Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

Correlational analysis of immunological and physiological parameters in patients with diabetes mellitus in Anbar Province (Iraq)

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Article info

Received 18.09.2025
Received in revised form 21.10.2025
Accepted 28.11.2025

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Muhammed, T. M., Hamad, H. M., & Allawi, Q. H. (2025). Correlational analysis of immunological and physiological parameters in patients with diabetes mellitus in Anbar Province (Iraq). Regulatory Mechanisms in Biosystems, 16(4), e25211. doi:10.15421/0225211

Diabetes mellitus (DM) type 2 is a chronic condition that occurs when the body cannot use insulin effectively or does not produce enough of it. This leads to high blood sugar levels and can cause serious health complications if not managed properly. The purpose of the presented research was to measure a few hematological and immunological parameters in patients with diabetes mellitus (DM). There were 80 blood samples in all, 50 of which came from patients with DM (cases). They were 16 to 50 years old, the remaining 30 samples were healthy individuals who served as controls and visited the Ramadi General Teaching Hospital in Ramadi City between October, 2023, and December, 2024. The study examined the correlation between the variables under investigation, demonstrating the presence of both positive and negative correlations. The results showed a notable change in the concentrations of IL4, IL17, IFNγ, and IL10 using ELISA. A comparison of the two groups (control and patients) revealed significant difference in the levels of IL17, IL10, IFNγ, and IL4. The mean values of IL17, IFNγ, and IL10 were significantly increased, while IL4 decreased significantly in comparison with the control group. Additionally, blood levels of Hb and PLTs revealed a significant difference, the level of Hb decreased significantly, while the PLTs level increased significantly in contrast with the control group. We conclude that the levels of IL-17 and IFN-γ were much higher in DM patients compared to the healthy individuals. Accordingly, a substantial drop in IL-4 and IL-10 was noted in DM patients compared with healthy individuals. Also the study examined the correlation between the variables under investigation, demonstrating the presence of both positive and negative correlations. The results of the correlation analysis showed a significant negative and positive correlation between IL-17 and both IL-10 and IFN-γ, respectively. However, the results did not demonstrate significant correlations between immune and physiological factors. Our results demonstrate that diverse and independently regulated cytokine pathways define the immunological dysregulation associated with diabetes, indicating that cytokine networks, rather than specific targets, should be the focus of effective treatment approaches.

Keywords: diabetic mellitus; interleukins; interferon gamma.

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition defined by persistent hyperglycemia. Insulin resistance can be induced by a combination of mechanisms, including reduced insulin secretion by pancreatic β-cells and inability of insulin-sensitive organs to respond effectively to insulin (Abdulridha et al., 2023). Diabetes can cause a variety of metabolic problems, including nephropathy, retinopathy, and neuropathy, particularly when poorly treated (Saini et al., 2021).

Oxidative stress can harm cells and tissues. Cytokines such as TNF-α and IL-1 affect hepatocytes and contribute to insulin resistance, dyslipidemia, obesity, and diabetes (Čolak & Pap 2021). In both humans and animals, cytokine therapy has been associated with insulin resistance and hypertriglyceridemia. TNF-α, a potent insulin receptor inhibitor, has been linked to insulin resistance in both diabetes and obesity (Wondmkun, 2020). A previous study indicates that diabetes is linked to increased cytokine production, which raises the hypothesis that cytokine overproduction could be the cause of or a contributing factor in metabolic abnormalities in diabetes. Rats given IL-1β injections repeatedly had decreased insulin release without changing the islet ultrastructure or insulin content (Saini et al., 2022).

The relationship between the immune system and diabetes pathogenesis has drawn attention to the pattern of some immune cells and their released cytokines associated with T2DM progression (Hammad et al., 2021). The burden of type 2 diabetes (T2D) is large and anticipated to grow. In 2021, there were around 8.4 million people worldwide living with T2D. A 10-year-old diagnosed with T2D has an average life expectancy of 13 years in low-income nations and 65 years in high-income ones (Klimontov et al., 2023). The processes behind the detrimental effects of excess hyperglycemia on target organs in diabetes have been extensively researched in recent years. The cardiovascular system, pancreas, adipose and muscular tissues, gastrointestinal tract, and kidney have been identified as the regions with the highest expression of glucose-related genes (Saik & Klimontov, 2020). Current evidence suggests that glucose impacts can manifest as oxidative stress, non-enzymatic glycation, chronic low-grade inflammation, endothelial dysfunction, platelet activation, poor angiogenesis, and renal fibrosis. At the molecular level, these pathophysiological processes may be mediated by changes in the production of cytokines and growth factors, which play significant roles in intercellular interactions (Klimontov et al., 2021). TNF-α, IFN-γ, and IL-17 production, as well as T cells, were found to be significantly increased during obesity-induced insulin resistance and T2DM development (Mathis, 2013).

Research indicates that the frequency of IFN-γ-producing CD3+ T-cells is favorably linked with body mass index (BMI) (Francisco et al., 2016). Previous research has shown that other types of lymphocytes can alter cytokine frequency. B-cells support Th17 inflammation in T2DM patients but not in healthy people, whereas monocytes support Th17 inflammation regardless of T2DM status (Cao et al., 2016; Rashied et al., 2020). The purpose of the presented research was to assess serum levels of IL4, IL17, IFNγ, and IL10, and several diabetic parameters in patients with DM and compare their serum levels to those of normal control.

Materials and methods

The Ethical Approval Committee of the University of Anbar in Iraq approved all research methods used in the study (Approval No. 32, March 13, 2025).

This research involved 80 participants from both sexes, ranging in age between 16 and 50, with 30 healthy participants serving as the

control group and 50 diabetes mellitus (type 1 and 2) patients who visited the General Teaching Hospital in Ramadi City for monthly clinical examination and laboratory investigation between October, 2023, and December, 2024.

Inclusion criteria: the age range is between 16 and 50 for diabetes mellitus type 1 and 2.

Exclusion criteria: thyroid disease, patients with pregnancy, kidney disease patients liver disease and any other chronic disease.

Ten milliliters of venous blood were drawn from an appropriate vein. About 2.5 mL of the blood sample was quickly transferred to a clean, dry EDTA tube. It was then gently shaken and utilized straight for the blood count blood test, the remaining blood sample was put into a glass tube without anticoagulant and allowed to coagulate for serum separation for five minutes in a 4000 rpm centrifuge. To be employed for serological research, the separated serum was gathered and stored at –20 °C in sterile, clean white tubes.

In the research, commercially available kits of enzyme linked immunosorbent assay (ELISA) have been utilized in order to quantitatively determine IL-17 using Human IL-17 ELISA Kit(Bioworld Technology, Inc. USA-CEK1759), IL-10 using Human IL-10 ELISA Kit (Bioworld Technology, Inc. USA -CEK1740), IL-4 using Human IL-4 ELISA Kit (Bioworld Technology, Inc. USA -CEK1734) and IFN-γ using Human IFN gamma ELISA Kit (Bioworld Technology, Inc. USA, CEK1743), as well as determine Insulin Ab using ELISA kit for the quantitative measurement of IgG class autoantibodies against insulin in human serum (Demeditec Diagnostics GmbH, Germany, DE7430). The determination of Hb and PLTs parameters were performed by complete blood count (CBC) test (Coulter HMX Inc.) CBC is a very common blood test to evaluate the types of cells in blood.

Data were analyzed statistically using GraphPadPrism 10.4.0, a statistical analysis program. Mean, SE of mean, independent t-test (two-tailed), and Pearson's correlation (two-tailed) were used to analyze the numerical data. Probability less than 0.001 is considered significant.

Results

To evaluate the patients' condition in comparison to controls, many laboratory analyses were carried out. To determine the progression of the disease and monitor interventions, the study conducted an anti-insulin antibody test. The results of the study showed a significant increase in antibody levels in patients compared to the control group (Table 1, Fig. 1).

Table 1
Comparison between patient and control groups in terms of anti-insulin Ab status

Anti-insulin Ab status	Patients group, no. (%)	Control group, no. (%)
Positive	20 (100.0)	0 (0.0)
Negative	0 (0.0)	10 (100.0)

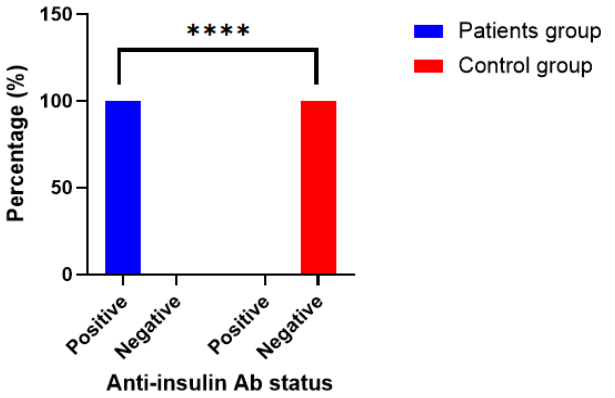

Fig. 1. Anti-insulin Ab of patients is shown compared to controls

As illustrated in Figure 2, the current study demonstrated a considerable decrease in the levels of IL-4 in DM patients when compared to normal individuals (i.e., controls), with a $P < 0.001$. The average levels of IL-4 in the patients were lower when compared to those in the controls (with respective means ± SE) of 14.0 ± 1.3 and 73.6 ± 4.2 pg/mL, respectively.

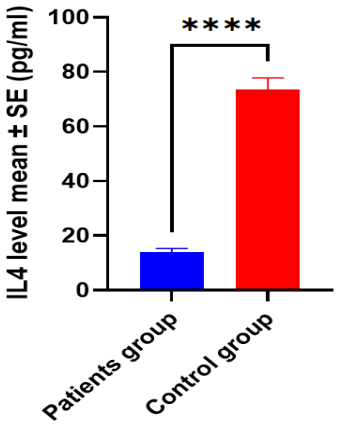

Fig. 2. Average IL-4 (14.0 ± 1.3 and 73.6 ± 4.2 pg/mL) levels in the patients as well as the controls

As illustrated in Figure 3, the current study demonstrated a non-considerable decrease in IL-10 levels in patients when put in comparison with normal individuals (controls) with $P > 0.05$. Average IL-10 levels in the cases were lower than those in the controls (with respective means ± SE) of 10.1 ± 2.2 and 24.9 ± 10.0 pg/mL, respectively.

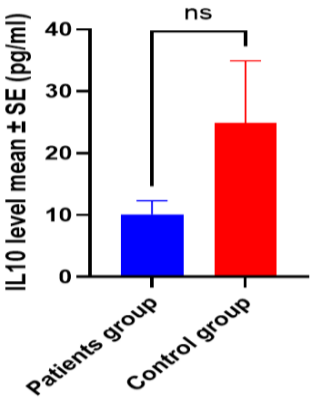

Fig. 3. Average IL-10 (10.1 ± 2.2 and 24.9 ± 10.0 pg/mL) levels in the patients as well as the controls

As illustrated in Figure 4, the current study demonstrated a considerable raise in IL-17 levels in patients with DM (i.e., the cases) in comparison with normal individuals (i.e., controls), with $P < 0.001$. Average levels of IL-17 in the patients were higher when compared to those in the controls of 78.5 ± 3.5 and 17.7 ± 0.9 pg/mL.

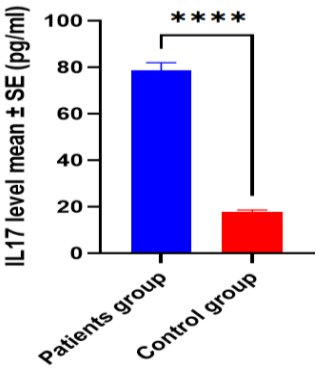

Fig. 4. Average IL-17 (78.5 ± 3.5 and 17.7 ± 0.9 pg/mL) levels in the patients as well as the controls

The result of IFN-γ is shown in Figure 5. The results demonstrated a considerable increase in IFN-γ levels in DM patients when put in comparison with normal people (control), with a $P < 0.001$).

The IFN-γ levels in cases were higher compared with those in controls, 84.6 ± 3.7 and 16.7 ± 0.6 pg/mL, respectively.

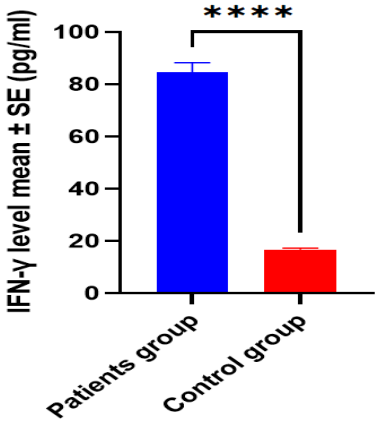

Fig. 5. Mean levels of IFN-γ (84.6 ± 3.7 and 16.7 ± 0.6 pg/mL) in patients and controls

As illustrated in Figure 6, the current study demonstrated a significant difference in Hb concentration between cases and controls, with a p-value ($P < 0.001$). The means ± SE of Hb for the two groups were 9.62 ± 0.33 and 14.45 ± 0.75 g/dL, respectively.

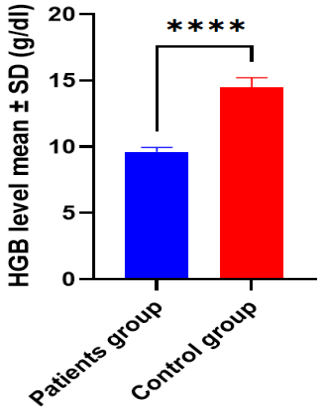

Fig. 6. Mean levels of HB in patients and control

With a $P < 0.001$, the current research demonstrated a considerable difference between the number of PLTs in the patients and controls. According to Figure 7, the PLT mean ± SE for the two groups were, respectively, 643.0 ± 34.8 and 234.3 ± 44.4 c/mm³.

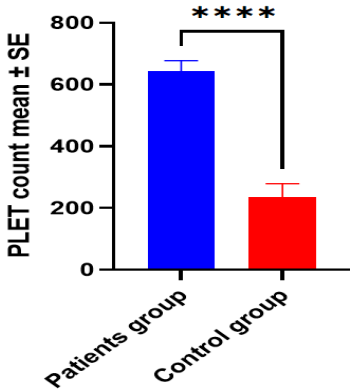

Fig. 7. Mean levels of platelet (c/mm³) in patients and control

In the current study, the associations between immunological and hematological parameters in the patient group were assessed by a thorough examination of correlation coefficients (Fig. 8).

Discussion

Persistent hyperglycemia, or increased blood glucose levels, is a hallmark of diabetes mellitus, a chronic metabolic disease caused by decreased insulin activity, secretion, or both. In addition to causing major long-term harm to organs including the heart, blood vessels, eyes, kidneys, and nerves, it causes disruptions in the metabolism of proteins, lipids, and carbohydrates (Mayer-Davis et al., 2018; Khalaf et al., 2024). According to a recent evaluation, diabetes should be viewed as a group of metabolic diseases joined by hyperglycemia, reflecting a variety of underlying causes and requiring specialized treatment approaches (Yameny, 2025). To evaluate the general condition of the patients, the current study performed the anti-insulin Ab test. Compared to the healthy control group, diabetes patients in this study demonstrated significantly higher levels of anti-insulin antibodies and showed noticeably greater levels of anti-insulin antibodies (anti-insulin Ab). The development of insulin autoantibodies (IAA) is a hallmark of the autoimmune response in type 1 diabetes mellitus (T1DM), and it can also happen in insulin-treated patients with type 2 diabetes mellitus (T2DM) as a result of exogenous insulin exposure, according to earlier reports (Ismail, 2015). It's interesting to note that the control group had either no anti-insulin Ab levels or none at all, which is consistent with research showing that healthy, non-diabetic people seldom ever produce these antibodies unless they are exposed to insulin through treatment or unique autoimmune diseases (Winter et al., 2022).

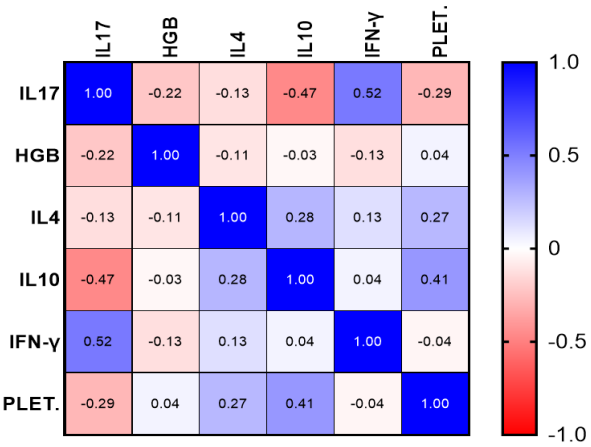

Fig. 8. The correlation between parameters in patients

The autoimmune nature of the illness and the immunogenicity of insulin treatment may both be responsible for the higher anti-insulin Ab levels seen in our diabetic sample. In general, some interleukins contribute to the development of diabetes and increased inflammatory processes, while others are considered anti-inflammatory in diabetics. Therefore, the current study investigated the relationship between four interleukins and the development or reduction of diabetes complications.

According to the study's findings, the patient group's IL-4 levels significantly decreased when compared to the control group. According to experimental research, IL 4 can improve hepatic glucose absorption, increase insulin sensitivity, encourage glycogen synthesis, and decrease hepatic lipid accumulation – all of which are advantageous for maintaining metabolic homeostasis. These regulatory functions are diminished by IL 4 deficiency, exacerbating lipid imbalance and insulin resistance (Yang et al., 2018). Therefore, low IL-4 levels can be a clear sign of diabetes in general. The reason for the decrease in IL-4 can be explained by a number of mechanisms. Peripheral blood mononuclear cells (PBMCs) activated *in vitro* generate considerably less IL 4 at the protein and mRNA levels in people with recent-onset type 1 diabetes mellitus (IDDM). Although it somewhat improves after diagnosis, this impairment is still greater than that of non-diabetic controls (Berman et al., 1996). This implies that early in the pathophysiology of T1D, there are compromised Th2/IL 4 anti-inflammatory responses.

Other studies found reduced IL-4 production from pancreatic-draining lymph node NKT cells in human T1D, suggesting that a crucial immunoregulatory cell type is unable to offer IL-4-mediated protection (Liu et al., 2020).

This IL-4 deficiency might be a factor in uncontrolled β cell autoimmunity. There may be a genetic predisposition to low IL 4 in metabolic dysfunction, as some T2DM patients have specific IL 4 gene polymorphisms (e.g., B2B2 genotype) that are significantly linked to decreased IL 4 gene expression and serum IL 4, as well as negative lipid profiles (e.g., lower HDL, higher LDL) and elevated blood pressure (Badr et al., 2018).

Circulating IL 4 levels in T2DM are variable, despite the fact that IL 4 is widely regarded as anti-inflammatory and helpful in metabolic control. According to a recent comprehensive meta-analysis, certain T2DM cohorts actually had higher levels of IL 4, which may be an anti-inflammatory compensatory response to chronic inflammation (Cao et al., 2025). Data, however, are sparse and varied.

Based on the results of our study, we can say that diabetic patients continue to suffer from impaired anti-inflammatory responses, impaired insulin sensitivity, and dysregulation of lipids. Since there is no therapeutic or genetic mechanism to enhance IL-4 production in diabetic patients, the decline in other interleukins may have an effect, as they work synergistically to reduce autoimmune disorders in patients.

Regarding IL-10 levels, the study results showed a non-significant decrease in the patient group compared to the control group. In general, IL-10 levels were decreased in the patient group compared to the control group, and the reason for the decrease can be explained by several mechanisms. Immune cells like regulatory T cells and macrophages produce less IL-10 when there is chronic hyperglycemia and metabolic stress. A pro-inflammatory environment is maintained because oxidative stress and advanced glycation products (AGEs) suppress the production of the IL-10 gene, and immune cells' compromised IL-10 signaling pathways lessen the anti-inflammatory effects of IL-10 (Pouvreau et al., 2018). By blocking pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, IL-10, a crucial anti-inflammatory cytokine, aids in immune response regulation. Chronic, low-grade inflammation is a characteristic of diabetes in general, and it is caused by high amounts of pro-inflammatory mediators. Low levels of IL-10 hinder the body's capacity to regulate inflammation, worsening insulin resistance and beta cell malfunction (Novianti & Nur'aeny, 2024). Clinical research consistently demonstrates that individuals with type 2 diabetes have lower levels of circulating IL-10 than healthy controls. Poor control of glucose and elevated inflammatory markers are associated with this decline. The anti-inflammatory feedback loop is disrupted by low IL-10, which leads to persistent inflammation that exacerbates insulin resistance and diabetes consequences (Acharya et al., 2015).

An elevated risk of diabetes sequelae, including retinopathy, cardiovascular disease, and nephropathy, is linked to low levels of IL-10. Prolonged inflammation and tissue damage are caused by deficiencies in anti-inflammatory chemicals (Chatterjee et al., 2024). To lessen these issues, it is crucial to investigate and create treatment plans that raise IL-10 levels or its signaling.

The results of our present investigation conflict with those of other research that found that patients had higher levels of IL-10 than controls. This might be explained by the fact that high levels of IL-10 are a sign of the severity of consequences from diabetes, including cardiovascular disease or nephropathy, which could be a result of the body's attempt to regulate excessive inflammation and chronic immune activation (Jin et al., 2024).

Patients in our study, however, did not experience these conditions. Additionally, the length of the disease, the course of treatment, metabolic management, and the immunological condition of each patient can all have a substantial impact on IL-10 levels in diabetic patients (Yaghini et al., 2011). Therefore, rather than being a methodological artifact, the lack of a statistically significant decrease in IL-10 levels in our research population may represent the complex and context-dependent role of IL-10 in diabetes. When evaluating cytokine data in metabolic illness studies, this study highlights the need for taking into account both patient-specific characteristics and larger immunological networks.

Regarding IL-17 levels, the research results showed a significant increase in the patient group compared to the control group. The present study's findings are consistent with a meta-analysis by Zi et al. (2022), which found that patients with type 2 diabetes mellitus (T2DM) have significantly higher levels of circulating IL-17 and Th17 cell proportions than individuals with a healthy state. The inflammatory bias toward Th17 dominance is further supported by the same research, which also reveals fewer Treg cells and a lower Treg/Th17 ratio. Additionally, IL-17 levels were the highest increased interleukin among those analyzed in a large-scale systematic analysis involving 2,646 T2DM patients, surpassing even IL-4, IL-6, and IL-18 (Cao et al., 2025).

IL-17 levels increase and worsen the course of diabetes in general when it comes to comorbidities like periodontitis. IL-17 contributes to periodontal bone loss by promoting gingival inflammation, osteoclast activation, and oral microbiota dysbiosis (Huang et al., 2020). Considering that obesity and type 2 diabetes are often co-occurring conditions, it is noteworthy that obesity is related with increased levels of IL-17 and Th17-associated inflammation, which are likely to work in concert in diabetic patients (Ohshima et al., 2012). Since IL-17 is regarded as an indicator and inducer of inflammation, as was previously indicated, it can be used as a therapeutic target to break this pathological cycle.

The results of our current study are inconsistent with studies that found lower levels of IL-17 in the patient group compared to the control group. Results from a research by Kumar et al. (2014), revealed that people with type 2 diabetes (DM) or prediabetes with latent *Mycobacterium* TB infection had lower blood levels of L-17F and type 1 cytokines like IFN-γ and IL-2 than a non-diabetic control group. This implies that people with diabetes may have systemic immunosuppression or deregulation of Th17 responses. Another study found that patients with type 2 diabetes and diabetic retinopathy had a decreased number of Th17 cells in their blood and IL-17A in their peripheral blood mononuclear cells (PBMC) compared to people in good health (Chen et al., 2016). Therefore, this disagreement can be explained, as we mentioned previously, by the fact that the current study population did not suffer from other disorders. Also, depending on the tissue and stage of the disease, IL-17 can have a protective or destructive effect. Regarding interferon gamma levels, the study results showed a significant increase in the patient group compared to the healthy group.

Interferon-gamma (IFN-γ) levels are considerably higher in diabetes patients than in healthy people, according to a number of studies. Numerous pathogenic and immunological processes that are common to both type 1 and type 2 diabetes mellitus might be blamed for this rise. Dysregulation of the immune system and persistent low-grade inflammation are key factors in the development of type 2 diabetes (T2D). The change in T helper (Th) cell populations toward a Th1-dominant phenotype, which encourages the release of pro-inflammatory cytokines like IFN-γ, is one noteworthy aspect (Bahgat and Ibrahim, 2020). According to this study, T2D patients had higher levels of IFN-γ, indicating a strong Th1 polarization, but there were no increases in Th2-associated cytokines such as IL-4 and IL-5. The inflammatory environment that supports insulin resistance and metabolic dysfunction is exacerbated by this cytokine imbalance. Laffranchi & Spinas (1996) demonstrated that interferon-gamma directly reduces insulin production in the setting of beta cell failure. Interferon-gamma has a negative impact on pancreatic beta cell activity and glucose homeostasis, as evidenced by the dramatic 82% reduction in glucose-stimulated insulin production seen in human pancreatic islets exposed to it.

Because type 1 diabetes (T1D) is an autoimmune illness, IFN-γ plays an even more significant role in the condition. IFN-γ has a role in autoreactive T cell activation and homing into pancreatic islets, where they exert cytotoxic effects that result in the death of β-cells (Savinov et al., 2001). In NOD (non-obese diabetic) mice models, treatments that inhibit IFN-γ or its receptor have demonstrated a delayed development and decreased severity of type 1 diabetes, further corroborating its harmful involvement (Yi et al., 2012). All of these findings point to tissue-specific pathogenic reactions, chronic inflammation, and immune system activation as the causes of high IFN-γ levels in diabetes patients. Chronic IFN-γ production has a role in

the development of problems associated with diabetes as well as the underlying processes of insulin resistance and β-cell malfunction.

Our diabetic cohort's lack of statistically significant relationships between all interleukin levels most likely reflects the presence of compensatory immunological systems, the temporal variability of cytokine release, and the separate control of cytokine production by different immune pathways. Furthermore, possible connections may be further obscured by significant inter-individual variability and technical limitations in cytokine quantification.

In diabetes, monitoring Hb and platelet parameters is more than just standard blood work; it provides insight into possible vascular problems, glycemic control validity, and patient risk. Therefore, the current study investigated hemoglobin levels and platelet counts in patients compared to the control group. The study results showed a significant decrease in hemoglobin levels in the patient group compared to the control group and a significant increase in platelet counts in the patient group compared to the control group.

The results of the correlation analysis showed no positive or negative correlation between hemoglobin levels and platelet counts. Recent studies support the biological plausibility of the absence of association between hemoglobin and platelet count in diabetes individuals. It represents distinct clinical variables and regulatory processes influencing RBC and platelet lineages (Ebrahim et al., 2022).

A better understanding of the pathophysiology of diabetes can be gained by tracking platelet indices rather than counts and taking hemoglobin into account in relation to anemia-related processes.

Our diabetic cohort's lack of statistically significant correlations between interleukin concentrations and hematological parameters like hemoglobin and platelet count may be due to the high inter-patient variability that comes with diabetes, the temporal mismatch between rapidly fluctuating cytokines and relatively stable blood indices, and the fundamentally different regulatory mechanisms of the immune and hematopoietic systems.

Conclusion

We came at the following conclusion based on findings of this work: levels of IL-17 and IFN-γ have been much higher in DM patients compared to it in the healthy individuals. Accordingly, a substantial drop in IL-4 and IL-10 has been noted in DM patients compared with healthy individuals. Hb levels in patients who have diabetes mellitus are significantly lower when compared to those in the healthy individuals. PLT and platelets are also much higher in diabetic mellitus patients than in healthy individuals. The immunomodulatory processes behind these interleukin changes should be investigated in future studies in order to find possible biomarkers and direct the creation of cytokine-based or focused anti-inflammatory treatments for better diabetes control.

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