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RESEARCH ARTICLE

Impact of Ischemic Heart Disease on Serum Visfatin, Chemerin and High Sensitivity C - reactive protein in Iraqi Patients with T2 DM

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Abstract

Objectives: Ischemic heart disease is a major cause of mortality among diabetic patients leading to about three-quarters of deaths among them. The study aimed to estimate serum visfatin, chemerin and hsCRP levels and other biochemical parameters in Iraqi diabetic patients with ischemic heart disease and compares it with newly diagnosed diabetic patients and control individuals. Methods: This study was carried out between October 2016 and March 2017 in Baghdad, Iraq, and involved 66 subject divided equally into three groups; 22 diabetic patient without IHD (P1), 22 diabetic patients with IHD (P2) and 22 non-diabetic healthy subjects (C). Serum visfatin, chemerin, hsCRP and other biochemical parameters were measured. Results: The results clarified that diabetic with IHD group had the highest levels of serum visfatin, chemerin and hsCRP in comparison with diabetic without IHD and control groups with means of (67.68±4.38 ng/ml, 59.73±9.42 ng/ml and 52.46±14 ng/ml respectively), (130.87±5.34 ng/ml, 127.85±4.30 ng/ml and 63.98±14.74 ng/ml respectively) and (8.37±1.03 mg/L, 7.54±1.19 mg/L and 4.55±2.31 mg/L respectively). These adipokines were found to be significantly correlated with some biochemical parameters. Conclusion: High levels of serum visfatin among diabetic patients indicate that there is an association between visfatin and hyperglycemia and it may be an independent risk factor for CHD. Although, both of the two inflammatory markers chemerin and hsCRP can be considered as markers of subclinical atherosclerosis and IHD, and they may be utilized for the early detection of macrovascular disease in type 2 diabetics.

Keywords: *CHD, Chemerin, Hscrp, IHD, T2DM, Visfatin.*

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia which results from defect in insulin secretion, defective insulin action or both [1]. Elevation of blood glucose level for a long time causes serious complications [2]. The diabetic patient is at increased risk of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes [3].

Macrovascular complications of diabetes are primarily diseases of the coronary arteries, peripheral arteries, and cerebrovasculature. Early macrovascular disease is associated with atherosclerotic plaque in the vasculature supplying blood to the heart, brain, limbs, and other organs. Late stages of macrovascular disease involve complete obstruction of these vessels, which can increase the risks of myocardial infarction (MI), stroke, claudication, and gangrene [4]. Ischemic heart disease is a major cause of mortality among diabetic patients leading to about three-quarters of deaths among them [5].Visfatin is a newly discovered adipocyte hormone (adipocytokin) which also known as pre-B-cell colony-enhancing factor and nicotinamide phosphoribosyl transferase.

Fat cells secret this novel adipokine and because of it's highly expression in visceral fat cells it was named as "visfatin" [6]. The expression of visfatin is regulated by cytokines that promote insulin resistance such as tumor necrosis factor-a (TNF-a),

interleukin-6 (IL-6) and lipopolysaccharide [7]. Visfatin known for his insulin-mimetic effect, as well as it has a regulation function in proinflammatory and immunomodulatory processes, which have been implicated in numerous disease processes, including atherosclerosis [8]. Several Studies about visfatin properties showed the involvement of this adipokine is in all syndromes characterized by increased resistance to insulin like; type II diabetes, gestational diabetes, and polycystic ovary syndrome [9].

Raised levels of circulating visfatin have been reported in patients not only with metabolic disease such as obesity but also with inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, inflammation-related bone disease, and symptomatic atherosclerosis, however, some studies showed that the positive correlations between visfatin and inflammation markers like hs-CRP and artery occlusion may cause myocardial infarction [9,10].Chemerin is a specific adipokine involved in both metabolic and immune dysregulation. It is highly expressed in liver and white adipose tissue [11].

This chemoattractant protein regulates the chemotaxis and activation of dendritic cells and macrophages, as well as regulates adipocyte differentiation in an autocrine/paracrine way and modulates adipocyte genes expression that involved in glucose and lipid metabolism [12]. Several studies on the association between serum chemerin levels and obesity, diabetes and coronary atherosclerosis have been conducted. High chemerin levels were found in obese subjects, in prediabetic states, overweight, and obese T2DM patients [13]. Raised levels of chemerin have been associated with insulin resistance and systemic inflammation [14].

Inflammation is significant in development of arterial hypertension, heart failure, valvular disease and atrial fibrillation, as well as, it considered to be a fundamental factor in atherosclerosis and acute coronary syndromes (ACS) development by stimulating atheroma formation, destabilization of damaged atherosclerotic plaques and formation of occlusive thrombi [15].The aim of this study is the estimation of serum visfatin, chemerin and hsCRP levels and other biochemical parameters in Iraqi diabetic patients with ischemic heart disease and compares it with newly diagnosed diabetic patients and control individuals.

Materials and Methods

Subject

This study was conducted with cooperation of the National Diabetes Center for Treatment and Research, Al-Mustansiriya University in Baghdad city, Republic of Iraq. Our study consisted of forty-four T2DM patients (17 female & 27 male) with age range of (20-70) year divided into two groups; twenty-two of them were newly diagnosed diabetic patients without ischemic heart diseases (P1) and twenty-two diabetic patients with ischemic heart diseases (P2).

The control group (C) was twenty-two healthy individuals (8 female & 14 male) with age range (20-60) year that had no family history of diabetes, hypertension, high cholesterol, or ischemic heart diseases. The diagnosis of type 2 diabetic patients was done according to World Health Organization criteria [16].Patients with type one diabetes mellitus, T2DM patients who use insulin as a treatment for the hyperglycemia, chronic liver disease, chronic kidney diseases, and acromegaly were excluded from this study. The study was permitted by the human research ethics committee of the center, and informed agreement was obtained from each patient.

Blood Pressure Records and Anthropometric Measurements

On the same day of the assessment, each patient submitted to physical examination consisting of blood pressure measurements that were used for calculating mean arterial pressure (MAP) according to the following equation [17]:

$$MAP = DBP + (SBP-DBP)/3$$

Series of anthropometric indices, including weight, height, and waist circumference were measured in light indoor clothing without shoes.

Body mass index (BMI) was determined by dividing the weight over height square.

Blood Sample Collection and Laboratory Measurements

Eight milliliter of venous blood were collected after (10-12 h) of fasting from each participant, then divided into two parts. The first part (2ml) was distributed in EDTA containing tube that used for assessment of fasting plasma glucose, while the second part (6ml) was distributed in biochemistry tube with gel separator. After 30 minutes, an incubation period, the samples were centrifuged (at 1500 × g for 15 min). A portion of the obtained serum was used for the assessment of lipid profile and uric acid. The second portion of serum was stored at -20^{o}C for subsequent assay of insulin, hs-CRP, chemerin and visfatin.

The assessment of fasting plasma glucose was achieved by a glucose oxidase method. Total serum cholesterol was assessed by enzymatic colorimetric experiments with cholesterol esterase and cholesterol oxidase, while serum triglycerides estimation was done by enzymatic colorimetric tests with glycerol phosphate oxidase. HDL-cholesterol was assessed after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol was calculated by the Friedewald formula. HOMA2 parameters were calculated from fasting insulin and glucose measurements by using HOMA2 calculator. Atherogenic index of plasma (AIP) was calculated using the equation below [18]:

AIP =Log (TG /HDL-C)

The commercially available ELISA kits those were used are; Monobind Inc. (U.S.A) kit to estimate fasting serum insulin (FSI), Bioactive diagnostic (Germany) kit for estimation of high sensitivity C-reactive protein (hs-CRP), Ray Biotechnology (U.S.A) kits to assess chemerin and visfatin levels. All ELISA procedures were carried as given by the manufacturer's instructions.

Statistical Analysis

IBM SPSS software package version 22.0 was used for the purpose of analyzing the data statistically. The variables were reported as means ± standard deviation. One way ANOVA and post hoc Tukey test were used for comparing the groups. Pearson's correlation analysis was used to detect the correlations between serum visfatin, chemerin and other variables, with a *P* value of <0.05 indicating statistically significant difference.

Results

This study consisted of sixty-six participants divided equally into three groups; T2DM without IHD group (P1), T2DM with IHD group (P2) and control group (C). Anthropometric and biochemical characteristics of diabetics and control subjects are illustrated in Table (1). Age showed significant differences (*P*<0.001) between control and both patients groups (P1&P2). BMI showed highly significant differences in the comparison between P2 and C groups, as well as between P1 and P2 groups at (*P*<0.001). FPG & PPBG levels were significantly elevated in both diabetic groups in comparison with control group (*P*<0.001). Furthermore, highly significant differences were observed between FSI levels and HOMA-IR index in both diabetic groups (P1&P2) in comparison with control group, as well as between P1 and P2 groups (*P*<0.001). A significant decrease at (*P*<0.001) in HOMA-S index in P1 and P2 groups was found when compared to C group. No significant differences were observed in serum TC and LDL-C levels of both diabetic groups compared to control group.

Both of serum TG and VLDL-C showed highly significant differences in the comparison of P1 with C groups at (*P*<0.001). However, serum HDL-C levels in P1 & P2 groups showed a significant decrease in comparison with C group. Levels of SBP & AIP showed highly significant differences in the comparison of P1 & P2 with control group at (*P*<0.001). A significant elevation in DBP and MAP levels of P1 group was observed when compared to control group. Serum uric acid showed no significant differences between the three groups. Serum levels of visfatin in P2 group showed highly significant differences in comparison with P1 and C groups, Figure (1).

As shown in Figures (2 & 3) a high significant elevation in both of serum chemerin and hs-CRP was observed in P1 & P2 when compared to control group C. Table (2) clarified that visfatin in diabetic patients without IHD (P1) has a highly significant negative correlation with TG and VLDL-C (*P*<0.01), and a significant negative correlation with AIP (*P*<0.05).

In contrast, chemerin showed a significant positive correlation with TG, VLDL-C and AIP (P<0.05), whereas hs-CRP showed a significant positive correlation with TC at (P<0.05). Serum visfatin in diabetic patients with IHD (P2) showed no significant correlation with any parameter among these patients, while serum chemerin showed a significant positive correlation with both SBP and hs-CRP at (P<0.05). Moreover, hs-CRP showed a highly significant positive correlation with SBP, DBP and MAP at (P<0.01) and a significant positive correlation with chemerin at (P<0.05), as illustrated in Table (3).

Discussion

The incidence of diabetes is accompanying with an increases risk for the development of CAD by 2 to 4 folds [4]. Ischemic heart disease is a major cause of mortality among diabetic patients leading to about three-quarters of deaths among them [5]. Macrovascular diseases in diabetic are related to both of vascular and metabolic abnormalities.

The vascular abnormalities include endothelial dysfunction, vascular smooth muscles and platelets dysfunction, while the metabolic abnormalities characterizing diabetes includes hyperglycemia and insulin resistance [19]. In the present study, levels of serum visfatin, chemerin and hs-CRP and their correlations with type two diabetes mellitus and ischemic heart diseases were examined. Our data showed that serum levels of visfatin were significantly elevated in diabetic patients with and without IHD in comparison with healthy individuals.

These results are in agreement with the findings of Esteghamati *et al.,* Kara *et al.*, and Rabo *et al.* who found that serum visfatin levels in diabetic patients were higher than in healthy individuals [20, 21, and 22]. Several authors reported that the elevated levels of visfatin in type 2 diabetic and its correlations with many metabolic markers might play a role in the pathogenesis of T2DM [23].

AL-ghasham *et al.* partially disagree with our results; they measured serum visfatin levels in type 2 diabetic with and without macroangiopathy. They found that visfatin concentrations in T2DM patients without macroangiopathy were higher than those with macroangiopathy, as well as, they concluded that visfatin concentrations increased regardless of body mass index (BMI) [24]. Both of Wang *et al.* and Gürsoy *et al.* found significant increase levels of visfatin in patients with coronary heart diseases in comparison to healthy individuals. Moreover, visfatin might be related to lipid metabolism as well as may be associated with inflammation and atherosclerotic cardiovascular diseases, and hence it may be an independent risk factor for CHD [25, 26]. Many researchers studied the properties of visfatin and showed the involvement of this adipokine in all syndromes characterized by increased resistance to insulin such as type II diabetes, gestational diabetes, metabolic syndrome and CHD.

Liu *et al.* studied the correlation of visfatin with IR in patients with coronary heart disease. They found that CHD patients with IR had higher levels of serum visfatin compared to those with CHD but without IR and healthy subjects, also a positive correlation between serum visfatin with both of IR and CHD was found [27], however, the mechanism of inducing high levels of plasma visfatin by hyperglycemia is not clear. Serum levels of chemerin increased significantly among diabetic patients with and without IHD compared to healthy subjects, as elucidated in Figure (2).

These data are in agreement with those of Lachine *et al.*, they determined chemerin levels among 160 subjects equally divided into four groups; T2DM with CAD, T2DM without CAD, CAD without diabetes and healthy control group. Higher levels of chemerin were observed in CAD & T2DM with CAD groups as compared with T2DM without CAD and control groups [28].

El-Mesallamy *et al.* assessed the levels of this adipokine in diabetic patients with and without ischemic heart diseases. They found an elevation in serum chemerin levels in diabetic patients with & without IHD compared to healthy subjects [29].

Coimbra *et al.* found that circulating chemerin concentrations are elevated in diabetic patients [13], as well as other investigators reported an increase in chemerin levels in diabetic patients with hypertension [30]. Previous studies revealed

that serum level of chemerin is higher in individuals with metabolic syndrome compared to healthy individuals [31, 32, and 33]. Elevation in serum chemerin levels among MetS patients with CAD compared with those without CAD lead to the suggestion that chemerin may be an independent predictive marker of the presence of CAD in patients with MetS. Moreover, some chemerin targeted therapy may decrease the incidence of CAD and mortality in MetS patients [34]. Our result showed that higher levels of serum hs-CRP were reported among diabetic patients with IHD, as well as those without IHD in comparison with healthy individuals, Figure (3).

In a study by Berezin *et al.*, 54 diabetic subjects and 35 healthy controls were included. An elevation in hs-CRP level in diabetic patients was observed in comparison with control subjects [35]. hs-CRP is an inflammatory marker that is closely associated with abdominal obesity, metabolic syndrome, and atherosclerotic cardiovascular disease [36]. It was identified as a risk factor for both CAD morbidity and secondary mortality [37]. A positive association between serum hsCRP and mortality among Chinese CAD patients was found by Ding *et al.*

This indicates that the acute-phase inflammatory process may play a harmful role in the prognosis of CAD patients [38]. As hs-CRP is considered to be a sensitive marker of inflammation, a raised hs-CRP level in type 2 diabetic patients may suggest that inflammation could be involved in the pathogenesis of diabetes and early atherosclerotic processes [39]. According to Table (2), visfatin showed a significant negative correlation with TG, VLDL-C and AIP in P1 group. Mu *et a*l. (2011) and Wang *et al.* (2014) found a strong correlation between visfatin levels and serum TG [40, 25]. Gligor *et al.* also found a negative correlation of visfatin with triglycerides, in diabetic patients [41]. The above mentioned results suggested that visfatin could be involved in lipid metabolism, and these correlations with metabolic factors may lead to the possibility of CHD occurrence. Serum chemerin showed positive correlations with TG, VLDL, AIP, hs-CRP and SBP in diabetic groups, as illustrated in Figures (2 & 3). Chemerin was found to be associated with many components of the MetS, including BMI, triglycerides, high-density lipoprotein cholesterol, and hypertension, and also with systemic markers of inflammation, such as high sensitivity C-reactive protein (hs-CRP), interleukin-6 [42].

The increasing of serum chemerin level in diabetic patients and its correlation with various metabolic risk factors, atherogenic index of plasma and atherosclerotic cardiovascular disease leads to that chemerin may have a pathological relevance to adipose dysfunction and associated disorders like dyslipidemia and insulin resistance, T2DM and CVD. The highest hsCRP levels were detected in T2DM patients with uncontrolled hypertension and high BP variability [43]. These data are in concordance with our data in Table (2 & 3), that clarified the positive correlation of hs-CRP with total cholesterol, blood pressure parameters and chemerin. Lachine *et al.* also found a positive correlation between hs-CRP and chemerin [28].

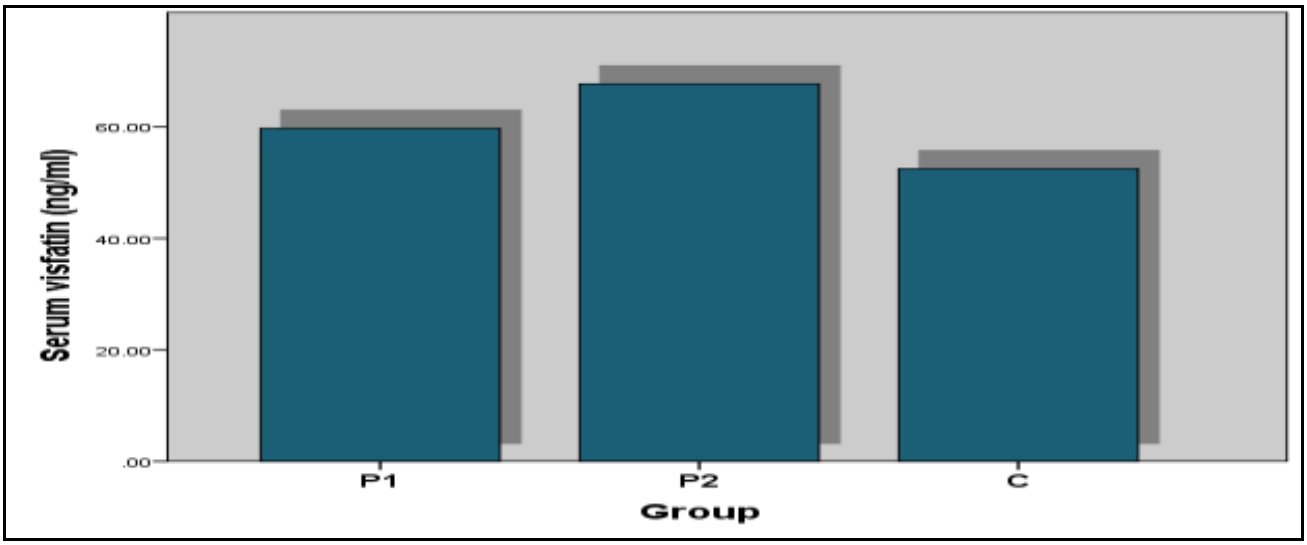

Fig. 1: Levels of serum visfatin

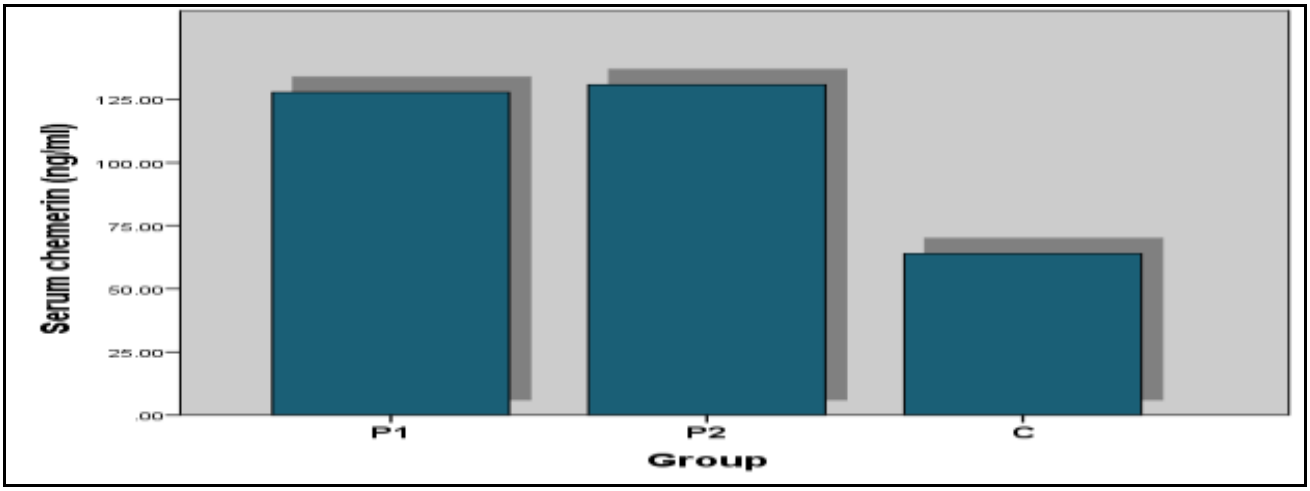

Fig. 2: Levels of serum chemerin

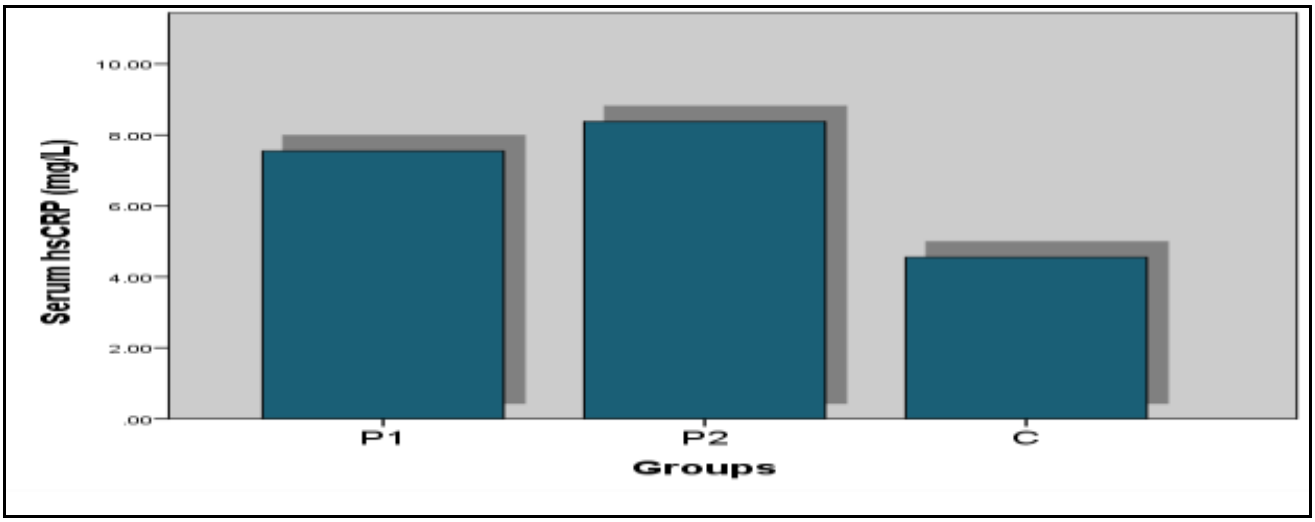

Fig. 3: Levels of serum hsCRP

Table 1: Anthropometric and biochemical characteristics of diabetic and control subjects

Parameter	Control N=22	T2DM N=22	T2DM with IHD N=22	*P*-value
Age(year)	33.41±9.55	54.09±9.36**a	59.27±6.11**b	<0.001
Gender(F/M)	8/14	9/13	8/14	_
BMI(kg/m²)	24.77±3.48	26.91±2.02** c	30.15±4.27 **b, c	<0.001
FPG(mg/dl)	87.95±10	168.54±56**a	173.72 ± 51**b	<0.001
PPBG(mg/dl)	123.95±21	228.04±72**a	237.45 ± 70**b	<0.001
FSI(µlU/ml)	7.55±1.8	11.88±1.9**a, c	14.38±0.7**b, c	<0.001
HOMA-IR%	0.97±0.25	1.77±0.33**a, c	2.15±0.22**b, c	<0.001
HOMA-S%	113.24±46.7	58.26±10.5**a	46.92±4.9**b	<0.001
TC(mg/dl)	168.90±36.96	194.09±44.05	169.31±40.90	0.071
TG(mg/dl)	77.18±29.26	168.36±107**a	128.81±74.50	<0.001
HDL-C(mg/dl)	47.38±12.09	36.18±8.33**a	38.59±10.93*b	0.002
LDL-C(mg/dl)	106.06±38.14	127.09±45.82	104.90±29.72	0.107
VLDL-C(mg/dl)	15.02±6.3	33.63±21.4**a	25.77±15.0	0.001
SBP(mmHg)	118.9±16	143.86±23**a	139.81±23**b	0.001
DBP(mmHg)	74.5±10.7	84.77±13.04*a	78.40±14.25	0.033
MAP(mmHg)	89.3±11	104.46±15**a	98.87±16	0.005
AIP	0.11±0.05	0.60±0.31**a	0.50±0.25**b	<0.001
U. Acid(mg/dl)	5.3±2.61	4.89±1	4.81±1.07	0.611
Visfatin(ng/ml)	52.46±14.05	59.73±9.42	67.68±4.38**b, *c	<0.001
Chemerin(ng/ml)	63.98±14.74	127.85±4.30**a	130.87±5.34**b	<0.001
hsCRP(mg/L)	4.55±2.31	7.54±1.19**a	8.37±1.03**b	<0.001

Results were expressed as mean ± SD, anova test was used for the purpose of comparison between the three groups. *P< 0.05 is significant, **P<0.01 is highly significant. a; refer to the significant differences between control and T2DM. b; refer to the significant differences between controls and T2DM&IHD c; refer to the significant differences between for T2DM and T2DM&IHD. T2DM =Type 2 diabetes mellitus, T2DM with IHD=Type 2 diabetes mellitus with ischemic heart diseases, BMI=body mass index, FPG=fasting plasma glucose, PPBG= Postprandial blood glucose, FSI=Fasting serum insulin, HOMA-IR= homeostasis model of assessment-insulin resistance, HOMA-S%= homeostasis model of assessment-insulin sensitivity, TC=total cholesterol, TG= triglycerides, HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL; ,very low-density lipoprotein, SBP= systolic blood pressure, DBP=diastolic blood pressure, MAP= mean arterial pressure ,AIP= atherogenic index of plasma, U.A= uric acid, hsCRP=high-sensitivity C-reactive protein

Table 2: Correlations of visfatin serum and chemerin levels with laboratory data of T2DM without IHD group (n=22)

Parameter	Visfatin	Chemerin	hs-CRP
	r	***r***	***r***
Age(y)	0.160	-0.285	-0.365
Gender(M/F)	0.367	-0.165	0.280
BMI	-0.200	0.040	0.300
FPG(mg/dl)	0.133	0.094	0.292
PPBG(mg/dl)	0.138	0.157	0.336
FSI (µlU/ml)	-0.086	0.034	-0.011
HOMA-IR (%)	-0.021	0.060	0.137
HOMA-S (%)	0.093	-0.052	-0.151
TC(mg/dl)	-0.019	0.264	0.478*
TG(mg/dl)	-0.591**	0.432*	0.166
HDL(mg/dl)	0.231	-0.245	-0.085
LDL(mg/dl)	0.243	0.113	0.415
VLDL(mg/dl)	-0.590**	0.429*	0.160
SBP(mmHg)	0.114	-0.265	0.046
DBP(mmHg)	0.197	-0.261	0.158
MAP(mmHg)	0.167	-0.278	0.111
AIP	-0.435*	0.476*	0.207
U. Acid(mg/dl)	-0.365	0.177	-0.162
hsCRP(mg/L)	0.186	0.337	1
Chemerin(ng/ml)	-0.135	1	0.337
Visfatin(ng/ml)	1	-0.135	0.186

R, Pearson coefficient.*Statistically significant at p ⩽ 0.05, **highly significant at *P*⩽ 0.01 BMI=body mass index, FPG=fasting plasma glucose, PPBG= Postprandial blood glucose, FSI=Fasting serum insulin, HOMA-IR= homeostasis model of assessment-insulin resistance, HOMA-S%= homeostasis model of assessment-insulin sensitivity, TC=total cholesterol, TG= triglycerides, HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL; very low-density lipoprotein, SBP= systolic blood pressure, DBP=diastolic blood pressure, MAP= mean arterial pressure, AIP= atherogenic index of plasma, U.A= uric acid, hs-CRP=high-sensitivity C-reactive protein

Table 3: Correlations of visfatin serum and chemerin levels with laboratory data of T2DM with IHD group (n=22)

Parameter	**Visfatin**	**Chemerin**	**hs-CRP**
	r	***r***	***r***
Age(y)	-0.067	0.243	-0.349
Gender(M/F)	0.253	0.360	0.293
BMI	-0.038	0.393	0.328
FPG(mg/dl)	-0.320	-0.019	0.220
PPBG(mg/dl)	-0.087	-0.055	0.400
FSI (µlU/ml)	0.224	0.002	0.230
HOMA-IR (%)	-0.143	-0.021	0.280
HOMA-S (%)	0.133	0.012	-0.265
TC(mg/dl)	-0.034	0.253	0.360
TG(mg/dl)	-0.143	-0.137	0.161
HDL(mg/dl)	0.036	0.253	0.229
LDL(mg/dl)	0.010	0.323	0.326
VLDL(mg/dl)	-0.143	-0.130	0.166
SBP(mmHg)	-0.072	0.529*****	0.662**
DBP(mmHg)	-0.120	0.269	0.596**
MAP(mmHg)	-0.103	0.404	0.654**
AIP	-0.148	-0.258	-0.068
U. Acid(mg/dl)	-0.103	0.313	0.137
hsCRP(mg/L)	0.079	0.440*****	1
Chemerin(ng/ml)	-0.064	1	0.440*
Visfatin(ng/ml)	1	-0.064	0.079

R, Pearson coefficient.*Statistically significant at p ⩽ 0.05, **highly significant at *P*⩽ 0.01 BMI=body mass index, FPG=fasting plasma glucose, PPBG= Postprandial blood glucose, FSI=Fasting serum insulin, HOMA-IR= homeostasis model of assessment-insulin resistance, HOMA-S%= homeostasis model of assessment-insulin sensitivity, TC=total cholesterol, TG= triglycerides, HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL; very low-density lipoprotein, SBP= systolic blood pressure, DBP=diastolic blood pressure, MAP= mean arterial pressure, AIP= atherogenic index of plasma, U.A= uric acid, hs-CRP=high-sensitivity C-reactive protein

Conclusion

In conclusion, high levels of serum visfatin among diabetic patients indicate that there is an association between visfatin and hyperglycemia and it may be an independent risk factor for CHD. As well as, both of the two inflammatory markers (chemerin & hsCRP) can be considered as markers of subclinical atherosclerosis and IHD and they may be utilized for the early detection of macro vascular disease in type 2 diabetic.

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