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The Correlation Between Higher of Human Interleukin-6 and C-reactive Protein in Female Patients with Diabetes Type 2

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P A P E R I N F O

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A B S T R A C T

Insulin resistance, glucose intolerance, fat deposition, dyslipidemia, and systemic inflammation are all symptoms of type (2) diabetes (T2D). Giving to the Universal Diabetes Confederation, millions of people worldwide will get diabetes. Genetic and environmental variables play a character in the development of T2D. In this investigation, samples were taken from 40 healthy women and 46 female patients with diabetes mellitus type 2. The serum levels of insulin, C-reactive protein, and Human interleukin-6 were measured in all patients and control groups. The results revealed that patient levels of these parameters were significantly more advanced than those in the control group, but the P value was less than 0.001.

1. INTRODUCTION

The umbrella term diabetes mellitus (DM) refers to a group of metabolic disorders brought on by either excessive or inadequate insulin synthesis. It typically presentes hyperglycemia and glucose intolerance, in addition to disrupting the processes that regulate the loading and enlistment of metabolic fuel and producing abnormalities in the metabolism of proteins, lipids, and carbohydrates [1].The International Diabetes Federation (IDF) estimates that 4.2 million individuals worldwide lost their lives to diabetes in 2019. Compared to the current 463 million, it is predicted that 700 million people between the ages of twenty and seventy will have diabetes by millions. The main reason for the at least several billion US dollars that were spent on healthcare in 2019 was diabetes [2].
Furthermore, gestational diabetes significantly increases the patient's offspring's genetic and environmental risk of developing diabetes and obesity due to the intrauterine diabetic environment. Financial statistics for Type 2 Diabetes (T2DM) date back to 1990, and 95% of all instances of diabetes reported in the US and worldwide are on the rise [3]. The aging population, urbanization, socioeconomic advancement, consumption of more highly processed food, and a decline in physical activity are some of the factors behind the exponential expansion. Nearly half of those with T2.DM are unaware that they have it because there are not many symptoms or markers in the early stages of the disorder.
Diabetes problems develop prior to a diagnosis being confirmed due to undiagnosed symptoms [4]. Despite the concerning prevalence of diabetes mellitus, around 193 million individuals lack a diagnosis. Many people are unaware that they have the condition due to factors such as a lack of symptoms or indicators and restricted access to medical care [5].
Based on where it originated, the American Diabetes Association (ADA) has divided diabetes mellitus into the following categories:
The first is
-Type 1 autoimmune idiopathic diabetes (T1DM).
-Type 2 Diabetes Mellitus (T2DM).
- Different forms of diabetes, including gestational diabetes mellitus (GDM) [6].

1.1. Diabetes Mellitus Type 2

Type 2 diabetes is the cause of 90–95 percent of cases of diabetes. In the context of hyperinsulinemia, which is characterized by both metabolic inefficiency and insufficient insulin production to meet the body's needs, insulin resistance leads to hyperglycemia [7]. Because of reduced insulin-mediated glucose uptake by muscle and fat in peripheral tissues, inadequate hepatic glucose output decrease, and ineffective fat-mediated triglyceride uptake, insulin resistance must be fought with increased insulin production [8]. The primary symptoms of this condition are polyuria, polydipsia, polyphagia, weight loss, fatigue, and eyes that seem far from objects. If their chronic hyperglycemia is not treated, diabetic patients may experience serious

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consequences [9].

the reasons for type 2 diabetes

For the past ten years, the sole significant element in identifying the congenital etiology of type 2 diabetes (T2DM) has been hypothesis-free genome-wide association studies (GWAS). More than 100 related genetic loci have been discovered using GWAS. Overindulgence and idleness are indicators of excess fat; genetic research has addressed this extensively. Comprehensive evaluations of BMI and related metrics indicate that among people of different descents, genes with high expression of the central nervous system are associated with general obesity [10].

1.2. Human Interleukin-6

Human interleukin-6 (IL-6) was once known by a number of names, including interferon, 26 K factor, B-cell stimulatory factor 2 [11], hybridoma growth factor, plasmacytoma growth factor, hepatocytestimulatory factor [12], hematopoietic factor, and cytotoxic T-cell differentiation factor. The biological activity linked to each name was tested using the same protein. Nowadays, most people are aware of the critical function IL-6 plays in several host defense mechanisms, including immunological response, acute-phase reactions, and hematopoiesis [13,14]. While IL-6 does not seem to have much impact on the body's "housekeeping" duties, when combined with other cytokines, it acts as the body's first line of defense against tissue damage or infection [15]. The functional pleiotropic effect of IL-6 has been shown, wherein. The pathophysiology of IL-6 has been linked to a number of diseases, including psoriasis, osteoporosis, rheumatoid arthritis, multiple myeloma, meningeal proliferative glomerulonephritis, AIDS, and Kaposi's sarcoma [16, 17]. Given the connection between clinical illnesses and abnormal IL-6 production, there has been a lot of interest in understanding the biochemical pathways regulated by IL-6 and in developing functional agonists and antagonists as potential therapeutic drugs for the treatment of IL-6-associated disorders [18]. Depending on the type of target cell, IL-6 influences a variety of proliferative, differentiated, and maturation events. The majority of cytokines and growth factors involved in the immunohemopoietic system share this functional pleiotropy [19].

There may be biological activities that overlap (functional redundancy) or that these cytokines are regulated at their receptors or along their intracellular signal transduction pathways, given that a single cell frequently reacts to several cytokines and growth factors that cooperate. Additionally, it has been demonstrated that several cytokines can function similarly or identically on the same cell. Numerous cells spread throughout the body create cytokines, which are distinct from traditional hormones.

It is a widely accepted belief that the body can more affordably produce pleiotropic biological effects by acting locally on the same cytokine. It is commonly known that the body can manufacture the same cytokine and use it locally to produce pleiotropic biological activity, more reasonably priced [20].

1.3. C.reactive Protein

An acute-phase protein called C-reactive protein (CRP) is a marker for inflammation or infection. When the level of blood protein falls below 10 mg/L, the liver begins to produce the protein. CRP levels rise quickly during the first six to eight hours of an infectious or inflammatory disease and peak 48 hours later at 350–400 mg/L [21]. CRP binds to Pepto saccharides and polysaccharides found on bacteria, parasites, and fungus in addition to the phosphocholine produced on the surface of injured cells. The immune system's classical complement cascade is triggered by this binding, which modifies the activity of phagocytic cells and strengthens the action of CRP in the opsonization of harmful microbes, boosting pathogen and living or dead cell opsonization by CRP, production is a good indicator of disease activity since it reduces when tissue damage or inflammation is treated [22]. Anemia, protein levels, red blood cell shape, patient age, or sex have no effect on CRP levels. However, by the conclusion of pregnancy, women usually have greater CRP levels [23].

The iron of the body and vitamin A status have been measured by serum ferritin, serum retinol, and other acute-phase proteins, which have all been used to compare the various levels of CRP in response to inflammation or infection. In any viral or inflammatory disease, serum ferritin levels increase along with a drop in serum retinol levels. As a result, an inflammatory or viral state could cause an overestimation whereas an underestimating could take place [24].

2. METHOD

In this study, the first group included 46 female patients with type 2 diabetes mellitus who were all between the ages of 35 and 60; the control group included 40 healthy female patients. The patients were seen at Al-Hussein Hospital in Kerbala. Name, age, weight, height, other diseases, and duration were among the details collected from patients and the control group in questionnaires. Each participant in the groups had their antecubital veins punctured with disposable sterile plastic syringes to collect three milliliters of venous blood. The blood samples were drawn into simple tubes without any anticoagulant, and they were left in a 37°C water bath for 15 minutes to clot. To extract serum samples, centrifugation was employed. Using a kit, the levels of human Interleukin-6, high Sensitivity C-reactive protein, and insulin were measured.

3. RESULTS

The results of the study showed that, in contrast to the control group, the patient group had considerably higher concentrations of serum insulin, C-reactive protein, and IL-6. Nevertheless, there was no significant difference in age or BMI, as Table 1 illustrates.

TABLE1. Serum biomarkers in women patients with diabetes type 2 and control subjects.

Parameter	Subject	Mean ± SD	P value
Age year	Patients	38.50 ± 9.12	NS
	Control	36.08 ± 8.55	
BMI kg/m2	Patients	55.22 ± 18.33	NS
	Control	53.10 ± 15.70	
Insulin ng/ml	Patients	18.66 ± 4.22	≤ 0.001
	Control	3.80 ± 1.71	
C-reactive protein(mg/l)	Patients	2.00 ± 2.61	≤ 0.001
	Control	0.52 ± 0.33	
Human IL-6 (pg/ml)	Patients	2.60 ± 1.82	≤ 0.001
	Control	1.32 ± 0.95	

Figure 1 shows the distribution of patients of diabetes mellitus according to age (years) including (35-60 years). Majority of patients (N=23, 58%) presented with age 46-60 years and 17 patients (42%) with age 35-45 years.

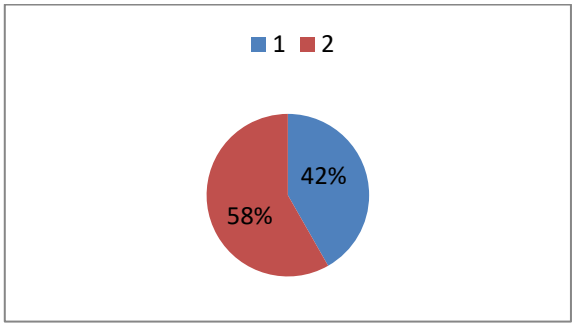

Figure 1. Distribution of patients with diabetes mellitus according to age (N=40).
1: patients of age 35-45 years 2: patients of age 46-60 years.

TABLE 2. Results of relation of age on parameters in women patients and healthy women.

Parameter	Subject	number	Mean ± SD	P value
Insulin ng/ml	35-45 years	17	17.88 ± 4.23	NS
	23			
	46-60 years		18.56 ± 3.31	
C-reactive protein (mg/l)	35-45 years	17	2.10 ± 0.74	≤ 0.001
	23			
	46-60 years		3.41 ± 0.52	
Human IL-6 (pg/ml)	35-45 years	17	2.06 ± 1.87	≤ 0.001
	23			
	46-60 years		3.85 ± 1.11	

4. DISCUSSION

The results in Table 1 of our investigation are explained by recent research showing a correlation between obesity and the development of type 2 diabetes (T2D) and greater amounts of IL-6, C-reactive proteins, and intestinal symbiosis [25]. Because adipocytes produce the essential CRP stimulators, tumor necrosis factor (TNF-) and interleukin 6 (IL-6), high CRP levels have been linked to excess body weight. Furthermore, it is known that under healthy conditions, hepatocytes create substantially less CRP than do T2DM patients, who have elevated levels of inflammatory markers like CRP.

Elevated CRP levels are closely associated with endothelial dysfunction, the synthesis of vasodilators, metabolic syndrome, and vascular system disease. Furthermore, insulin-based therapies may alter CRP levels in T2DM patients [26]. CRP production may be triggered by a number of metabolic and inflammatory factors, such as high blood glucose, adipokines, and free fatty acid levels, which are associated with the onset of type 2 diabetes. Moreover, a high CRP level in individuals with diabetes is a reliable indicator of vascular issues and the onset of cardiovascular disease [27].

Moreover, numerous studies on humans and animals have demonstrated connections between obesity and elevated serum CRP levels, as well as the progression of insulin resistance into type 2 diabetes. These findings provide credence to the hypothesis that the inflammatory state suggested by high CRP levels plays a major role in the pathogenesis of type 2 diabetes. Numerous studies have found a substantial positive correlation between elevated CRP levels and the probability of acquiring type 2 diabetes (28). However, when adjusting for a number of factors known to cause type 2 diabetes, including obesity and hyperinsulinemia, several studies fail to discover this connection. Owing to the fact that obesity and elevated body fat are significant risk factors for the development of type 2 diabetes and they are associated with a higher risk of inflammation and the advancement of insulin resistance (29).

Age, obesity, and inactivity are probably the main factors that affect the onset of type 2 diabetes. Long before the clinical signs of type 2 diabetes appear, IR, which is characterized by hyperinsulinemia and is commonly linked to obesity, hypertension, and dyslipidemia, starts [30]. During insulin resistance (IR), compensatory hyperinsulinemia keeps blood glucose levels normal. Yet, cells lose their capacity to do so due to hypersecretion, which causes hyperglycemia. Subclinical inflammation is a key component of inflammatory response (IR), and there is a positive link between IR and a number of inflammatory markers, including CRP. The innate immune system also produces serum amyloid A and fibrinogen in addition to CRP, the amounts of which change noticeably in response to inflammation, tissue injury, or infection. High concentrations of fibrinogen, sialic acid, CRP, and other

Low levels of albumin, transferrin, and serum amyloid A have all been linked to an increased risk of type 2 diabetes [31]. Inflammation of the adipose tissue and high levels of TNF-, IL-6, and IL-1 in obese people are factors that influence the onset and progression of type 2 diabetes. According to some writers, TNF-inhibits Akt substrate and increases IL-18 synthesis, which helps induce inflammation (IR) in human skeletal muscle. Moreover, TNF-reduces insulin-induced endothelial vasodilation and glucose absorption. TNF- receptors also have an impact on proteins that interfere with insulin signaling, trigger an inflammatory response, and make it easier for the NF-B pathway to activate [32].

However, in the liver and skeletal muscle tissues, IL-6 affects the production and activity of the insulin-degrading enzyme, and the manipulation of this enzyme may be connected to type 2 diabetes and obesity. In fact, a recent meta-analysis found that IL-6 contributes to chronic inflammation in people with T2DM. Because the general population appears to be exposed to insufficient amounts of IL-6, targeting the IL-6 pathway may not reduce the risk of developing type 2 diabetes. Although there is some evidence that CRP contributes to the microvascular effects of diabetes, such as neuropathy, retinopathy, and nephropathy, IL-6 is required for liver homeostasis [33].

Despite the fact that there is some evidence linking CRP to the microvascular effects of diabetes, such as nephropathy, retinopathy, and neuropathy. Elevated glucose levels may lead to increased production of inflammatory factors such TNF-, IL-6, and CRP, which may also cause microvascular alterations. Serum HS-CRP is linked to the development of diabetic neuropathy, one of the most prevalent effects of diabetes. Still, in both male and female patients, peripheral diabetic neuropathy symptoms and inflammation are connected with endothelial dysfunction and elevated CRP blood levels. It is assumed that in individuals with T2DM peripheral neuropathy, increased CRP levels are positively correlated with inflammatory grade [34]. Even though these results provide new insight into the pathophysiology of diabetes, further research is still needed to address unresolved issues.

Animal studies have shown that CRP plays a critical role in infections and inflammatory processes, and that it is produced in response to monocytic mediators such as IL-1 and IL-6 during the acute phase of infections [35]. CRP recognizes and attaches to specific polysaccharides in the bacterial wall to opsonize infections. The complement pathway is further triggered by this. Moreover, evidence suggests that CRP contributes to both proliferative and apoptotic processes by activating Fc receptors, which causes proapoptotic and proinflammatory mediators to produce cytokines. Male Sprague-Dawley rats given streptozotocin show greater serum CRP levels than untreated rats [36].

The antioxidant qualities of vitamin E, according to the same investigators, significantly decreased CRP levels and vascular issues in diabetic mice. A link between elevated CRP levels and the development of type 2 diabetes has been observed in certain human investigations, even after adjusting for other variables such as obesity, hyperinsulinemia, hypertriglyceridemia, and low HDL cholesterol [37]. Additionally, middle-aged diabetic women with elevated CRP levels have higher levels than the group of healthy controls, as reported by Pradhan et al. This finding raises the possibility that inflammation contributes to the etiology of type 2 diabetes. Han et al. also observed variations in the association between the prevalence of T2DM and elevated CRP levels by sex. This significant correlation may be explained by women's higher fat content and distinct hormone profiles [38, 39].

In 44% of the patients, Magrinelli et al. found a significant inverse relationship between serum IL-6 levels and compound muscle action potentials as well as sensory nerve action potentials. They argue that IL-6 plays a role in peripheral nerve axonal damage [40]. According to the study by Brazil, Lebro et al., there was a 19% occurrence of self-reported diabetes among women up to the age of 60 in the United States and Canada between 2005 and 2008. This study explains why the majority of women with type 2 diabetes between the ages of 46 and 60 were in the second group and had higher levels of inflammatory factors than the first group of female patients.

According to estimates, 26.9% of adults over 65 had diabetes. Previous studies using occupational cohorts have suggested that the self-rated health is mainly a reflection of physical and mental health problems and, to a lesser degree, of age, early life circumstances, family history, sociodemographic traits, psychosocial factors, and behavior related to health. It was found that living alone was linked to type 2 diabetes in men but not in women in a population cohort comprising both sexes [42].

The results of the study by Lidfeldt et al. [43] may be explained by the fact that women in Brazil who are most likely to have type 2 diabetes are older and live with others because they require care. It is also feasible that these women are in worse health and have lower incomes than other women. An rise in BMI between the ages of 20 and 30 was another factor that led to the onset of diabetes and its effects on inflammatory variables. Studies have shown that being obese or overweight when you are younger may increase your risk of developing diabetes [44].

Kim et al. found that among women in the Diabetes Prevention Program who were at high risk for the condition, going through a normal menopause did not increase their risk of developing diabetes. The lack of correlation between menopausal state and diabetes risk may be explained by the fact that the majority of women were postmenopausal at the time the condition developed [45]. The doctor's diagnosis report also established the age at which diabetes first became apparent. Other levels of aberrant glucose tolerance were not taken into account.

5. CONCLUSION

Human IL-6, C-reactive" protein, and type" 2 diabetes in women are strongly correlated.

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Arabic Abstract

مقاومة الأنسولين، عدم تحمل الجلوكوز، ترسب الدهون، دسليبيدميا، والالتهابات الجهازية كلها أعراض لمرض السكري من النوع (2) T2D من خلال التبرع للاتحاد العالمي للسكري، سيصاب ملايين الأشخاص في جميع أنحاء العالم بمرض السكري. تلعب المتغيرات الجينية والبيئية دورًا في تطور مرض السكري من النوع الثاني. في هذا البحث، تم أخذ عينات من 40 امرأة سليمة و46 مريضة مصابة بداء السكري من النوع 2. تم قياس مستويات الأنسولين والبروتين التفاعلي C والإنترلوكين البشري 6 في جميع المرضى ومجموعات المراقبة. وكشفت النتائج أن مستويات هذه المعلمات لدى المرضى كانت متقدمة بشكل ملحوظ عن تلك الموجودة في المجموعة الضابطة، ولكن قيمة P كانت أقل من 0.001.