Original Article

Evaluation of IL-6 and IL-17A Levels in Diabetic Iraqi Patients Infected with COVID-19

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Abstract

Background: Patients with diabetes mellitus (DM) have compromised innate and acquired immunity. DM is an independent predictor of morbidity and mortality in severe acute respiratory syndrome. Type 2 diabetes mellitus (T2DM) with severe coronavirus disease 2019 (COVID-19) illness is further prone to a cytokine storm characterized by elevated titers of inflammatory cytokines. **Objective:** This study aimed to evaluate interleukin-6 (IL-6) and interleukin-17A (IL-17A) in COVID-19 and T2DM in Iraqi patients. **Materials and Methods:** The clinical and immunological characteristics of 40 hospitalized confirmed COVID-19 patients, including 20 COVID-19 patients with T2DM as group 1 (G1), 20 COVID-19 patients without T2DM as group 2 (G2), and 20 patients with T2DM only as group 3 (G3). Furthermore, 20 individuals as healthy controls were analyzed. The serum IL-6 and IL-17A levels were measured by the enzyme-linked immunosorbent assay technique, and the results were compared among the study groups. **Results:** IL-6 increased significantly ($P < 0.05$) in G1, G2, and G3 (268.62 ± 41.74, 241.94 ± 38.29, and 107.56 ± 9.58), respectively, compared with the control group (88.77 ± 3.5). There were highly significant differences ($P < 0.05$) in IL-17A mean values of the study groups G1, G2, and G3 (38.33 ± 1.84, 34.46 ± 1.83, and 30.19 ± 1.54), respectively, compared with the control groups (28.30 ± 2.03). **Conclusions:** Patients with both T2DM and COVID-19 indicated higher IL-6 and IL-17 levels than patients with COVID-19 only, also higher than those infected with T2DM only. T2DM patients have higher levels of IL-6 and IL-17A compared with the control group.

Keywords: COVID-19, IL-6, IL-17A, T2DM

Introduction

In December 2019, a novel viral pneumonia associated with an acute severe respiratory tract disease developed in Wuhan, China, and spread quickly all around the world, becoming a community health emergency of international concern, officially called the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2). Its genome sequence is strongly related but distinct from the SARS and Middle East respiratory syndrome (MERS) virus, which were primarily isolated as pathogens of the novel coronavirus disease 2019 (COVID-19) by the Chinese Center for Disease Control and Prevention.[1]

Diabetic patients are at high risk of developing severe disease when infected with COVID-19. Diabetes mellitus (DM) is the second principal cause of mortality among COVID-19 hospitalized patients, after cardiovascular disease, rendering people more susceptible to severe consequences.[2]

Accumulating evidence proposes that a subgroup of patients infected with severe COVID-19 might experience a cytokine storm syndrome, which has been suggested to play a major role in the pathogenesis of COVID-19.[3] Particularly, considerably increased interleukin (IL)-6 levels might be related to mortality because of the virally driven hyper-inflammation.[4]

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Levels of IL-6, C-reactive protein, ferritin, and D-dimer were notably increased in diabetic patients, proposing that a marked inflammatory cytokine storm was associated with a more negative prognosis in comparison with patients without diabetes. Furthermore, IL-17 has been observed to play an important role in inflammation, insulin resistance, and type 2 DM (T2DM).[5,6] So far, the detailed effects of hyperglycemia or diabetes on the immune system and immune cells in COVID-19 patients remain unclear.[1]

In general, the rate of diabetes in COVID-19 patients is from 7.4% and 20%.[7-9] DM has been demonstrated to be a high risk for mortality in two earlier coronavirus infections: SARS, as well as MERS.[10,11] Enhanced disease severity and increased inflammatory susceptibility are found in COVID-19 patients with diabetes, which are linked to increased admissions to the intensive care unit. The cytokine storm is frequently associated with dysregulation in glucose metabolism, which causes metabolic and energetic failure.[12] This study aimed to investigate the influence of IL-6 and IL-17 cytokine levels in COVID-19 patients with or without diabetes.

Materials and Methods

Blood samples were obtained from patients hospitalized at Ibn-Al Khateeb Hospital during the period from February to March 2022. The patient–control study was performed based on four groups. Group 1 (G1) included 20 severe cases infected with both SARS-CoV-2 and T2DM, group 2 (G2) included 20 patients infected with COVID-19 only, group 3 (G3) included 20 T2DM patients, and in addition to 20 healthy individuals was taken as a control group. Diagnosis of T2DM was performed depending on the specialist, whereas infections with COVID-19 were investigated by polymerase chain reaction and computed tomography scan, and then confirmed by immunoglobulin (Ig)G and IgM concentrations by fluorescence immune assay. Fasting blood sugar and hemoglobin A1C tests were performed for all the study groups. Three milliliters of peripheral blood was collected by vein puncture from 80 participants. Blood samples were obtained by disposable syringe under aseptic conditions and drawn into a gel tube, then centrifuged to obtain serum for chemical and immunological investigations. The serum was kept in separate Eppendorf tubes and stored at −20°C until used later.

The kits of enzyme-linked immunosorbent assay for human IL-6 (Demeditec Diagnostics, Kiel, Germany) and human IL-17 (Elabscience Company, Wuhan, Hubei, China) were used to estimate the concentrations of IL-6 and IL-17A in all the participants following the guidelines provided by the manufacturers.

Statistical analysis

Statistical Package for the Social Sciences version 21 (SPSS Inc., Chicago, IL, USA) is used to interpret the data. The information is given in the form of a mean, standard error, and range. Frequencies and percentages are used to display categorical data. Analysis of variance was used to compare the tested mean data expressed as mean ± standard error (SE). The Least Significant Difference test was used to calculate the significant differences between the tested means. Values of $P > 0.05$ were considered statistically nonsignificant, whereas $P < 0.05$ were considered significant results.

Ethical approval

This study was reviewed and approved by the College of Science Research Ethics Committee, Mustansiriyah University (Ref.: BCSMU/1221/0004M, December 1, 2021). All procedures were conducted in accordance with the College of Science guidelines on biomedical research, and informed consent was obtained from all participants before inclusion in the study.

Results

The present study showed that IL-6 levels increased significantly ($P < 0.05$) in all groups (G1, G2, and G3), compared with a healthy control group (268.62 ± 41.74, 241.94 ± 38.29, 107.56 ± 9.58, and 88.77 ± 3.5, respectively). Patients infected with both T2DM and COVID-19 have higher IL-6 levels than patients with COVID-19 only, also higher than those infected with T2DM only. T2DM patients have a significantly higher level of IL-6 compared with the control group, as presented in Table 1.

There were highly significant differences ($P < 0.05$) in IL-17A mean value in the tested groups compared with the healthy control group Table 2. The means and SE of G1, G2, G3, and control groups were 38.33 ± 1.84, 34.46 ± 1.83, 30.19 ± 1.54, and 28.30 ± 2.03, respectively. The mean IL-17A levels in COVID-19 with the T2DM group (G1) were higher than those in COVID-19 without

Table 1: Distribution of IL-6 levels among the study groups

IL-6 (pg/mL)	G1	G2	G3	Control
Mean ± SE	268.62 ± 41.74 A	241.94 ± 38.29 B	107.56 ± 9.58 C	88.77 ± 3.5 D
P value		0.01		

IL: interleukin, SE: standard error, *P*: probability, G: group.A: Highest significant value.B: Lower than A and significantly different.C: Lower than B and significantly different.D: Lowest value and significantly different from all other groups

Table 2: Distribution of IL-17A levels among the tested groups

IL-17A (pg/mL)	G1	G2	G3	Control
Mean ± SE	38.33 ± 1.84 A	34.46 ± 1.83 B	30.19 ± 1.54 C	28.30 ± 2.03 D
P value		0.01		

IL: interleukin, SE: standard error, *P*: probability, G: group.A: Highest significant value.B: Lower than A and significantly different.C: Lower than B and significantly different.D: Lowest value and significantly different from all other groups

the T2DM group (G2) and the T2DM group (G3). Furthermore, the mean value of IL-17A in G3 was significantly higher compared with the control group, as shown in Table 2.

Discussion

IL-6 is one of the most important pro-inflammatory cytokines. Increased IL-6 levels are registered in COVID-19 patients, especially those with severe to critical disease. Evidence has accumulated on the relevance of IL-6 as a predictive marker in COVID-19 infection. The elevation of IL-6 levels has been previously exhibited in an inflammatory state for various conditions. The pathophysiological feature of COVID-19 is severe inflammation, as well as a chemokine storm, which explains the elevation of IL-6 levels.[13]

After binding to its receptor, angiotensin-converting enzyme 2, SARS-CoV-2 enters type II lung cells (pneumocytes) and replicates. Following this invasion, macrophages, neutrophils, and dendritic cells are activated to capture SARS-CoV-2. Damaged cells release pathogen-associated molecular patterns, stimulating more recruitment of immune cells, which release a large amount of pro-inflammatory cytokines, including IL-6. These cytokines are responsible for the raised permeability of alveolar vessels and the additional recruitment of immune cells to the site of infection.[14]

Some earlier studies reported that the IL-6 level helps determine if patients need mechanical ventilation during the hospitalization period.[15,16] Another study found that the mortality risk model is based on IL-6 levels, lactate dehydrogenase levels, neutrophil/lymphocyte ratio, and age. In addition, an Italian study recommended that IL-6 is a helpful predictor for the endpoint of severe COVID-19.[17,18]

The role of IL-6 in the immunopathology of COVID-19 is crucial. IL-6 plays an important role in predicting disease severity and mortality in COVID-19. Elevated IL-6 levels are associated with acute respiratory distress syndrome, raised requirement of mechanical ventilation, prolonged hospitalization, multiple organ failure, and admission to the intensive care unit.[19]

Dysregulation production of IL-6 is associated with the pathogenesis of T2DM. However, IL-6 effects on insulin sensitivity and glucose metabolism are noticeably divergent in various tissues and contexts. This nature is dependent on a signaling pathway that is activated by IL-6, a multi-functional cytokine that has been involved in the pathophysiology of T2DM. The increased circulating IL-6 level is an independent predictor of T2DM and is considered to be implicated in the development of insulin resistance, β-cell dysfunction, and inflammation. On the other hand, accumulated evidence suggests that IL-6 has an anti-inflammatory function and improves glucose metabolism. The complex mechanism of IL-6 signal transduction may aid in explaining the pleiotropic nature of this cytokine. IL-6 acts through two distinct signaling pathways, called classic signaling and trans-signaling. While both pathways lead to the activation of the same receptor subunit, their ultimate biological effects are completely different.[20]

A study showed that serum levels of inflammation-related biomarkers (such as IL-6, C-reactive protein, D-dimer, serum ferritin, and coagulation index) were significantly higher ($P < 0.05$) in diabetic patients in comparison with those without, suggesting that diabetic patients are more predisposed to an inflammatory storm, ultimately leading to the rapid deterioration of COVID-19.[6]

Numerous pro-inflammatory mediators may develop an exacerbation of the immune response, causing hyper-inflammation. Patients with severe COVID-19 infection exhibit high levels of IL-17. Furthermore, it has been shown that the destruction of lung tissue might be explained by neutrophil recruitment, mediated by T helper 17 (Th17) cells.[21]

Pro-inflammatory cytokine storms have been detected in critically ill COVID-19 patients, which progress to multi-organ dysfunction and death.[22] The excessive IL-6 level promotes the creation of Th17 cells, and the resulting IL-6 and IL-17 synergistically support viral persistence by protecting virally infected cells from apoptosis.[23]

IL-17A (as a pro-inflammatory cytokine) has double functions, stimulating early immune responses to infections and participating in destructive and autoimmunity inflammatory conditions. Furthermore, IL-17A plays a vital role in the development of T2DM and its related disorders by upregulation of numerous inflammatory molecules, including angiotensin II type 1 receptor, as well as Janus kinase 2/signal transducer and activator of transcription 3 pathway-related molecules.[24]

A study showed that there was a significant difference in serum IL-17 concentrations in Iraqi COVID-19-infected

patients compared with healthy controls, indicating IL-17 appears to be involved in immune-mediatory responses in patients infected with COVID-19.[25]

Conclusion

The increase in serum levels of IL-6 and IL-17A was considerably noted among the three studied groups of patients with COVID-19 and T2DM ($P < 0.05$). Patients infected with both T2DM and COVID-19 have higher IL-6 and IL-17 levels than patients with COVID-19 only, also higher than those infected with T2DM only. T2DM patients have significantly higher levels of IL-6 and IL-17 compared to the control group. This study has recommended frequent checking of blood sugar and prompt management of hyperglycemia and hypoglycemia.

Author contributions

Dr. QAK: Study design, overall supervision, data analysis, and manuscript drafting. Dr. KHR: Sample collection, laboratory experiments, and statistical analysis. Dr. ENN: Literature review, result interpretation, and final manuscript revision. All authors have read and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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