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A Study of Interleukin-18 (IL18) and High Sensitive C-Reactive Protein (CRP) in Type 2 Diabetes (T2D) with or without Obesity

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ABSTRACT

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Both diabetes and obesity are associated with chronic low-grade inflammation. IL-18 is a cytokine that stimulates various cell types and has pleiotropic functions. It is elevated in obesity, metabolic syndrome and type 2 diabetes (T2D).The hypothesis that serum level of IL-18 and high sensitive C-reactive protein can be used as markers for presence of chronic low-grade inflammation in type 2 diabetes more than in obesity per se was tested.

The study recruited 80 subjects. They comprised 20 diabetic obese cases (DM-OB group), 20 diabetic non-obese cases (DM-NOB group), : 20 non-diabetic obese cases (NDM-OB group) and 20 non-diabetic non-obese subjects (NDM-NOB group). All participants were submitted to careful history taking, through clinical investigations and laboratory assessment.

It was found that hs-CRP was significantly high in DMOB group (3.4±0.5 mg/dl) followed by NDM-OB group (2.9±0.4 mg/dl) then DM-NOB group (2.3±0.3 mg/dl) and least in NDM-NOB (0.8±0.3 mg/dl). It was also found that serum IL-18 was significantly highest in DMOB group (397.8±33.9 pg/mL) followed by NDM-OB (368.8±26.7 pg/mL) group followed by DM-NOB group (335.9±18.4 pg/mL) and least in NDM-NOB group (281.1±22.9 pg/mL). Serum IL-18 levels are directly correlated with BMI, waist circumference, hip circumference and waist/hip ratio in all the studied groups and with HbA1c in the diabetic groups.

It could be concluded that Serum IL-18 and hs-CRP are related to diabetes and obesity. They are associated with dyslipidemia, poor glycemic control, insulin resistance and impaired liver and renal functions

Keywords: Diabetes mellitus, obesity, interleukin-18, high-sensitivity C-reactive protein

Introduction

Body weight homeostasis is regulated by central and peripheral mechanisms, in which cytokines appear to have an important role. The circulating levels of the cytokines interleukin 1 (IL-1) and interleukin 18 (IL-18), and other inflammatory mediators such as prostaglandin E2 (PG-E2), and C-reactive protein (CRP) are elevated in obese individuals [1].Many factors are known to contribute to the development of diabetes and its complications. These include genetics, diet, sedentary lifestyle, prenatal factors, age, and obesity[2].

Nevertheless, an inflammatory basis for diabetes and its complications has been gaining interest. However, the distinct etiology of the two types of diabetes suggests that different causal mechanisms are involved [3]. There is increasing evidence supporting a role for inflammation in type 1 and type 2 diabetes. The mechanism for such process

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includes the release of inflammatory cells, cytokines, and profibrotic growth factors including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18) [4]. Interleukin-18 (IL-18), a recently described member of the IL-1 cytokine super family is considered as a proinflammatory cytokine secreted from mononuclear cells [5]. It has been shown that adipocytes are also a source of IL-18 [6]. Some studies suggest another effect of IL-18 on glomerulus in addition to its proinflammatory effect [7] and that serum levels of IL-18 might be a predictor of progression of diabetic nephropathy as well as cardiovascular diseases [5]. IL-18 might also be a predictor of insulin resistance[8].The current study aims to test the hypothesis that the serum level of IL-18 and high sensitive C-reactive protein, as markers for presence of chronic low-grade inflammation, are related to type 2 diabetes and insulin resistance more than being related to obesity per se through comparing their levels in diabetic obese patients with diabetic non obese patients.

SUBJECTS AND METHODS

The present study is a cross-sectional case control study. It was conducted at Internal Medicine Department at El-Zahraa University Hospital. The study protocol was approved by the local ethical committee and all subjects gave informed consent to participate in the study. The study recruited 80 subjects. They comprised 20 diabetic obese cases (DM-OB group), 20 diabetic non-obese cases (DM-NOB group), : 20 non-diabetic obese cases (NDM-OB group) and 20 non-diabetic non-obese subjects (NDM-NOB group). Inclusion criteria were age from 18-70 years old, obese and non-obese individuals and diabetic and non-diabetic patients. The diagnosis of type 2 diabetes was made in accordance to the criteria of the World Health Organization with fasting plasma glucose ≥ 126 mg/dl and 2-hour postprandial glucose ≥ 200 mg/dl. Exclusion criteria comprised age>70 years, chronic inflammatory diseases as systemic lupus erythematosus, rheumatoid arthritis, serious infections, chronic granulomatous diseases as sarcoidosis and tuberculosis, cancers and metastatic diseases. All participants were submitted to careful history taking, through clinical investigations and laboratory assessment including CBC, fasting and postprandial blood sugar, HbA1c, fasting insulin, HOMA-IR, lipid profile, liver enzymes, renal functions in addition to hs-CRP and IL-18.

Data obtained from the present study were computed using SPSS versions 22 (IBM, USA). Continuous data were expressed in the form of mean ± SD while categorical data were expressed in the form of count and percent. Comparison of continuous data were performed utilizing student t test or one-way ANOVA, while categorical data were done using Chi-square test. P value less than 0.05 was considered statistically significant

RESULTS

The present study shows that obese groups had significantly higher BMI, waist circumference, hip circumference and waist-hip ratio. Comparison between DM-OB group and DM-NOB group regarding HbA1c revealed significantly higher HbA1c in the former group. Also, diabetic patients whether obese or not had significantly higher fasting serum insulin and HOMA-IR levels when compared with non-diabetic patients. Cholesterol and LDL were significantly highest in the DM-OB group, followed by NDM-OB group, followed by DM-NOB group and least in the NDM-NOB group. Triglycerides were significantly highest in DM-OB group, followed by DM-NOB group, followed by NDM-OB group and least in NDM-NOB group. HDL was significantly lowest in the DM-OB group, followed by NDM-OB group, followed by DM-NOB group and highest in NDM-NOB group. AST and ALT were significantly elevated in obese patients irrespective of their diabetic status. Diabetic groups had significantly higher BUN and serum creatinine levels in comparison to non-diabetic groups.

In this study, hs-CRP was significantly highest in the DMOB group (3.4±0.5 mg/dl) followed by NDM-OB group (2.9±0.4 mg/dl) followed by DM-NOB group (2.3±0.3 mg/dl) and least in NDM-NOB (0.8±0.3 mg/dl). It was also found that serum IL-18 was significantly highest in DMOB group (397.8±33.9 pg/mL) followed by NDM-OB (368.8±26.7 pg/mL) group followed by DM-NOB group (335.9±18.4 pg/mL) and least in NDM-NOB group (281.1±22.9 pg/mL) (Table-1).

The correlational analysis in the present study revealed that serum IL-18 levels are directly correlated with BMI, waist circumference, hip circumference and waist/hip ratio in all the studied groups. In addition, a significant direct association was observed between serum IL-18 levels and HbA1c in the diabetic groups. Furthermore, a significant direct correlation was found between serum IL-18 levels and total cholesterol and

triglycerides levels in all the studied group. Moreover, our study detected a significant correlation between IL-18 and serum creatinine in the diabetic patients groups. Also, the present study found significant correlation between IL-18 and hs-CRP in all the studied groups (Table-2).

Regarding the correlations between hs-CRP and the various clinical and laboratory data in the studied groups, the current study documented significant direct correlation between hs-CRP and BMI, waist circumference, hip circumference and waist/hip ratio. In addition, the study found a significant positive correlation between hs-CRP and HbA1c. Moreover, a significant direct correlation was found between hs-CRP and total cholesterol, triglycerides, LDL and inverse correlation between hs-CRP and HDL. Also, a significant direct correlation between hs-CRP and serum creatinine levels in diabetic patients was detected (Table-3). BMI: body mass index, FBG: fasting blood glucose, PPBG: post-prandial blood glucose, HOMA-IR: Homeostatic model assessment, LDL: low density lipoprotein, HDL: high density lipoprotein, ALT: alanine amino transferase, AST: aspartate amino transferase, BUN: blood urea nitrogen, HsCRP: high sensitivity c-reactive protein

Table (1): Comparison between the studied groups regarding clinical and laboratory data

	DM&Ob N=20	**DM&Nob N=20**	**NDM&Ob N=20**	**NDM&Nob N=20**	**P value**
Age (years)	49.0±3.1	49.9±2.8	50.0±2.8	50.2±3.3	0.603
Duration of DM	4.8±2.0	5.1±1.6	-	-	0.604
Sex					
Male	8 (40.0%)	8 (40.0%)	11 (55.0%)	13 (65.0%)	0.604
Female	12 (60.0%)	12 (60.0%)	9 (45.0%)	7 (35.0%)	
BMI (Kg/m^2)	33.8±1.0	26.2±0.9	33.9±1.0	26.4±0.6	<0.001*
Waist circumference (cm)	103.6±2.9	95.0±3.4	103.8±3.3	96.1±2.5	<0.001*
Hip circumference (cm)	140.1±16.2	79.9±10.1	139.8±18.6	83.9±9.8	<0.001*
Waist- Hip ratio	1.35±0.12	0.84±0.08	1.34±0.13	0.87±0.08	<0.001*
FBG (mg/dL)	146.0±15.3	136.9±7.1	109.8±3.8	104.1±7.2	<0.001*
PPBG (mg/dL)	192.0±16.9	181.0±15.3	128.5±4.5	124.8±4.3	<0.001*
HbA1c %	7.3±0.6	6.7±0.4	-	-	<0.001*
Fasting insulin (mIU/L)	23.6±6.1	19.4±5.8	8.2±1.7	6.5±1.9	<0.001*
HOMA-IR	8.7±3.0	6.7±2.4	2.2±0.5	1.7±0.6	<0.001*
Cholesterol (mg/dL)	217.7±31.4	168.4±10.9	199.5±16.0	141.6±9.6	<0.001*
Triglycerides (mg/dL)	152.5±21.3	131.3±14.6	114.4±12.4	68.2±11.3	<0.001*
LDL (mg/dL)	132.8±18.4	96.9±12.9	119.2±14.4	78.1±10.0	<0.001*
HDL (mg/dL)	25.9±4.1	34.2±3.4	29.4±3.5	41.1±5.3	<0.001*
ALT (IU/L)	37.1±2.1	20.5±3.1	35.4±2.2	21.4±2.0	<0.001*
AST (IU/L)	33.0±2.0	19.8±2.6	32.4±2.5	18.5±2.0	<0.001*
BUN (mg/dL)	14.7±1.4	14.4±1.0	11.4±1.3	11.2±1.1	<0.001*
Creatinine (mg/dL)	1.19±0.20	1.13±0.09	0.87±0.12	0.84±0.13	<0.001*
HsCRP (mg/dL)	3.4±0.5	2.3±0.3	2.9±0.4	0.8±0.3	<0.001*
IL-18 (pg/mL)	397.8±33.9	335.9±18.4	368.8±26.7	281.1±22.9	<0.001*

Table(2): Correlations between serum IL-18 and clinical and laboratory data in the studied groups

		DM &Ob	DM &NOb	NDM &Ob	NDM &NOb
		IL-18	IL-18	IL-18	IL-18
Age	**r**	0.359	-0.184	0.152	0.055
	p	0.120	0.436	0.524	0.819
Duration of DM	**r**	0.069	0.004	--	--
	p	0.772	0.988	--	--
BMI	**r**	0.548	0.743	0.953	0.565
	p	**0.012***	**<0.001***	**<0.001***	**<0.001***
Waist	**r**	0.599	0.644	0.967	0.630
	p	**0.005***	**<0.001***	**<0.001***	**0.003***
Hip	**r**	0.545	0.730	0.981	0.682
	p	**0.013***	**<0.001***	**<0.001***	**<0.001***
Waist- Hip ratio	**r**	0.519	0.744	0.982	0.689
	p	**0.019***	**<0.001***	**<0.001***	**<0.001***
FBG	**r**	0.398	-0.076	0.342	0.105
	p	0.082	0.751	0.140	0.660
PPBG	**r**	0.109	-0.221	0.356	0.078
	p	0.648	0.348	0.124	0.743
HbA1c	**r**	0.644	0.728	--	--
	p	**0.002***	**<0.001***	--	--
Fasting insulin	**r**	0.123	-0.054	0.364	0.087
	p	0.605	0.820	0.114	0.715
HOMA-IR	**r**	0.241	-0.051	0.368	0.094
	p	0.306	0.829	0.110	0.693
Cholesterol	**r**	0.828	0.925	0.921	0.801
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Triglycerides	**r**	0.817	0.908	0.940	0.859
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***
LDL	**r**	0.766	0.952	0.947	0.897
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***
HDL	**r**	-0.593	-0.944	-0.800	-0.809
	p	**0.006***	**<0.001***	**<0.001***	**<0.001***
ALT	**r**	0.564	0.576	0.931	0.574
	p	**0.010***	**0.008***	**<0.001***	**0.008***
AST	**r**	0.547	0.641	0.920	0.504
	p	**0.013***	**0.002***	**<0.001***	**0.023***
BUN	**r**	0.328	0.035	0.052	0.033
	p	0.157	0.884	0.826	0.891
Creatinine	**r**	0.690	0.833	0.046	-0.054
	p	**<0.001***	**<0.001***	0.848	0.821
Hs-CRP	**r**	0.964	0.952	0.962	0.971
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***

Table (3): Correlations between serum hs-CRP and clinical and laboratory data in the studied groups

		DM&Ob Hs-CRP	DM&NOb Hs-CRP	NDM&Ob Hs-CRP	NDM&NOb Hs-CRP
Age	**r**	0.359	-0.128	0.092	0.077
	p	0.120	0.591	0.700	0.747
Duration of DM	**r**	0.124	0.034	--	--
	p	0.602	0.886	--	--
BMI	**r**	0.552	0.830	0.950	0.595
	p	**0.012***	**<0.001***	**<0.001***	**0.006***
Waist	**r**	0.600	0.761	0.970	0.644
	p	**0.005***	**<0.001***	**<0.001***	**0.002***
Hip	**r**	0.555	0.834	0.981	0.679
	p	**0.011***	**<0.001***	**<0.001***	**<0.001***
Waist- Hip ratio	**r**	0.529	0.842	0.976	0.679
	p	**0.016***	**<0.001***	**<0.001***	**<0.001***
FBG	**r**	0.387	-0.064	0.343	0.216
	p	0.091	0.789	0.138	0.360
PPBG	**r**	0.106	-0.175	0.353	0.179
	p	0.657	0.462	0.126	0.449
Fasting insulin	**r**	0.114	-0.032	0.355	0.186
	p	0.631	0.894	0.125	0.433
HOMA-IR	**r**	0.231	-0.032	0.359	0.193
	p	0.327	0.893	0.120	0.415
HbA1c	**r**	0.628	0.759	--	--
	p	**0.003***	**<0.001***	--	--
Cholesterol	**r**	0.811	0.987	0.973	0.840
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Triglycerides	**r**	0.777	0.979	0.953	0.898
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***
LDL	**r**	0.669	0.987	0.926	0.886
	p	**<0.001***	**<0.001***	**<0.001***	**<0.001***
HDL	**r**	-0.515	-0.981	-0.775	-0.845
	p	**0.020***	**<0.001***	**<0.001***	**<0.001***
ALT	**r**	0.607	0.699	0.959	0.591
	p	**0.005***	**<0.001***	**<0.001***	**0.006***
AST	**r**	0.559	0.775	0.920	0.515
	p	**0.010***	**<0.001***	**<0.001***	**0.020***
BUN	**r**	0.294	0.146	0.086	0.043
	p	0.209	0.539	0.719	0.857
Creatinine	**r**	0.689	0.778	0.078	-0.051
	p	**<0.001***	**<0.001***	0.743	0.830

* Significant results

DISCUSSION

Diabetes (DM) as well as obesity, due to their increasing incidence, were recognized as epidemic by the World Health Organization [9].Due to the strong association of obesity and diabetes, the term “diabesity” was coined, suggesting a causal pathophysiological link between both phenomena. In fact, nutritional excess is a major forerunner of type 2 diabetes. It enhances the secretion of insulin, but attenuates insulin's metabolic actions in the liver, skeletal muscle and adipose tissue [10,11].

Both conditions are associated with chronic low-grade inflammation, which has been indicated as a potential mediator of endothelial dysfunction and cardiovascular disease. Visceral adiposity is thought to be the starting condition of the inflammatory state through the release of inflammatory cytokines, including TNF-alpha, CRP, and IL-6, which in turn promote endothelial dysfunction, endothelial expression of chemokines (IL-1) and adhesion molecules (ICAM-1, VCAM-1, and P-selectin), and the inhibition of anti-atherogenic factors (adiponectin) [12].

IL-18 is a cytokine that stimulates various cell types and has pleiotropic functions. IL-18 is a member of the IL-1 family of cytokines [13]. It is regarded as a proinflammatory cytokine that facilitates type 1 responses [14].It is elevated in obesity, metabolic syndrome and type 2 diabetes (T2D) as a part of the chronic low-grade inflammatory process in these states [15].

The present study sought to test the hypothesis that serum level of IL-18 and high sensitive C-reactive protein can be used as markers for presence of chronic low-grade inflammation in type 2 diabetes more than in obesity per se through comparing their levels in diabetic obese patients with diabetic non-obese patients.

In the current study, diabetic patients whether obese or not had significantly higher fasting serum insulin and HOMA-IR levels when compared with non-diabetic patients. Insulin resistance (IR) is defined as a series of clinical manifestations for diminished effectiveness of insulin in lowering blood sugar levels caused by decreased sensitivity to insulin of liver, muscle and adipose tissue. IR is the major contributor to the etiology and pathogenesis of type 2 diabetes mellitus (T2DM) [16].

Regarding the reported lipid profile in the studied groups, it was found that cholesterol and LDL were significantly highest in DM-OB group, followed by NDM-OB group, followed by DM-NOB group and least in NDM-NOB group. Triglycerides were significantly highest in DM-OB group, followed by DM-NOB group than NDM-OB group and least in NDM-NOB group. HDL was significantly lowest in DM-OB group, followed by NDM-OB group, followed by DM-NOB group and highest in NDM-NOB group. These results are in full agreement with the study of Johari et al [17] which has similar design to our study and found corresponding results.

Moreover, our results are in line with those reported by Edo and Adediran[18] who showed that diabetic patients, regardless their BMI had significantly higher serum triglycerides levels when compared with non-diabetics. In the study of Giannini et al [19] obese patients irrespective of their diabetic status had significantly higher total cholesterol, triglycerides and LDL levels and significantly lower HDL levels in contrast to non-obese complements. Likewise, Amole et al [20] concluded that obese patients had significantly higher prevalence of dyslipidemia when compared with non-obese patients.

Furthermore, Yadav et al [21], who compared obese diabetic and obese non-diabetic patients regarding their lipid parameters, found that the former group experienced statistically significant increase in the levels of serum total cholesterol, serum triglycerides, serum LDL-cholesterol while serum HDL-cholesterol levels did not show statistically significant difference in the two groups. This latter finding in particular opposes the results of our study and may be explained by the different clinical and laboratory characteristics of the studied populations.

Considering liver enzymes, the current study found that AST and ALT were significantly elevated in obese patients irrespective of their diabetic status. These data are in accordance with the report of Al-Sultan [22] who assessed the relationship of hepatic enzymes and serum albumin to obesity and insulin resistance in adults.

The study found significantly higher AST and ALT in obese patients as compared to non-obese controls.

Concerning renal functions, our study showed that diabetic groups had a significantly higher BUN and serum creatinine levels in comparison to non-diabetic groups. These conclusions are in agreement with the study of Barakat et al [23]. In their work, they compared various laboratory markers in three groups of patients including non-obese non-diabetic group, obese non-diabetic group and obese diabetic group. The study found that both creatinine and urea levels were significantly higher in the diabetic group when compared with the other two groups.

In this study, hs-CRP was significantly highest in the DMOB group followed by NDM-OB group than DM-NOB group and least in NDM-NOB. These results are supported by the previous study of Barakat et al [23]who found that obese diabetic patients had significantly higher hs-CRP levels than non-obese non-diabetic and obese non-diabetic patients. Also, the study of Zang et al [24], who investigated serum hs-CRP concentrations of type 2 diabetes mellitus and controls, found that diabetic patients had significantly higher hs-CRP levels when compared with healthy controls.

It was also shown that serum IL-18 was significantly highest in DMOB group followed by NDM-OB group followed by DM-NOB group and least in NDM-NOB.

Our results are in agreement with the study of Mabrouk et al [8] in which the relationship between serum IL-18 concentrations and insulin resistance in lean, obese diabetic and obese non-diabetic was assessed. The reported levels of serum IL-18 levels were 3181 ± 970, 2896 ± 985 and 170.6 ±139.4 pg/ml (p=0.01) in obese diabetic, obese non diabetic and lean groups respectively.

This is consistent with the results reported in the study of Zaharieva et al [15] who evaluated the interleukin-18 level in T2D subjects in comparison to healthy controls and found that serum concentration of IL-18 was higher in patients with T2D (389.04 ± 203.44 pg/mL) than that in control subjects (219.88 ± 91.03 pg/mL), $P < 0.05$.

Conclusions of the present study are supported by the work of Ahmad et al [25]. In their research, they determined the adipose tissue expression of IL-18R and IL-18 mRNA/protein in lean, overweight, and obese individuals with and without T2D, 15 each, using qRT-PCR, immunohistochemistry, and confocal microscopy. Results revealed upregulated gene/protein expression of IL-18R and IL-18 in non-diabetic obese/overweight as compared with lean individuals. Also, in T2D individuals, gene and protein expression of IL-18R/IL-18 was significantly higher in obese as compared with overweight/lean individuals.

The study of Zilverschoon et al [26] provided an explanation to the elevated IL-18 levels in obese and diabetic patients. They noted that patients with obesity or type 2 diabetes mellitus are characterized by lower responses after stimulation with IL-18. This IL-18 resistance explains the association of obesity and diabetes with high IL-18 circulating concentrations, similar to hyper in sulinemia and hyper leptinemia. IL-18 resistance may represent an important mechanism of the increased susceptibility of these patients to a number of infections.

Correlational analysis in our study revealed that serum IL-18 levels are directly correlated with BMI, waist circumference, hip circumference and waist/hip ratio in all the studied groups. Similar findings were reported in the study of Sun et al [27] who noted signification direct correlation between serum IL-18 levels and BMI and waist circumferences in normal weight and overweight/obese subjects. In contrast, there were no significant correlation between IL-18 levels and BMI in the study of Thorand et al [28].

In addition, a significant direct association was found between serum IL-18 levels and HbA1c in the diabetic groups in accordance with the study of Dezayee et al [29] who studied the association between the levels of cytokines notably IL-4, IL-12, IL-18 and, the atherogenicity and glycemic control in 75 patients with type 2 diabetes mellitus. They showed significant association between serum IL-18 and both BMI and HbA1c. Likewise, the study of Ahmad et al [30] on role of osteopontin and IL-18 in obese individuals found that serum IL-18 is significantly correlated with BMI and HbA1c.

Furthermore, a significant direct correlation was noticed between serum IL-18 levels and total cholesterol and triglycerides levels in all the studied group. In harmony with these

data, the study of Al-Rubeaan et al [31] who found significant correlation between IL-18 and total cholesterol and triglycerides levels in diabetic patients.

In contradiction to our conclusions, the study of Jung et al [32] showed that no significant correlation was found between IL-18 levels and total cholesterol and triglycerides levels. Also, the previously mentioned study of Zaharieva et al [15] failed to document a significant correlation between serum IL-18 levels and lipid profile components in diabetic and normal subjects. The only exception for this was the inverse correlation between HDL and IL-18 in diabetic patients.

Moreover, our study detected a significant correlation between IL-18 and serum creatinine in the diabetic patients groups in agreement with the study of Al-Rubeaan et al [31] who found significant correlation between IL-18 and deteriorated renal function as assessed by albumin/creatinine ratio.

Also, the present study found significant correlation between IL-18 and hs-CRP in all the studied groups, but the study of Zaharieva et al [15] found a significant correlation between IL-18 and hs-CRP only in diabetic patients.

Regarding the correlations between hs-CRP and the various clinical and laboratory data in the studied groups, the current study documented significant direct correlation between hs-CRP and BMI, waist circumference, hip circumference and waist/hip ratio. This is in agreement with the study of Huffman et al [33] who studied the relationship between high-sensitivity C-reactive protein (hs-CRP) and adiposity by diabetes status and gender. In their study, WC and BMI were associated with hs-CRP ($P < 0.001$).

In addition, the present study found a significant positive correlation between hs-CRP and HbA1c. Likewise, in the study of Sarinnapakorn and Wanicagool[34], the investigators assessed the relationship between hs-CRP and HbA1c levels in diabetic patients. The authors found that hs-CRP levels correlated with HbA1c levels. Mean HbA1c levels were significantly higher in patients who had hs-CRP levels of 1 mg/L or more (p-value < 0.001).

Besides, the present study found significant direct correlation between hs-CRP and total cholesterol, triglycerides, LDL and inverse correlation between hs-CRP and HDL. These findings are in accordance with conclusions of Ebrahimi et al [35] who studied hs-CRP levels, as a marker of inflammation, in a large sample of population without a history of cardiovascular or inflammatory disease and cancer, and to relate this to fasting blood glucose (FBG) and the presence of diabetes mellitus. The study, similar to the present investigation included four groups: group I (n = 4,953): normal weight without diabetes, group II (n = 2,116): obese without diabetes, group III (n = 448): diabetes nonobese and group IV (n = 245): obese with diabetes. In univariate correlation analysis, total cholesterol, triglycerides and LDL but not HDL levels correlated with hs-CRP. Also, in partial agreement with our data, the study of Elizondo-Montemayor et al [36] who found significant association between hs-CRP and only serum triglycerides and HDL levels in diabetic patients.

In the present research, a significant direct correlation between hs-CRP and serum creatinine levels in diabetic patients could be detected. This concurs with Zelniker et al [37] recent work which hypothesized that cardiac and inflammatory biomarkers may assist in identification of patients with type 2 diabetes mellitus (T2DM) at high risk of worsening renal function. Their results revealed that hs-CRP were each associated with worsening of renal function in patients with T2DM.

Finally, the present study found a high reliability for hs-CRP in diagnosis of diabetic patients. This finding is supported by the study of Tutuncu et al [38] who concluded that hs-CRP has good discriminative power in detection of newly diagnosed diabetes. Use of IL-18 in distinguishing DM is a novel finding by the present study. However, it is supported by the previous data linking IL-18 to the various clinical and laboratory characteristics of DM.

In conclusions, serum IL-18 and hs-CRP are related to diabetes and obesity. They are associated with dyslipidemia, poor glycemic control, insulin resistance and impaired liver and renal functions.

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