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Association of C- Reactive Protein and Glycated Hemoglobin among Type 2 Diabetic Adults

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Abstract **Original Research Article**

***Background*:** Diabetes mellitus (DM) is a complex metabolic disorder and is a major global health problem. An increasing amount of evidence suggests that chronic subclinical inflammation is one of the triggering factors in the onset of type 2 diabetes mellitus (T2DM). ***Objective*:** The current study was designed to determine the association of C-reactive protein **(**CRP) and glycated hemoglobin **(**HbA1c) in T2DM patients. ***Methods*:** This cross-sectional study was carried out at Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between March 2017 to February 2018. Total 80 adult patients of newly diagnosed T2DM were included in this study. A detailed clinical history was recorded and relevant physical examinations were done. The complete blood count (CBC), C-reactive protein (CRP), fasting blood glucose (FBG) and HbA1c were done accordingly. Data were analyzed and compared by statistical tests. ***Results*:** The mean age of the study patients was 45.06±11.08 years with female predominance. More than half (53.7%) of the study patients were in age group 41-59 years. Majority (65%) of the study patients was overweight/obese. It was observed that, mean(±SD) FBG, HbA1c and CRP levels were 8.97±2.41 mmol/L 8.54±2.08% and 8.98±4.85 mg/L respectively. Pearson correlation analysis revealed that CRP has a significant positive correlation with HbA1c (r= 0.457, p< 0.001). ***Conclusion*:** This study concluded that CRP has a significant positive association with HbA1c in adult T2DM patients. CRP can be used as a valuable and effective tool for monitoring T2DM.

Keywords: C-Reactive Protein (CRP), Diabetes Mellitus (DM), Glycated Hemoglobin (HbA1c), Type 2 Diabetes Mellitus (T2DM).

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is recognized as one of the major health issues worldwide. Diabetes mellitus (DM) is a chronic, metabolic disorder characterized by uncontrolled hyperglycemia that results from a decrease in the physiologic efficiency of insulin, an absolute or relative lack of insulin secretion, or both [1]. The estimated global prevalence of DM was 8.8% in 2015, and by 2040, it is expected to increase up to 10.4% [2]. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs particularly the eyes, kidneys, nerves, heart and blood vessels [1]. DM is regarded as one of the leading causes of death and disability globally [3].

Glycated hemoglobins are glucose-derived products of normal adult hemoglobin. Glycated hemoglobin (HbA1c), produced by the condensation of glucose with N-terminal valine of each β-chain of HbA [4]. It is formed by a slow irreversible non-enzymatic reaction between hemoglobin and glucose. It represents the integrated values for glucose over the preceding 6-8 weeks [5]. HbA1c is now regarded as a much more robust parameter than fasting plasma glucose for detecting and monitoring the impairment of glucose homeostasis in the general adult population [6].

Previous studies suggest that chronic subclinical inflammation may be associated with insulin resistance and precede the development of clinically overt type-2 diabetes mellitus [7-11]. Patients with type-

2 diabetes were found to have greater resting serum levels of acute-phase reactants than healthy people [7]. However, elevated concentrations of inflammatory marker such as C- reactive protein (CRP) and interleukin-6 have been implicated in the development and progression of long term diabetic macrovascular complications [8]. During recent years C- reactive protein (CRP) is uprising as a new inflammatory marker associated with health and diseases. CRP is becoming recognized as an independent risk factor for chronic diseases [9]. A higher chance of developing diabetes in the future has also been connected to elevated CRP levels [10]. Moreover, individuals with diabetes had greater CRP levels than those without DM [11]. There is scarce information available regarding the relationship between glycemic control and CRP in diabetic adults. Wu T *et al*., documented a correlation between CRP and HbA1c levels; however, the study did not include participants with diabetes [12]. Another study, reported a correlation between CRP and uncontrolled diabetes; although, the study was limited on small sample size [13]. Previous data indicates a substantial correlation between poor glycemic control and the onset of macrovascular consequences of diabetes [14]. Research has demonstrated the significance of C-reactive protein (CRP) as a risk factor for the diabetic complications [14, 15]. CRP is a simple, less expensive and easily available parameter and claimed to have a role in the disease process of DM and its complication. Routine CRP measurement might be regarded as a potential innovative biomarker for improving risk assessment of individuals with diabetes. In this background, this study was aimed to assess the relationship between CRP and HbA1c among type 2 diabetic adults.

2. METHODOLOGY

This cross-sectional study was carried out at Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from March, 2017 to February, 2018. The study was approved by the ethical review committee, BSMMU, Dhaka, Bangladesh. A total of eighty (80) newly diagnosed patients with diabetes mellitus [according to American Diabetic association (ADA) criteria] were included in this study [1]. Adult (age >18 years) type 2 diabetic patients of both sexes were enrolled. Gestational diabetes mellitus, diabetic patients having other comorbidities like- cardiovascular disease, acute or chronic renal/liver disease, patients with known inflammatory conditions and any type of malignancy were excluded from the study.

Study Procedure

After selection; the objective, procedure and benefits of the study were explained to the study population. Informed written consent was taken from each study patient prior to enrollment. A detailed clinical history was recorded and relevant physical examinations were done accordingly. All demographic, anthropometric and clinical data were recorded in a data collection sheet. The body mass index (BMI) was calculated from patient's weight and height. According to the BMI categories, "overweight" was defined as having a BMI of 25.0-29.9 kg/m^2, and "obesity" was labelled as having a BMI of ≥30 kg/m^2. Their complete blood count (CBC), C-reactive protein (CRP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c) levels were measured following standard procedure. In this study CRP level <5 mg/L was considered within normal limit and HbA_1C was considered within normal limit if <6.4%.

Statistical Analysis

All collected data were cleaned, verified and compiled. Data were analyzed using windows-based software statistical package for social sciences (SPSS) version 26. Quantitative data were expressed as mean with standard deviation (±SD) and qualitative data were expressed as frequency with percentage. Unpaired t test was done to compare different quantitative variables. Finally, association of CRP and HbA1c was examined by using Pearson's correlation coefficient test. Statistical significance was considered if p value less than 0.05.

3. RESULTS AND OBSERVATIONS

This cross-sectional study was intended to assess the relationship between CRP and HbA1c among diabetic adults. A total of eighty (80) adult diabetic patients were enrolled. The mean age of the study patients was 45.06±11.08 years that was ranged from 33 to 70 years. It was observed that, more than half [43(53.7%)] of the study patients belonged to age group 41-59 years, but 28(35%) patients were ≤40 years and 9(11.3%) patients were ≥60 years (Figure- 1). Of them 46(57.5%) patients were female and 34(42.5%) were male (Figure- 2).

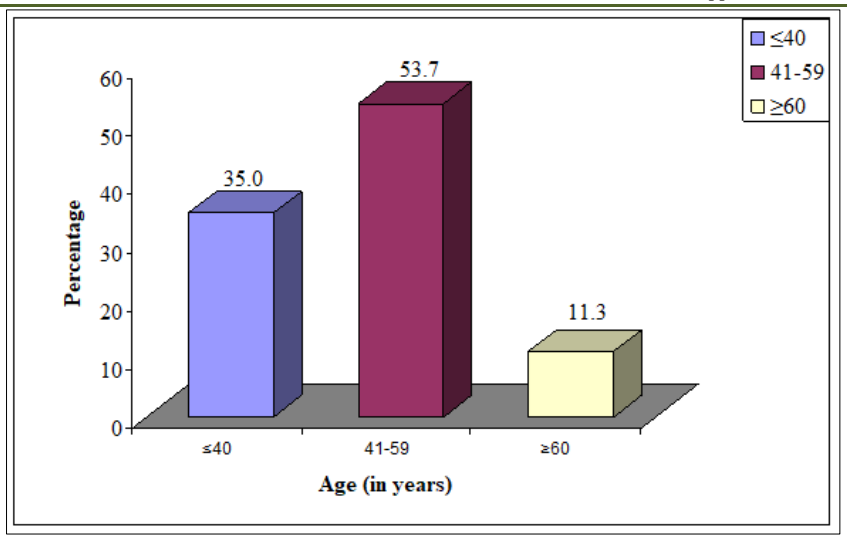

Figure 1: Age distribution of the study patients (N= 80)

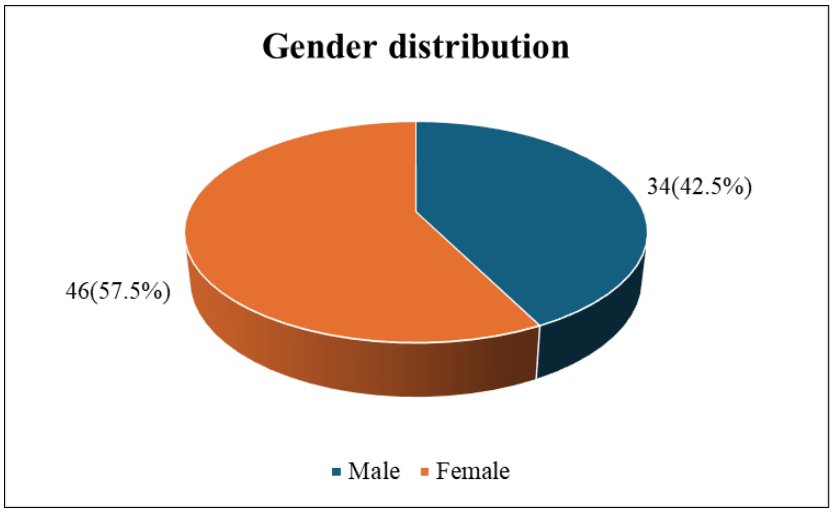

Figure 2: Gender distribution among the study patients (N= 80)

In body mass index (BMI) categories; 28(35%) patients had normal bodyweight, 45(56.2%) patients were overweight and 7(8.8%) patients were obese. Mean BMI (kg/m^2) was 26.34±3.26 which ranged from 17.79 to 36.29 kg/m^2 (Table- 1).

Table 1: Distribution of the study patients according to BMI categories (N= 80)

BMI (kg/m^2) categories	Number of patients (n)	Percentage (%)
Normal bodyweight (18.5-24.9)	28	35.0
Overweight (25-29.9)	45	56.2
Obese (≥30)	7	8.8
Mean±SD	26.34±3.26 kg/m^2	
Range (minimum-maximum)	17.79 - 36.29 kg/m^2	

Analyzing the laboratory parameters revealed that, the mean (±SD) hemoglobin (Hb) level of the study patients was 13.12±1.4 gm/dl with ranged from 11.5 to 16.1 gm/dl. Mean (±SD) fasting blood glucose (FBG) was 8.97±2.41 mmol/L with ranged from 6.4 to 16 mmol/L. Mean (±SD) glycated hemoglobin (HbA1c) was 8.54±2.08% with ranged from 6.8% to 15%. Mean (±SD) C-reactive protein (CRP) was 8.98±4.85 mg/L with ranged from 5.3 mg/L to 14.14 mg/L (Table- 2).

Table 2: Laboratory findings of the study patients (N= 80)

Variables	Mean±SD	Range (minimum-maximum)
Hb (gm/dl)	13.12±1.4	11.5- 16.1
FBG (mmol/L)	8.97±2.41	6.4- 16
HbA1c (%)	8.54±2.08	6.8-15
CRP (mg/L)	8.98±4.85	5.3- 14.14

It was found that, the mean (±SD) hemoglobin (Hb) level was 15.4±2.3 g/dl with ranged from 13.2 to 16.8 g/dl in CRP≤10 mg/L and mean (±SD) Hb was 15.6±3.3 g/dl with ranged from 14.2 to 17.3 g/dl in CRP>10 mg/L, the difference was not significant (p= 0.820). The mean (±SD) fasting blood glucose (FBG) level was 5.8±1.41 mmol/L with ranged from 5.6 mmol/L to 6.6 mmol/L in CRP≤10 mg/L, but mean (±SD) FBG was 6.18±1.81 mmol/L with ranged from 6.1 mmol/L to 7.8 mmol/L in CRP>10 mg/L, which was not significant (p= 0.327). Mean (±SD) glycated hemoglobin (HbA1c) was 6.8±1.34% with ranged from 6.5% to 7.2%. in CRP≤10 mg/L, while mean(±SD) HbA1c was 8.7±1.8% with ranged from 6.6% to 9.8%. in CRP>10 mg/L, the difference was statistically significant (p<0.001) (Table-3)

Table 3: Comparison of laboratory data with CRP ≤10 mg/L and CRP>10 mg/L (N= 80)

Variables	CRP		p value*
	≤10 mg/L (n=16)	>10 mg/L (n=64)	
Hemoglobin (g/dl)	15.4±2.3 (13.2-16.8)	15.6±3.3 (14.2-17.3)	0.820^{ns}
FBG (mmol/L)	5.8±1.41 (5.6-6.6)	6.18±1.81 (6.1-7.8)	0.327^{ns}
HbA1c (%)	6.8±1.34 (6.5-7.2)	8.7±1.8 (6.6-9.8)	<0.001^{s}

Data were expressed as mean±SD, figures in the parentheses indicate corresponding ranges,
s= significant, ns= not significant, *p value obtained from unpaired t test.

On the other hand, the mean (±SD) CRP level was 6.88±1.5 mg/L in patients having HbA1c <7% and that was 9.98±2.8 mg/L among patients with HbA1c ≥7%. The difference was statistically significant (p<0.001) between the groups (Table- 4).

Table 4: **Comparison of CRP with HbA1c <7% and ≥ 7% (N= 80)**

Variable	HbA1c (%)		
	<7 (n=14)	≥7 (n=66)	p value*
	Mean±SD	Mean±SD	
CRP (mg/L)	6.88±1.5	9.98±2.8	<0.001^{s}

s= significant, *p value obtained from unpaired t test

It was observed that CRP was significantly correlated with HbA1c (r= 0.457, p<0.001), although FBS (mmol/L) was not significantly correlated with CRP (r= 0.161, p>0.05) (Table- 5).

Table 5: Correlations (r and p-values) of C-reactive protein (CRP) with FBS and **HbA$_1$c (N= 80)**

Variables	r	p value*
FBS (mmol/L)	0.161	>0.05^{ns}
HbA$_1$c (%)	0.457	0.001^{s}

s= significant, ns= not significant,
*Pearson correlation test was performed

3. DISCUSSION

Diabetes mellitus (DM) is a chronic metabolic disorder, widely recognized as one of the leading causes of death and disability worldwide [3]. The prevalence of type-2 diabetes mellitus (T2DM) has been increasingly prevalent globally. Immune system activation is strongly associated with the development and occurrence of type 2 diabetes mellitus (T2DM). The inflammation of adipose tissue involves both innate and adaptive immunity. It was reported that inflammatory marker C-reactive protein (CRP) has been connected to a higher chance of developing diabetes later in life [15-16]. Additionally, previous studies have demonstrated that individuals with diabetes had higher CRP levels, which are associated to elevated HbA1c concentrations compared to non-diabetics [12-17]. Therefore, assessment of CRP and HbA1c among diabetic individuals in order to forecast future complications is necessary. This study was aimed to examine the

association of CRP and HbA1c in adult patients with type-2 diabetes mellitus.

In this study, 80 adult patients of newly detected type-2 diabetes mellitus were included. The mean (±SD) age of the study patients was 45.06±11.08 years and the age range were 33 to 70 years. A previous study found the mean (±SD) age was 60.2(±10.9) years for diabetic patients [18]. One related study documented that the mean (±SD) age was 56.80(±11.95) years in diabetic patients [19]. In another study the mean (±SD) age of the diabetic adults was 58.6(±7.8) years [20]. The mean age of the current study population was not consistent with these related previous studies, possibly due to demographical variation. A female predominance was observed among our study population, which was supported by a couple similar previous study [21-22].

In our study, the mean (±SD) body mass index (BMI) of the study patients was 26.34±3.26 kg/m²; majority of them were overweight or obese. One previous study found mean BMI of their study patients was 31.49±5.14 kg/m² [18]. Another study on diabetic adults showed that, mean BMI was 28.4±4.3 kg/m² among their study population [20]. So, our findings were consistent with related previous studies [18, 20]. In this study, mean (±SD) glycated hemoglobin (HbA1c) concentration was 8.54±2.08%, that was ranged from 6.8% to 15%. The measurement of glycated hemoglobin (HbA1c) has now been established as an essential criterion for diagnosing diabetes in the general population [1]. In accordance, Dilara DA *et al.*, found mean HbA1c in diabetic patients was 7.7% (ranged: 6%-14.9%) [19], while Malandrino N *et al.*, found a mean HbA1c was 7.0±1.9% among their study patients [23]. Therefore, our result was near similar to the other studies [19, 23].

In our study, mean (±SD) C-reactive protein (CRP) level was 8.98±4.85 mg/L which was ranged from 5.3 mg/L to 14.14 mg/L. In this context Sherif H *et al*., found a significant higher CRP level in diabetic patients (p= 0.02) [24]. Our finding was in a line of related previous studies; which demonstrated that individuals with diabetes had higher CRP levels [12-17].

It was found that, the mean (±SD) hemoglobin (Hb) level was almost similar in CRP level ≤10 mg/L and in CRP level >10 mg/L (15.4±2.3 g/dl and 15.6±3.3 g/dl with p= 0.820). The mean (±SD) fasting blood glucose (FBG) level was not significantly different between CRP ≤10 group and CRP >10 mg/L group (5.8±1.41 mmol/L and 6.18±1.81 mmol/L, p= 0.327). On the other hand, mean (±SD) glycated hemoglobin (HbA1c) concentration was significantly higher among patients with CRP level >10 mg/L than patients having CRP level ≤10 mg/L (8.7±1.8% versus 6.8±1.34%, p<0.001). These findings were reflected in similar related studies [15, 26].

In this present study, the mean (±SD) CRP level was significantly higher among patients with HbA1c concentration ≥7% than patients having HbA1c concentration <7% (9.98±3.8 mg/L versus 6.88±1.5 mg/L, p <0.001). This result was comparable with a couple of previous study [14, 26].

Pearson correlation analysis revealed that CRP has a significant positive correlation with HbA_1C (r= 0.457, p<0.001), however FBS (mmol/L) was not significantly correlated with CRP (r= 0.161, p>0.05). Although the clinical correlation between diabetes and elevated CRP being well documented, but molecular processes which allow elevated CRP to cause diabetes is still unclear [15]. The generation of CRP could be triggered by numerous inflammatory and metabolic variables linked to the onset of type 2 diabetes mellitus (T2DM), including elevated blood glucose, adipokines, and free fatty acid levels [15]. Moreover, a large body of research on humans [10, 27], and animals [28-30], has shown that high serum CRP levels are linked to obesity and the development of insulin resistance (IR) that leads to type 2 diabetes mellitus (T2DM). These results support the hypothesis that a key element in the pathophysiology of type 2 diabetes mellitus (T2DM) is the inflammatory state as indicated by elevated CRP levels.

In our study, adult newly detected type-2 diabetic patients were selected, CRP and HbA1c levels were measured and correlate them. CRP and HbA1c levels were found elevated in the adult diabetic subjects. According to Pearson correlation, these variables had a significant positive correlation. From the findings of this study, we can conclude that all type-2 diabetic patients could be screened by measuring CRP level. High CRP level provides a reflection of high HbA1c concentration in T2DM.

4. CONCLUSION

In conclusion, our research revealed a significant positive correlation between CRP and HbA1c in type 2 diabetic adults. This study documented that increased CRP level is associated with elevated HbA1c. Increased CRP level reflects the presence of active inflammatory condition and oxidative stress. It is also helpful for follow up the adult T2DM patients by evaluating CRP level. Therefore, CRP can be used as a valuable and effective tool for monitoring T2DM among adults.

Conflicts of Interest: All authors declared that there is no conflict of interest regarding this publication.

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