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Serum Visfatin and Chemerin Levels in Iraqi Diabetics and Obese Individuals.

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ABSTRACT

Visfatin and chemerin have been identified as novel adipokines that may modulate insulin action. Also, they have been suggested to be linked to obesity-induced insulin resistance. The aim of this study is to analyze the correlations between these two adipokines and insulin resistance, anthropometric, hsCRP, lipid profile, and AIP in patients with Type 2 diabetes mellitus and in obese non diabetic patients. Our study consisted of forty-four diabetic patients, twenty-two obese individuals and twenty-two healthy individuals. Serum visfatin and chemerin were measured in these three groups and their correlations with other parameters were found. SPSS software was used to analyze the collected data by independent two-sample t-test and the Pearson correlation coefficient. Serum insulin and HOMA-IR were higher in obese group compared to T2DM and control respectively (19.25±1.09 *vs.*13.13±1.92 *vs.*7.55±1.86) and (2.56±0.16 *vs.* 1.96±0.34 *vs.* 0.97±0.25). hsCRP was higher in obese and T2DM (8.1±1.1 and 7.96±1.18) in comparison with control group (4.55±2.31). Serum visfatin levels were higher in T2DM group (63.71±8.30) compared to obese group (56.03±10.58) and control group (52.46±14.05). Moreover chemerin concentration was higher in obese group (151.77±10.43) and T2DM group (129.36±5.03) compared to control group (63.98±14.74). These two adipokines were found to be correlated to some anthropometric, biochemical parameters. Also, there wasn't any significant correlation between them. Form these results we found that visfatin is sensitive to Type two diabetes mellitus and obesity, while level of chemerin is correlated to increasing adipose tissue macrophage infiltration and expression of inflammatory mediators.

Keywords: Visfatin, Chemerin, Adipokines, hsCRP, T2DM, Obesity.

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INTRODUCTION

Type two diabetes mellitus is a chronic disease in which blood glucose levels are elevated. T2DM is also associated with several other metabolic abnormalities such as central obesity, hypertension, and dyslipidemia, which contributes to the very high rate of cardiovascular morbidity and mortality [1]. The main cause of hyperglycemia is lack in endogenous secretion of insulin or the resistance to the insulin action [2]. Excess adiposity is the most important risk in the development of insulin resistance, T2DM, mortality and cardiovascular diseases. Moreover, obese individuals have 7 times higher the risk of developing diabetes than individuals of a normal BMI [3]. The influence of obesity on type 2 diabetes risk is determined not only by the degree of obesity but also by where fat accumulates. Increased upper body fat including visceral adiposity, as reflected in increased abdominal girth or waist-to-hip ratio, is associated with the metabolic syndrome, type 2 diabetes, and cardiovascular disease, although underlying mechanisms remain uncertain [4]. Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipose tissue has a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines.

These chemical messengers, collectively known as “adipocytokines or adipokines,” include tumor necrosis factor alpha (TNF-α), adiponectin, leptin, resistin and visfatin [5]. Visfatin has recently been identified as a protein preferentially expressed in visceral adipose tissue compared with subcutaneous adipose tissue. It can be found in skeletal muscle, liver, bone marrow, and lymphocytes [6]. Visfatin (also known as NAMPT or PBEF), is a multifunctional protein that has at least three known specific functional properties: (a) it functions as an enzyme in the catalysis of the rate‑limiting step of NAD+ production from nicotinamide; (b) it is a novel insulin‑mimetic fat‑secreted factor; and; (c) it is a regulatory factor in proinflammatory and immunomodulatory processes, which have been implicated in numerous disease processes [7]. Moreover, circulating visfatin concentrations were shown to increase in parallel with hyperglycemia. Elevated plasma visfatin levels have recently been reported in a group of patients with type 2 diabetes mellitus (T2DM) on hypoglycemic treatment [8]. Visfatin has been widely studied as a potential factor linking obesity and diabetes mellitus type 2. Although results of these studies are often conflicting, there is evidence that visfatin concentration increases with progressive B-cell dysfunction in patients with longer-standing diabetes mellitus type 2 [9]. Chemerin is another adipokines that secreted by adipose tissue, it is a pro-inflammatory cytokine that recruits and activates immune cells and contributes to inflammation by promoting macrophage adhesion to vascular cell adhesion molecule-1(VCAM-1) and fibronectin [10]. Chemerin is a multifunctional peptide involved in lipid and glucose metabolism. Elevated levels of this peptide have been associated with insulin resistance and systemic inflammation [11]. The level of chemerin has been shown to increase in obese subjects and correlates with obesity markers, so its alteration may have a pathological relevance to adipose dysfunction associated disorders like dyslipidemia and insulin resistance [12].

The aim of this study is to find the correlation of visfatin and chemerin with other anthropometric and biochemical parameters in type 2 diabetes mellitus and obese individuals.

MATERIALS AND METHODS

Subjects and anthropometric measurements

This study enrolled participants who were attending to the National Diabetes Center for Treatment and Research at Al-Mustansiriya University. Eighty eight participants divided into three groups: Group 1, consist of 44 diabetic patients (17 female and 27 male) with age range (20-70) year and BMI (28.35±3.68) kg/m^2. Group 2, consist of 22 obese non diabetic patients (9 female and 13 male) with age range (20-60) year and BMI (38.71±6.24) kg/m^2. Group 3, is the control group which consist of 22 healthy people (8 female and 14 male) who had no family history of T2DM with range of age (20-60) year, BMI (24.77±3.48) kg/m^2. Obese patients were chosen according to body mass index (BMI) (> 30 kg/m2). The diagnosis of T2DM was based on the World Health Organization Criteria [13]. Body fat% was calculated according to the following equation:

$$BF\% = (1.20 \times BMI) + (0.23 \times age) - (10.8 \times sex) - 5.4 \quad [14]$$

The exclusion criteria were patients with T1DM, patients with T2DM who taking insulin as hypoglycemic therapy, acromegaly, chronic liver and kidney diseases.

This study was approved by the human research ethics committee of the hospital, and informed consent was obtained from each patient.

Blood sample collection

Venous blood samples were collected from an antecubital vein (8.00-10.00 a.m.) after10-12h overnight fasting period. The obtained 10 ml of venous blood from each patients were divided into two portion; 2 and 8 ml. The first portion was dispensed for tube containing ethylene diamine tetra acetic acid (EDTA) and used for the estimation of FPG, while the second portion was dispensed in biochemistry tubes with gel separator. Biochemistry tubes were centrifuged at 3000 x g for 10 min after an incubation period of 30 min. Fasting glucose measurement was performed in the same day. Remaining serum specimens were divided into portions (250 µl) in Eppendorff tubes kept at -20°C until visfatin, chemerin, hs-CRP and other biochemical parameters analyses were performed.

Clinical and Laboratory Tests

Fasting plasma glucose was measured by a glucose oxidase method. Serum triglycerides assay was done by enzymatic colorimetric tests with glycerol phosphate oxidase. Total serum cholesterol was assayed by enzymatic colorimetric tests with cholesterol esterase and cholesterol oxidase. HDL-cholesterol was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol was calculated by the Friedewald formula [15]. Atherogenic index of plasma was calculated using the equation:

$$AIP = \text{Log } (Tg/HDL\text{-}C) \quad [16]$$

The homeostasis model assessment of insulin resistance (HOMAIR) was calculated from fasting insulin and glucose by the following equation:

$$HOMAIR = \text{insulin (micro units per milliliter)} \times \text{glucose (mg/dl)} / 405$$

The cutoff point to define insulin resistance corresponds to HOMA-IR ≥ 3.8 [17]. Fasting serum insulin was estimated by ELISA using commercially available ELISA kit (Monobind Inc., U.S.A). High sensitivity C-reactive protein was measured by bioactive diagnostic (Germany) ELISA kit. Human serum chemerin level was measured using commercially available chemerin ELISA assays kit (Ray Biotechnology Company, U.S.A). Serum visfatin level was estimated also by using Ray Bio Visfatin Enzyme Immunoassay (EIA) Kit (U.S.A). All ELISA procedures were carried as given by the manufacturer's instructions.

Statistical Analysis

IBM SPSS software package version 22.0 was used for data statistical analysis. The variables are reported as means ± standard deviation. A Student's t-test was used for comparison of significance between two groups. More than two groups were compared by one way ANOVA using least significant difference as a post hoc test to compare individual groups. The correlation between serum visfatin, chemerin and other variables was detected using the Pearson correlation analysis, with a P value of <0.05 indicating statistically significant difference.

RESULTS

All anthropometric and biochemical characteristics of the eighty eight participants, control group (group Ⅰ) n = 22, T2DM group (group Ⅱ) n = 44, obese group (group Ⅲ) n = 22, were illustrated in Table (1). Both of BMI and BF% showed highly significant differences between the three groups at ($P < 0.01$). Waist and WHtR showed highly significant differences in the comparison of T2DM group with healthy subjects and obese patients group with healthy group, while they didn't show any significant differences between T2DM and obese groups. A high significant difference in FPG ($P < 0.01$) was observed between the studied groups (T2DM,

control and obese group). PPBG showed highly significant differences ($P < 0.01$) in the comparison of T2DM group with healthy subjects and obese patients group, while they didn't show any significant differences between obese and control groups.

Table 1: Clinical and biochemical characteristics of the study

Factor	Control (n=22)	T2DM (n=44)	Obese (n=22)	*P1*	*P2*	*P3*
Age(y)	33.41±9.55	56.68±8.24	37.59±10.15	<0.001	0.142	<0.001
Gender(M/F)	14M/8F	27M/17F	13M/9F	—	—	—
Waist(cm)	82.27±7.80	97.64±14.63	103.0±10.57	<0.001	<0.001	0.131
BMI(kg/m^2)	24.77±3.48	28.35±3.68	38.71±6.24	<0.001	<0.001	<0.001
BF%	25.05±7.56	35.23±7.84	43.16±9.02	<0.001	<0.001	<0.001
WHtR	0.48±0.03	0.58±0.09	0.62±0.06	<0.001	<0.001	0.091
FPG(mg/dl)	87.95±10.81	171.09±53.76	109.64±7.16	<0.001	<0.001	<0.001
PPBG(mg/dl)	123.95±21.66	232.75±70.71	125.45±25.52	<0.001	0.835	<0.001
Insulin(µlU/ml)	7.55±1.86	13.13±1.92	19.25±1.09	<0.001	<0.001	<0.001
HOMA-IR(%)	0.97±0.25	1.96±0.34	2.56±0.16	<0.001	<0.001	<0.001
TC(mg/dl)	168.90±36.96	181.70±43.84	128.27±33.13	0.244	0.074	0.538
TG(mg/dl)	77.18±29.26	148.59±93.32	84.31±40.40	0.001	0.506	0.003
HDL-C(mg/dl)	47.38±12.09	37.38±9.86	44±8.83	0.001	0.295	0.009
LDL-C(mg/dl)	106.06±38.14	116±39.78	128±32.29	0.336	0.046	0.225
VLDL-C(mg/dl)	15.02±6.31	29.70±18.72	16.86±7.90	0.001	0.398	0.003
AIP	0.11±0.05	0.55±0.28	0.26±0.19	<0.001	<0.001	<0.001
Visfatin(ng/ml)	52.46±14.05	63.71±8.30	56.03±10.58	<0.001	0.346	0.002
Chemerin(ng/ml)	63.98±14.74	129.36±5.03	151.77±10.43	<0.001	<0.001	<0.001
hs-CRP(mg/L)	4.55±2.31	7.96±1.18	8.1±1.1	<0.001	<0.001	0.465

Results were expressed as mean ± SD. P1, for controls and T2DM; P2,for controls and obese: P3, for T2DM and obese.T2DM =Type 2 diabetes mellitus, BMI=body mass index, BF%=body fat percent, WHtR=waist to height ratio,FPG=fasting plasma glucose, PPBG=post prandial blood glucose, HOMA-IR=homeostasis model of ssessment-insulin resistance,TC=total cholesterol, TG=triglycerides,HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL; ,very low-density lipoprotein ,AIP=atherogenic index of plasma, hsCRP, high-sensitivity C-reactive protein.

Serum insulin levels showed a highly significant increase in obese group compared to T2DM and control groups (19.25 *vs*. 13.13*vs*. 7.55 µIU/ml) respectively at ($P < 0.01$). HOMA-IR (%) also revealed a highly significant increase in obese group compared to T2DM and control groups (0.97 *vs*. 1.96 *vs*. 2.56) respectively at ($P < 0.01$). By comparing the means of serum total cholesterol of the three groups, it was found that there were no significant differences between them. The means of (TG, HDL-C and VLDL-C) showed highly significant differences (at $P < 0.01$) when comparing T2DM group with control and obese groups respectively. Serum LDL-C showed a significant difference (at $P < 0.05$) between obese group and control group only. The means of AIP showed a highly significant increase in T2DM, obese and control groups (0.55 *vs.* 0.26 *vs.* 0.11) respectively. hsCRP means showed highly significant differences in the comparison of T2DM and obese groups with control group (at $P < 0.01$) but no significant difference were observed between obese and diabetic groups.

Serum visfatin levels were significantly elevated in T2DM group (63.71ng/mL) compared with control group (52.46ng/ml). A positive correlation was observed at the comparison of T2DM with control and obese group respectively (at $P < 0.01$), while serum chemerin levels showed a highly significant increase (at $P < 0.01$) between obese, T2DM and control groups (151.77 *vs*.129.36 *vs*.63.98 ng/ml) respectively. Figures (1) & (2) showed the differences of serum visfatin and chemerin among the studied groups.

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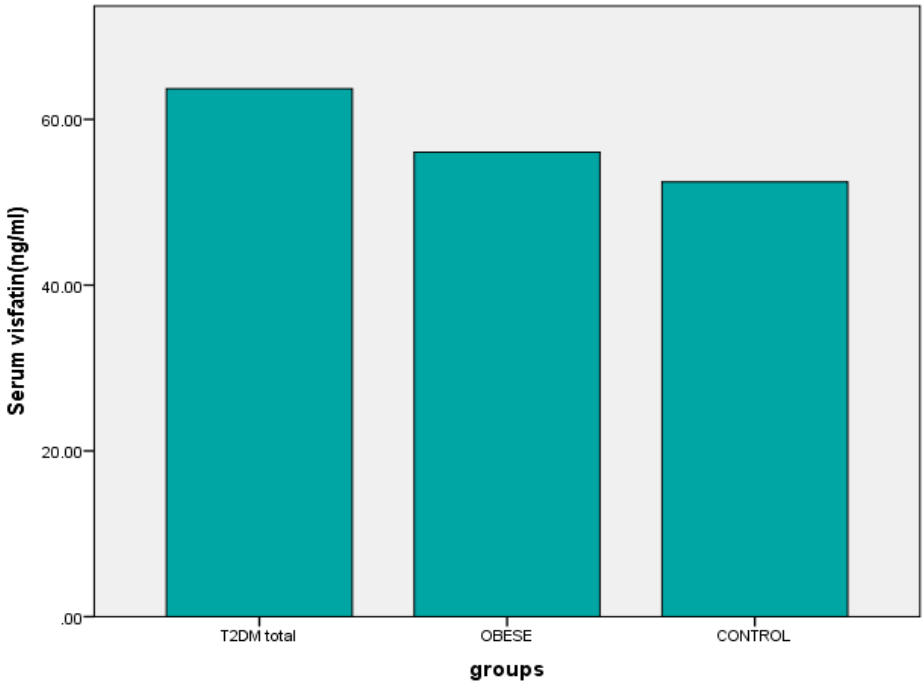

Figure 1: Serum visfatin levels among the studied groups.

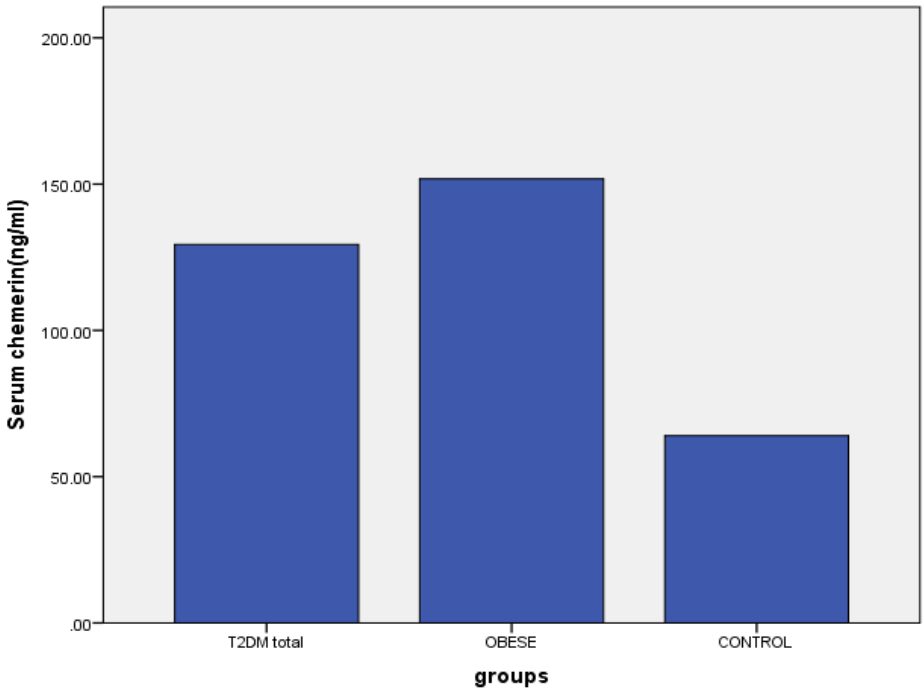

Figure 2: Serum chemerin levels among the studied groups

The correlations of serum visfatin and chemerin with other biochemical parameters in T2DM and obese groups were summarized in Table (2) and Table (3). Serum visfatin levels in diabetic patients were positively correlated with BF% (*r* = 0.310, *P* = 0.041), and negatively correlated with triglycerides (r = -0.509, P = < 0.001), VLDL (r = -0.507, P=< 0.001) and AIP (r = -0.382, P = 0.01). While in obese group; serum visfatin levels were positively correlated with BMI (r = 0.380, P = 0.011), BF% (r = 0.299, P = 0.049) and waist to height ratio WHtR (r = 0.318, P = 0.036), and negatively correlated with gender (r = -0.445, P = 0.038). Serum chemerin level in T2DM group was positively correlated with BMI (r = 0.380, P =0.011), BF% (r = 0.299, P = 0.049), WHtR (r = 0.318, P = 0.036) and hsCRP (r = 0.449, P = 0.002), while Serum chemerin levels in obese group was

positively correlated with gender (r = 0.648, P = 0.001), BF% (r = 0.458, P = 0.032), triglycerides (r = 0.672, P = 0.001), VLDL (r=0.661,P=0.001) and AIP (r = 0.587, P = 0.004).

Table 2: Correlations between serum visfatin and chemerin levels with anthropometric and laboratory data of T2DM group (n=44)

Parameter	Serum visfatin		Serum chemerin	
	R	*P*	*R*	*P*
Age(y)	0.242	0.114	0.055	0.723
Gender(M/F)	0.251	0.101	0.102	0.510
Waist(cm)	-0.172	0.256	0.211	0.180
BMI	0.143	0.353	0.380	0.011*
BF%	0.310	0.041*	0.299	0.049*
WHtR	-0.103	0.507	0.318	0.036*
FPG(mg/dl)	0.022	0.888	0.047	0.761
PPBG(mg/dl)	0.088	0.569	0.059	0.704
Insulin(µlU/ml)	0.293	0.054	0.215	0.162
HOMA-IR(%)	0.239	0.119	0.189	0.219
TC(mg/dl)	-0.157	0.307	0.147	0.342
TG(mg/dl)	-0.509	< 0.001**	0.085	0.584
HDL(mg/dl)	0.182	0.238	0.098	0.525
LDL(mg/dl)	0.020	0.895	0.094	0.544
VLDL(mg/dl)	-0.507	< 0.001**	0.086	0.578
AIP	-0.382	0.01**	0.044	0.779
Visfatin(ng/ml)	1	-	0.066	0.673
Chemerin(ng/ml)	0.066	0.673	1	-
hs-CRP(mg/L)	0.294	0.053	0.449	0.002**

r, Pearson coefficient.
*Statistically significant at $p \leqslant 0.05$.
**highly significant at $p \leqslant 0.01$.
BMI:body mass index,BF%:body fat percentage,WHtR:waist to height ratio.
FPG:fasting plasma glucose,PPBG:post prandial blood glucose,HOMA-IR:Homeostasis Model Assessment for insulin resistance,TC:totalcholesterol,TG:Triglycerides,HDL:highdensity lipoprotein ,LDL:low density lipoprotein, VLDL:very low density lipoprotein.
AIP: Atherogenic index of plasma,hs-CRP :high sensitivity C-reactive protein.

Table 3: Correlations between serum visfatin and chemerin levels with anthropometric and laboratory data of Obese group (n=22)

Parameter	Serum visfatin		Serum chemerin	
	R	*P*	*r*	*P*
Age(y)	0.038	0.868	0.080	0.725
Gender(M/F)	-0.445	0.038*	0.648	0.001**
Waist(cm)	0.211	0.180	0.160	0.478
BMI	0.380	0.011*	0.060	0.790
BF%	0.299	0.049*	0.458	0.032*
WHtR	0.318	0.036*	0.333	0.130
FPG(mg/dl)	-0.077	0.733	-0.003	0.991
PPBG(mg/dl)	0.059	0.704	0.069	0.761
Insulin(µlU/ml)	-0.238	0.287	-0.132	0.558
HOMA-IR(%)	-0.222	0.320	-0.110	0.625
TC(mg/dl)	0.147	0.342	0.388	0.075

TG(mg/dl)	0.085	0.584	0.672	0.001**
HDL(mg/dl)	0.098	0.525	0.093	0.680
LDL(mg/dl)	0.094	0.544	0.199	0.374
VLDL(mg/dl)	0.086	0.578	0.661	0.001**
AIP	0.044	0.779	0.587	0.004**
Visfatin(ng/ml)	1	-	-0.364	0.096
Chemerin(ng/ml)	-0.364	0.096	1	-
hs-CRP (mg/L)	0.233	0.297	-0.011	0.961

r, Pearson coefficient.
*Statistically significant at $p \leqslant 0.05$.
**highly significant at $p \leqslant 0.01$.
BMI:body mass index, BF%:body fat percentage,WHtR:waist to height ratio.
FPG: fasting plasma glucose ,PPBG:post prandial blood glucose,HOMA-IR:Homeostasis Model Assessment for insulin resistance,TC:totalcholesterol,TG:Triglycerides,HDL:high density lipoprotein ,LDL:low density lipoprotein, VLDL:very low density lipoprotein.
AIP: Atherogenic index of plasma,hs-CRP :high sensitivity C-reactive protein.

DISCUSSION

This study has been prepared to evaluate serum levels of visfatin and chemerin in type two diabetic patients and obese non diabetic patients, and to examine the correlation between these two adipokines. Our results revealed that plasma visfatin levels were higher in T2DM group compared to obese and healthy individuals, while serum chemerin levels were higher in obese subjects compared to T2DM and control groups. Also there wasn't any correlation between visfatin and chemerin among studied groups. Adipocytes are important endocrine cells, which secrete several hormones and cytokines that are involved in metabolic diseases such as obesity and T2DM. Adipose tissue derived cytokines such as TNF-α, IL-6, hsCRP, leptin, adiponectin, visfatin and resistin which contribute to the development of insulin resistance as well as diabetes mellitus [8]. The biological mechanisms involving visfatin in the pathogenesis of T2DM still not well understood. Visfatin defined as an adipokine that has recently been identified and named as such because of its much greater expression in visceral fat than in subcutaneous adipose tissue. In keeping with its insulin-mimetic effects, visfatin was as effective as insulin in reducing hyperglycemia in insulin-deficient diabetic mice. Visfatin was also bound to and activated insulin receptors, causing receptor phosphorylation and the activation of the downstream signaling molecules [18]. Our research findings confirm that T2DM is associated with increased circulating levels of visfatin and this compatible with the findings of Dogru, *et al.* [8], who found that visfatin levels were higher in patients with T2DM compared to controls. Moreover, the results of the current study show that visfatin is sensitive to type two diabetes mellitus and obesity. Hala *et al.* [19], found that visfatin may play an important role in the pathogenesis of T2DM. As shown in Figure (1) the levels of serum visfatin in obese group were slightly higher than control subjects. Our result is in agreement with Haider *et al.* [20], as they found a positive correlation between plasma concentration of visfatin and obesity. The role of visfatin in insulin sensitivity and obesity is controversial. Daniel *et al.* [21], found that there wasn't any correlation between visfatin and anthropometric parameters such as waist circumference and fat mass, while our results showed a positive correlation between visfatin and anthropometric parameters like body mass index, body fat percentage and waist to height ratio, Table (3). However, Mabrouk *et al.*[22], found that serum levels of visfatin in obese non-diabetic are higher than that of control subjects and this result is similar to that of our study.

Chemerin is recently described as adipokine which has dual roles in adipose tissue metabolism and regulation of immune response. Chemerin serum concentrations are elevated in obese, insulin-resistant, and inflammatory states in *vivo* and suggested to be an obvious cause of insulin resistance in obesity [23, 24]. Previous surveys examining total chemerin concentrations in humans and animals have resulted in the hypothesis that chemerin is relevant to obesity and obesity-associated comorbidities [25, 26].

The result of our study showed that serum chemerin levels in obese non diabetic patients were higher than diabetic patients and control subjects, Figure (2). These results are in agreement with that of Peter *et al.* [27], who found that serum chemerin levels in obese non diabetic patients were higher than in healthy

individuals, and positively correlated to inflammation markers like high-sensitivity C-reactive protein. Youlany *et al.* [28], also found that serum chemerin levels in obese subjects are higher than their levels in healthy subjects, for that, Chemerin is suggested to be linked to obesity-induced insulin resistance in type 2 diabetes mellitus [29].

Ali and his colleagues demonstrated that serum chemerin levels were significantly increased in patients with type 2 diabetes compared with non-diabetic individuals [10, 30]. This result is compatible to our finding, as illustrated in Table (2), which demonstrated that serum chemerin in T2DM group showed a positive correlation with anthropometric parameters like BMI, body fat percentage, and waist to height ratio which may reflect the association of visceral obesity with a higher level of chemerin secretion. Also, our result revealed a positive correlation between chemerin and hs-CRP, and this result is similar to that of Lachine *et al.* [31], while in obese group, chemerin had a positive correlation with gender, BF%, Triglycerides, VLDL and AIP (Atherogenic Index of Plasma).

CONCLUSION

All these findings propose that:

- chemerin is an important link between obesity and inflammation in Type 2 diabetes mellitus. The rising in chemerin levels that occurs in moderate and severe obesity suggested to be correlated with increasing adipose tissue macrophage infiltration and expression of inflammatory mediators such as CRP, and IL-6.
- T2DM is associated with increased circulating levels of visfatin, and as its insulin-mimetic effects visfatin was as effective as insulin in reducing hyperglycemia in insulin-deficient diabetic individuals.

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