that was first isolated from bovine bone matrix.[4] Its growth-stimulatory activity is mediated by bone morphogenetic proteins (BMP)-2 and 3. Additionally, it affects lipid and glucose metabolism, browning of white fat, bone formation, and endothelial cell function by modulating the circuit among bone, pancreas, and hypothalamus.[5,6] Its role in the pathogenesis of DM can be mediated by vascular endothelial injury, angiogenesis, and atherosclerosis of renal arteries.[7]

Previous research suggested that glomerular insult is detected even in normoalbuminuric diabetic patients. Thus, detecting potential risk factors for early DN is essential. Earlier research revealed that serum OGN could be a potential

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 ISSN: 2279-7165 - Available on-line at www.embj.org

discriminatory marker for early DN.[8] However, OGN in DN gave contradictory results.[7,8] Thus, this research was conducted to investigate the association between serum OGN levels and DN, its potential role as a biomarker for disease occurrence and severity, and as a potential discriminatory marker for detecting early DN among Egyptians.

Materials and Methods

This case-control study included 92 subjects distributed in 4 groups. Group I (control group) included 23 healthy subjects. Group II included 23 normoalbuminuric type 2 diabetic patients (<30 mg of albumin per g of creatinine). Group III included 23 type 2 diabetic patients with microalbuminuria (30-300 mg of albumin per g of creatinine), and Group IV included 23 type 2 diabetic patients with macroalbuminuria (> 300 mg of albumin per g of creatinine). The study was carried out in the Outpatient Clinic and Internal Medicine Department, Zagazig University Hospitals with the Medical Biochemistry Department, Zagazig University (Egypt), from March 2023 to March 2024. A random sampling method was used to recruit the participants.

T2DM was diagnosed according to the American Diabetes Association (2020) standards (fasting blood glucose [FBG]≥126 mg/dL, 2-hour postprandial blood glucose ≥ 200 mg/dL, or random blood glucose ≥ 200 mg/dL). Written informed consent was received from all participants. The participants were of both sexes, and their ages ranged from 40 to 70 years. Exclusion criteria comprised acute metabolic disturbances (including ketoacidosis, hyperosmolar status, and acute severe infections), acute or chronic renal diseases on dialysis, bone fracture within 3 months, autoimmune diseases, malignancy, severe cardiac insufficiency, coronary heart disease, liver disease, and acute cerebral infarction.

Personal and family history was obtained from participants. Physical examination included a full general examination and measurement of height, weight, and brachial blood pressure. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters (kg/m^2). Five mL of peripheral venous blood was obtained from each subject after 10 hours of fasting under complete aseptic conditions. The obtained blood was divided into 3 portions: 1 mL collected on fluoride oxalate for colorimetric estimation of FBG, 1 mL collected on potassium ethylenediaminetetraacetic acid (EDTA) for measurement of glycated hemoglobin (HbA1c) using an immunoturbidimetric assay and complete blood count (CBC) using the Sysmex XF-500 cell counter (Kobe, Hyōgo, Japan), and 3 mL was left for 30-60 minutes for spontaneous clotting, then centrifuged at 2000 rpm for 10 minutes for serum preparation. Serum samples were separated into another set of tubes and kept frozen at -20ºC until use for assessment of other parameters. Fresh, midstream urine was collected from all patients for estimation of urinary albumin-creatinine ratio (ACR). Kidney function tests included blood urea nitrogen (BUN) and serum creatinine. Liver function tests included alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin, total protein, and serum albumin. Lipid profile included total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C).

All colorimetric tests were performed using Sunostik (China). The kits were provided by Spectrum (Obour City, Cairo, Egypt). LDL-C was calculated with the Friedewald formula. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration; 2009) creatinine-based equation. Serum C-peptide and OGN levels were measured using an enzyme-linked immunosorbent assay (ELISA). ELISA kits were provided by ELK Biotechnology (Wuhan, China). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Software, version 28. The Kolmogorov-Smirnov test was used to check data normality. Categorical data were represented as absolute frequencies and were compared using the chi-square test and Monte Carlo tests when appropriate. Quantitative data were represented as means ± standard deviations (SD) or medians and interquartile ranges. To compare quantitative data between more than two groups, the Kruskal-Wallis test (for not normally distributed data) and the one-way analysis of variance (ANOVA) test (for normally distributed data) were used. Pairwise comparisons and Tukey's honest significant difference test were conducted to identify differences between each pair of individual groups. The receiver operator curve (ROC) was used to determine the best cutoff of serum OGN. The Spearman rank correlation coefficient was used to assess the strength and direction of correlation between OGN and the studied parameters. Linear regression analysis was performed to detect independent factors for serum OGN levels. The level of statistical significance was set at $p<0.05$.

Results

Concerning demographic and clinical data, Group I had 43.5% females and 56.5% males. In Group II, 52.2% were females and 48.8% were males. In Groups III and IV, 56.5% were females and 43.5% were males, with no significant difference between the groups regarding gender (p=0.79). The mean age for Group I was 59.91±8.73 years, for Group II was 60.65±7.39 years, for Group III was 65.65±8.74 years, and for Group IV was 62.26±8.67 years, with no statistically significant difference among the groups regarding age (p=0.103). Additionally, there were no significant differences between the groups regarding BMI and diastolic blood pressure (p=0.515 and 0.052). However, there was a statistically significant difference between the groups regarding systolic blood pressure (p=0.04). with higher systolic blood pressure in the diabetic patients with macroalbuminuria compared to the control (p=0.029) (Table 1).

Regarding blood picture, hemoglobin levels showed a significant difference across the groups (p=0.014), with Group I having the highest mean (12.69±1.58 g/dL) and Groups III and IV having lower means (11.15±2.6 and 11.14±1.32 gm/dL, respectively). Significantly higher hemoglobin levels were detected in Group I compared to Groups III and IV (p=0.029 and 0.026, respectively). White blood cell (WBC) count also differed significantly among groups (p=0.045), with Group II having the lowest median (5.6; range: 5-8.9 $10^3/mm^3$) and Group III having the highest median (9; range: 6.7-10.5 $10^3/mm^3$), with a significant difference between them (p=0.005) (Figure 1A). Platelet count did not show a significant difference between the groups (p=0.075) (Table 1).

Concerning liver functions, albumin levels exhibited a highly significant difference ($p<0.001$), with Group I having the highest mean (4.08±0.42 g/dL), while Group IV had the lowest mean (2.99±0.47 g/dL), with significantly higher levels in Group I compared to other groups ($p<0.001$ for each). Additionally, Group II had higher albumin levels compared to Group IV (p=0.003). Total protein levels also differed significantly among the groups (p=0.002). Groups I and II had higher levels than Group IV (p=0.002 and 0.015, respectively) (Figure 1B). No significant differences were observed in the international normalized ratio (INR; p=0.079), total bilirubin (p=0.113), or direct bilirubin levels (p=0.547) among the groups. ALT levels were significantly different (p=0.018), with the highest values in Group II, with significantly higher levels in Group II compared to Groups I and III (p=0.01 and 0.005, respectively). AST levels were also significantly different among the groups ($p<0.001$), with Group II showing the highest values. Significant differences were detected between Group III and other groups (p=0.013, <0.001, and 0.025, in order) (Table 1).

Regarding kidney functions, there was a statistically significant difference between the groups in creatinine ($p<0.001$). Significantly higher levels were detected in Group III compared to Groups I and II ($p<0.001$ and 0.032, respectively). Also, higher levels were detected in Group IV compared to Groups I and II (both $p<0.001$). Additionally, there was a statistically significant difference between the groups in BUN ($p<0.001$); significantly lower levels were detected in Group I compared to other groups (p=0.048, <0.001, and <0.001, respectively). Significantly lower levels were also detected in Group II compared to Group IV (p=0.016). Moreover, there was a statistically significant difference between the groups regarding ACR ($p<0.001$), with significant pairwise differences detected between all groups. Furthermore, there was a statistically significant difference between the groups regarding eGFR ($p<0.001$), with significant differences detected between every two groups except when comparing Groups III and IV (p=0.112) (Figure 1C). However, there were statistically non-significant differences between the studied groups regarding calcium and phosphorus (p=0.356 and 0.603) (Table 1).

Regarding lipid profile, there were statistically significant differences between the groups in TG, LDL-C, and HDL-C ($p<0.001$ for each). Group IV exhibited significantly higher levels of TG and LDL-C compared with the other groups, whereas HDL-C levels were significantly lower in Group IV than in all other groups. Also, TC showed a significant difference between the groups (p=0.002) with significantly higher levels in Group IV than Group I ($p<0.001$) (Table 1).

Regarding glycemic profile, a statistically significant difference in HbA1c was observed among the groups ($p<0.001$), with all pairwise comparisons reaching statistical significance. Additionally, there was a statistically significant difference between the groups in FBG ($p<0.001$), with significantly higher levels in Group IV compared to Groups I and II (both $p<0.001$) and significantly higher levels in Group III compared to Group I ($p<0.001$). Moreover, C-peptide levels showed a significant difference between the groups (p=0.017), with Groups I and II having higher levels than Group IV (p=0.004 and 0.011, respectively) (Table 1). Serum OGN showed a statistically significant difference among the groups ($p<0.001$). Significantly lower levels were observed in

Group I compared with Groups III and IV (p<0.001 for each), and Group II also exhibited significantly lower levels than Groups III and IV (p<0.001 for each). There were also significantly lower levels in Group III than in Group IV (p=0.04) (Table 1, Figure 1D).

Correlation analyses revealed statistically significant negative correlations between serum OGN and HDL-C (r=−0.462, p<0.001), total protein (r=−0.333, p=0.001), serum albumin (r=−0.462, p<0.001), eGFR (r=−0.619, p<0.001), and C-peptide (r=−0.24, p=0.021). There were statistically significant positive correlations between serum OGN and TC (r=0.4, p<0.001), TG (r=0.348, p<0.001), LDL-C (r=0.481, p<0.001), FBG (r=0.495, p<0.001), HbA1c (r=0.701, p<0.001), systolic blood pressure (r=0.22, p=0.035), creatinine (r=0.59, p<0.001), BUN (r=0.499, p<0.001), and ACR (r=0.802, p<0.001) (Table 2, Figures 2 and 3 A,B).

The multivariate linear regression analyses revealed that HbA1c (β=3.457, 95% confidence interval [CI]: 1.753-5.162, p<0.001), LDL-C (β=0.114, 95% CI: 0.051-0.177, p<0.001), BUN (β=0.134, 95% CI: 0.058-0.209, p<0.001), and ACR (β=0.005, 95% CI: 0.002-0.009, p=0.006) were independently associated with serum OGN, while HDL-C showed a significant inverse association (β=−0.154, 95% CI: −0.298 to -0.009, p=0.038) (Table 3).

ROC curve results revealed that the best cutoff value of serum OGN in the prediction of microalbuminuria was ≥12.75 pg/mL with an area under the curve (AUC) of 0.919, with 87% sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy (p<0.001). The best cutoff value of serum OGN in the prediction of macroalbuminuria was ≥22.9 pg/mL with an AUC of 0.885, 82.6% sensitivity, 78.3% specificity, PPV of 65.5%, NPV of 90%, and overall accuracy of 78.3% (p<0.001) (Table 4, Figure 3 C,D)

Table 1. Comparison of clinical and laboratory data across the study groups.

	Group I n=23 (%)	Group II n=23 (%)	Group III n=23 (%)	Group IV n=23 (%)	χ^2	p
Gender						
Female	10 (43.5)	12 (52.2)	13 (56.5)	13 (56.5)	1.045	0.79
Male	13 (56.5)	11 (48.8)	10 (43.5)	10 (43.5)		
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**F**	**p**
Age (years)	59.91±8.73	60.65±7.39	65.65±8.74	62.26±8.67	2.121	0.103
BMI (kg/m^2)	23.58±2.49	24.4±2.6	24.63±2.89	23.84±2.65	0.768	0.515
Systolic BP (mmHg)	116.96±8.49	120.96±12.6	124.57±15.66	130.0±22.41^a	2.886	0.04*
Diastolic BP (mmHg)	69.78±7.46	74.57±11.57	77.87±11.09	78.48±15.26	2.678	0.052
Hemoglobin (g/dL)	12.69±1.58	11.4±1.58	11.15±2.6^a	11.14±1.32^a	3.729	0.014*
Albumin (g/dL)	4.08±0.42	3.51±0.63^a	3.18±0.37^a	2.99±0.47^{ab}	22.561	<0.001**
Total protein (g/dL)	6.95±0.47	6.82±0.63	6.61±0.67	6.29±0.62^{ab}	5.513	0.002*
INR	1.04±0.07	1.08±0.1	1.05±0.11	1.11±0.11	2.34	0.079
Calcium (mg/dL)	8.75±0.41	8.71±0.67	8.53±0.49	8.54±0.52	1.094	0.356
Phosphorus (mg/dL)	3.52±0.82	3.35±0.87	3.62±0.9	3.68±1.01	0.621	0.603
Total cholesterol(mg/dl)	153.39±35.25	170.52±42.77	174.17±37.66	198.0±34.65^a	5.458	0.002*
Triglycerides (mg/dL)	119.74±16.07	129.65±37.75	130.48±37.78	157.17±28.25^{abc}	6.409	<0.001**
LDL-C (mg/dL)	89.57±24.69	99.3±32.81	108.17±35.6	140.74±37.02^{abc}	10.49	<0.001**
HDL-C (mg/dL)	50.23±14.47	48.33±19.16	43.47±14.51	31.43±7.2^{abc}	7.827	<0.001**
FBG (mg/dL)	88.35±12.17	119.57±20.65	154.83±59.75^a	191.61±75.95^{ab}	18.442	<0.001**
HbA1c (%)	5.05±0.48	6.61±0.73^a	7.68±0.66^{ab}	8.81±1.09^{ab}c	98.29	<0.001**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**KW**	**p**
WBC count (10^3/mm^3)	7 (6.5-9.2)	5.6 (5-8.9)	9 (6.7-10.5)^b	8.3 (6-10)	8.044	0.045*
Platelet count (10^3/mm^3)	256 (220-330)	183 (158-312)	249 (185-347)	225 (175-269)	6.891	0.075
C-peptide (ng/mL)	2.5 (2.1-3.1)	2.7 (0.7-5)	1.2 (0.4-4.8)	0.6 (0.4-2.2)^{ab}	10.222	0.017*
Total bilirubin (mg/dL)	0.55 (0.35-0.9)	0.55 (0.45-0.87)	0.45 (0.25-0.66)	0.48 (0.34-0.64)	5.963	0.113
Direct bilirubin (mg/dL)	0.25 (0.15-0.35)	0.26 (0.22-0.35)	0.18(0.13-0.44)	0.25 (0.17-0.45)	2.123	0.547
ALT (U/L)	12 (9-17)	15 (12-25)^a	12 (11-14)^b	13 (12-17)	10.101	0.018*
AST (U/L)	15 (12-16)	17 (14-19)	12 (9-14)^{ab}	15 (12-17)^c	17.668	<0.001**
Creatinine (mg/dL)	0.6 (0.53-0.7)	0.72 (0.6-1.45)	1.6 (0.7-2.4)^{ab}	2.25 (1.1-4.6)^{ab}	38.504	0.001*
BUN (mg/dL)	12 (9.5-17)	22 (14-39)^a	44 (16.2-52)^a	50 (25-81)^{ab}	27.848	<0.001**
ACR (mg/g)	7.2 (4.5-15.2)	8.39 (5.17-18.17)^a	178 (55-231)^{ab}	750 (406-1350)^{abc}	77.001	<0.001**
eGFR (mL/min/1.73 m^2)	110 (105-117)	101 (42-109)^a	45 (25-96)^{ab}	30 (11-66)^{ab}	38.918	<0.001**
Serum OGN (pg/mL)	6.9 (5.4-9.9)	8.4 (5.9-11.9)	20.6 (15.7-35.6)^{ab}	44 (37.7-53.2)^{abc}	61.742	<0.001**

SD, standard deviation; BMI, body mass index; BP, blood pressure; INR, International Normalized Ratio; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; WBC, white blood cell count; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; ACR, albumin creatinine ratio; eGFR, estimated glomerular filtration rate. F, one-way ANOVA test; χ^2, chi square test; IQR, interquartile range; KW, Kruskal-Wallis test; *p<0.05 is statistically significant; **p≤0.001 is statistically highly significant; ^{a}difference with Group I; ^{b}difference with Group II; ^{c}difference with Group III.

Discussion

T2DM is characterized by hyperglycemia due to defects in insulin action, secretion, or both. DM is associated with multiple organ damage. Prolonged DM is associated with microvascular complications, including nephropathy.[9] DN is characterized by high morbidity and mortality mediated by hyperglycemia and oxidative stress.[10] OGN is a proteoglycan with endocrine effects on bones and pancreas.[11] It participates in bone metabolism, being expressed by osteoblasts.[12]

Regarding demographic data, our study revealed no significant differences between the studied groups in gender or age. These findings are supported by Zhang *et al.*[13] This can be attributed to the nature of our study, being a case-control study with an age- and sex-matched population.

Concerning CBC, hemoglobin levels in Group I had the highest mean, and Groups III and IV had the lowest means. Significantly higher hemoglobin levels were detected in Group I compared to Groups III and IV. Our results are consistent with those of Unsal *et al.*,[12] who reported a significant decrease in hemoglobin with GFR decline.[14] This is attributed to the progression of DN, where declining kidney function reduces erythropoietin production, leading to anemia.[15,16] Additionally, Ito *et al.* attributed the association between DN and anemia to severe interstitial fibrosis and tubular atrophy regardless of the renal function. Moreover, anemia helped clinicians discriminate between isolated DN and non-diabetic kidney diseases.[17] Another important CBC element is the WBC count, which had the lowest median in Group II, while Group III showed the highest median. The elevated WBC count in Group III suggests an inflammatory response, a key mechanism in DN progression, with the lower WBC count in the normoalbuminuric diabetic group indicating less systemic inflammation. Regarding platelet count, it did not differ significantly between the groups, suggesting that platelet dysfunction is not a prominent mechanism in the early stages of DN.[18]

Concerning liver functions, Group I had the highest albumin mean, and Group IV had the lowest mean, with significantly higher levels in Group I than in the other groups. Additionally, Group II had higher levels compared to Group IV. Total protein levels also differed significantly, with Groups I and II having higher levels than Group IV. The significant decline in albumin and total protein levels in the macroalbuminuric diabetic group is indicative of advanced DN, where kidney damage leads to increased urinary protein loss and impaired synthesis. This reflects the impaired filtration capacity of the kidneys as DN progresses.[19] However, no significant differences in INR or total bilirubin levels were observed, indicating that liver and coagulation functions were not significantly impaired. Regarding liver enzymes, Groups I and III showed lower ALT and AST levels compared to Group II, which exhibited the highest values. Notably, AST levels in Group III were significantly different from those observed in the other groups. Elevated ALT and AST levels in the normoalbuminuric diabetic group suggest early liver involvement, potentially linked to

Table 2. Correlation between serum OGN and the studied parameters.

	r	p
Age (years)	0.058	0.58
BMI (kg/m^2)	0.067	0.503
Systolic BP (mmHg)	0.22	0.035*
Diastolic BP (mmHg)	0.161	0.125
FBG (mg/dL)	0.495	<0.001**
HbA1c (%)	0.701	<0.001**
Hemoglobin (g/dL)	−0.191	0.068
WBC count (10^3/mm^3)	0.158	0.132
Platelet count (10^3/mm^3)	−0.035	0.738
Total protein (g/dL)	−0.333	0.001**
Serum albumin (g/dL)	−0.462	<0.001**
INR	0.186	0.075
ALT (U/L)	0.014	0.894
AST (U/L)	−0.16	0.128
Total bilirubin (mg/dL)	−0.181	0.083
Direct bilirubin (mg/dL)	−0.049	0.642
Creatinine (mg/dL)	0.59	<0.001**
BUN (mg/dL)	0.499	<0.001**
ACR (mg/g)	0.802	<0.001**
eGFR (mL/min/1.73 m^2)	−0.619	<0.001**
C-peptide (ng/mL)	−0.24	0.021*
Total cholesterol (mg/dL)	0.4	<0.001**
Triglycerides (mg/dL)	0.348	<0.001**
LDL-C (mg/dL)	0.481	<0.001**
HDL-C (mg/dL)	−0.462	<0.001**
Calcium (mg/dL)	−0.156	0.137
Phosphorus (mg/dL)	0.055	0.605

r, Spearman rank correlation coefficient; BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; WBC, white blood cell count; INR, International Normalized Ratio; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; ACR, albumin creatinine ratio; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; *p<0.05 is statistically significant; **p≤0.001 is statistically highly significant.

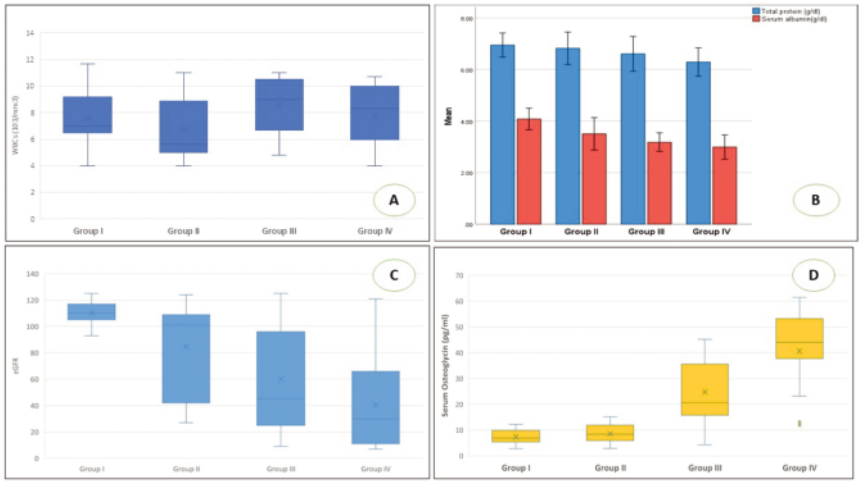

Figure 1. A) Boxplot comparing WBC count across groups. **B**) Multiple bars comparing serum albumin and total protein across groups. **C**) Boxplot comparing eGFR across groups. **D**) Boxplot comparing serum OGN across groups.

metabolic syndrome, which often accompanies T2DM.[20]

Concerning glycemic indices, Groups I and II had higher C-peptide levels than Group IV. This result was similar to that found by Mousa *et al.*[21] They detected a significant rise in HbA1c, FBG, fasting insulin, homeostatic model assessment for insulin resistance (HOMA-IR), and C-peptide among elderly diabetic and DN groups compared to the elderly control group and among the DN group compared to the diabetic group. Additionally, Yang *et al.* detected the highest C-peptide levels in patients with the smallest annual eGFR decline.[22] The lower C-peptide levels in Group IV indicate worsening of β-cell dysfunction and reduced insulin secretion as DM advances.[23] Moreover, Huang *et al.* reported that C-peptide levels between 1.71 and 2.51 ng/mL in patients with T2DM were associated with a higher rate of glycemic control.[24]

Regarding renal function, BUN and ACR significantly increased with disease progression, while eGFR significantly decreased. These results were similar to those found by Mousa *et al.*[21] They found significant increases in creatinine, BUN, and ACR, and a significant decrease in eGFR in elderly DN compared to elderly control and diabetic patients. In contrast to our results, they detected no significant differences in BUN, ACR, and eGFR between elderly diabetics and the control group. Additionally, Yu *et al.* reported a significant rise in creatinine and BUN in patients with T2DM, which correlated with the incidence of DN.[25] Furthermore, Coughlan *et al.* revealed a statistically significant decrease in eGFR in micro- and macroalbuminuric patients with T2DM.[26] The rise in creatinine, BUN, and ACR in macroalbuminuric patients can be attributed to chronic hyperglycemia and inflammation, which lead to impaired filtration, causing waste accumulation and severe proteinuria.[27] The decrease in eGFR in micro- and macroalbuminuric patients further reflects the progressive loss of kidney function, as glomerular damage worsens with DN. These markers highlight the key mechanisms of DN-glomerular damage and reduced filtration capacity, driven by prolonged DM, oxidative stress, and inflammation.[28-30] In line with our study, Kondaveeti *et al.* demonstrated that microalbuminuria increased significantly with poor glycemic control and was correlated with elevated serum creatinine levels, which indicated renal damage.[31]

Concerning OGN, Group I had the lowest median, and Group IV had the highest. Although there was no significant difference between controls and nor-

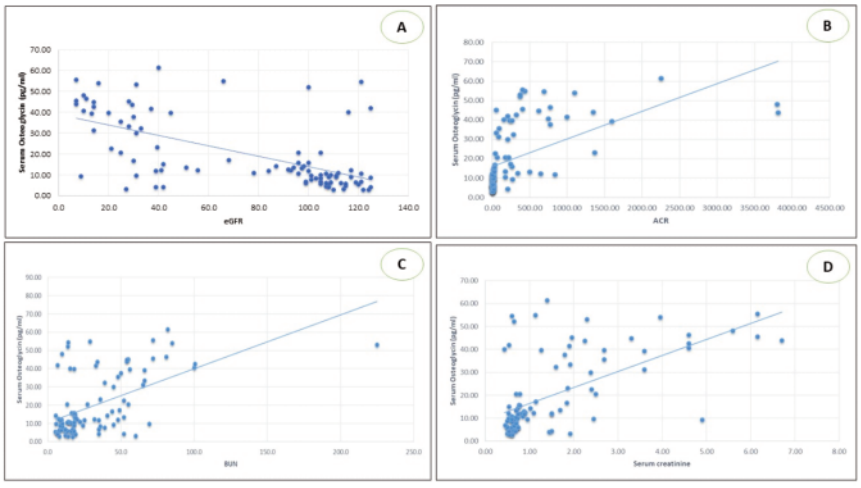

Figure 2. Scatter dot plots showing **A**) significant negative correlation between serum OGN and eGFR; **B**) significant positive correlation between serum OGN and ACR; **C**) significant positive correlation between serum OGN and BUN; and **D**) significant positive correlation between serum OGN and serum creatinine.

Table 3. Linear regression analysis of factors associated with serum OGN.

	Unstandardized coefficients		Standardized coefficients	t	P	95% confidence interval	
	β	Std. Error	Beta			Lower	Upper
Constant	−15.891	6.896		−2.305	0.024*	−29.599	−2.183
HbA1c (%)	3.457	0.857	0.326	4.032	<0.001**	1.753	5.162
LDL-C (mg/dL)	0.114	0.032	0.256	3.612	<0.001**	0.051	0.177
BUN (mg/dL)	0.134	0.038	0.246	3.527	<0.001**	0.058	0.209
ACR (mg/g)	0.005	0.002	0.204	2.793	0.006*	0.002	0.009
HDL-C (mg/dL)	−0.154	0.073	−0.146	−2.108	0.038*	−0.298	−0.009

HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; BUN, blood urea nitrogen; ACR, albumin creatinine ratio; *p<0.05 is statistically significant; **p≤0.001 is statistically highly significant.

Table 4. Performance of serum OGN in the prediction of the presence of microalbuminuria and macroalbuminuria among diabetic patients.

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
Microalbuminuria	≥12.75 pg/mL	0.919	87%	87%	87%	87%	87%	<0.001**
Macroalbuminuria	≥22.9 pg/ml	0.885	82.6%	78.3%	65.5%	90%	78.3%	<0.001**

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; **p≤0.001 is statistically highly significant.

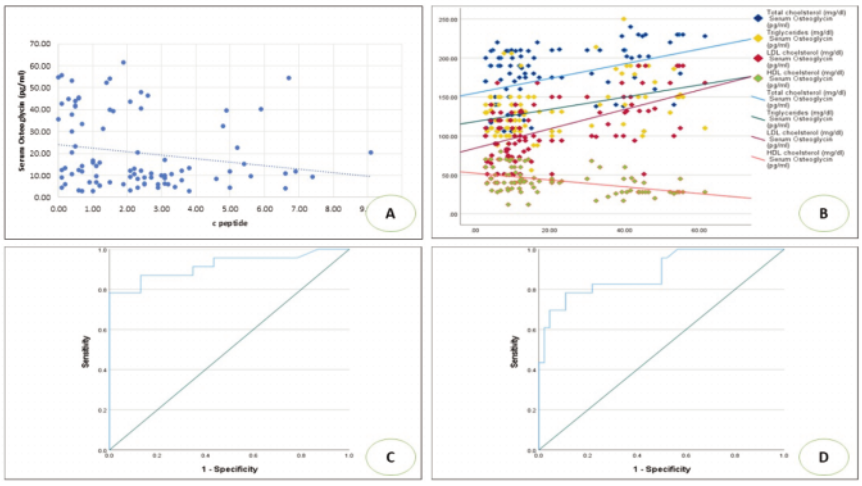

Figure 3. A) Scatter dot plot showing significant negative correlation between serum osteoglycan and C-peptide. **B**) Scatter dot plot showing significant positive correlations between serum OGN and total cholesterol, LDL cholesterol, and triglycerides and a negative correlation between it and HDL cholesterol. **C**) ROC curve showing the performance of serum OGN in the prediction of the presence of microalbuminuria among diabetic patients. **D**) ROC curve showing the performance of serum OGN in the prediction of the presence of macroalbuminuria among diabetic patients.

moalbuminuric diabetics, OGN levels increased among diabetics. Our study agrees with El-Behiry *et al.*, who found a substantial elevation in OGN in microalbuminuria compared to normal control and normoalbuminuric, and no substantial variations among healthy control and normoalbuminuric.[32] Although González-Salvatierra *et al.* found that circulating OGN was significantly higher in patients with T2DM than in controls, they found a progressive increase in serum OGN with the severity of kidney impairment in harmony with other findings.[12] The significant increase in serum OGN levels among diabetic groups suggests that OGN is closely linked to DN progression, as it plays a role in inflammation and tissue remodeling and likely rises in response to increasing kidney damage and chronic inflammation in advanced DN. The level stability between controls and normoalbuminuric diabetics indicates that OGN may not rise in early DM, but becomes markedly higher as kidney function deteriorates in Groups III and IV. This suggests that OGN may be a marker for more advanced renal damage and inflammation in DN.[33]

Correlation analyses revealed that serum OGN was not significantly correlated with age, hemoglobin, WBC count, platelet count, ALT, AST, total bilirubin, direct bilirubin, or INR. However, significant negative correlations were found with total protein, serum albumin, eGFR, and C-peptide. Conversely, significant positive correlations were observed with HbA1c, FBG, creatinine, BUN, ACR, TC, TG, and LDL. Similar results were found by El-Behiry *et al.* Additionally, they found that OGN was directly proportional to the degree of albuminuria.[32] This is also consistent with González-Salvatierra *et al.*, who showed a negative correlation between OGN and eGFR in diabetic patients, indicating a strong correlation between OGN levels and deteriorating renal function in DN.[12] Moreover, Wang *et al.* demonstrated that serum OGN had a negative correlation with eGFR and a positive correlation with BUN and creatinine.[8] In contrast to our findings, Wei *et al.* found that serum OGN had a weak inverse correlation with the degree of albuminuria and showed a weak positive correlation with eGFR.[34] This discrepancy can be attributed to patient selection and criteria in that study. Our findings suggest OGN involvement in the pathophysiology of DN. The significant negative correlations with total protein, serum albumin, and eGFR indicate that higher OGN levels are associated with declining kidney function, increased proteinuria, and associated inflammation. Additionally, the positive correlations with creatinine, BUN, and the ACR reinforce the association between elevated OGN levels and renal dysfunction and damage, suggesting its potential role as a biomarker for kidney injury in DN.[35]

The multivariate linear regression analyses revealed that ACR and BUN were independently associated with serum OGN. Additionally, ROC curve results revealed that serum OGN levels were good predictors of microalbuminuria and macroalbuminuria among diabetic patients, with 87% sensitivity and specificity for microalbuminuria and 82.6% sensitivity and 78.3% specificity for macroalbuminuria. In concordance with our study, El-Behiry *et al.* revealed that OGN was a significant predictor for early detection of microalbuminuria with 86.7% sensitivity and 95% specificity.[32] Additionally, Wang *et al.* revealed that serum OGN level was a good marker for microalbuminuria with a sensitivity of 86.7% and specificity of 95%, as well as for macroalbuminuria with a sensitivity of 90% and a specificity of 95%.[8] Serum OGN can help reduce false results by potentially discriminating structural kidney alterations earlier, even before significant albuminuria appears.[36]

Limitations

Some limitations of the study need to be acknowledged. Case-control studies are prone to selection bias, as cases and controls may not be fully representative of the general population despite matching and inclusion criteria. Additionally, the participants were recruited from a single center, which may limit the external validity of the findings. Moreover, measurement bias, biological variability, and single-time-point measurements of biochemical parameters may not fully reflect long-term metabolic status. Furthermore, the relatively modest sample size may reduce statistical power to detect weak associations and may increase the risk of type II error. Also, residual unmeasured confounding factors such as medications, dietary habits, and inflammatory markers were not included in the analysis. Finally, caution should be used when applying the results to other ethnic or clinical settings.

Conclusions

In patients with T2DM, correlation analyses revealed that serum OGN levels were significantly positively correlated with markers of kidney impairment (creatinine, BUN, ACR) and significantly negatively correlated with markers of protein loss (total protein, serum albumin). Additionally, multivariate analyses revealed that HbA1c, LDL-C, BUN, and ACR were independently associated with serum OGN, while HDL-C showed a significant inverse association. ROC curve results demonstrated that serum OGN may serve as a potential biomarker for the early detection of microalbuminuria with 87% sensitivity and specificity. This suggests that monitoring serum OGN could help early diagnosis and intervention strategies, ultimately improve patient outcomes, and delay the progression of kidney-related complications in T2DM.

Contributions: Mohamed M. M. Hassan, Emam M. M. Ismail, Hamed A. Deraz, Atef G. Hussien: conception and design; Samar Mohamed A. Mohaseb, Samia Hussein, Al-Shabrawy M. Abdelnabi, Alhoussein Alsayed AbdelAal: methodology and statistical analysis of data; Samar Mohamed A. Mohaseb,

Samia Hussein: writing – original draft. All authors read and approved the final manuscript.

Conflict of interest: the authors have no conflict of interest to declare.

Ethics approval and consent to participate: this study obtained approval from the Institutional Review Board of the Faculty of Medicine, Zagazig University (ZU-IRB#6591-13-1-2021). Informed consent was obtained from the patient included in this study.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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