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Evaluation of hs-CRP in Type 2 Diabetes Mellitus and its Relationship with Glycemic Control and Disease Complications

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ABSTRACT

Background: *Type 2 diabetes mellitus is the predominant kind of condition characterized by impaired insulin production. It is linked to a disturbance in the metabolism of lipids, proteins, and carbohydrates.* ***Aim of the study:*** *The present study try to explore the role of inflammation process in type 2 diabetes mellitus (T2DM) through assessment the level of High Sensitivity-CRP (hs-CRP).* ***Subject and Methods:*** *The study is a case-control study conclude 78 randomly selected patients with mean age 60.44 ± 11.18 years old and they had a documented medical records of T2DM, they invited to participation in the study when they attended to The Specialist Centre for diseases of Endocrine and Diabetes in Babylon for medical checkup. The healthy control group consists of 57 randomly selected non diabetic volunteers, with mean age 57.37 ± 9.16 years old, all of them had normal fasting blood glucose and normal HbA1c. Both diabetic and healthy control groups were matched in regard to age and sex and other demographic characters while there is difference between them in regard family history for diabetes as well as in RBS & HbA1c. Serum levels of hs-CRP were measured by ELISA technique.* ***Results****: The results showed that the mean serum concentrations of hs-CRP were significantly higher in diabetic patients than control, 0.93 ± 0.27 ng/ml in patients versus 0.36 ± 0.18 ng/ml in controls, respectively) with p< 0.001, the mean level of hs-CRP inpatients with poor glycemic control had approximately double the mean level of than those with good glycemic control,, P=0.02.* ***Conclusion****: the high levels of hs-CRP among diabetes strength the inflammatory hypothesis that predispose to T2DM.*

Keywords: hs-CRP, T2DM, Complications, Glycemic Control.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that is characterized by hyperglycemia owing to abnormalities in insulin production, insulin action, or a combination of both (1). The World Health Organization (2011) reports that approximately 90% of individuals develop type 2 diabetes, primarily due to an excess of body fat. The onset of diabetes is determined by the interaction of a number of different risk factors. The main risk factors for prediabetes and DM include genetics, sedentary lifestyle, lack of physical activity, smoking, alcohol consumption, dyslipidemia, reduced sensitivity of β-cells (insulin resistance), hyperinsulinemia, and increased glucagon activity (2). Researchers have shown that both pro- and anti-inflammatory cytokines impact insulin signaling pathways, leading to insulin resistance, so the trend of type 2 diabetes pathogenesis has shifted from metabolic dysfunction to inflammation (3). Additionally, Oxidative stress, dyslipidemia(that is usually trigger

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due to obesity), and hyperglycemic circumstances which often seen in diabetes patients may create an inflammatory environment and enhance the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), these cytokines cause persistent inflammation (even low grade) that lead macro angiopathy and micro angiopathy which contributed to different diabetic related complications like cardiovascular disease , neuropathy, retinopathy and nephropathy, by the above mentioned mechanisms a vicious cycle between inflammation and insulin resistance lead to disease developments (4).

C-reactive protein (CRP) is mostly synthesized in the liver via the stimulation of inflammatory cytokines; also, local production of CRP by lymphocytes, smooth muscle cells, and monocytes within atherosclerotic lesions has been documented in a limited number of instances (5). CRP can be measured by the routine method or by high-sensitivity CRP (hs-CRP), which is regarded as a sensitive method, and one can detect the level of CRP even in very low concentration, which is an indicator of subclinical low-grade inflammation (6). A higher level of hs-CRP in a diabetic patient may suggest a combination of chronic and acute inflammation. C-reactive protein is the primary marker for acute inflammation, and its level decreases rapidly when the inflammation subsides. Detecting hs-CRP in the blood of diabetic individuals may provide insight into the long-term presence of inflammation (7). Hyperglycemia in individuals with diabetes results in elevated levels of inflammatory mediators, such as CRP. This is due to the fact that hyperglycemia is a condition that triggers inflammation, leading to alterations in both macro- and micro-vascular systems (8).

Furthermore, hyperglycemia promotes the production of advanced glycation end products (AGEs). AGEs may exacerbate oxidative stress and inflammation, and they bind to their receptors in different tissues throughout the body, including blood vessels, resulting in harm and difficulties (9). In their study, Stanimirovic et al. (10) conducted a comprehensive review of various studies that examined the association between elevated levels of CRP and the development of diabetes and its complications in both animal and human models. They concluded that understanding the link between CRP and diabetes has clinical significance, as it could lead to the development of new preventive and diagnostic strategies in addition to the commonly used FBS and HbA1c tests. Furthermore, CRP levels could serve as a useful indicator for monitoring the effectiveness of diabetes management. Unlike Stanimirovic's review, Thorand et al. (11) and others have a different perspective, where the research aims to evaluate the link between highly sensitive C-reactive protein (hs-CRP), glycemic control, and disease complications in Iraqi diabetic patients. This study will not consider any correlation that may arise due to confounding variables such as obesity.

PATIENTS AND MATERIALS

135 participants were included in the case control research. The patient group consisted of 78 patients with T2DM who attended the Specialist Centre for Diseases of Endocrine and Diabetes in Babylon for a medical checkup. The patients ranged in age from 35 to 90 years. The sample included 37 females and 41 males. The control group consists of 57 randomly selected non-diabetic volunteers, with a mean age of 57.37 ± 9.16 years old. They match the patient group in regard to age, sex residence, and BMI. All controls were examined for fasting blood sugar and HbA1c to exclude diabetes.

Patients with complications were divided into either macrovascular (cardiovascular) or microvascular complications, including neuropathy, retinopathy, and nephropathy. The diagnosis of each complication depended on a

physical examination by a specialist physician, relevant investigations, and medical reports. Patients with HbA1c ≥ regarded as poor glycemic control, while those with HbA1c < regarded as good glycemic control. Patients with a BMI ≥ 30 are classified as obese, and those <30 are classified as non-obese, according to the WHO classification.

Tests were carried out on a volume of 4 ml of venous blood that was collected from diabetes patients as well as controls. 2 ml of blood were collected in a gel tube and left to clot at room temperature. The tube was then spun at a speed of 3000 revolutions per minute for 5 minutes. Half of the resulting serum was immediately used for the biochemical test known as fasting blood sugar. After collecting the remaining serum in an Eppendorf tube, we kept it at -20 °C for the ELISA assays to evaluate the levels of hs-CRP. The other 2 ml were collected in tubes with anticoagulant (EDTA tubes) to measure HbA1c.

Approval of the Ethical Committee

Prior to commencing the research endeavor, the ethics committee of the Faculty of Medicine at the University of Kufa granted its approval. All participants in the study supplied their informed permission, and the Institutional Review Board of the Endocrine and Diabetes in Babylon authorized the study.

STATISTICAL ANALYSIS

The information from both research groups was analyzed using the Statistical Package for the Social Sciences (SPSS) software, specifically version 26, produced by Inc. in Chicago, USA. The independent t-test was used to compare the means, while the ANOVA test was used to examine the differences among the three groups under study. The frequencies and means of categorical variables were compared using a chi-square test and bar graphs. A significance level of $P \leq 0.001$ and $P \leq 0.05$ was used to determine whether there was a meaningful difference.

RESULTS

The Mean level of hs-CRP was 0.93±0.27 in patients in comparison to 0.36±0.18 in control with a significant difference at ($P < 0.001$), as show in table (1) and figure (1).

Table (2) shows that the mean level of hs-CRP was not significantly associated with age of patients ($P< 0.05$), also females had higher hs-CRP level than male 0.98 ± 0.28 vs. 0.85 ± 0.26 but without statistical difference ($P= 0.16$), while hs-CRP level was higher in patients with positive family history in compared to patients with negative family history with significant difference, (0.98 ± 0.22 vs 0.73 ± 0.19) respectively, ($P = 0.01$), also smokers had higher hs-CRP level than non-smokers(0.97 ± 0.24 vs. 0.89 ± 0.25) and patients with disease duration more than10 years had higher level of hs-CRP than those with duration less than 10 years,also non obese patients shows higher levels of hs-CRP than obese patients (1.00 ± 0.20 vs. 0.96 ± 0.23) , however all the above results were statistically not significant $p>0.05$.

Table (1): hs-CRP level in patients with T2DM and healthy control.

	Cases –control comparison		
	Patients ***n*** **= 78**	**Healthy control** ***n*** **= 58**	***P***
hs-CRP levels			
Mean± SD	**0.93 ± 0.27**	**0.36 ± 0.18**	**< 0.001 † HS**
Range	0.11 – 2.60	0.01-1.69	

n: number of cases; SD: standard deviation; †: independent samples t-test; HS: Highly significant at P ≤ 0.001.

Table (2): Mean levels of hs-CRP level according to some characteristics

Characteristics		N	Mean ± SE	*P*
Age groups	< 50 years	10	0.95 ± 0.25	0.83 A NS
	50-59 years	22	0.94 ± 0.21	
	≥ 60 years	46	0.89 ± 0.26	
Sex	Male	41	0.85 ± 0.26	0.16 † NS
	Female	37	0.98 ± 0.28	
Family History	Positive	56	0.98 ± 0.22	0.01 † S
	Negative	22	0.73 ± 0.19	
Smoking	Positive	21	0.97 ± 0.24	0.48 † NS
	Negative	57	0.89 ± 0.25	
Duration of disease	< 10 years	28	0.93 ± 0.22	0.43 † NS
	≥ 10 years	50	1.20 ± 0.24	
BMI	None obese	40	1.00 ± 0.20	0.8 † NS
	Obese	38	0.96 ± 0.23	

n: represents the number of cases, SD stands for standard error, † denotes an independent samples t-test, A refers to a one-way ANOVA test, S indicates significance at P ≤ 0.05, and NS represents non-significance at P < 0.05.

Figure (3) shows that patients with poor glycemic control had approximately double mean level of hs-CRP than those with good glycemic control, P=0.0.

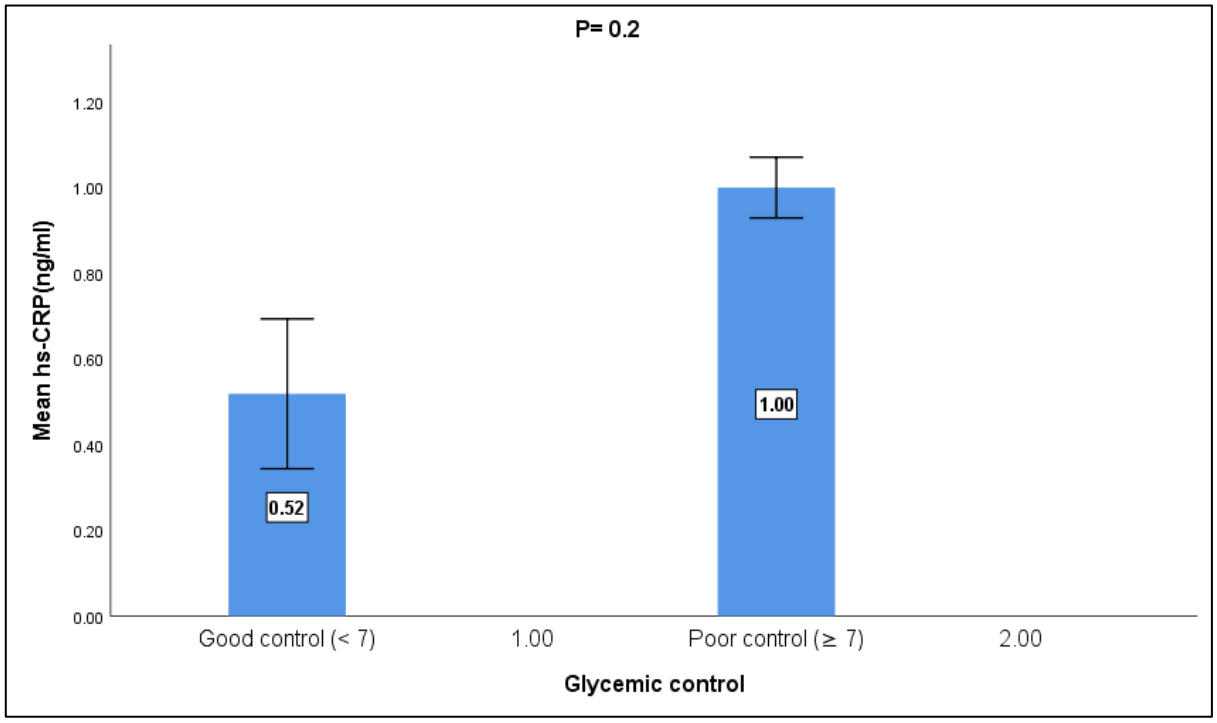

Figure (3): Mean hs-CRP levels according to glycemic control.

A comparison of the levels of hs-CRP in accordance with the complications has been carried out, and the findings are shown in Table 4. The present results show the mean hs-CRP level was higher in those with cardiovascular complications (1.28 ± 0.26 vs. 0.85 ± 0.21 in those without cardiovascular complications), while the level was lower in those with neuropathy in comparison with those patients without such complications (0.94 ± 0.22 vs. 0.86 ± 0.23). Also, the levels of hs-CRP were 0.94 ± 0.21 and 0.91 ± 0.23, respectively, in patients with and without retinopathy, and 0.98 ± 0.36 and 0.91 ± 0.22 in patients with or without nephropathy, although all the results of hs-CRP levels in association with the above studied complications were with no significant differences (P< 0.05), Table (4).

Table (4): Mean serum levels of hs-CRP according to complications.

Characteristics		N	Mean ± SE	*P*
Macro vascular complications				
CVD	**Present**	**46**	**1.28 ± 0.26**	**0.20 † NS**
	Absent	**22**	**0.85 ± 0.21**	
Micro vascular complications				
Neuropathy	**Present**	**32**	**0.86 ± 0.23**	**0.43 † NS**
	Absent	**46**	**0.94 ± 0.22**	
Retinopathy	**Present**	**13**	**0.94 ± 0.21**	**0.76 † NS**
	Absent	**65**	**0.91 ± 0.23**	
Nephropathy	**Present**	**5**	**0.98 ± 0.36**	**0.72 † NS**
	Absent	**73**	**0.91 ± 0.22**	

N: represents the number of cases, SD stands for standard error, † denotes an independent samples t-test, A refers to a one-way ANOVA test, S indicates significance at P ≤ 0.05, and NS represents non-significance at P < 0.05.

DISCUSSION

The mean level of hs-CRP was significantly higher in patients than controls (P<0.001), and this result in line with many studies carried out in different populations around the word like Lee and shin (12) study who observed increased levels of hs-CRP and CRP in individuals with diabetes, indicating a potential involvement of CRP in inflammation and the development of diseases. However, earlier in 2009, Lee et al. (13) in nested case control study determined that high CRP levels were not connected with developing diabetes In addition, CRP promotes the expression of several molecules, such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). This, in turn, leads to endothelial cell dysfunction, dilation of blood vessels, and an increase in fluid permeability from the blood vessels to the surrounding tissue, these events will reduce blood flow, which will lower insulin levels in the tissue and eventually lead to insulin resistance (14); (10).Further perspectives regarding the involvement of CRP in the pathogenesis of type 2 diabetes suggest that oxidative stress from inflammation causes hyperglycemia, which in turn triggers inflammation and raises CRP, and this vicious cycle appears to be what raises CRP, Additionally, oxidative stress prevents endocytosis from taking up insulin, which leads to insulin resistance in endothelial cells (10).The

present study observed no significant variations in the average levels of hs-CRP across different age groups. These findings align with the results reported by Yang et al. (15), who identified a similar elevation in hs-CRP levels among middle-aged and older Chinese individuals and suggest that hs-CRP might be used in conjunction with other indicators like blood pressure and blood lipid profiles for CVD screening in all or high-risk individuals. Kanmani et al. (16), in a study including 22,946 individuals aged 40 years or older in Korea, revealed a significant relationship between CRP levels and the development of T2DM in the older age group.

Researchers have shown that chronic inflammation, which is common with ageing, plays a role in the development of type 2 diabetes. While it is well recognized that becoming older increases the likelihood of developing certain diseases, it would be difficult to pinpoint an exact age at which therapeutic measures should begin. Previous research has suggested multiple causes of ageing-associated chronic inflammation, including age-related accumulation of damaged cells, changes in the gut microbiota over age, increasing cellular senescence and the subsequent secretion of proinflammatory cytokines, namely the senescence-associated secretory phenotype, or SASP, and age-associated modification of the immune system, among others (17). Women exhibited greater levels of hs-CRP than men (0.98 ± 0.28 vs. 0.85 ± 0.26); however, the difference was not statistically significant. Tong et al. (18) discovered no evidence of a connection between sex and hs-CRP. Conversely, Julia et al. (19) showed a noteworthy link between hs-CRP and T2DM in both genders.

The sex difference in the correlation might be attributed to an interplay between adiposity percentages, sex hormones, and inflammation; however, this suggestion should be tested in future research that quantifies endogenous sex hormones with CRP (15).

The current findings indicate that the average hs-CRP level was substantially greater in patients with a positive family history compared to individuals with a negative family history (0.98 ± 0.22 vs. 0.73 ± 0.19), respectively (P = 0.016). This data is in line with what Behre et al. (20) found: that those who had a first-degree relative with diabetes also had higher levels of inflammatory markers, including adiponectin and hs-CRP. Also, Dehghan et al. (21) discovered that a high CRP is a significant independent contribution to the risk of type 2 diabetes, particularly among individuals with non-modifiable risk variables such as a positive family history and advanced age.

The current results suggest that non-obese people have higher levels of hs-CRP compared to obese patients (1.00 ± 0.20 vs. 0.96 ± 0.23); however, this difference is not statistically significant. The results agree with Effoe et al. (22), who found an association between higher levels of hs-CRP and developing type 2 diabetes mellitus in non-obese female participants. Furthermore, the results align with the findings of Tong et al. (18) in Norway, who state that neither obesity nor hypertension can fully account for the relationship between hs-CRP and diabetes. The current findings contradict the research conducted by Reilly and Saltiel. (23) in Korea, which revealed significant links between CRP and those with a BMI of 25 kg/m2 or above compared to those with a lower BMI, for both men and women. The relationship between hs-CRP levels and central obesity, insulin resistance, and the metabolic syndrome is complex and not well understood (24). Serum CRP serves as an indicator of inflammation, but it is also strongly associated with obesity. We posit that the fluctuation of serum CRP, which is associated with obesity, serves as an indicator of an inflammatory condition. The elevated

concentration of blood CRP in obese people is a result of the heightened release of interleukin-6 and tumor necrosis factor-β by adipocytes; these factors regulate CRP synthesis in hepatocytes and contribute to the development of a persistent inflammatory condition (21).

The findings indicate that individuals with poor glycemic control had a mean hs-CRP level that was about twice as high as those with good glycemic control, and this result is consistent with the findings of the study that was carried out by Dayoub et al. (25), which indicated a positive correlation between serum hs-CRP and HbA1c in patients who were diagnosed with type 2 diabetes mellitus, independent of whether or not coronary heart disease was present. Moreover, Sarinnapakorn and Veerasak (26) showed that there is a connection between the levels of hs-CRP and the levels of HbA1c in patients who were overweight and had type 2 diabetic mellitus. Shi et al. (27) conducted an analysis of the relationship between hs-CRP and HbA1c, and the findings revealed that HbA1c is a risk factor for hs-CRP rises. Therefore, when planning glycemic control treatment, it is important to prioritize the reduction of HbA1c levels because lowering HbA1c levels helps to decrease the inflammatory response, thereby delaying the onset and progression of complications associated with diabetes mellitus.

The mean level of hs-CRP in diabetic patients with cardiovascular disease does not differ from the mean level in those patients who do not have cardiovascular diseases. This result fits with Zhang et al.'s (28) suggestion that hs-CRP is not a good indicator of vascular disease in type 2 diabetes, and monitoring the rise in serum hs-CRP concentration was not very useful for figuring out how bad vascular inflammation was and predicting the risk of coronary microvascular disease. The current findings are in contrast to the study conducted by Shah et al. (29), which examined the additional value of measuring hs-CRP in the general population for predicting coronary heart disease, as they assume that hs-CRP may be a good predictor in the general population when added to traditional risk variables such as age, smoking status, systolic blood pressure, history of diabetes, total cholesterol, and HDL cholesterol. Mor et al. (24) showed that those who exhibited both the metabolic syndrome and elevated levels of C-reactive protein (CRP) had a heightened risk of cardiovascular mortality in comparison to those without the metabolic syndrome and with low levels of CRP.

In an attempt to explain the role of CRP in CVD development, Bian et al. (30) in 2014 assumed that hs-CRP had a direct effect on increasing the transcytosis of LDL across endothelial cells. Consequently, this process enhances the development of atherosclerosis by augmenting the accumulation of LDL in the endothelial lining of blood vessels. Also, reduced glucose absorption into muscle and adipose tissue is a significant pathogenetic element that contributes to the development of diabetic macrovascular problems because this reduction in glucose uptake results in persistent extracellular hyperglycemia, which in turn causes vascular damage (31). Regarding neuropathy, the current study indicates that there is no relationship between the average level of hs-CRP and the incidence of neuropathy. This aligns with the findings of Herder et al. (32), who also observed no significant variations in the mean CRP levels between individuals with and without neuropathy.In contrast to the present findings, Papanas et al. (33) conclude that serum hs-CRP is independently linked to the development of diabetic neuropathy and diabetic foot ulcers, and hs-CRP may be used as a predictor of diabetic neuropathy.

The precise impact of subclinical inflammation that happens in diabetes on the progression of neuropathy remains uncertain. Aryan et al. (34) have shown a connection

between inflammatory cytokines and the negative impact they have on the vascular responsiveness of the skin microcirculation that may lead to neuropathic complications. Regarding retinopathy, the study indicates that there is no difference in hs CRP levels between patients with diabetic retinopathy and those without; however, patients with retinopathy had a higher mean hs-CRP level compared to those without retinopathy. This aligns with the findings of Eun et al. (35), who also observed no significant variations in mean hs CRP levels between individuals with and without retinopathy; furthermore, they found no variations in the average hs CRP levels based on the stage of retinopathy. Surprisingly, an across-sectional study done in Singapore by Lim et al. (36) showed that those in the highest quartiles of hs-CRP had a reduced probability of developing diabetic retinopathy. Regarding nephropathy, the study shows that the presence or absence of diabetic nephropathy did not result in any statistically significant change in his CRP levels. This result aligns with the observations made by Otto et al. (37), who propose that there is no link between the level of CRP and the amount of urine albumin excretion; moreover, Zhang et al. (2019) (38) study have shown no correlation between the progression of diabetic nephropathy and the initial level of CRP.

Our findings contradict the findings of Zbaar et al. (39), who found that the levels of C-reactive protein (CRP) in blood samples were elevated in diabetic individuals with nephropathy compared to those without nephropathy. This finding may be attributed to the impact of CRP on causing inflammation in the kidneys via the activation of a CD32b-NFκB-dependent pathway. This leads to an increase in the infiltration of T cells and macrophages, as well as the stimulation of IL-1bata, TNF-α, and MCP-1 in the renal tubules of diabetic individuals. Also, CRP caused kidney fibrosis by activating the CD32b-Smad3-mTOR signaling pathway and boosting TGF-β/S made signaling, which led to extracellular matrix accumulation and renal fibrosis in T2DM (40).

CONCLUSIONS

The level of hs-CRP is significantly higher in diabetic patients. It is associated with glycemic control, but there is no significant association with complications. The high levels of inflammatory markers among diabetes patients strengthen the inflammatory mechanism that predisposes to T2DM.

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