



# The Relationship between Plasma Osteopontin Level and Proteinuria in Diabetic Patients

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## Abstract

**Background:** Elevated serum levels of osteopontin (OPN) have been associated with cardiovascular disease, diabetic nephropathy, and autoimmune disease activity. The aim of this study was to investigate the relationship between OPN serum levels and renal damage in type 2 diabetes patients.

**Methods:** This analytical cross-sectional study was carried out in Yazd, Iran from April to September 2017. Micro-albuminuria and creatinine (Cr) in 750 patients were measured and 180 included patients were divided into the three groups of 60 subjects based on the level of micro-albuminuria; normal (group A), micro proteinuria (group B) and macro proteinuria (group C). Body weight, height, blood pressure, body mass index (BMI), HbA1c and OPN were assessed.

**Results:** Among 179 patients, 60 of them were normal for proteinuria, 59 patients had micro-proteinuria and 60 ones had macro-proteinuria. The mean age of participants was 58.96 ( $\pm 11.10$ ) years (range 26-80 years), 90 patients (50.8%) were males and 88 ones (49.2%) were females. The mean OPN levels were significantly higher in group C compared to group B, and in group B compared to group A ( $P=0.0001$ ). Serum OPN was correlated positively with HbA1c ( $P: 0.012$ ), Cr ( $P=0.010$ ) and glomerular filtration rate (GFR) ( $P=0.002$ ). There was a significant difference in the mean of OPN level among the subgroups with the history of ischemic heart disease (IHD) and HbA1C ( $P=0.035$ , and  $0.047$  respectively).

**Conclusion:** These findings suggest that OPN is involved in chronic disease activity, and there is an independent association between plasma levels of OPN, and nephropathy in diabetic patients.

**Keywords:** Type 2 diabetes, Nephropathy, Osteopontin

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## Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide. DM incidence will increase to 500 million by 2030 (1). Complications of micro- and macro-vasculopathy, such as nephropathy and coronary artery disease (CAD), are common in diabetes and increase mortality (2,3). Diabetic nephropathy occurs in approximately 30% of diabetic patients and leads to renal failure (4). The first sign of diabetic nephropathy in most patients is microalbuminuria, which is caused by severe renal failure due to high blood pressure and glomerular basement disorder (4,5).

Osteopontin (OPN) is an extracellular glycoprotein that is secreted by osteoclasts, lymphocytes,

chromosomes, macrophages, endothelial cells, and smooth blood vessels and plays a key role in cellular immunity as a proinflammatory cytokine and growth factor (6). Animal studies have shown that OPN expression in diabetic nephropathy increases glomerular damage and is involved in the pathogenesis of diabetic nephropathy (7-10).

Given that animal studies have shown the potential role of OPN in diabetic nephropathy and because before the advent of classical biomarkers of nephropathy such as albuminuria, there are some new biomarkers such as plasma OPN (11), Therefore, the aim of this study was to evaluate the association between OPN and diabetic nephropathy in humans.



## Material and Methods

### Study population and data collection

This analytical cross-sectional study was conducted from April to September 2017 on 180 patients with T2DM, referred to Yazd diabetic research center. They were selected by convenient sampling method. The inclusion criteria were the age range of 20-60 years, patients with type 2 diabetes and the exclusion criteria consisted of history of diabetic foot ulcer, liver disorders, heart failure, malignancy, acute inflammatory diseases and hypothyroidism. Demographic data and medical history including history of retinopathy and ischemic heart disease (IHD) were collected by one researcher. One case was excluded from the study due to the unwillingness to continue cooperation. Weight was measured without shoes and wearing only light clothing using an electronic weighing scale (Glamor, BF-1041-A) and recorded to the nearest 100 g. Height was measured once at baseline without shoes with the subject stretching to the maximum height and the head positioned in the plane using a portable stadiometer and was recorded to the nearest 0.1 cm. Body mass index (BMI) was also calculated ( $\text{kg}/\text{m}^2$ ).

Micro-albuminuria and creatinine (Cr) in 750 patients were evaluated. With regard to the clinical findings, patients were divided into the three groups of 60 subjects: normal (group A), micro-proteinuria (group B) and macro-proteinuria (group C). Diabetic nephropathy was graded as: no micro-albuminuria (albumin concentration  $\leq 30$  mg/L), micro-albuminuria (albumin concentration 30-300 mg/L and proteinuria (albumin concentration  $\geq 300$  mg/L) (12). Glomerular filtration rate (GFR) was calculated based on the four-variable modification of diet in renal disease (MDRD).

Laboratory tests including HbA1c, and serum Cr levels

were measured in all participants. In patients with macro-proteinuria, and 24-hour urine protein, 24-hour urine Cr were also measured to confirm macro-proteinuria levels of the patients in this group. Lab tests such as serum Cr levels, 24-hour urine protein, 24-hour urine Cr were obtained using BA400 and A25 analyzer. HgbA1C was measured by high-performance liquid chromatography on a Diamat Analyzer (Bio-Rad, München, Germany).

The level of OPN was measured in three groups of patients by enzyme-linked immunosorbent assay kit (Human Osteopontin ELISA Kit, E1525Hu 96 tests).

### Statistical analyses

The obtained data was coded for statistical evaluations. Statistical analysis was performed using SPSS software version 23 (SPSS Inc., Chicago, USA). Data are presented as mean  $\pm$  standard deviation (SD). In this study, one-way analysis of variance (ANOVA) was used for quantitative comparison and chi square analysis for qualitative variables. Logistic regression analysis was performed to identify independent risk factors. *P* value  $< 0.05$  was considered statistically significant.

### Results

Among 179 patients, 60 patients had normal proteinuria, 59 ones had micro proteinuria and 60 patients had macro-proteinuria. One of the samples in micro proteinuria group did not cooperate for repeated blood sampling. The mean age of participants was  $58.96 \pm 11.10$  years (range 26-80 years), 90 patients (50.8%) were males and 88 ones (49.2%) were females. Demographics and clinical characteristics of participants with diabetes have been summarized in Table 1.

The mean of DM duration ( $\pm$ SD) was  $9.98 \pm 6.95$

**Table 1.** Demographics and clinical characteristic of participants

Variables	Group A	Group B	Group C	P value
Age (y)	57.13 $\pm$ 1.51	60.76 $\pm$ 1.42	59.01 $\pm$ 1.35	0.216
Gender (Female)	30 (50%)	30 (50%)	29 (50%)	0.719
BMI	29.31 $\pm$ 4.95	28.93 $\pm$ 4.66	27.83 $\pm$ 4.27	0.195
Diabetes duration (year)	8.9 $\pm$ 0.79	9.96 $\pm$ 0.98	11.1 $\pm$ 0.9	0.177
Retinopathy				
Yes	5 (8.3%)	8 (13.6%)	14 (23.3%)	
No	55 (91.7%)	51 (86.4%)	46 (76.7%)	0.388
GFR	87.76 $\pm$ 4.05	62.71 $\pm$ 2.62	41.62 $\pm$ 1.44	0.002
IHD	1 (1.7%)	6 (10.2%)	11 (18.3%)	0.288
Micro-albuminuria	10.51 $\pm$ 0.98	94.87 $\pm$ 7.78	-	0.0001
HbA1c	7.8 $\pm$ 0.16	8.26 $\pm$ 0.20	8.44 $\pm$ 0.2	0.127
Cr	1.03 $\pm$ 0.03	1.09 $\pm$ 0.04	1.37 $\pm$ 0.04	0.008
OPN	8.01 $\pm$ 0.24	8.92 $\pm$ 0.25	9.95 $\pm$ 0.18	0.0001
24-Hour urine protein	-	-	716 $\pm$ 47.1	-
24-Hour urine creatinine	-	-	876 $\pm$ 46.7	-

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; IHD, ischemic heart disease; Cr, creatinine; OPN, osteopontin. Values reported as mean  $\pm$  standard error or No. (%). *P* value was obtained from independent samples *t* test (2-tailed).

years (range 1-40 years). Sixty (33%) of the patients were treated with insulin before and during the study.

The mean OPN level was significantly higher in group C compared to group B, and group B compared to group A. The level of OPN was significantly different in the comparison of each of the two groups (groups A- with B: 0.022, A- with C: 0.001, B- with C: 0.007). Also, the difference of OPN in the three studied groups did not change after adjustments for GFR ( $P=0.001$ ).  $P$  value for trend analysis was significant ( $P=0.0001$ ) which means the increasing trend of OPN in A, B, C groups was statistically significant.

There was a significant difference in the mean of OPN level among the subgroups of the history of IHD and HbA1C ( $P=0.035$ ,  $P=0.047$ , respectively) (Table 2).

Serum OPN correlated positively with HbA1c ( $P=0.012$ ), Cr ( $P=0.010$ ) and GFR ( $P=0.002$ ). However, OPN did not correlate with age, weight, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Table 3).

Using the multinomial logistic regression for the predictive value of OPN and proteinuria and after adjusting for the other variables including Cr, BMI, HbA1c, and GFR, the relationship of OPN and protein binding remained significant (Table 4).

## Discussion

Diabetic Nephropathy is the most common complication of diabetes and leads to renal failure. Early diagnosis of nephropathy in diabetic patients is necessary to initiate appropriate treatment.

This study tried to find a sensitive biomarker for the diagnosis of early phase of diabetic nephropathy (13-15).

**Table 2.** Comparison of the OPN level in some of the subgroups of the studied variables

Variable	Sub-groups	N	Mean ( $\pm$ SD)	P value
Gender	Women	80	8.54 ( $\pm$ 1.72)	0.070
	Men	81	9.01 ( $\pm$ 1.57)	
IHD	Yes	22	9.37 ( $\pm$ 1.34)	0.035
	No	140	8.67 ( $\pm$ 1.69)	
Retinopathy	Yes	22	9.13 ( $\pm$ 1.40)	0.213
	No	140	8.71 ( $\pm$ 1.69)	
HbA1c	Good control*	40	8.23 ( $\pm$ 2.05)	0.047
	Poor control**	120	8.95 ( $\pm$ 1.48)	

Abbreviation: IHD, ischemic heart disease.

$P$  value was obtained from independent samples  $t$  test (2-tailed).

\*HbA1C < 7 %; \*\* HbA1C  $\geq$  7 %.

Increased serum Cr and microalbuminuria are common markers for detecting kidney failure. Recent studies have shown that serial changes in cystine, OPN and erythropoietin can improve sensitivity for early detection (9,13,15).

In this analytical cross-sectional study, the relationship between OPN levels and proteinuria degree in patients was significant. In our study, the relationship between OPN levels and proteinuria was significant. The odds ratio for group B was 1.29 (CI: 1.00-1.67) and for group C was 1.63 (CI: 1.11-2.46), and this correlation was obtained after adjusting for Cr, BMI, HbA1c, and GFR.

Mean serum OPN levels had a significant correlation with GFR, Cr and HbA1C. In addition, mean serum OPN levels were found to be significantly higher in subjects with a worse blood glucose control situation.

In a cohort study by Gordin et al, patients with higher baseline OPN levels had a significantly higher incidence of albuminuria, cardiovascular disease, and death. In addition, in this study, there was a significant independent association of OPN with albumin, cardiovascular disease and death after adjustment for other variables (15). Steinbrenner et al proposed that higher levels of OPN are associated with lower eGFR and higher risk of chronic kidney disease and mortality (16). Findings from another study in 2022 showed that OPN level was significantly higher in patients with microvascular complications (17).

Current evidence supports the hypothesis that OPN may induce inflammation of the kidney, proteinuria, intracellular fibrosis (18), reduced GFR, and increase the release of this cytokine from damaged kidneys, resulting in increased levels of plasma (19), leads to the strengthening of systemic inflammation and the deterioration of nephropathy and possibly other kidney diseases too (11,20,21).

Although, in laboratory conditions, OPN serum concentrations are associated with vascular disease in diabetes (22), clinical data suggest a relationship between OPN and late vascular complications in patients with DM. In the study of Mohamadpour et al, the level of OPN was significantly higher in patients with chronic disease activity than in the control (healthy) group (23). A similar result has been observed in the study of Ohmori et al (24). According to a study by Kase et al in 2018, OPN levels were significantly higher in diabetic patients with nephropathy (25). However, in the study by Yamaguchi et al (6), plasma urine OPN was associated with the progression of diabetic nephropathy. In the present study, we also found

**Table 3.** The correlation between osteopontin and other variables in the studied participants

Variable		Age	Duration	Weight	HbA1C	Cr	GFR	SBP	DBP	OPN
Osteopontin	Pearson correlation	0.053	0.061	0.129	0.199	0.203	-0.244	-0.112	-0.124	1
	$P$ value	0.501	0.439	0.102	0.012	0.010	0.002	0.158	0.117	-
	N	162	161	162	160	162	162	161	161	162

Abbreviations: GFR, glomerular filtration rate; Cr, creatinine; OPN, osteopontin; SBP, systolic blood pressure; DBP, diastolic blood pressure.

$P$  value was obtained from independent samples  $t$  test (2-tailed).

**Table 4.** The multinomial logistic regression for the predictive value of osteopontin and proteinuria

Groups*	Odds ratio	95% CI	P value
B	1.29	1.001-1.671	0.049
C	1.63	1.111-2.46	0.013

\*Adjusted for Cr, BMI, HbA1c, GFR. The reference category is A.

a relationship between OPN and IHD ( $P < 0.05$ ) and OPN predicts the development of kidney disease in patients with T2D independently.

The significant strengths of this study were comparison of three groups of diabetic patients with OPN in varying degrees of nephropathy, accurate data collection and the use of expert colleagues to identify any of the variables requiring expert opinions. The cross-sectional nature of the study and the impossibility of causal relationships can be an important limitation of this study.

### Conclusion

These findings suggest that OPN is involved in chronic disease activity, and there is an independent association between plasma levels of OPN, and nephropathy in diabetic patients.

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### Competing Interests

None.

### Ethical Approval

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences in Yazd (IR.SSU.REC.1393.113682). Informed consent was obtained from all participants.

### Authors' Contribution

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