Levels of serum vaspin and tumor necrosis factor-α in patients with type 2 diabetes mellitus in relation to kidney function and glycemic control

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Background
Diabetes mellitus type 2 (T2DM) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Vaspin (visceral adipose tissue-derived serpin) is a member of the broadly distributed serpin (a protein superfamily of serine protease inhibitors of ~500 genes) and is identical to serpin A12. The upregulation of vaspin can improve insulin resistance. Thus, identification of the protease inhibited by vaspin may lead to the development of novel strategies in the treatment of diabetes and insulin resistance. In patients with chronic kidney disease, the levels of vaspin appear to increase mostly because of reduced renal metabolism of vaspin. Tumor necrosis factor-α (TNF-α) is a cytokine involved in systemic inflammation. Its increased production has been observed in adipose tissue, and it has been implicated as a causative factor in obesity-associated insulin resistance, the pathogenesis of T2DM, and the development of diabetic nephropathy (DN) through several mechanisms. The association of T2DM patients (with and without impaired renal function) with serum vaspin and TNF-α levels is not clearly understood. This study aimed to evaluate the levels of vaspin and tumor necrosis factor (TNF) in T2DM patients and compare their levels with impairment in renal function in T2DM to determine whether circulating vaspin and TNF could be a biomarker of DN.

Patients and methods
This case–control observational prospective study was conducted on 73 patients with T2DM classified into two groups; group I included 20 T2DM patients with reduced renal function, and group II included 53 T2DM patients with normal renal function. The studied groups were recruited from the Diabetic Unit Outpatient Clinic, Department of Internal Medicine, Sohag University Hospitals, from December 2014 to December 2015. T2DM was diagnosed according to the American Diabetes Association Criteria. Totally, 12 age and sex matched apparently healthy individuals who served as the control group (group III) were enrolled in the study. The study was approved by the ethical committee of Faculty of Medicine, Sohag University, and written informed consent was obtained from each participant. All participants were subjected to thorough history taking, full clinical examination, and anthropometric measurements, including weight, height, and BMI. In addition, peripheral hemogram, random blood glucose evaluation, HbA1c determination, liver function tests, kidney function tests, lipid profile, and serum vaspin and serum TNF-α evaluation were carried out.

Results
In essence, significant correlations of vaspin and TNF were found with age of T2DM patients, hypertension, BMI, and lipid profile, but not with HbA1c. Moreover, higher levels of vaspin and TNF-α were significantly correlated with the degree of impaired renal function in T2DM patients. Notably, multivariate linear regression shows that BMI and age are negatively correlated with vaspin but not with TNF-α levels in T2DM patient with more impaired renal function.

Conclusion
Strict monitoring of T2DM can reduce the morbidity and mortality rate and will also improve the quality of life of diabetic patients. The association of renal insufficiency due to diabetes mellitus with serum vaspin and TNF-α levels is not clearly understood. However, vaspin may be beneficial as a positive biomarker for T2DM patients with impaired renal function and can be considered as a new

prognostic marker for DN. Large studies are required to establish vaspin and TNF-α efficacy and safety in T2DM.

Keywords:
diabetes mellitus, tumor necrosis factor-α, type 2 diabetic patients

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Introduction

Diabetes mellitus type 2 (T2DM) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [1]. T2DM is the leading cause of chronic kidney disease (CKD) worldwide. CKD is a public health problem worldwide. These patients are at an increased risk not only for end-stage kidney disease but also for cardiovascular disease (CVD) [2]. The high burden of CKD in T2DM and the associated adverse outcomes result in high healthcare costs to both public and private payers [3]. T2DM is associated with a high risk for CVD, which is the leading cause of death in patients with T2DM [4]. Diabetic nephropathy (DN) is the leading cause of end-stage renal failure worldwide [5]. The pathogenesis of DN is still not fully elucidated. The association between microvascular and macrovascular diseases in diabetes mellitus (DM) and the importance of early detection of microangiopathy for vascular risk assessment in DM have been determined [6]. Moreover, the association between DN, inflammation, and coronary artery disease has been defined [7]. T2DM is associated with a 10-year-shorter life expectancy. This is partly due to a number of complications with which it is associated, including two-to-four times the risk for CVD (ischemic heart disease and stroke) and a 20-fold increase in lower limb amputations and increased rates of hospitalizations [8]. It has also been associated with an increased risk for cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia [9]. In the developed world, and increasingly elsewhere, T2DM is the largest cause of nontraumatic blindness and kidney failure [10]. Other complications such as acanthosis nigricans, sexual dysfunction, and frequent infections are frequent in T2DM [11]. Risk factor modification in diabetes is crucial given that these patients are at high risk for stroke, myocardial infarction, and heart failure. On the basis of the significant impact of CKD, Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) recommend a focus on the early identification of CKD. This early identification may allow for treatment directed at CKD to slow or prevent progression and the treatment of associated complications and comorbidities such as CVD [3]. This is even more important when acknowledging the fact that no significant randomized clinical trial of glucose-lowering therapy demonstrates a significant decrease in major adverse cardiovascular events, although glucose-lowering therapy significantly decreases microvascular events such as nephropathy and retinopathy [12]. Vaspin (visceral adipose tissue-derived serine proteinase inhibitor) was identified in the visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of obesity and T2DM [13]. Vaspin is also expressed in the skin, hypothalamus, pancreatic islets, and stomach [14]. The serum vaspin levels in the patients with T2DM have been demonstrated to be higher than that reported by Brosius and colleagues [15,16] or similar to that reported by Gulcelik *et al.* [17] than those observed in individuals with normal glucose tolerance. However, plasma visfatin levels reduced in chronic hemodialysis (HD) patients [18]. The association between serum vaspin levels and renal dysfunction in T2DM is still not fully elucidated. Tumor necrosis factor α or TNF-α (which was known formerly as cachexin or cachectin) is an adipokine involved in systemic inflammation and it is a member of a group of cytokines that stimulate the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as $CD4^+$ lymphocytes, natural killer cells, neutrophils, mast cells, eosinophils, and neurons. The synthesis of human TNF-α starts with the elaboration of a prohormone, a 26 kDa membrane associated form, which either serves as a precursor for the soluble molecule or binds without processing to the TNF-α receptors through cell-to-cell contacts [19]. This cytokine is synthesized primarily by monocytes/macrophages, although diverse studies have demonstrated that intrinsic renal cells, including glomerular, mesangial, endothelial, and tubular cells, are able to produce inflammatory cytokines that play a role in controlling growth, biosynthetic activities, and functions of cells. The experimental investigations have demonstrated that renal mRNA expression for TNF-α is significantly increased by ~2.5-fold in diabetic rats compared with normal rats [20]. A variety of bioactivities suggest that this cytokine may promote the development of diabetic microvascular complications. TNF-α has been implicated in the hemodynamic misbalance between vasodilatory and vasoconstrictive mediators, which may result in alterations of glomerular blood flow and glomerular filtration rate

(GFR) [21]. It has also been reported that this cytokine is cytotoxic to glomerular, mesangial, and epithelial cells, and may induce direct renal damage. Bertani and colleagues [22–24] demonstrated that TNF-α was able to promote the local generation of reactive oxygen species with a subsequent alteration of the barrier function of the glomerular capillary wall, resulting in enhanced albumin permeability, independently of hemodynamic factors or effects of recruited inflammatory cells. In addition to the observations from experimental investigations, clinical studies have found a direct and significant association between serum TNF-α and urinary protein excretion in diabetic patients with normal renal function and microalbuminuria, as well as in individuals with overt nephropathy and renal insufficiency [25,26]. However, urinary TNF-α levels are also elevated in diabetic patients with increased urinary albumin excretion. Furthermore, there was a significant rise in urinary TNF-α excretion as DN progressed. Moreover, multivariate analysis showed a significant and independent relationship between urinary TNF-α and urinary albumin excretion. The primary role of tumor necrosis factor (TNF) is in the regulation of immune cells; TNF, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, and inflammation, inhibits tumorigenesis and viral replication, and responds to sepsis through interleukin-1) and interleukin-6 producing cells. Dysregulation of TNF production has been implicated in a variety of human diseases, including Alzheimer's disease [27], cancer [28], major depression [29], psoriasis [30], and inflammatory bowel disease [31]. Some studies reported that the levels of TNF-α and vaspin were correlated with decreased GFR and increased albuminuria. However, to date, in the literature, there have been no studies demonstrating their relationships with DN. This study aimed to evaluate the levels of vaspin and TNF in T2DM patients and compare their levels with impairment in renal function in T2DM to determine whether circulating vaspin and TNF could be a prognostic biomarker of DN.

Patients and methods

This case–control observational prospective study was conducted on 73 patients with T2DM classified into two groups. Group I included 20 T2DM patients with reduced renal function (range: 45–75 years with a mean age of 58.5±8.98 years; 16 female and four male) and group II included 53 T2DM patients with normal renal function (range: 25–70 years with a mean age of 50.79±10.52 years; 45 female and eight male). The studied groups were recruited from the diabetic unit outpatient clinic, Department of Internal Medicine, Sohag University Hospitals, from December 2014 to December 2015. T2DM was diagnosed according to the American Diabetes Association Criteria. Totally, 20 age and sex matched apparently healthy individuals (range: 33–52 years with a mean age 41.58±5.68 years; 11 female and one male) who served as a control group (group III) were enrolled in the study. The study was approved by the ethical committee of Faculty of Medicine, Sohag University, and written informed consent was obtained from each participant. All participants were subjected to thorough history taking, full clinical examination, fundus examination, and anthropometric measurements including weight, height, and BMI. In addition, blood samples were drawn in the morning after an overnight fast of 12–16 h. After centrifugation to yield platelet-poor plasma from samples on anticoagulant (3.8% sodium citrate) and serum from clotted blood samples, serum and plasma samples were stored in aliquots at −20°C until assay. Complete blood count was performed on whole blood samples on EDTA (Beckman Coulter Hmx, Brea, CA, USA). Random blood glucose evaluation, HbA1c determination, liver function tests, kidney function tests, and lipid profile tests were carried out using standard laboratory methods with Hitachi 911 autoanalyser (Roche). Creatinine clearance was estimated using Cockcroft and Gault formula. Serum vaspin was measured using ELISA with a commercially available kit (Code No. WH-940; Wkea Med Supplies, China) and serum TNF-α was evaluated using ELISA with a commercially available kit (Assay Pro LLC No. ET2010–1; Roche).

Statistical analysis

Data were analyzed using STATA intercooled version 12.1 (Roche). Quantitative data were presented as mean, SD, median, and range. Data were analyzed using Student's *t*-test to compare the mean of two groups. When the data were not normally distributed the Mann–Whitney test was used to compare two groups. Qualitative data were presented as number and percentage and compared using the Fisher's exact test. To evaluate the correlation between serum vaspin and TNF-α level with other variables such as age, BMI, systolic blood pressure (BP), diastolic BP, creatinine, creatinine clearance, etc. Pearson's correlations and multivariate regression analyses were performed. *P* value was considered significant if it was less than 0.05.

Results

Demographic and laboratory parameters in T2DM patient groups (with or without reduced renal function; groups I and II) and the control group (group III) are summarized in Table 1 and Fig. 1). There were highly significant statistical differences in

Table 1 The demographic and biochemical characteristics of studied population

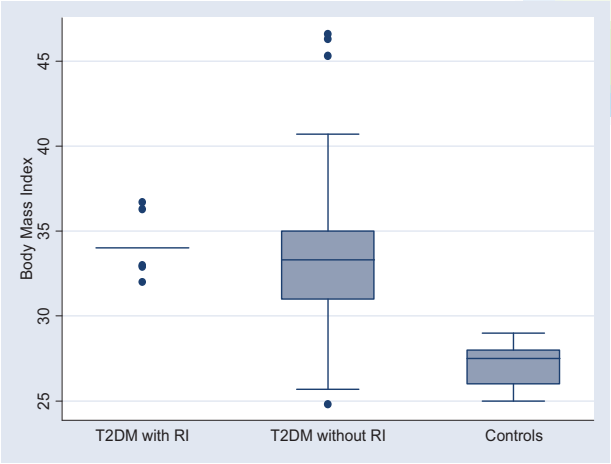
Variables	T2DM with RI (group I) (*N*=20)	T2DM without RI (group II) (*N*=53)	Controls (group III) (*N*=12)	P_1	P_2	P_3
Age						
Mean (SD)	58.55 (8.98)	50.79 (10.52)	41.58 (5.68)	0.005	<0.0001	0.005
Median (range)	59 (45–75)	51 (25–70)	42 (33–52)			
Sex [*n* (%)]						
Female	16 (80.00)	45 (84.91)	11 (91.67)	0.73	0.63	1.00
Male	4 (20.00)	8 (15.09)	1 (8.33)			
BMI						
Mean (SD)	34.05 (0.99)	33.27 (4.73)	27.25 (1.29)	0.47	<0.0001	0.0001
Median (range)	34 (32–36.7)	33.3 (24.8–46.6)	27.5 (25–29)			
SBP						
Mean (SD)	136.25 (20.58)	122.36 (14.20)	110.41 (9.64)	0.002	0.0003	0.008
Median (range)	135 (110–180)	120 (100–160)	110 (100–130)			
DBP						
Mean (SD)	83.5 (12.26)	77.83 (6.89)	72.5 (7.54)	0.02	0.009	0.02
Median (range)	90 (60–100)	80 (60–90)	70 (60–80)			
Creatinine						
Mean (SD)	4.33 (2.08)	0.92 (0.13)	0.98 (0.09)	<0.000	<0.0001	0.08
Median (range)	4.27 (1.4–7.9)	0.9 (0.6–1.2)	1 (0.82–1.1)	1		
Creatinine clearance						
Mean (SD)	38.57 (13.21)	124.62 (36.87)	126.18 (29.60)	<0.000	<0.0001	0.83
Median (range)	38.56 (12.4–72)	124.62 (73.2–269)	122.31 (98.5–187)	1		
Blood urea						
Mean (SD)	97.71 (60.29)	28.50 (8.49)	31.75 (5.18)	<0.000	0.0004	0.07
Median (range)	97.7 (25–296)	27 (16–56)	31 (25–40)	1		
Uric acid						
Mean (SD)	12.20 (4.44)	6.85 (1.49)	5.83 (2.04)	<0.000	0.0001	0.11
Median (range)	12 (4–23.1)	7 (3–9)	6 (3–9)	1		
Random blood sugar						
Mean (SD)	171.65 (69.09)	209.96 (79.70)	101.67 (15.26)	0.06	0.001	<0.0001
Median (range)	177.5 (84–364)	208 (81–353)	99 (76–130)			
HbA1c						
Mean (SD)	7.02 (1.34)	8.93 (2.01)	5.29 (0.38)	0.0003	0.0001	<0.0001
Median (range)	7 (5.1–10.2)	9 (5–13.3)	5.15 (4.9–6.2)			
Total cholesterol						
Mean (SD)	126.55 (42.63)	182.40 (51.54)	160.83 (27.54)	0.0001	0.02	0.11
Median (range)	120 (48–217)	180 (100–420)	160 (100–195)			
Triglycerides						
Mean (SD)	147.85 (79.66)	209.60 (158.23)	161.25 (24.87)	0.16	0.36	0.89
Median (range)	147 (25–345)	155 (45–925)	170 (110–190)			
HDL-C						
Mean (SD)	34.08 (12.22)	37.85 (12.12)	46.08 (5.05)	0.08	0.002	0.005
Median (range)	34 (17–66)	40 (12–68.4)	47.5 (40–55)			
LDL						
Mean (SD)	63.56 (28.69)	101.69 (54.14)	85.83 (22.39)	0.002	0.009	0.26
Median (range)	63 (6–135)	105.8 (9–348)	88.5 (38–112)			
VLDL-C						
Mean (SD)	30.3 (15.24)	41.92 (31.60)	32.25 (4.97)	0.22	0.37	0.86
Median (range)	30 (5–69)	31 (9–185)	34 (22–38)			

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein; P_1, T2DM with RI and T2DM without RI; P_2, T2DM with RI and controls; P_3, T2DM with RI and controls; RI, renal impairment; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; VLDL-C, very low-density lipoprotein-cholesterol.

the age of T2DM patients (mean: 58.5±8.98 for group I, 50.79±10.52 for group II, and 41.58±5.68 for controls; $P<0.005$) when compared with controls. However, in T2DM patients, no sex differences had been found, as well as in controls, with no significant statistical differences. As regards BMI, there were highly significant statistical differences in BMI of T2DM patients when compared with controls (mean: 43.05±0.99 for group I, 33.27±4.73 for group II, and 27.25±1.29 for controls; $P<0.0001$).

Meanwhile, BMI was nearly equal in both studied T2DM patient groups with no statistical difference. The mean serum creatinine, blood urea, creatinine clearance (CrCl), and uric acid levels in the studied patient groups (4.33±2.08 and 0.92±0.13 µmol/l for serum creatinine, 97.71±60.3 and 28.5±8.94 mmol/l for blood urea, 38.57±13.21 and 124.62±36.87 ml/min/surface area^2 for CrCl, and 12.2±4.44 and 6.85±1.49 mg/dl for serum uric acid with *P* less than 0.005 in both groups, respectively) were statistically significantly higher than that in the control group (0.98±0.09 µmol/l for serum creatinine, 31.75±5.12 mmol/l for blood urea, 126.18±29.6 ml/min/surface area^2 for CrCl, and 5.8±2.04 mg/dl for serum uric acid, respectively with $P>0.05$). The highest mean levels of blood sugar and HbA1c were found in the T2DM patients with reduced renal function (group II) with high statistically significant differences (209.96±79.7 and 8.93±2.01 mg/dl, respectively; $P<0.001$ for each). As regards lipid profile of studied groups, statistically significantly higher levels of total cholesterol (TC), triglycerides (TG), and low-density lipoproteins-cholesterol (LDL-C) in groups II and III (182.4±51.54 mg/dl and 160.83±27.54 for TC, 209.46±158.23 and 161.25±24.87 mg/dl for TG, and 101.69±54.1, and 85.83±22.39 for LDL-C, respectively) were found when compared with group I (126.55±42.63 for TC, 147.85 7±9.66 for TG, and 63.56±28.69 for LDL-C, respectively). However, the mean levels of high-density lipoproteins-cholesterol (HDL-C) were statistically significantly lower in the studied groups I and II (34.08±12.22 and 37.85±12.12 mg/dl, respectively) than in the control group (group III) (46.08±5.05 mg/dl; $P<0.005$). The significantly higher levels of vaspin and TNF-α were found in our studied T2DM patients when compared with the control group (4.30±0.77 and 3.87±0.80 for vaspin and 4.28±0.29 and 3.40±0.21 for TNF-α in T2DM patients vs 0.32±0.07 for vaspin and 2.47±0.19 TNF-α in controls, respectively; *P*? 0.001 for each) with significant statistically highest levels in group I (Table 2 and Fig. 2).

Figure 1



Comparison among the three groups as regards BMI. RI, renal impairment; T2DM, type 2 diabetes mellitus

In single variate linear regression analyses in T2DM patients and controls (Tables 3, 4and Figs 5–7), there was a positive linear regression between TNF-α and vaspin with high statistically significant differences. As regards vaspin, there was a statistically significant negative linear regression with age and BMI in studied group I T2DM patients. Notably, in studied group I, other parameters such as creatinine, creatinine clearance, uric acid, and HDL-C showed significant negative linear regression with vaspin but in narrow scale. However, there was a statistically significant negative linear regression with lipid profile in both groups T2DM patients. However, there was a positive linear regression for vaspin with hypertension, TNF-α, HbA1c and random blood glucose in both T2DM groups with high statistically significantly differences. As regards TNF-α, there was a statistically significant negative linear regression with age and BMI in studied group I T2DM patients. However, there was a statistically significant negative linear regression with urea, creatinine clearance, uric acid and lipid profile in both groups T2DM patients. Notably, there was a positive linear regression for TNF-α with hypertension, vaspin, HbA1c and random blood glucose in both T2DM groups with high statistically significantly differences. In multivariate linear regression analyses (Tables 5 and 6, Figs 3 and 4) in T2DM

Table 2 The mean levels of vaspin and tumor necrosis factor-α of studied population

Variables	T2DM with RI (group I) (*N*=20)	T2DM without RI (group II) (*N*=53)	Controls (group III) (*N*=12)	P_1	P_2	P_3
Serum vaspin (ng/ml)						
Mean (SD)	4.30 (0.77)	3.87 (0.80)	0.32 (0.07)	0.04	<0.0001	<0.0001
Median (range)	4.29 (3.09–5.68)	3.78 (2.64–7.03)	0.35 (0.2–0.41)			
TNF-α						
Mean (SD)	4.28 (0.29)	3.40 (0.21)	2.47 (0.19)	<0.0001	<0.0001	<0.0001
Median (range)	4.31 (3.7–5.02)	3.4 (3.1–4.48)	2.5 (2.1–2.8)			

P_1, T2DM with RI and T2DM without RI; P_2, T2DM with RI and controls; P_3, T2DM with RI and controls; RI, renal impairment; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α.

patients, serum vaspin was independently related to sex (β=–0.03; *P*=NS for group I, β=0.0009; *P*=NS for group II) and BMI (β=0.32; *P*=0.04 for group I, β=0.02; *P*=NS for group II). However, serum TNF-α was independently related to sex (β=0.008; *P*=NS for group I and β=0.004; *P*=NS in group II) but not to BMI (β=0.02; *P*=NS for group I and β=–0.00001; *P*=NS in group II) (Figs 5–8).

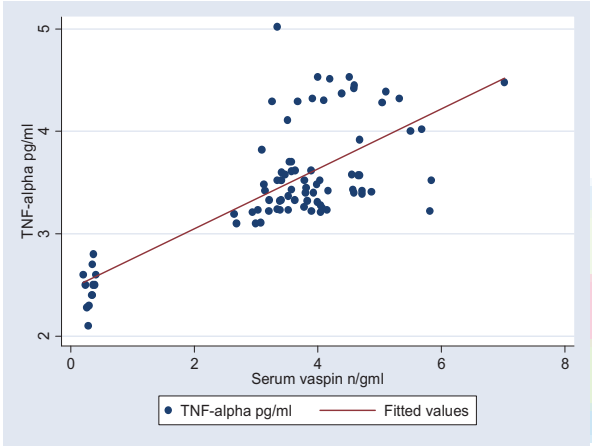
Discussion

T2DM is one of the most common chronic diseases worldwide and is associated with a high risk for CVD, which is the leading cause of death in patients with T2DM [4,32]. DN is the leading cause of end-stage renal failure worldwide [2,5]. The pathogenesis of DN is still not fully elucidated. The association between microvascular and macrovascular disease in DM and the importance of early detection of microangiopathy for vascular risk assessment in DM has been determined [6]. Moreover, the association between DN, inflammation, and coronary artery disease has been defined [7].

Adipose tissue is a highly active endocrine organ secreting a number of bioactive molecules called adipokines [15,16,33] such as vaspin and TNF-α. Vaspin (visceral adipose tissue-derived serpin) is a member of the broadly distributed serpin (a protein superfamily of serine protease inhibitors of ~500 genes) and is identical to serpin A12. Upregulation of vaspin can improve the insulin resistance. Hida and colleagues [13,34] suggested that vaspin may play a role in the pathophysiology of T2DM by its influence on insulin sensitivity and its lowering effect on glucose levels in animal models. Thus, they stated that identification of the protease inhibited by vaspin may lead to the development of novel strategies in the treatment of diabetes and insulin resistance. The mechanism of vaspin and the downstream signal pathway are not fully clear. Some studies show that vaspin increases nitric oxide bioavailability through the reduction of asymmetric dimethyllarginine in vascular endothelial cells [35] or inhibits platelet-derived growth factor-BB-induced migration of vascular smooth muscle cells [36].

TNF-α is a cytokine involved in systemic inflammation and its increased production has been observed in adipose tissue; it has been implicated as a causative

Figure 2



Correlation between vaspin and tumor necrosis factor-α (ng/ml) in all participants. TNF-α, tumor necrosis factor-α

Table 3 Single univariate linear correlations between clinical and biochemical data with serum vaspin levels

Variables	T2DM with RI (group I) (*N*=20)		T2DM without RI (group II) (*N*=53)		Controls (group III) (*N*=12)		All	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
TNF-α	0.07	0.78	0.55	<0.0001	0.35	0.27	0.73	<0.0001
Age	–0.46	0.09	0.16	0.24	–0.01	0.97	0.37	<0.0001
BMI	–0.46	0.04	0.002	0.99	0.22	0.49	0.43	<0.0001
SBP	0.008	0.97	–0.12	0.40	0.0003	0.99	0.28	0.009
DBP	0.16	0.50	–0.17	0.22	0.59	0.04	0.25	0.02
Creatinine	–0.03	0.89	–0.11	0.43	–0.16	0.62	0.24	0.03
Creatinine clearance	–0.003	0.99	–0.13	0.35	–0.16	0.62	–0.21	0.049
Blood urea	0.005	0.98	0.31	0.03	–0.16	0.62	0.22	0.04
Uric acid	–0.36	0.12	0.12	0.10	0.39	0.22	0.26	0.02
Random blood sugar	0.39	0.09	0.10	0.47	0.32	0.32	0.42	0.0001
HbA1c	0.14	0.54	0.08	0.56	0.24	0.46	0.42	0.0001
Total cholesterol	–0.27	0.25	–0.06	0.65	0.20	0.52	–0.01	0.90
Triglycerides	–0.009	0.97	–0.23	0.10	0.05	0.88	–0.04	0.69
HDL-C	–0.19	0.43	–0.38	0.005	0.49	0.11	–0.36	0.0007

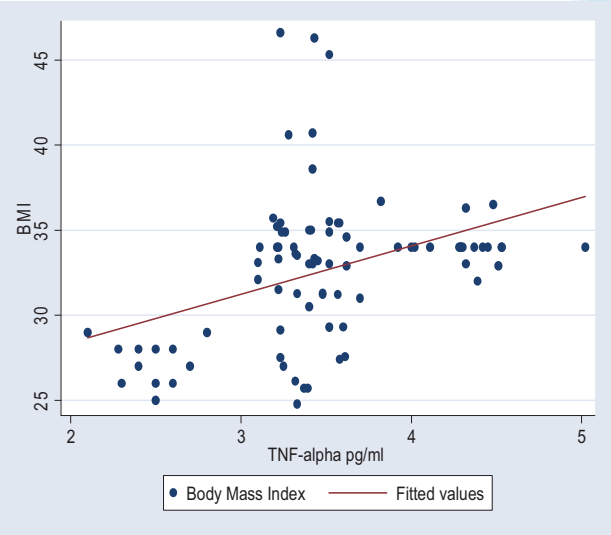
DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; P_1, T2DM with RI and T2DM without RI; P_2, T2DM with RI and controls; P_3, T2DM with RI and controls; RI, renal impairment; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α.

Table 4 The single univariate linear correlations clinical and biochemical findings with tumor necrosis factor-α

Variables	T2DM with RI (group I) (*N*=20)		T2DM without RI (group II) (*N*=53)		Controls (group III) (*N*=12)		All	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Serum vaspin	0.07	0.78	0.55	<0.0001	0.35	0.27	0.73	<0.0001
Age	−0.08	0.72	0.23	0.10	−0.04	0.89	0.48	<0.0001
BMI	−0.30	0.20	0.02	0.88	−0.09	0.79	0.39	0.0003
SBP	0.17	0.48	0.15	0.30	−0.55	0.06	0.41	0.0001
DBP	0.07	0.78	0.26	0.06	0.30	0.34	0.32	0.003
Creatinine	0.77	0.0001	0.04	0.76	0.10	0.76	0.72	<0.0001
Creatinine clearance	−0.49	0.03	−0.12	0.39	0.10	0.76	−0.61	<0.0001
Blood urea	−0.05	0.82	−0.03	0.86	0.11	0.72	0.51	<0.0001
Uric acid	−0.13	0.59	−0.03	0.83	−0.41	0.19	0.57	<0.0001
Random blood sugar	0.14	0.57	0.02	0.86	−0.12	0.71	0.19	0.08
HbA1c	0.05	0.83	0.07	0.64	−0.25	0.44	0.14	0.21
Total cholesterol	−0.11	0.65	−0.12	0.41	0.51	0.09	−0.27	0.01
Triglycerides	−0.18	0.44	−0.10	0.48	0.13	0.68	−0.10	0.37
HDL-C	−0.18	0.44	−0.21	0.14	0.26	0.42	−0.29	0.007
LDL	−0.02	0.92	−0.07	0.62	0.51	0.09	−0.18	0.09
VLDL-C	−0.19	0.42	−0.10	0.49	0.13	0.68	−0.09	0.42

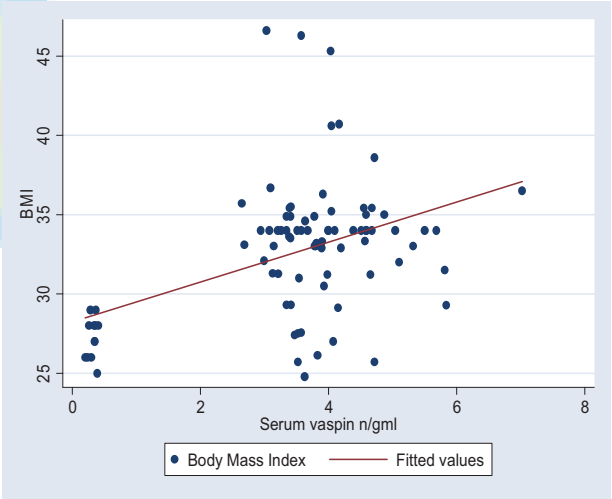
DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein; P_1, T2DM with RI and T2DM without RI; P_2, T2DM with RI and controls; P_3, T2DM with RI and controls; RI, renal impairment; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; VLDL-C, very low-density lipoprotein-cholesterol.

Figure 3



Correlation between serum tumor necrosis factor-α and BMI in all participants. TNF-α, tumor necrosis factor-α

Figure 4

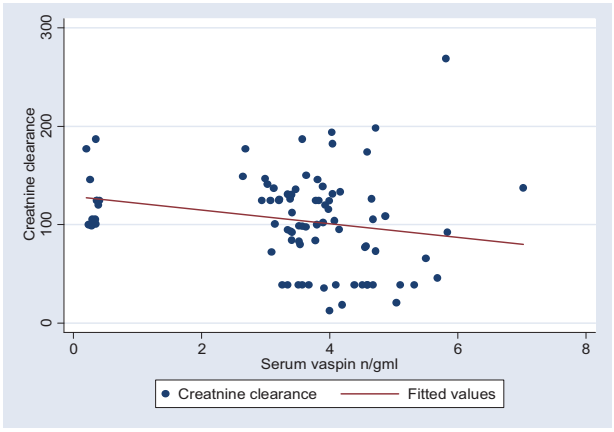


Correlation between serum vaspin and BMI in all participants

factor in obesity-associated insulin resistance and the pathogenesis of T2DM. TNF-α can contribute to the development of DN through several mechanisms, including reduction of the glomerular blood flow and GFR, vasoconstriction induced by increased endothelin-1 production, and disruption of the glomerular filtration barrier, which is mediated by the interaction with the intercellular junctions and leads to proteinuria. Navarro-González *et al.* [37]. The association of renal insufficiency due to DM with serum vaspin and TNF-α levels is not clearly understood.

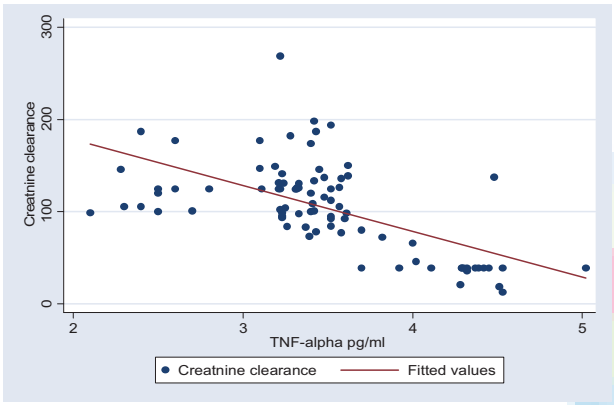
This study aimed to evaluate the levels of vaspin and TNF-α in T2DM patients and compare their levels with degree of diabetic control and reduction in renal function in T2DM to determine whether circulating vaspin and TNF-α could be prognostic biomarkers of DN and other diabetic complications. In the current study, our T2DM patients showed elevated mean serum levels of vaspin and TNF-α with more increments with progression of renal dysfunction. These findings are in accordance with [13,38–40], who reported that, in patients with CKD, the levels of adipokines (vaspin and TNF-α) appear to increase in association with declines in the GFR. This is most

Figure 5



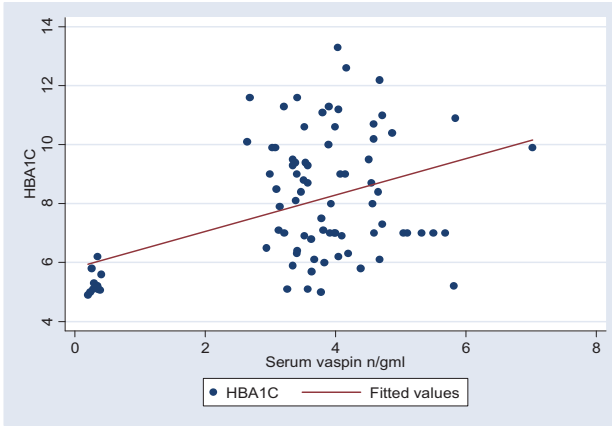
Correlation between serum vaspin and creatinine clearance in all participants

Figure 6



Correlation between serum tumor necrosis factor-α and creatinine clearance in all participants. TNF-α, tumor necrosis factor-α

Figure 7



Correlation between serum vaspin and HbA1c in all participants

likely due to reduced renal metabolism of adipokines, which may not increase vascular risks in patients with a reduced renal function. Thus, the decrease in vaspin in patients with reduced renal functions will increase the risk for coronary heart disease. Therefore, measuring the levels of adipokines in patients with renal dysfunction may be beneficial for predicting cardiovascular events and patient survival.

Notably, [41,42] stated that serum TNF-α has been elevated in diabetic patients, and even in patients with only impaired glucose tolerance, compared with healthy individuals. These findings could be attributed to the fact that vaspin serves as an insulin sensitizer with anti-inflammatory effects and might act as a compensatory mechanism with target white adipose tissue, which is activated in response to the decreased insulin sensitivity. Notably, an increased TNF-α production had been observed in adipose tissue derived from obese rodents or humans; thus, TNF-α has been implicated as a causative factor in obesity-associated insulin resistance and the pathogenesis of T2DM. Inoue *et al.* [18] stated that, as vaspin is a small protein size with the molecular mass of 50 kDa, which would be freely filtered by the kidneys, it is reasonable to presume that vaspin levels should be increased in patients with renal insufficiency.

As regards BMI, our study showed that BMI was nearly equal in both studied T2DM patient groups with no statistically significant difference but with highly significant statistical differences when compared with controls. Moreover, T2DM patients with impaired renal function who have higher BMIs (of more than 27) with higher waist-to-hip ratio that increased with increasing BMI exhibited significant highest levels of vaspin when compared with their counterparts of patients with BMIs of less than or equal to 27. These findings are in agreement with the findings of Klöting *et al.* [34], who stated that vaspin is an adipokine secreted from visceral adipose tissue, and hence it increased with increasing BMI and mainly increases with increasing waist-to-hip ratio. This in contrast to that reported by Fatema *et al.*, who reported that these changes might only occur in early diagnosed patients with DM before renal affection. Notably, our results showed a statistically significant negative correlation between BMI and TNF-α but not with glycemia. This finding is in agreement with the findings of Bertin and colleagues [43–45], who reported that serum TNF-α concentration in obese individuals with T2DM depends on the degree of their insulin resistance but does not depend on BMI. As regards sex, our study showed that there was no significant statistical differences in the mean levels of vaspin and TNF-α between male and female patients in all studied groups in contrast to other studies. Youn *et al.* [46]

Table 5 Multivariate linear regression analyses using the serum vaspin levels as dependent variables

Models	Independent variables	*B*	β	*t*-Value	*P* value	Model r^2
1	T2DM with RI					
	Age	−0.03	−0.34	−1.79	0.09	0.44
	BMI	−0.32	0.41	−2.19	0.04	
	Random bl. sugar	0.003	0.30	1.56	0.14	
2	T2DM without RI					
	Age	0.0009	0.01	0.11	0.91	0.50
	BMI	0.02	0.12	1.09	0.28	
	TNF-α	1.83	0.49	4.45	<0.0001	
	Blood urea	0.03	0.37	3.36	0.002	
	HDL-C	−0.02	−0.32	−3.00	0.045	
3	Controls					
	Age	−0.0003	−0.02	−0.08	0.94	0.36
	BMI	−0.004	−0.09	−0.27	0.79	
	DBP	0.006	0.64	1.96	0.09	
4	All participants					
	Age	0.001	0.008	0.11	0.91	0.76
	BMI	−0.007	−0.02	−0.27	0.79	
	TNF-α	2.66	1.06	9.13	<0.0001	
	SBP	0.002	0.03	0.33	0.75	
	DBP	0.007	0.04	0.49	0.62	
	Creatinine	−0.42	−0.49	−3.84	<0.0001	
	Creatinine clearance	0.005	0.16	1.51	0.14	
	Blood urea	0.004	0.12	1.35	0.18	
	Uric acid	−0.01	−0.03	−0.29	0.77	
	Random Blood sugar	0.003	0.16	1.79	0.08	
	HbA1c	0.03	0.04	0.43	0.67	
	HDL-C	−0.008	−0.06	−0.94	0.35	

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; RI, renal impairment; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α.

reported that, in normal glucose-tolerant participants, the circulating vaspin was statistically significantly higher in female participants when compared with male participants, whereas in participants with T2DM, no sex differences have been found.

As regards degree of glycemic control, the current study showed that there is no significant statistical difference in the mean serum levels of vaspin with HbA1c in all studied groups. This finding is in contrast with Refaat *et al.* [47], who stated that the serum vaspin level was higher in diabetic patients when compared with normal glycemic patients. Yan *et al.* [39] related this result to significant difference in BMI, which need other investigations. Moreover, our study showed that there is no significant statistical difference in the mean serum levels of TNF-α with HbA1c in all studied groups. This finding is in accordance with Lele *et al.* [48], who explained that serum levels of TNF-α are essentially determined by the systemic production of this adipocytokine by adipose tissue, unrelated to metabolic factors such as HbA1c. This difference in results could be attributed to the fact that Lele *et al.* [48] conducted his study on Asian Indians. He reported that Asian Indians have unique biochemical and hormone features, which may be considered as additional features to the so-called 'Asian Indian Phenotype'.

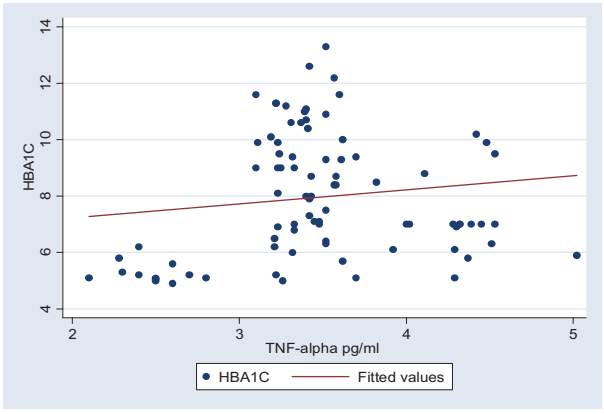
Hypertension is a complex polygenic disorder that is highly modifiable through environmental influences such as salt intake and obesity. It is exceedingly common among patients with DM. This strongly correlates with the degree of albuminuria and progression of diabetic kidney disease. In the current study, our T2DM patients experienced high BP with more prevalence in those with more reduction in renal function. This finding is in concordance with that of Laffin and George [49], who reported that there are four significant pathogenic contributors to the high coincidence of diabetes and hypertension. The development of DN is clearly a factor, as noted above. Other chief factors include volume expansion, hyperinsulinemia, and increased arterial stiffness. The contribution of volume expansion is likely due to sodium retention induced through insulin and an increase in filtered glucose load due to hyperglycemia. In contrast, the relationship between BP and albuminuria is not as closely correlated in T2DM where very high albuminuria (>300 mg/day)

Table 6 Multivariate linear regression analyses using the tumor necrosis factor-α as dependent variable

Models	Independent variables	*B*	*β*	*t*-Value	*P* value	Model r^2
1	T2DM with RI					
	Age	0.0008	0.02	0.14	0.89	0.60
	BMI	0.02	0.07	0.39	0.71	
	Creatinine	0.11	0.77	3.65	0.002	
	Creatinine clearance	−0.001	−0.06	−0.27	0.79	
2	T2DM without RI					
	Age	0.004	0.17	1.46	0.15	0.36
	BMI	−0.00001	−0.0002	−0.0001	0.99	
	Serum vaspin	0.13	0.49	4.07	<0.0001	
	DBP	−0.006	−0.19	−1.61	0.11	
3	Controls					
	Age	0.002	0.06	0.26	0.80	0.67
	BMI	0.02	0.12	0.53	0.61	
	SBP	−0.01	−0.64	−2.87	0.02	
	LDL	0.005	0.63	2.73	0.03	
4	All patients					
	Age	0.002	0.04	0.75	0.46	0.89
	BMI	0.02	0.13	2.52	0.01	
	Serum vaspin	0.21	0.53	9.51	<0.0001	
	SBP	0.0001	0.003	0.05	0.96	
	DBP	−0.00003	−0.0005	−0.01	0.99	
	Creatinine	0.15	0.45	5.59	<0.0001	
	Creatinine clearance	−0.003	−0.21	−2.94	0.004	
	Blood urea	−0.001	−0.10	−1.60	0.11	
	Uric acid	0.006	0.04	0.63	0.53	
	Random Blood sugar	−0.0004	−0.05	−1.17	0.24	
	Total Cholesterol	0.0001	0.008	0.08	0.94	
	HDL-C	−0.003	−0.06	−1.05	0.30	
	LDL	−0.001	−0.06	−0.68	0.50	

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein; RI, renal impairment; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α.

Figure 8



Correlation between serum tumor necrosis factor-α and HbA1c in all participants. TNF-α, tumor necrosis factor-α

does not necessarily serve as a prelude to the development of hypertension but ultimately is a predictor of nephropathy progression.

Our study showed that significant higher levels of vaspin and TNF-α in T2DM patients with hypertension reduced renal function. This finding is in agreement with Demirbas *et al.* [50], who reported that, in patients with hypertension, serum TNF-α concentration was increased together with an increase in concentrations of insulin. Notably, in the setting of moderate hyperglycemia [49] reported that excess glucose is reabsorbed in the proximal tubule of the kidney by a sodium–glucose cotransporter and contributes to a rise in sodium reabsorption. Elevated serum levels of insulin, due to exogenous insulin or insulin resistance in T2DM can also cause a significant hypertensive response, although it has not been noted in all studies. It may be caused by concurrent weight gain with insulin treatment. Finally, in patients with diabetes, evidence suggests that they have increased vascular stiffness that produces a reduction in arterial distensibility that likely contributes to a rise in systolic BP and, ultimately, an increased risk for death.

In our study, we found that there is a positive correlation between vaspin and HDL-C in all studied groups, mainly T2DM, without reduced

renal function. This finding is in contrast to that of Jian *et al.* [51]. Hyperlipidemia has been incriminated as a risk factor for atherosclerotic vascular disease in T2DM patients regardless of their renal function. Therefore, CKD should be regarded as a high-risk condition and that strict control of dyslipidemia would be beneficial in preventing CVD at least at early stages of CKD [52,53]. In the current study, we found significantly lowest mean levels of TG, TC HDL-C, and LDL-C in our T2DM patients (group II) with impaired renal function in contrast to their levels in T2DM patients (group I) and controls. This finding is in agreement with the findings of Ansari *et al.* [54], who stated that dyslipidemia is highly prevalent in diabetic patients on maintenance hemodialysis with predominance of atherogenic triad – that is hypertriglyceridemia, elevated very LDL, and reduced HDL. Notably, Attman and Samuelsson [55] stated that hypertriglyceridemia is one of the most common quantitative lipid abnormalities in patients with CKD, and decreased HDL concentrations with elevated very LDL are common in HD diabetic patients particularly in the presence of hypertriglyceridemia.

Moreover, Tsimihodimos and Elisaf [56] reported that TC is usually normal or reduced and may be occasionally elevated in ESRD patients in accordance with Ansari *et al.* [54], who stated that hyperlipidemia has been incriminated as a risk factor for atherosclerotic vascular disease, both in nondialyzed and dialyzed patients and is characterized by hypertriglyceridemia without cholesterol accumulation. Moreover, Kaysen and colleagues [57,58] stated that these variations depend on the degree of renal impairment, the etiology of primary disease, the presence of nephrotic syndrome, and the method of dialysis (HD or peritoneal dialysis) for patients undergoing renal replacement therapy. Abrass [59] claimed that the pathogenesis of hypertriglyceridemia in patients with CKD is related to an alteration in the composition of circulating TG (which become enriched with apolipoprotein C-III) and their diminished clearance with reductions in the activity of lipoprotein lipase and hepatic TG lipase, which are involved in TG removal and has been thought to reflect increased inhibitor activity.

Notably, Ansari *et al.* [54] reported that apart from quantitative plasma lipoprotein abnormalities [hypertriglyceridemia and hypo-HDL cholesterolemia and elevated lipoprotein(a) concentrations], CKD also displays important qualitative alterations in LDL metabolism (small dense LDL, which is considered to be highly atherogenic) and HDL particles. Other dyslipidemias consist of decreased HDL-C, elevated serum lipoprotein(a), and LDL cholesterol (which is usually not elevated) were reported. Al-Hwiesh [60] reported that lower serum concentrations of HDL-C is thought to be due to impaired maturation of these particles. Nevertheless, Ahmadi *et al.* [61] stated that a possible contributing mechanism is the downregulation of lecithin–cholesterol acyltransferase, leading to reduced etherification of cholesterol that is incorporated into HDL in TG removal. The elevated levels of intact parathyroid hormone may play an important role in the pathogenesis of dyslipidemia in HD patients, but the underlying mechanisms are not clearly defined.

In the current study, we found that there was a significant positive correlation between the age of patients and their lipid profile. This finding is in agreement with Mitwalli *et al.* [62], who stated that lipids increased with age and more dramatically at age greater than 60 years. Therefore, younger patients had less-disturbed lipid profile compared with elderly patients, and female patients had higher lipid values compared with male patients. Factors such as hormones and individual capability to degrade excess lipids may play a role. The nonassociation of dyslipidemia with serum vaspin and TNF-α levels is not clearly understood, and further large clinical studies are needed to understand this association better. Much work remains to be conducted in this high-risk patient group with a significant burden of illness pertaining to CVD. Large randomized controlled trials are necessary to establish evidence-based guidelines in the management of these patients.

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Conflicts of interest
There are no conflicts of interest.

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