

The Impact of Glycemic Control on Procalcitonin Level in Patients with Type II Diabetes

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Abstract

Background: Diabetes mellitus is a chronic condition characterized by hyperglycemia that can lead to serious complications. It results from a defect in insulin secretion, insulin resistance, or both. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes and mainly affects adults. It is associated with insulin resistance and low-grade chronic inflammation in the adipose tissue, muscles, and liver. Measurement of hemoglobin A1c (HbA1c) is one of the most widely used tests to monitor diabetes. The aim of this study was to shed light on the effect of glycemic control of type 2 diabetes on procalcitonin (PT) levels in order to prevent future complications. **Materials and Methods:** This case-control study included 68 patients with type 2 diabetes mellitus. At Biochemistry Department, College of Medicine, and University of Baghdad and at Al-Sadiq Teaching Hospital in Al-Hilla City, during the period from July 2020 to October 2020. Hemoglobin A1C (HbA1c) was estimated by using an affinity chromatography assay. These patients were divided according to HbA1c level into bad control group (HbA1c $\geq 7\%$) which included 36 patients, and good control group (HbA1c $< 7\%$) which included 32 patients. Another group of 32 nondiabetic apparently healthy subjects (HbA1c $< 5.7\%$) served as control group. Patients with type 1 diabetes mellitus (T1DM), gestational diabetes, insulin-treated type 2 diabetes, history of recent infection, diabetic foot, ischemic heart disease, cerebrovascular disease, or recent trauma or surgery were excluded. PCT of each participant was estimated using an enzyme-linked immunosorbent assay (ELISA). **Results:** The mean PCT values of bad control group, good control group, and control groups were 871.3776, 834.5005, and 208.5313 pg/mL, respectively. The study showed that there was no significant difference in mean PCT between good control and bad control groups ($P > 0.05$). In addition, there was no significant correlation between PCT and HbA1c among diabetic patients ($r = 0.072$, $P > 0.05$). However, there is a significant differences in mean of PCT values between diabetic patients and control group ($P < 0.05$). **Conclusion:** There was no effect of glycemic control on PCT level in patients with T2DM. However, the level of PCT was increased in comparison with non-diabetic healthy subjects.

Keywords: Glycemic control, procalcitonin level, the impact, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone.^[1] The global prevalence of diabetes is estimated to be 9.3% in adults aged 20–79 years in 2019.^[2] Over the past decade, the prevalence of diabetes has risen rapidly due to an increase in the average age of the community, hereditary background, unhealthy dietary habits, sedentary lifestyle, and increased obesity in line with the growth of urbanization. Various estimates suggest that the number of affected people will be risen

from 422 million to 642 million in the world by 2040.^[3] In 2019, approximately 54.8 million adults aged 20–79 years, or 12.8% of the population of Middle East and North Africa in this age group, have diabetes. This includes 24.5 million adults with undiagnosed diabetes. The Region has the highest age-adjusted diabetes prevalence (12.2%) of all the International Diabetes Federation (IDF) Regions. Eighty-five to ninety-five % of all diabetes in high-income countries are of T2DM accounting for an even higher

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dominance in developing countries.^[4] The prevalence is lowest in rural areas of developing countries, generally intermediate in developed countries, and highest in certain ethnic groups, particularly those that have adopted western lifestyle patterns. The age of onset is usually >25 but the incidence increasing in adolescents, paralleling the increasing rate of obesity in children and adolescents.^[5] Type 1 diabetes mellitus (T1DM) is an autoimmune disease encompassing the T-cell-mediated destruction of pancreatic β -cells and the production of autoantibodies against islet proteins.^[6] These autoantibodies include islet cell autoantibodies, and autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2 β), and zinc transporter protein (ZnT8A).^[7] Autoimmune T1DM has strong HLA associations, with linkage to *DR* and *DQ* genes.^[1] Hemoglobin A1c (HbA1c), also called glycosylated hemoglobin, is a hemoglobin compound in which glucose molecule is attached to one or both N-terminal valines of the β -polypeptide chains of normal adult hemoglobin. The HbA1c formation is proportional to the blood glucose concentrations. Because the average red blood cell life is approximately 120 days, the glycosylated hemoglobin level reflects the average blood glucose level during the previous 2 to 3 months.^[8] Procalcitonin (PCT) is the precursor of the hormone calcitonin. It is synthesized in thyroid C-cells. It is an 116-amino acid peptide with a molecular weight of 14.5 kDa.^[9] Serum PCT concentration in healthy individuals is typically <0.1 μ g/L. In the presence of bacterial infection, PCT increases, and the degree of rise correlates with the severity of the infection. Patients with localized infection have smaller increases of PCT in comparison to those with generalized sepsis, severe sepsis, and septic shock. A declining concentration usually reflects resolution of disease.^[9] Despite being the most accepted biomarker in sepsis, PCT is far from being an ideal biomarker. PCT has many limitations that should be taken into consideration when incorporating PCT in the management of a potentially septic patient. Falsely low PCT in localized infections like cellulitis, appendicitis, abscess, and empyema can be misleading.^[10-12] However, some data shows a modest performance of PCT in differentiating para-pneumonic effusion from malignant or transudative effusions.^[13] The aim of this study was to shed light on the effect of glycemic control of type 2 diabetes on PT levels in order to prevent future complications.

MATERIALS AND METHODS

A case-control study was performed. Hundred subjects were included in this study; sixty-eight of them were patients with T2DM who were already diagnosed by consultant physicians according to the criteria of the American Diabetes Association.^[14] These patients were divided into two groups based on their HbA1c levels: thirty-two well-controlled (HbA1c below 7%^[15] with age ranging between 38 and 75 years old (female = 20, male = 12) and 36 poor-controlled

(HbA1c equal or above 7%) with age ranged between 39 and 70 (female = 23, male = 13). Thirty-two non-diabetic apparently healthy participants with age ranging between 40 and 55 years old (female = 20, male = 12) were included as control group. History and questionnaire taken from all participants included in this study. Patients with type 1 diabetes mellitus T1DM, gestational diabetes, insulin-treated T2DM, history of recent infection, diabetic foot, ischemic heart disease, cerebrovascular disease, or recent trauma or surgery excluded. Verbal consent was obtained from all participants. Weight and height of each participant were measured and body mass index (BMI) was calculated as weight (kg)/square of height (M).^[15] Five milliliters of venous blood were aspirated from each participant from antecubital vein by puncture using disposable syringe. Tow mL was put in ethylenediaminetetraacetic acid (EDTA) tube for measurement of HbA1c and the remaining blood was collected in gel tube for PT measurement and waiting for 15–30 minutes for blood to clot and then centrifuged for 5 minutes at 5000 $\times g$.^[16] Serum was obtained and put in Eppendorf tube and stored frozen at -80°C using deep freeze until time of analysis. PT was determined by enzyme-linked immunosorbent assay (ELISA) using a kit provided by Bioassay Technology Laboratory/ China.^[17] A standard curve was constructed by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and a best fit curve was drawn through the points on the graph with computer-based curve-fitting software.^[18] Statistical analysis was carried out using SPSS version 23. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (means $\pm$ SD). Student t-test was used to compare means between two groups. One-way ANOVA test was used to compare means between three groups or more. Pearson chi-squared and fisher-exact test were used to find the association between categorical variables. Pearson correlation coefficient was used to assess the relationship between two continuous variables. A value of $P \leq 0.05$ was considered significant.^[19]

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 123 (including the number and the date in 01/05/2020) to get this approval.

RESULTS

The results of Table 1 and Figure 1 show that the age range of diabetic patients was 38–75 years and the mean $\pm$ SD was (56.50 $\pm$ 9.86 years). The gender distribution of diabetic patients was 25 (36.8%) males and 43 (63.2%)

Table 1: Distribution of diabetic patients according to socio-demographic characteristics including (age, gender, and body mass index)

Sociodemographic characteristics		
Age (years)	(56.50 ± 9.86)	(38-75)
Gender		
Male	25	36.8%
Female	43	63.2%
Total	68	100.0%
BMI (kg/m ²)		
Normal (18.5–24.9)	7	10.3%
Overweight (25–29.9)	29	42.6%
Obese (≥ 30)	32	47.1%
Total	68	100.0%

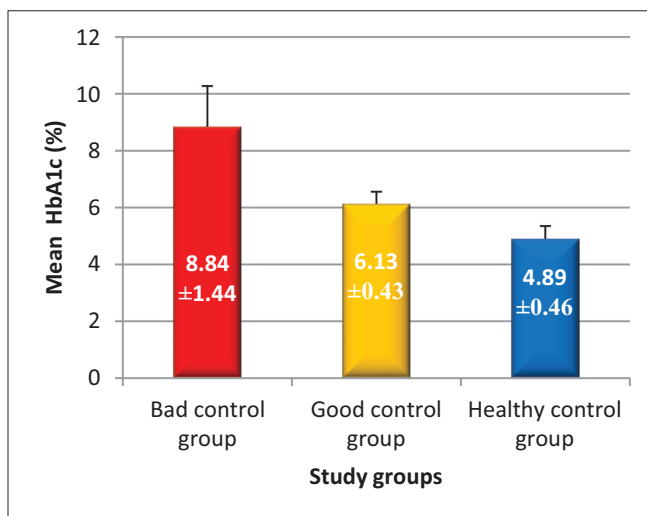


Figure 1: Mean (±SD) differences of HbA1c according to study group

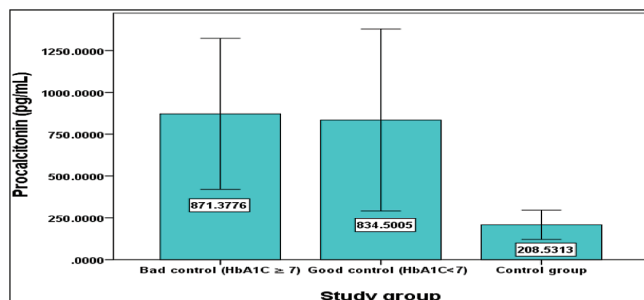


Figure 2: Mean differences of procalcitonin according to study group

females. The mean + SD of Body mass index (BMI) was (30.05±4.41) kg/m² and the range was 20.32–40.90 kg/m². The BMI distribution was 7 (10.3%) normal, 29 (42.6%) overweight and 32 (47.1%) obese.

The mean age of participants according to study group including diabetic patients with bad control (HbA1c >7%), diabetic patients with good control (HbA1c <7%), and healthy control group (HbA1c <5.7%) was 54.41±9.35, 58.84±10.03, 48.12±4.27 years respectively. Figure 2 shows

that the mean of HbA1c The mean HbA1c of participants according to study group including diabetic patients with bad control (HbA1c >7%), diabetic patients with good control (HbA1c <7%), and healthy control group (HbA1c <5.7%) was 8.84 + 1.44, 6.13±0.43, and 4.89±0.46% respectively and there was among these groups. The mean BMI of participants according to study group including diabetic patients with bad control (HbA1c >7%), diabetic patients with good control (HbA1c <7%), and healthy control group (HbA1c <5.7%) was 31.25±4.54, 28.69±3.90, 25.99±2.55 kg/m², respectively. All these result had been shown to be significantly different among study groups ($P < 0.05\%$) [Table 2].

The mean values of PCT according to study groups including diabetic patients with bad control (HbA1c ≥ 7), diabetic patients with good control (HbA1c < 7), and control group (HbA1c <5.7) were 871.3776, 834.5005, and 208.5313 respectively. There were significant differences in mean PCT values according to study group ($P < 0.001$). However, there was no significant difference in mean PCT values between bad control and good control groups ($P = 0.464$) [Table 3 and Figure 2].

The mean values of age, HbA1c, BMI, and PCT in diabetic patients were 56.50±9.86 years, 7.57±1.74%, 30.05±4.41 kg/m², and 854.0236±247.2747 pg/mL, respectively. There was no significant correlation between procalcitonin and study parameters [Table 4 and Figure 3].

DISCUSSION

Diabetes mellitus is a chronic condition that grows significantly, especially in developing countries, and is marked for the severity of its complications.^[20] Procalcitonin has been identified as a novel systemic inflammatory marker and has been shown to be increased in case of advanced atherosclerosis and in patients with acute coronary syndrome and to predict future cardiovascular mortality after myocardial infarction.^[21-24] There was no significant association between glycemic control and duration of disease in our study. While other studies Kapur *et al.*, and Ufuoma *et al.* showed that there were an association between higher level of HbA1c and longer duration of type 2 DM.^[25,26] This may be explained by delayed diagnosis of type 2 DM in our community due to asymptomatic and gradual onset and absence of screening which results in falsely shorter duration of disease. Also, there was a significant difference in age among all study groups, the patients with good control showed the highest mean, while healthy participants showed the lowest mean. These results disagree with Wang *et al.* and AL-Shammaree *et al.*^[23,24] The explanation may be due to the fact that older healthy participants with normal HbA1c could not be obtained in our study. Furthermore, older diabetic patients with poor glycemic control who are free of complications could not be found.

Table 2: Mean differences of study parameters according to study group

Study variables	Study group	N	Mean	SD	F-test	P-value
Age (years)	Diabetic patients with bad control (HbA1C $\geq$ 7)	36	54.41	9.35	13.35	<0.001*
	Diabetic patients with good control (HbA1C < 7)	32	58.84	10.03		
	Healthy control group	32	48.12	4.27		
HbA1c %	Diabetic patients with bad control (HbA1C $\geq$ 7)	36	8.84	1.44	158.24	<0.001*
	Diabetic patients with good control (HbA1C < 7)	32	6.13	0.43		
	Healthy control group	32	4.89	0.46		
BMI (kg/m ²)	Diabetic patients with bad control (HbA1C $\geq$ 7)	36	31.25	4.54	16.25	<0.001*
	Diabetic patients with good control (HbA1C < 7)	32	28.69	3.90		
	Healthy control group	32	25.99	2.55		

* Significant < 0.05

Table 3: Multiple comparison (post hoc test)

Study variables	Study group	P Value	95% confidence interval
Procalcitonin (pg/mL)	Bad control (HbA1C $\geq$ 7)	0.464	-62.66
	Good control (HbA1C < 7)	<0.001*	563.30
	Control group		136.42
			762.39
Procalcitonin (pg/mL)	Good control (HbA1C < 7)	0.464	-136.42
	Bad control (HbA1C $\geq$ 7)	<0.001*	523.53
	Control group		62.66
			728.39

*Significant < 0.05

Table 4: Correlation between procalcitonin (pg/mL) and studied parameters

Study variables	N	Mean	SD	r	P-value
Procalcitonin (pg/mL)	68	854.0236	247.2747	-0.039	0.751
Age (years)	68	56.50	9.86		
Procalcitonin (pg/mL)	68	854.0236	247.2747	0.072	0.558
HbA1C (%)	68	7.57	1.74		
Procalcitonin (pg/mL)	68	854.0236	247.2747	0.036	0.77
BMI (kg/m ²)	68	30.05	4.41		

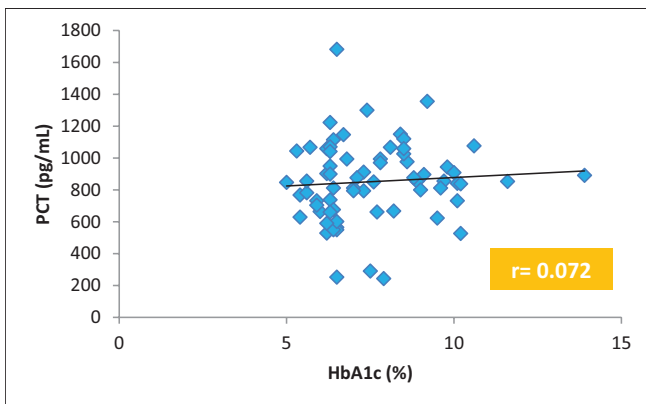


Figure 3: Correlation between PCT and HbA1c

In this study, diabetic patients treated with insulin were excluded. Several studies have suggested that insulin may exert an anti-inflammatory effect, independent of its effects on glycemia. Insulin has been shown to reduce inflammation through several mechanisms, including increased endothelial nitric oxide release and decreased expression of proinflammatory cytokines and immune

mediators, such as NF- κ B, intercellular adhesion molecule-1, and MCP-1, as well as several TLRs.^[27] In a randomized parallel-group study in patients with T2DM, serum concentrations of hs-CRP and IL-6 were markedly reduced in insulin-treated patients compared with metformin, despite similar glycemic control. This may suggest that insulin reduces inflammation, irrespective of its effects on glycemia.^[28] This may explain the relatively low PCT levels among diabetic patients in the study of AL-Shammaree *et al.* in which insulin-treated patients were not excluded from the study. No correlation was found between PCT and HbA1c of diabetic patients in this study. This result disagrees with Ahmed *et al.* who found a significant positive correlation.^[29] This may be related to the difference in sample size between the two studies (40 diabetic patients and 20 healthy subjects in the study of Ahmed *et al.* compared to 68 diabetic patients and 32 healthy subjects in our study). Also there was no correlation between BMI and PCT of diabetic patients in our study. This result disagrees with Ghanem *et al.* and Ahmed *et al.* who found a positive correlation. This may be related to the difference in sample size (106 diabetic

patients and 44 healthy subjects in the study of Ghanem *et al.*, and—as mentioned above—40 diabetic patients and 20 healthy subjects in the study of Ahmed *et al.* compared to 68 diabetic patients and 32 healthy subjects in our study).^[29,30]

CONCLUSION

There was no effect of glycemic control on PCT level in patients with T2DM. However, their PCT level increased in comparison with non-diabetic healthy subjects.

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Conflicts of interest

There are no conflicts of interest.

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