



Correlation between (Procalcitonin, CRP and interleukin-6) with cystatin C in type-2 diabetes mellitus patients

Nesreen Ahmed Nasser^{1*}, Anas H. Sadek², Zainab Sadeq Yuosif³, Rayah Sulaiman Baban⁴

^{1,3}Department Of Medical Lab Techonology, Mazaya University College, Dhi Qar , Iraq

²Department Ibn Sina university of medical and pharmaceutical sciences, Baghdad, Iraq

⁴Department of Chemistry and Biochemistry, College of Medicine, Al- Nahrain University, Baghdad, Iraq

*Corresponding author: Nesreen Ahmed Nasser, Department Of Medical Lab Techonology, Mazaya University College, Dhi Qar , Iraq, Email: nisreen.ahmed@mpu.edu.iq

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ABSTRACT

All nucleated cells consistently synthesize and secrete cystatin C, a basic protein that is not glycosylated. Because it is less influenced by outside variables including gender, race, and muscle mass, cystatin C is a more trustworthy measure than blood creatinine. Serum cystatin C levels in type 2 diabetes mellitus are not well understood in individuals with obesity, nevertheless. A low-molecular weight protein called cystatin C that is readily filtered by the kidneys has just come to light as a potential biomarker that may be utilized to identify early renal failure in people with type 1 or type 2 diabetes. Additionally, it has been demonstrated that cystatin C can be used to identify cardiovascular disease in diabetics, and it may possibly be connected to the occurrence of type II diabetes in obese individuals. This study aimed correlation cystatin C (Cys C) levels in type II diabetes and Procalcitonin , CRP and interleukin-6 .inflammatory marker

Material and methods: the blood samples of Type II diabetes mellitus (30 cases) and control (30 normal) groups were collected in private laboratory through the study dated between February 2022 and june 2022. HbA1c test was done immediately then the blood sample was centrifuged. Serum divided into two part. The first part was used for the following test : random blood sugar, total protein, albumin, GPT, GOT, ALP. The other was refrigerated for Procalcitonin , CRP, interleukin-6 and cystatin C tests by using enzyme-linked immunosorbent assay (ELISA).

Results: The mean cystatin-c levels were increased in Type II diabetes patients significantly ($P \leq 0.0001$) compared with healthy groups (2.55 ± 1.12 pg/ml, 0.55 ± 0.21 pg/ml) respectively. Also, CRP ,IL-6 and procalcitonin levels were bigger in Type II diabetes patients significantly ($P > 0.0001$) in Type 2 diabetes linked with healthy groups (30.45 ± 16.4 ng/ml, 2.19 ± 1.27 ng/ml , 16.19 ± 4.32 ng/ml 6.06 ± 3.10 and 4.92 ± 4.00 , 0.315 ± 0.22) respectively.

Conclusions: According to our research, individuals with Type II diabetes have circulating Cys C levels that are higher than those of healthy individuals. To determine the cause of abnormal Cys C concentrations in Type II diabetes, more research is still required.

Keywords: Type II diabetes, cystatin C, Procalcitonin, interleukin-6, cystatin C

INTRODUCTION

Diabetes is a chronic disease brought on by either insufficient pancreatic insulin production or ineffective body insulin utilization. The insulin hormone regulates blood sugar levels. Hyperglycemia, commonly referred to as high blood glucose or elevated blood sugar, is a common side effect of uncontrolled diabetes that over time can gravely affect a variety of internal systems, including the neurons and blood vessels. (1)

Type 2 diabetes mellitus, one of the most common diseases in western society, is connected to a significant cardiovascular risk due to both the fundamental risk factors and a persistent low-grade inflammation. (2)

Type 2 diabetes-related long-term microvascular and macrovascular issues can increase morbidity and mortality. (3) Additionally, type 2 diabetes might be undiagnosed in up to one-third of patients. Nonetheless, growing evidence connects type 2 diabetes to a number of frequently co-occurring disorders that are known to be caused by inflammatory pathways, suggesting that inflammation may operate as a significant intermediary in the development of type 2 diabetes (4)

Several investigations suggest a link between type 2 diabetes, interleukin-6 (IL-6), and CRP in this setting. (5,6)

Interleukin-6 (IL-6) is a proinflammatory cytokine that, by controlling cell proliferation, migration, differentiation, and death, greatly contributes to the pathogenesis of type II diabetes (T2DM) and the emergence of insulin resistance. Although IL-6 is naturally present in tissues, its irregular synthesis and extended exposure lead to inflammation, which in turn causes overt T2DM and insulin resistance. There is a mechanistic connection between insulin resistance and IL-6 activation. By altering the phosphorylation of the insulin receptor and insulin receptor substrate, IL-6 induces insulin resistance by raising the expression of SOCS-3, a potential inhibitor of insulin signaling. (7)

It has been claimed that chronic inflammation, which is partially explained by the interleukin 6 (IL-6) pathway, has a significant impact on the

pathophysiology of type II diabetes patients (T2D) [8].

Associated Obesity is linked to an increased risk of insulin resistance, T2D, coronary artery disease, and raised levels of IL-6 and other pro-inflammatory mediators [9].

The precursor of calcitonin, procalcitonin (PCT), is normally released by thyroidal para follicular C-cells. However, during an infection, neuroendocrine cells from the liver, peripheral blood monocytes, macrophages, spleen, lung, small intestine, and kidneys release PCT ectopically. With viral infections and non-specific inflammatory disorders like ulcerative colitis, serum jPCT levels are modest; nevertheless, as bacterial infections develop, they climb rapidly.

There hasn't been any research on how type II diabetes patients' serum mPCT levels vary when an infection first manifests. The use of PCT for predicting infection in type II diabetes patients was therefore examined in the current study by comparing it to different inflammation markers in patients with type II diabetes who were suffering from variable degrees of infection. (10)

All nucleated cells are capable of producing the cysteine proteinase inhibitor Cystatin C (Cys C), which has a molecular weight of 13,343 Da and mostly impacts extracellular protease activity [11,12].

It has been shown that Cys C can affect the lysosomal protein turnover pathway during cellular internalization, therefore showing the role of Cys C in controlling the homeostasis of the target tissue during cellular reuptake in vivo. Also, Cys C has in vitro angiogenic properties and leads to the development of endothelial cell (EC) tubules. [13].

Material and method : In our study, samples were collected for patients with type 2 diabetes, and they were taken from private laboratories, and the period in which samples were collected was between February 2022 and June 2022. The period is five months. 60 samples were obtained divided into 30 healthy samples, a group and 30 patients with type 2 diabetes. After that, some laboratory analyzes were measured for them, which include random sugar, cumulative sugar,

albumin, protein, and liver analyzes (GPT, GOT, ALK). compared to cystatin C and measurement of inflammatory markers, which include (procalcitonin, interleukin-6, CRP)

increases (P=0.001) in the average of Cyc-c. level ; also there were a highly significant difference increases of inflammatory marker (Procalcitonin , CRP and interleukin-6) (P=0.0001) between patients groups and control group (Table1). However, there was no significant different at the same period (P=0.062) between the patient groups and controls of level liver function test (GPT, GOT and ALK.Ph) .

RESULT

Between the patient's group and the control group, there was a significantly higher serum

TABLE 1: cystatin -c , procalcitonin , interlukein -6 and C-reactive protein for both control group and patients groups type 2 diabetes .

Variables	Control Mean± SD	Patients Mean± SD	P-Value
R.B.S	84.71±7.98	193.85 ± 41.42	<0.0001
HBA1C	4.82±0.47	9.72±1.49	<0.0001
Albumin	4.87 ± 0.29	4.30±0.30	< 0.001
Protein	6.72±0.81	5.82±0.50	< 0.002
Procalcitonin	0.315± 0.22	4.92±4.00	0.0008
CRP	2.19±1.27	30.45±16.4	< 0.0001
CYS- C	0.55±0.21	2.55±1.12	< 0.0001
GOT	20.42±6.40	17.85±6.06	0.28
GPT	18.28±5.38	21.07±8.29	0.30
ALK.Ph	82.71±25.9	114.35±40.7	0.02
IL-6	6.06±3.10	16.19±4.32	< 0.0001

In table-2, negative correlation was found between patient's and control for all (R.B.S , HBA1C, CYS-C,GPT and IL-6) while positive

correlation was found for all (Albumin , protein , procalcitonin, CRP , GOT and ALK-ph)

TABLE 2: Correlations between anthropometric and serum cys-c in study subjects

Variables	Correlation
R.B.S	- 0.45
HBA1C	- 0.146
Albumin	0.23
Protein	0.29
Procalcitonin	0.466
CRP	0.36
CYS-C	-0.19
GOT	0.32
GPT	-0.0091
ALK.Ph	0.27
IL-6	-0.28

DISCUSSION

Cystatin C is a serum-bound, non-glycosylated protein with a low molecular weight (13 kDa) that is highly correlated with the GFR (14) It is present in nearly all nucleated cells in the human

body and is unaffected by activity, gender, age, injury and inflammation states, or tissue specialization.(16). Since the kidney is the only organ that is able to remove Cys-C from the circulatory system, the GFR predominantly

affects the levels of serum Cys-C. Previous studies have shown that, independent of mild, moderate, or severe renal impairment, Cys-C can serve as an indicator for kidney function with a close relationship to GFR and good sensitivity, suggesting its promise as a diagnostic marker [17]

The current study discovered higher levels of cys-c in people with type 2 diabetes than in the control group. Many studies, like Cheng-Cheng Ma et al.2020, presented related results (15) .

There has been a lot of discussion on the connection between cystatin C and the emergence of type 2 diabetes mellitus. (Diabetes is described as being treated with insulin, oral hypoglycemic medications, diet changes, or all of these) (HbA1c). The incidence was greater in those with higher baseline cystatin C levels, independent of confounding risk variables. Future research should focus on figuring out whether cystatin C might have a role in the emergence of type 2 diabetes. Fasting glucose, renal function, and baseline HbA1c were all factors in this connection. Baseline insulin resistance, waist size, and BMI all showed interactions when cystatin C levels were also taken into account.

They came to the conclusion that only people with central obesity or insulin resistance and incident diabetes were associated to cystatin C. Cystatin C and cardiovascular disease are related. Independent of renal function, it was found that cystatin C levels were related to insulin resistance and inflammation. This may clarify how type 2 diabetes, cystatin C, and cardiovascular disease are related [18].

A multifunctional cytokine called interleukin 6 (IL-6) has been linked to the etiology of type 2 diabetes (T2D). An independent predictor of T2D, the increased circulating amount of IL-6 is thought to play a role in the emergence of inflammation, insulin resistance, and beta-cell dysfunction. Contrarily, mounting data indicates that IL-6 has anti-inflammatory properties and enhances glucose metabolism. The pleiotropic properties of IL-6 may be explained by the cytokine's intricate signal transduction process. Classic signaling and trans-signalling are two different signaling pathways that IL-6 uses to

exert its effects. Although the identical receptor subunit is activated by both signaling mechanisms, their biological outcomes are entirely different. This review's objective is to provide an overview of what is currently known regarding how IL-6 contributes to the emergence of T2D. In addition, we will go over the significance of targeting IL-6 trans-signaling rather than both signaling routes as a therapeutic approach for the management of T2D and its related macrovascular problems. (19)

Comparing infectious and non-infectious diseases, PCT has greater sensitivity and specificity than CRP. PCT levels have a high sensitivity (92%) for helping to distinguish between bacterial and viral illnesses. PCT is typically produced in thyroid C cells, where it serves as a precursor to calcitonin. In contrast, bacterial cells and toxins act to create inflammatory cytokines in severe infections brought on by bacteria, parasites, and fungus. These cytokines stimulate PCT production by acting on organs such the lungs, kidneys, liver, adipose tissue, and muscles (20)

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