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SERUM VISFATIN; ITS ROLE IN DIABETIC NEPHROPATHY PREDICTION AND AS A RISK FACTOR OF CARDIOVASCULAR DISEASES IN TYPE 2 DIABETIC PATIENTS

Diabetology

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ABSTRACT

INTRODUCTION: Visfatin is synthesized and released by adipocytes and by inflammatory cells, like activated macrophages, whose infiltration in adipose tissues is markedly increased in relation with obesity . Elevated serum visfatin levels was reported in diabetic type 2 patients and in haemodialysis patients. Visfatin has been considered as a marker of endothelial dysfunction.

OBJECTIVE: Our aim was to study the role of serum visfatin levels as diagnostic marker of the degree of kidney disease in diabetic patients and its role as a risk factor of cardiovascular disorders in those patients.

SUBJECTS AND METHODS: 75 diabetic type 2 subjects categorized into 4 groups according to absence and presence of albuminuria and to its degree if present ,in addation to 15 age and sex matched healthy control subjects. All individuals included in the study were subjected to history taking, physical examination, Body mass index calculation, measurement of total cholesterol , serum triglecrides, high density lipoprotein cholesterol(HDL) , levels of haemoglobin(HB) , white blood cells(WBCs) and pletelets count , fasting blood glucose levels, Glycosylated Hb (HA1c), serum albumin ,serum creatinine ,urinary albumin creatinine ratio and serum visfatin levels.

RESULTS: Serum visfatin levels were significantly higher in macroalbuminuric diabetics (group4) than microalbuminuric diabetics(group3)[***P***=<0.001] and in diabetic patients on haemodialysis than in macroalbuminuric diabetics (group4) [***P***=<0.001]. We found significant positive correlations between serum visfatin levels and both total cholesterol levels and serum triglycerides levels [***P***=≤0.001 repeatedly] with significant negative correlation between serum visfatin levels and HDL serum levels [***P***=≤0.001] Hightly significant negative correlation between serum visfatin levels and serum albumin [P= 0.001] , together with highly significant positive correlations between serum visfatin levels and both serum creatinine [P= 0.001] , and UACR [P= 0.001].

CONCLUSION:serum visfatin levels can be considered not only as diagnostic marker for kidney disease and its degree in diabetic patients type2 but moreover it can be considered as a risk factor of cardiovascular disorders in those patients.

KEYWORDS

INTRODUCTION

Visfatin is a protein (adipocytokine) produced by fat tissue, it corresponds to a protein identified previously as pre-B cell colony-enhancing factor (PBEF), a cytokine detected in lymphocytes, acting on its maturation and inflammatory regulation (1). Visvatin is produced in human leukocytes, adipose tissue, hepatocytes and muscles (2),also, in animal adipocytes, hepatocytes, kidney and heart (3) It was found to be released by the macrophages infiltrating adipose tissue in response to inflammatory signals (4). Continuous glucose infusion in humans acutely increases visfatin levels, while insulin or somatostatin infusion suppresses its levels with a negative correlation of its levels with beta cell function (5). Patients with both long duration type 1 diabetes and type 2 diabetes were found to have higher visfatin levels than in the non-diabetic controls or recently diagnosed diabetic individuals, also, increased visfatin levels were associated with increased glycated hemoglobin (HA1C) levels in type 2 diabetic patients (6). Visfatin was found to bind to the insulin receptor and causes hypoglycemia by reducing glucose release from liver cells and stimulating glucose utilization in adipocytes and myocytes and its levels were upregulated by inflammation and hyperglycemia and down regulated by insulin and statins (7) Visfatin levels were elevated in patients and animals with type 2 diabetes associated with nephropathy (8)., Proteinuria, which is an important predictor of endothelial dysfunction (ED) in early diabetic nephropathy, was associated with increased visfatin levels in type 2 diabetic patients and visfatin levels was found to correlate with the degree of albuminuria (9) Song *et al.* (10), studied visfatin at the molecular level as they cultured mesangial cells with recombinant visfatin and found a marked increase in the synthesis of profibrotic molecules including transforming growth factor-b, plasminogen activation inhibiting factor 1, and type 1 collagen, which are well known to contribute toward the pathogenesis of diabetic nephropathy .This supports the concept that visfatin could be one of the cytokines responsible for renal damage in diabetic nephropathy. Also, Axelsson et al. (11) reported an elevated serum level of visfatin in chronic kidney disease (CKD) and that elevation was associated with soluble vascular adhesion molecule 1, which is a biomarker of endothelial damage in CKD. Visfatin found to be involved in the complex interactions between ED, inflammation, and atherosclerosis in CKD, suggesting that it is a surrogate biomarker for the prediction of ED and future cardiovascular risk in CKD patients (12).Our aim is to study visfatin levels in different stages of diabetic nephropathy and the probability of consideration of its levels as markers of worsening of kidney functions in diabetic patients.

Subjects and methods:

The patients in our study were selected from both the out patients clinics and the admitted patients in the internal medicine department in Mansoura University Hospitals. 75 diabetic type 2 subjects (39 males and 36 females) were included in the study and categorized into 4 groups according to absence and presence of albuminuria and to its degree if present , besides 15 age and sex matched healthy control subjects.

Group 1 included 15 control subjects. *Group 2* included 22 diabetic patients with normoalbuminuria. *Group 3* included 22 diabetic patients with detected microalbuminuria . *Group 4* included 15 diabetic patient with macroalbuminuria but not on haemodialysis .*Group 5* included 16 diabetic patients on haemodialysis. Individuals with systemic diseases, such as, liver failure, cardiovascular diseases, infectious diseases, inflammatory diseases, malignancies, neurodegenerative diseases, cerebrovascular diseases; and smokers were excluded from the study.

All individuals included in the study were subjected to complete history taking, detailed physical examination, body mass index calculation (BMI = weight in kilograms/height in m2), total cholesterol levels ,serum triglecrides , high density lipoprotein cholesterol(HDL) , levels of haemoglobin(HB) , white blood

cells(WBCs) and pletelets count , fasting blood glucose levels, Glycosylated Hb (HA1c), serum albumin ,serum creatinine and urinary albumin-creatinine ratio (UACR) .UACR was defined as milligram of albumin per gram of creatinine (mg/g). Normoalbuminuria was defined by a UACR< 30 mg/g, microalbuminuria was defined by a UACR of 30 to 300 mg/g and macroalbuminuria was defined by a UACR≥ 300 mg/g. . Plasma visfatin levels were measured using an enzyme-linked immunosorbent assay (ELISA).

Statistical Analysis

Data entry and analysis were performed using SPSS statistical package version 17. The data were expressed as mean ± SD for normally distributed variables . Comparisons among groups were performed using 1-way analysis of variance (ANOVA) with post hoc least significant difference (LSD) pair-wise comparisons. Pearson and Spearman correlations were done to study relation between different items.

RESULTS

Table 1. Clinical and biochemical characteristics of patients groups with type 2 diabetes and healthy controls

Groups		All groups	Group 1 Control group	Group 2 Normoalbuminuric diabetic patients	Group 3 Microalbuminuric diadetic patients	Group 4 Macroalbuminuric diabetic patients	Group 5 diabetic patients on haemodialysis
Number of subjects		90	15	22	22	15	16
Age (years)	Mean	49.27	44.00	50.32	47.55	53.20	44.13
	S.D	+6.70	+8.85	+6.85	+6.70	+7.68	+10.22
BMI (kg/m2)	Mean	30.75	29.89	30.59	32.13	33.01	27.76
	S.D	+4.68	+2.61	+4.61	+4.82	+4.19	+5.80
Duration of DM (years)	Mean	8.84	0.00	8.55	10.72	12.40	11.63
	S.D	+6.17	+0.00	+4.27	+5.62	+5.44	+4.94
Duration of haemodial-ysis (years)	Mean	.728	0.00	0.00	0.00	0.00	4.09
	S.D	+1.91	+0.00	+0.00	+0.00	+0.00	+2.65
Systolic BP (mmHg)	Mean	131.11	116.00	134.09	136.09	140.00	128.75
	S.D	+15.47	+6.32	+15.63	+14.36	+10.69	+17.46
Diastolic BP (mmHg)	Mean	83.11	79.67	84.09	84.55	87.67	78.75
	S.D	+7.95	+4.42	+8.54	+8.00	+6.78	+8.06
Total cholesterol (mg/dl)	Mean	188.52	157.13	197.00	198.09	200.60	202.81
	S.D	+35.55	+11.80	+25.54	+32.91	+40.85	+38.76
Serum triglycerids (mg/dl)	Mean	156.44	108.60	168.41	172.04	174.80	180.06
	S.D	+55.04	+16.04	+45.60	+65.42	+55.43	+55.15
HDL (mg/dl)	Mean	39.43	49.20	38.55	37.23	36.47	37.31
	S.D	+7.65	+3.32	+6.28	+6.99	+4.24	+8.93
FBG (mg/dl)	Mean	139.63	91.20	147.91	137.00	202.53	118.31
	S.D	+45.80	+7.61	+38.71	+36.43	+23.64	+31.92
HbA1c (%)	Mean	6.74	5.08	6.24	6.64	9.51	6.54
	S.D	+2.16	+0.48	+1.07	+1.47	+3.24	+1.46
S. creatinine (mg/dl)	Mean	3.00	0.867	1.15	1.66	3.81	8.64
	S.D	+3.26	+0.17	+0.39	+2.07	+1.16	+2.96
UACR (mg/gm)	Mean	382.13	5.51	10.40	126.84	357.67	682.81
	S.D	+613.45	+2.05	+6.97	+83.07	+33.42	+482.56
S. albumin (gm/dl)	Mean	3.92	4.39	4.16	3.99	3.10	3.82
	S.D	+.544	+.41	+.32	+0.25	+0.41	+0.46
Hemoglobin (g/dl)	Mean	11.29	12.65	11.10	11.90	10.29	10.36
	S.D	+1.97	+1.50	+2.42	+0.69	+1.98	+2.03
Platelet (x103)	Mean	230.14	208.87	181.36	277.91	159.47	180.25
	S.D	+95.81	+27.97	+97.98	+95.39	+65.09	+91.17
WBCs (x103)	Mean	5692.78	6210.00	4818.18	5040.90	7093.33	5993.75
	S.D	+2718.50	+1386.57	+2180.30	+2455.39	+3437.08	+3444.12
Visvatin (ng/ml)	Mean	103.79	27.15	49.85	102.83	147.87	209.81
	S.D	+71.74	+7.56	+16.27	+23.88	+23.38	+68.78

BMI: body mass index ,BP: blood pressure ,HDL: hight density lipoprotein , FBG: fasting blood glucose ,HbA1c: glycated haemoglobin,S. albumin: serum albumin ,UACR: Urinary Albumin Creatinine Ratio ,WBCs: white blood cell

Table (2): Comparison between healthy control group and diabetic patients groups

	Group 1 Control group	Group2 Normoalbuminuric diabetic patients	Group3 Microalbuminuric diadetic patients	Group4 Macroalbuminuric diabetic patients	Group5 diabetic patients on haemodialysis
Duration of DM(years)	0.00	8.55+4.27 (P=<0.001)*	10.72+5.62 (P=<0.001)*	12.40+5.44 (P=<0.001)*	11.63+4.94 (P=<0.001*)
BMI(kg/m2)	29.89+2.61	30.59+4.61 (P=O.640)	32.13+4.82 (P=0.137)	33.01+4.19 (P=0.058)	27.76+5.80 (P=0.185)
Systolic BP (mmHg)	116.00+6.32	134.09+15.63 (P=<0.001)*	136.09+14.36 (P=<0.001)*	140.00+10.69 (P=<0.001)*	128.75+17.46 (P=0.012)*
Diastolic BP(mmHg)	79.67+4.42	84.09+8.54 (P=0.081)	84.55+8.00 (P=0.055)	87.67+6.78 (P=0.004)*	78.75+8.06 (P=0.734)
Total cholesterol (mg/dl)	157.13+11.80	197.00+25.54 (P=<0.001)*	198.09+32.91 (P=<0.001)*	200.60+40.85 (P=<0.001)*	202.81+38.76 (P=<0.001)*
Serum triglycerids (mg/dl)	108.60+16.04	168.41+45.60 (P=<0.001)*	172.04+65.42 (P=<0.001)*	174.80+55.43 (P=<0.001)*	180.06+55.15 (P=<0.001)*
HDL(mg/dl)	49.20+3.32	38.55+6.28 (P=<0.001)*	37.23+6.99 (P=<0.001)*	36.47+4.24 (P=<0.001)*	35.31+8.93 (P=<0.001)*
FBG(mg/dl)	91.20+7.61	147.91+38.71 (P=<0.001)*	137.00+36.43 (P=<0.001)*	202.53+23.64 (P=<0.001)*	118.31+31.92 (P=0.018)*
HA1c (%)	5.08+0.48	6.24+1.07 (P=0.045)*	6.64+1.47 (P=0.008)*	9.51+3.24 (P=<0.001)*	6.54+1.46 (P=.020)*
S. albumin (gm/dl)	4.39+.410	4.16+.326 (P=0.073)	3.99+0.25 (P=0.002)*	3.10+0.41 (P=<0.001)*	3.82+0.46 (P=<0.001)*
S.creatinine (mg/dl)	0.867+0.17	1.15+0.39 (P=0.613)	1.66+2.07 (P=0.166)	3.81+1.16 (P=<0.001)*	8.64+2.96 (P=<0.001)*
S.visfatin (ng/ml)	27.15+7.56	49.85+16.27 (P=0.048)*	102.83+23.88 (P=<0.001)*	147.87+23.38 (P=<0.001)*	209.81+68.78 (P=<0.001)*
UACR (mg/gm)	5.51+2.05	10.40+6.97 (P=0.968)	126.84+83.07 (P=<0.001)*	1357.67+733.42 (P=<0.001)*	

P is significant *at the 0.05 level .

Table (3):Comparison between diabetic patients without kidney disease (group2)and diabetic patients with kidney disease (groups 3,4,5) .

	Group 2 Normoalbuminuric diabetic patients	Group3 Microalbuminuric diadetic patients	Group4 Macroalbuminuric diabetic patients	Group5 diabetic patients on haemodialysis
Duration of DM(years)	8.55+4.27	10.72+5.62 (P=0.122)	12.40+5.44 (P=0.015)*	11.63+4.94 (P=0.046)*
BMI(kg/m^2)	30.59+4.61	32.13+4.82 (P=0.254)	33.01+4.19 (P=0.107)	27.76+5.80 (P=0.056)
Systolic BP (mmHg)	134.09+15.63	136.09+14.36 (P=<0.001)*	140.00+10.69 (P=0.025)*	128.75+17.46 (P=0.242)
Diastolic BP(mmHg)	84.09+8.54	84.55+8.00 (P=0.841)	87.67+6.78 (P=0.158)	78.75+8.06 (P=0.033)*
Total cholesterol (mg/dl)	197.00+25.54	198.09+32.91 (P=0.841)	200.60+40.85 (P=0.014)*	202.81+38.76 (P=<0.001)*
Serum triglycerids (mg/dl)	168.41+45.60	172.04+65.42 (P=0.780)	174.80+55.43 (P=0.075)	180.06+55.15 (P=0.023)*
HDL(mg/dl)	38.55+6.28	37.23+6.99 (P=0.495)	36.47+4.24 (P=0.333)	35.31+8.93 (P=0.558)
FBG(mg/dl)	147.91+38.71	137.00+36.43 (P=0.251)	202.53+23.64 (P=<0.001)*	118.31+31.92 (P=0.005)*
HA1c (%)	6.24+1.07	6.64+1.47 (P=0.440)	9.51+3.24 (P=<0.001)*	6.54+1.46 (P=0.591)
S.albumin (gm/dl)	4.16+.326	3.99+0.25 (P=0.113)	3.10+0.41 (P=<0.001)*	3.82+0.46 (P=0.005)*
Serum Creatinine (mg/dl)	1.15+0.39	1.66+2.07 (P=0.322)	3.81+1.16 (P=<0.001)*	8.64+2.96 (P=<0.001)*
Vifatin (ng/ml)	49.85+16.27	102.83+23.88 (P=<0.001)*	147.87+23.38 (P=<0.001)*	209.81+68.78 (P=<0.001)*
UACR (mg/gm)	10.40+6.97	126.84+83.07 (P=<0.001)*	1357.67+733.42 (P=<0.001)*	

P is significant *at the 0.05 level .

Table (4) :Comparison between serum visfatin levels in the different studied groups

visfatin	Group1Control group	Group2 Normoalbuminuric diabetic patients	Group3 Microalbuminuric diadetic patients	Group4 Macroalbuminuric diabetic patients	Group5 diabetic patients on haemodialysis	
mean	27.15	49.85	102.83	147.87	209.82	P=
SD	+7.56	+16.27	+23.88	+23.38	+68.78	(< 0.001)*

P is significant at the 0.05 level .

Table (5): comparison between serum visfatin levels in diabetic patients groups with kidney disease ; groups 3, 4 and 5

Visfatin	P1	P2	P3
Group3 Microalbuminuric diadetic patients 102.83+23.88	(P=<0.001)*	(P=<0.001)*	(P=<0.001)*
Group4 Macroalbuminuric diabetic patients 147.87+23.38			
Group5 Diabetic patients on haemodialysis 209.81+68.78			

P is significant *at the 0.05 level .

Table (6): correlations between visfatin levels some clinical paramerters

Duration of DM(years)	r=.420 p=<0.001*
Duration of haemodialysis(years)	r=.605 p=<0.001*
Systolic BP(mmHg)	r=.134 p=0.209
Diastolic BP(mmHg)	r=.030 P=0.776
BMI(kg/m2)	r=.001p=0.992

P is significant *at the 0.05 level .

Table(7): correlations between visfatin levels some laboratory paramerters

Total cholesterol (mg/dl)	R=.383 p=0.001*
Serum triglycerids (mg/dl)	R=.414 p=0.001*
HDL(mg/dl)	R=-.340 p=0.001*
FBG(mg/dl)	r=.187 p=0.078
HbA1c (%)	r=.254 p=0.016*
HB(gm/dl)	r=-.310 p=0.033*
WBCs(x103)	r=.030 p=0.778
Pletelets(x103)	r=-.245 p=0.020*
S.albumin(gm/dl)	r=-.464 p=<0.001*
S.creatinine(mg/dl)	r=.745 p=<0.001*
UACR(mg/gm)	r=.469 p=<0.001*

P is significant *at the 0.05 level .

Table (8) : correlation between urinary albumin creatinine ratio (UACR)and some clinical and laboratory parameters :

Duration of DM(years)	r=.395 p==<0.001*
FBG(mg/dl)	r=.440 p=<0.001*
HbA1c(%)	r =.625 p=<0.001*
Serum albumin (gm/dl)	r =-.740 p=<0.001*
Serum creatinine (mg/dl)	r= .396 p=<0.001*
Serum visfatin (ng/ml)	r=.469 p=<0.001*

P is significant *at the 0.05 level .

In the current study, duration of DM were significantly higher in different patients groups (groups 2,3,4&5) than healthy control group (group1) [P=≤0.001 repeatedly] ,also duration of DM were significantly higher in macro-albuminuric group (group3) and diabetic patients on haemodialysis (group 4) than normo-albuminuric patients(group2)[P=0.015 & P=0.046 respectively]. BMI showed no difference between patients groups and control group ,or between normo-albuminuric group(group 2) and other patients groups. There were significant differences between systolic BP in diabetic patients groups (groups 2,3,4&5) and in healthy control group (group1)[P=≤0.001 ,P =≤0.001 , P=≤0.001 & P=0.012 respectively],besides significant differences between systolic BP in both micro & macro-albuminuric groups (groups 3 &4) and systolic BP in normo-albuminuric group (group2)[P =≤0.001 & P=0.025 respectively]. Diastolic BP was significantly higher in macro-albuminuric group (group 4) than in healthy control group (group1)[P=0.004], but was lower in diabetic patients on haemodialysis(group5) than nomo-albuminuric group (group2) [P=0.033]. Total cholesterol levels were significantly higher in diabetic patients (groups 2,3,4 &5) than healthy controls (group1)[P =≤0.001 repeatedly] , besides total cholesterol levels were significantly higher in macro-albuminuric diabetics and diabetics on hemodialysis (groups 4,5) than normoalbuminuric diabetic patients (group2) [P=0.014 &P=≤0.001 respectively]. In addation ,serum triglyceride levels were significantly higher in diabetic patients groups(groups 2,3,4&5)than in healthy control [P =≤0.001 repeatedly] ,but only diabetics on hemodialysis (group5) showed significantly higher serum triglyceride levels than normo-albuminuric (group2)[P=0.023] .HDL levels were significantly lower in diabetic patients groups (groups2,3,4&5)than control group (group1) [P=≤0.001 repeatedly] ,but no significant differences were detected between normo-albuminuric group(group2) and other diabetic groups (groups 3,4&5).

FBG levels were significantly higher in diabetic patients groups (groups2,3,4&5)than control group(group1)[P=≤0.001, ≤0.001, ≤0.001 & 0.018] respectively] , and also in both macro-albuminuric group & diabetics on haemodialysis (groups4&5) than normo-albuminuric group (group2)[P=≤0.001 & P=0.005 respectively]. HA1c % were significantly higher in all diabetic patients groups (groups2, 3,4&5) than in healthy controls (group1) [***P***=0.045, 0.008, ≤0.001, 0.020 respectively].

Serum creatinine levels were significantly higher in diabetics with macroalbuminuria (group4) and diabetics on haemodialysis (group5) than healthy control (group1)[***P***=≤0.001 and≤ 0.001 repeatedly], also in same two groups(groups 4&5) than in diabetics with normoalbuminuria (group2) [***P***=≤0.001 and≤ 0.001 repeatedly]. Serum albumin levels were significantly lower in all diabetic patients groups(groups 2,3,4&5) than in control group(group1)[***P***=0.002 ,≤0.001 and≤ 0.001 respectively],and in macro-albuminuric group (group4) and diabetics on haemodialysis(group5) than in

normoalbuminuric group(group2)[***P***=0.005 & ≤0.001 respectively] Serum visfatin levels were significantly higher in all diabetic patients groups(groups 2,3,4&5) than in healthy control (group1)[***P***=0.048, ≤0.001, ≤0.001 and ≤0.001 respectively],and also were significantly higher in micro-albuminuric, macro-albuminuric and diabetics on haemodialysis (groups 3,4&5)than in normo-albuminuric group (group2)[P=≤0.001 repeatedly].

UACR were significantly higher in diabetics with microalbuminuria (group3) and those with macroalbuminuria (group4), than healthy control (group1) with [***P***=≤0.001 repeatedly],and in micro- and macro- albuminuric groups(group3&4) than in normo –albuminuric group(group2) [P=≤0.001 repeatedly].

Serum visfatin levels were significantly higher in macroalbuminuric diabetics (group4) than microalbuminuric diabetics(group3)[***P***=<0.001] and also were significantly higher in diabetic patients on haemodialysis (group5) than microalbuminuric diabetics(group3)[***P***=<0.001] ,in addation serum visfatin levels were significantly higher in diabetic patients on haemodialysis than in macroalbuminuric diabetics (group4) [***P***=<0.001].

In our studied groups there were significant positive correlations between serum visfatin levels and both of duration of DM [***P***=<0.001] and duration of haemodialysis [***P***=≤0.001]. There were non significant positive correlations between serum visfatin levels and systolic blood pressure [P=0.209],diastolic blood pressure [P=0.776] and BMI [P=0.992].We found significant positive correlations between serum visfatin levels and both total cholesterol levels and serum triglycerides levels [***P***=≤0.001 repeatedly] with significant negative correlation between serum visfatin levels and HDL serum levels [***P***=≤0.001]. Also, there were non significant positive correlations between serum visfatin levels and both FBG [P=0.078] and WBCs [P= 0.778]. Significant positive correlation was found between serum visfatin levels and HbA1c % , besides significant negative correlations between serum visfatin levels and both hemoglobin levels [P=0.033] and pletelets counts [P=0.020] . Highly significant negative correlation between serum visfatin levels and serum albumin [P= 0.001] , together with highly significant positive correlations between serum visfatin levels and both serum creatinine [P= 0.001] , and UACR [P= 0.001].

Our study also detected highly significant positive correlations between UACR and each of FBG [P= 0.001] , HbA1c [P= 0.001] , and serum creatinine [P= 0.001].Besides highly significant negative correlations between UACR and serum albumin.

DISCUSSION

Diabetic nephropathy is one of the important complications of diabetes mellitus (DM) and is the most common cause of end-stage renal failure in clinical practice (13).Diabetic nephropathy is characterized by progressive albuminuria, glomerulosclerosis and decline in glomerular filtration rate GFR leading to end stage renal failure (14). Microalbuminuria has been identified as the most effective indicator of early diabetic nephropathy (15). It has been reported that elevated visfatin levels were associated with the progression of diabetic nephropathy and other vascular complications of diabetes (16). Plasma visfatin levels were positively correlated with urinary albumin excretion, and were inversely correlated with creatinine clearance (8).

In our study HbA1c was found to be significantly higher in diabetic patients groups than control groups and there was hight significant positive correlation between UACR and both FBG and HbA1c levels this agree with Varghese *et al.* who reported a correlation of the prevalence of microalbuminuria with the fasting blood sugar and with HbA1c levels (17).Also there was a significant positive correlation between visfatin levels and HbA1c levels however this is inconsistent with Gundus *et al*. who claimed that this correlation was not observed (18) . In this study Serum creatinine levels were significantly higher in diabetics with macroalbuminuria and diabetics on haemodialysis than diabetics with normoalbuminuria and healthy control while no significant difference was detected between microalbuminuric diabetic patients and either diabetics normoalbuminuric or healthy control. These resuls are similar to those of Grover et al. who found that serum creatinine values do not increase significantly in early stages of diabetic nephropathy (19), and with Hojs et al. who suggested that serum creatinine is considered relatively specific but not very sensitive diagnostic because serum creatinine remains in the normal range until 50% of kidney function is lost (20) however we found significant positive correlation between serum visfatin levels and serum creatinine. This observation agree with study of Tang et al that showed increase in serum visfatin levels in all stages of CKD (21) . In our study, serum visfatin levels were significantly higher in diabetic patients groups than control ,this agree with many studies that approved the elevation of visfatin level in type 2 diabetic patients.(22,6) and also with other studies that shown the elevation of visfatin levels in hemodialysis patients (23,24).Also visfatin levels were significantly higher in diabetic patients with macroalbuminuria than those with microalbuminuria and in diabetics on hemodialysis than in diabetic patients with macroalbuminuria with significant positive correlation between serum visfatin levels and urinary albumin creatinine ratio(UACR) which coincide with Yilmaz et al. who detected positive correlation between visfatin levels and the degree of albuminuria in type 2 diabetic patients also between visfatin levels and all stages of chronic kidney disease (25,9) , however this is inconsistent with Kathryna et al.who suggested decrease of serum visfatin levels in advanced stages of diabetic nephropathy and suggest two hypotheses: the CKD progression in T2DM increases the urinary excretion of visfatin, reducing its plasma concentration; or advanced stages of DN reduce local synthesis of visfatin by mesangial cells, decreasing its plasma levels (26).we detected significant negative correlations between s. visfatin levels and HB levels. Kaygusuz et al (27), suggested that high levels of visfatin may interact with iron ,however ,Van et al (28) reported that visfatin may play a role in erythropoietin insensitivity in addition to reduced erythropoietin production in renal failure patients .

Elevated levels of serum visfatin was detected in different metabolic abnormalities, such as obesity, type 2 diabetes mellitus, and the metabolic syndrome appearing as independent risk factors for inflammation-related atherothrombotic diseases (29) ,also serum visfatin has been suggested as a marker of endothelial dysfunction and the progression of the atherosclerotic process (30) Others, found contradicting results on studying the variation of visfatin levels in these disease states, as visfatin levels have been found not altered or even lower compared to healthy controls (31).

we found positive correlation between serum visfatin levels and BMI that was considered as simple indicator and mediator of CVD risk by Dudina et al (32) with other studies found positive association between high BMI and risk for CKD (33,34) however Ching-chu et al, found no correlations between visfatin levels and any anthropometric measures(35).Also, we found positive correlations between serum visfatin levels and both systolic and diastolic BP as CV risk factors, this was in the same context with Ozal et al (36) who found an independent correlation between higher visfatin levels and the presence left ventricular hypertrophy , however these positive correlations between serum visfatin and BMI, systolic BP and diastolic BP in our study were non significant. Serum visfatin levels showed significant positive correlations with both total cholesterol levels and serum triglycerides levels that were found to be significantly higher in diabetics on haemodialysis (group5) than those with normoalbuminuria (group 2)these agree with other studies that reported that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, and may result in the development of severe dyslipidemia(37,38). In the same side, serum visfatin levels showed significant negative correlation with serum levels of HDL . It has been reported that patients with CKD have, generally, reduced plasma HDL cholesterol levels compared to individuals with normal renal function (39, 40). In this study we found that systolic BP ,diastolic BP, total cholesterol, serum triglycerides and low HDL were significantly higher not only in diabetic groups with nephropathy but also in diabetics with normoalbuminuria than the control group so we can understand that these high levels not only due to the kidney disease.These correlations of serum visfatin with different risk factors of CV diseases agree with the hypothesis that serum visfatin can be suggested as CV risk factor in type 2 DM, it has been suggested that elevated serum visfatin levels are associated with advanced carotid atherosclerosis,estimated as the intima-media thickness (IMT) in this artery (41),and Kadoglou et al. have proposed serum visfatin levels as a marker of advanced carotid atherosclerosis for type 2 diabetic patients(42) .

CONCLUSION:

In our study, serum visfatin levels correlated with the degree of albuminuria and stages of kidney disease as it correlated positively

with the urinary albumin creatinine ratio , and its levels were higher in end stage renal disease in patients on haemodialysis than others not on haemodialysis, confirming the consideration of elevated serum visfatin as a marker of diabetic nephropathy and of degree of albuminuria. Also serum visfatin levels correlated positively with different cardiovascular risk factors in our patients represented in BMI , systolic and diastolic BP, serum triglycerides, total cholesterol and low HDL cholesterol suggesting that serum visfatin levels can be considered not only as diagnostic factor for kidney disease and its degree in diabetic patients type 2 but moreover it can be considered as a risk variable of cardiovascular abnormalities in those patients. More studies are needed to investigate for the relations of visfatin levels and different CV abnormalities in type2 diabetic patients .

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