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The Association between Type 2 Diabetes Mellitus and Some Immunological Parameters (IL-6, C3, Igg, WBC)

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Abstract

The study aimed to establish the connection between type 2 diabetes mellitus and IL-6, C3, IgG, and WBC in clinically diagnosed diabetes patients. Using a cross-sectional design, we compared the immunological parameters of 121 Iraqis from Basra City having type 2 diabetes mellitus with 50 healthy control people. Serum concentrations of total IgG and third complement compound C3 were determined by the turbidimetric method using Gesan production S. R. l-Italy. Piccolo chem. Serum concentrations of IL-6 were determined using enzyme-linked immune sorbent assay (ELISA). The CBC was measured. Demographic and laboratory data were distinguished. Our data indicated that type 2 diabetes was strongly associated with elevated levels of IL-6, C3, and WBC, with no significant difference in the IgG levels. Unregulated blood sugar levels change the normal concentration of immunological parameters, leading to an altered immune response in diabetic patients.

Keywords: immunological parameters, IL-6, C3, IgG, WBC, Diabetes mellitus.

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INTRODUCTION

Type 2 diabetes, especially when poorly controlled, is a disease of the innate immune system and shows up as chronic low-grade inflammation.[1]

Cytokines are substances that cells use to send messages and initiate the immune system's responses against outside invaders. [2]

IL-6 is a homodimer cytokine that ranges in size from 19 to 26 kD. It is made by cells in the body, such as endothelial cells, fibroblasts, and monocytes (macrophages). IL-6 is a multifunctional cytokine that controls many cellular processes, such as the growth of some types of cancer cells, the development and maturation of hemopoietic progenitors, and the metabolic processes of cells. It is becoming clearer that IL-6 changes both local and systemic inflammation and defense. A rise in IL-6 made by adipose tissue has been linked to both the start of DM2 and peripheral insulin resistance. [1]

High amounts of IL-6 encourage the manufacture of free fatty acids (FFA) and oppose insulin pathway signaling, decreasing tissues' alertness to insulin action. IL-6 stops lipoprotein lipase from working and triglycerides from building up, among other things related to controlling lipid metabolism. Through SOCS proteins, IL-6 can also interrupt the insulin route in muscle and liver. [3]

To get rid of bacteria wrapped in antibodies, the complement system in the immune system works. It is made up of about 25 proteins and is chemical in nature. There are different parts of the complement system that work together to send the attackers packing. In addition, they are part of the system that fights inflammation. If there is inflammation, the levels of the acute phase proteins C3 and C4 maybe 50% higher (Jayachandran et al., 2016) [4] . A study by Muscari et al. in 2007 [5] It was found that C3 is strongly linked to diabetes. Human plasma has the highest concentration of C3, which is part of the complement system. It acts as a link between normal and unusual activation. Hepatic cells still make C3 even though monocytes and fibroblasts cause bacterial endotoxins.

The protein immunoglobulin G (IgG), which makes up 10% to 20% of plasma protein, is one of the most common ones in human blood. It is the most important of the five types of immunoglobulins that people have, which are IgM, IgD, IgG, IgA, and IgE. These glycoproteins are very similar, but their heavy chain structures and effector roles are very different. 82% to 26% of them are protein, and 4% to 18% are carbs [6].

The amount of white blood cells (WBC) and cytokines in the body shows how inflamed the immune system is. It has been pointed out that problems with the immune system play a big role in the progression of type II diabetes because of the statistical link between signs of insulin resistance and inflammation. [7] A CBC factor that may be linked with the onset and advance of DM can exhibit a range of inflammatory markers. The CBC can serve as an economic assessment tool to determine the likelihood of diabetics developing complications and aid in preventing mortality and adverse health outcomes. [8]

MATERIALS AND METHODS

Study design

The study was an observational cross-sectional study conducted in Basra City, Iraq, from January 2023 to April 2023.

Participants

An entirety of one hundred and seventy-one participants of both sexes joined in this research. The subjects were divided into two general groups: 50 healthy controls (34% females and 16% males) were within the age interval of (40 - 50) years and had a mean of 46.100±1.619398. The other participants were 121 patients with diabetes mellitus type 2, parted into 2 groups based on how long they had type 2 diabetes mellitus: 64 old diagnosed patients and 57 newly diagnosed patients (within 5 years)[9]. This group comprised (77 females and 43 males), with a mean age of 46.53719±2.642730.

Subjects were randomly nominated as some inclusion and exclusion criteria were employed in this investigation. All patients were randomly collected from the laboratory of the 7th Wheat Medical Complex in the Al-abasia region, Basrah City, Iraq.

Inclusion and exclusion criteria: subjects with a pre-existing diagnosis of type 2 diabetes mellitus (DM2) who have not received insulin treatment for a minimum of one year. All patients exhibited glycosylated hemoglobin A1c (HbA1c) levels over 6.1%. A group of individuals who are in good health and do not have any current or long-term illnesses. In contrast, the study excluded patients with acute illnesses, chronic problems such as nephropathy, retinopathy, neuropathy, hypothyroidism, hyperthyroidism, chronic digestive diseases, autoimmune diseases, hepatitis, and individuals undergoing immunosuppressive drug therapy.

A questionnaire gathered demographics and descriptions of all individuals, for instance, sex, age, education, Marital status, Family history, Occupation, disease/drug history, and smoking status.

Measurements

HbA1c was assessed by the ready-to-use kits SD BIOSENSOR using apparatus SD BIOSENSOR F200, corresponding to the existing guidelines [10]. Patients were formerly diagnosed with diabetes mellitus type 2 based on signs and symptoms of diabetes plus clinical measurements: Fasting blood glucose level (126 mg/dL), random blood sugar (200 mg/dL), or glycated Hemoglobin A1c ≥ 6.5% [18].

ASSESSMENT OF IL-6:

Interleukin 6 (IL-6) Human Elabscience ® Kit ELISA,

This ELISA kit is used to quantify the levels of human IL-6 in serum, plasma, and other biological fluids in vitro.

Measurement of the Serum concentrations of Total IgG and Third Complement Component (C3):

The serum concentration of IgG and the third component of the complement system (C3) were measured by the turbidimetric method, using Gesan production S. R. l. -Italy Kits for the quantitative determination of C3 and IgG. By Piccolo Chem (Autoanalyzer Clinical Chemistry) [11]

WBC Assay

For all subjects, almost 5 mL of venous blood sample was assembled in a serum-separating tube, sodium citrate, and ethylenediaminetetraacetic acid (EDTA) bulb by means of aseptic safety measures. Mindray BC-5000 estimated a complete blood picture [12]

Statistical analysis

The data was analyzed utilizing statistical software for social sciences (SPSS version 26). The data were presented as the mean value plus or minus the standard deviation to facilitate comparison. By utilizing the Shapiro-Wilk and Kolmogorov-Smirnov tests to ascertain if the numerical data had a normal distribution. Using the independent sample t-test for data that had an ordinary distribution, whereas using the Mann-Whitney U-test for data that had a nonnormal distribution. The binary logistic regression analysis was employed by researchers to compute the confidence interval (CI) and odds ratio (OR) for patients with type 2 diabetes (DM2). The link between the two variables was calculated using Pearson's correlation and Spearman's rank coefficients. statistical significance determined as P value < 0.05.

Results and Discussion

the demographics of the controls and diabetic patients were matched in age, gender distribution (females/males' ratio), education, marital status, occupation, and family history; there was no statistically significant difference ($p > 0.05$), while HbA1c exposed significant differences between healthy controls and diabetic patients with a p value=0.001.

Immunological parameters can be modified by differences in age. [13], education, family history,

occupation, marital status, and gender [14]. Thus, participants involved in the present study were matched in most ultimate characteristics, e.g., age and gender distribution, to generate better statistical accuracy and enhance the transparency of the presentation of the results, particularly when analyzing subgroups.

We excluded obesity because it can affect immunity.[15], as reported by a previous study[16]. This factor, along with others in the exclusion criteria, such as hypertension and cardiovascular diseases that impact the immune system [17], was also excluded to acquire matching criteria. Even though serum complement factor 3 (C3) is mostly produced in the liver as an acute-phase reactant, adipose tissue (AT) has been found to express the C3 gene highly in several recent investigations. Nonetheless, there is still uncertainty regarding the connection between C3 and AT levels in people with type 2 diabetic mellitus (T2DM).[18]

In this research, we compared controls and all DM2 patients unrelatedly of the time of diagnosis and it showed that immunological parameters (IL-6, C3, and WBC, Neu, Lym, and Mon) were significantly higher in DM2 patients (2.53585±3.014738; 181.39575±50.838560; 8.82667±2.429345; 4.99508±2.070094; 3.19358±1.195580; 0.47041±0.151910) than healthy people (0.63806±0.389875; 148.30800±35.845108; 6.57440±1.366826; 3.58960±1.101474; 2.45940±.549721; 0.39980±0.117881) ($p < 0.05$) except for (IgG, Eos) which revealed a non-significant difference ($p > 0.05$) between controls and all DM2 patients (1711.74600±578.667296; 0.13760±0.116646 vs. 1615.61600±484.624396; 0.14025±0.081048), as showed in Table 1 and 2.

Table 1: Immunological parameters of DM2 patients and controls

parameters	control Mean ±SD N=50	patients Mean ±SD N=121	*P value
IL6(pg/ml)	0.63806±0.389875	2.53585±3.014738	**0.001***
C3(mg/dl)	148.30800±35.845108	181.39575±50.838560	**0.001***
IgG(mg/dl)	1711.74600±578.667296	1615.61600±484.624396	0.268

- ✓ Independent sample t-test to compare means. *P value is considered significant if it is less than 0.05; N: number; Mean±SD is the mean value + standard deviation,

Table 2: Hematological indices in healthy control and diabetic patients' groups

parameters	control Mean ±SD N=50	patients Mean ±SD N=121	*P value
WBC (10^9/L)	6.57440±1.366826	8.82667±2.429345	**0.001***
Neu (10^9/L)	3.58960±1.101474	4.99508±2.070094	**0.001***
Lym (10^9/L)	2.45940±.549721	3.19358±1.195580	**0.001***
Eos (10^9/L)	0.13760±0.116646	0.14025±0.081048	0.884
Mon (10^9/L)	0.39980±0.117881	0.47041±0.151910	**0.001***

- ✓ Independent sample t-test to compare means
- ✓ For Mon a Mann-Whitney U test was done

C3 concentrations and T2DM were strongly related to each other. C3 concentrations are expected to be a vital marker for adipose tissue accumulation, which is an important cause of IR worsening. Recent

investigations have shown that AT may also contribute to C3 synthesis. AT itself produces C3, that's why the results show that patients with type 2 diabetes mellitus have raised concentrations of complement C3 more than healthy controls[18]While other studies conclude that C3 concentration decreased in patients with diabetic complications (diabetic nephropathy)[19]

Studies on Japanese patients have confirmed that the serum concentration of C3 appears to be strictly related to insulin resistance, mainly in metabolic syndrome[20].

These differences may be due to the elevated WBC count in diabetic patients keeping up with the increasing oxidative stress induced by hyperglycemia, which reflects poor glycemic regulation. [21]

The increased WBC count is an important marker of inflammation that may contribute to endothelial dysfunction and diabetic complications. Consequently, mononuclear and polymorphonuclear WBCs can be triggered by cytokines and advanced glycation end-products AGEs in a hyperglycemic state, according to Chung F et al. They also showed that the number of WBCs is raised in diabetic patients, and this may add to the disease's vascular problems.

Epidemiological research studies revealed a link between abnormal WBC count, development of vascular problems, and diabetes risk. They also stated that differential and total WBC counts are increased in DM2 when comparing healthy subjects in resemblance to the current study. Many prior studies, like the current study, showed that a higher WBC count, despite being within the normal range, is associated with developing diabetes complications. They also showed that total WBC, neutrophil, and monocyte counts are greater as the disease complications progress further.[21]

Blood cell disruption and related indicators are a result of elevated blood glucose levels in type 2 diabetes.[22].

When comparing the healthy control group to the newly diagnosed group, it predicts the non-significant difference in the concentration of IL-6(p=0.055), while a highly significant difference(P=0.001) between controls with old diagnosed and newly diagnosed with old diagnosed (table 3.3). The result also indicated a highly significant difference (P=0.001) in the C3 level when compared the controls with newly and old diagnosed, while no significant difference between newly diagnosed versus old diagnosed.

there were no significant differences in the IgG level between the three groups(1vs2,1vs3,2vs3) (P=0.233, P=0.440, P=0.636) in that order,

There were significant differences between the three groups (controls vs. newly diagnosed, controls vs. old diagnosed, newly diagnosed vs. old diagnosed) in the level of WBC (P=0.001, P=0.001, P=0.001, P=0.001, P=0.017).

The neutrophil results showed significant differences between the three groups (1vs2,1vs3,2vs3) (p=0.013, P=0.001, P=0.003). Lymphocytes revealed a greater level in diabetic patients than in controls, so the P value results were (0.001, 0.001) for the following comparison (1vs2, 1vs3), respectively. There was no significant difference (P=0.637) in the comparison (2vs3) (Table 3).

Eosinophil levels did not significantly differ between the control healthy group and newly diagnosed and old diagnosed groups (P=0.605, P=0.854, P=460). There were significant differences in the monocyte levels in the comparisons (1vs2,1vs3) since the p-value equals (0.004, 0.016), but there was a non-significant difference in the 2vs3 comparison (P=1.00).

Table 3: Comparison of Immunological parameters between diabetic patients' groups and healthy controls

Parameters	control Mean ±SD 1	new Mean ±SD 2	old Mean ±SD 3	P value 1vs2	P value 1vs3	P value 2vs3
IL6(pg/ml)	0.63806±0.389875	1.55220±2.019330	3.38331±3.458454	0.055	**0.001**	**0.001**
C3(mg/dl)	148.30800±35.845108	179.45036±46.590662	183.09797±54.594788	**0.001***	**0.001***	0.673

IgG(mg/dl)	1711.74600±578.667296	1591.76464±417.297142	1636.48594±539.122934	0.233	0.440	0.636
WBC (10^9/L)	6.57440±1.366826	8.32161±2.220051	9.26859±2.533727	**0.000**	**0.000**	**0.017**
Neu# (10^9/L)	3.58960±1.101474	4.46393±1.653970	2.288229±5.45984	**0.013**	**0.000**	**0.003**
Lym# (10^9/L)	2.45940±.549721	3.24214±1.266476	1.138325±3.15109	**0.000**	**0.001**	0.637
Eos# (10^9/L)	0.13760±0.116646	0.14696±0.079975	0.082151±0.13438	0.605	0.854	0.460
Mon (10^9/L)	0.39980±0.117881	0.48125±0.162112	0.46262±0.143954	**0.004**	**0.016**	1.000

✓ ANOVA test

In this work, we demonstrated that DM2 participants had higher levels of the inflammatory cytokine IL-6 than controls. Precisely, the old-diagnosed patients had higher levels of IL-6 than newly diagnosed patients and controls. This is consistent with earlier research that found DM2 people had higher levels of IL-6 among cases than among controls.[3]

The three groups' serum IgG levels did not differ significantly from one another. Thus, this study's findings demonstrate that diabetes individuals produce enough serum IgG to fend against harmful germs.[23]

Research Guo et al., 2016 reported that IgG was negatively related to type 2 DM (they decreased in the group of patients with type 2 diabetes than in controls), and this disagrees with our result that they are not significantly different in all study groups.[24]

The old diagnosed diabetic patients showed higher blood concentrations of WBC than newly diagnosed diabetic patients and controls, and the newly diagnosed diabetic patients showed higher WBC levels than controls. This is in line with M.N, D. J, and D. K, who reported that Increased leukocyte count is linked to both macro and microvascular problems in diabetes as well as insulin resistance.[25]

Table 4: Correlation between HbA1c and immunological parameters for all patients

HbA1c	IL6	C3	IgG
Pearson Correlation	0.033	0.286	-0.036
P value	0.668	**0.001**	0.637

✓ Pearson correlation

We chose HbA1c to correlate with the immunological parameters in diabetes as it is the most sensitive index of glycemic control over a period (3-4 months)[26].

All DM 2 patients show significant correlation between C3 parameter and HbA1c levels.

Table 5: Correlation of HbA1c with Immunological parameters for old diagnosed patients

HbA1c	IL6	C3	IgG
Pearson Correlation	-.111	0.228	0.078
P value	0.380	0.068	0.535

✓ Pearson correlation

Table 6: Correlation of immunological parameters for newly diagnosed patients with HbA1c

HbA1c	IL6	C3	IgG
Pearson Correlation	-0.096	0.055	0.033
P value	0.482	0.687	0.811

✓ Pearson correlation

There was a non-significant correlation between these immunological parameters for newly and old diagnosed patients with glycemic control.

Regarding the immunity response, A recent Du et al., 2023 study suggests that type 2 DM patients displayed significantly higher levels of lymphocyte concentration that agree with our results, while plasma IgG levels were significantly lower compared to those without T2DM, but we get results of non-significant lowering in the levels of IgG of diabetic patients than in controls that's maybe because of our small size study, they exposed IgG levels showed a significant negative correlation with HbA1c, but we get non-significant negative correlation with HbA1c for all patients; also this may depend on the scale size of the study[27] . proposing that hyperglycemia or hyperinsulinemia in T2DM may contribute to changes in immunoglobulins [27]

CONCLUSION

Type 2 diabetes mellitus (DM) plays a crucial role in the advancement of communicable diseases. Additionally, the immune system, along with other bodily systems, is particularly vulnerable in individuals with diabetes. Immunological markers such as IL6, WBC, and C3 show a considerable increase in individuals with type 2 diabetes, although IgG levels are not significantly reduced. Preventing and managing diabetes is essential to avoid further loss of immunological function. White blood cell (WBC) assays can be regarded as the primary clinical diagnostic test for type 2 diabetes mellitus.

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