Inflammatory Modulation of Interleukin-17 and -23 in Long COVID Diabetic Patients

Esra Hassan Abd Ali [1]

Abstract

Background: The global COVID-19 pandemic has brought forth a persistent challenge in the form of Post-COVID-19 Syndrome (PCS) or Long COVID, affecting approximately 1 in 10 cases. Among the various risk factors, diabetes has emerged as a significant predictor of severe outcomes, with hyperglycemia and hyperinflammation playing pivotal roles. Despite the known association, the exact mechanisms linking diabetes to Long COVID remain elusive, prompting the need for further investigation. This study aimed to explore the relationship between immune responses, particularly interleukin-17 and -23 levels, and Long COVID severity in diabetic individuals. Method: Fifty diabetic patients with Long COVID were compared with fifty diabetic controls. Blood cytokine levels were measured, and Long COVID severity was assessed using the Long COVID Severity Scale (PCS-SS). Results: Results revealed elevated levels of interleukin-17 and -23 in diabetic patients with Long COVID compared to those without the condition. Additionally, participants with Long COVID and diabetes reported significantly higher symptom severity across physical, psychological, and cognitive domains, as indicated by the Long COVID Severity Scale. Conclusion: These findings underscore a strong association between heightened inflammatory responses and increased Long COVID severity in diabetic individuals. Understanding these mechanisms could inform targeted interventions to improve outcomes for this vulnerable population, highlighting the importance of tailored management strategies for Long COVID in diabetics.

Keywords: Interleukin-17, Interleukin-23, Long COVID, Diabetes, Hyperglycemia, Hyperinflammation, COVID-19 Pandemic, Immune Response

Significance | The global COVID-19 pandemic disrupted daily life. This study demonstrated Long COVID's severity, especially in diabetic individuals, highlighting inflammation's crucial role.

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Introduction

The global COVID-19 pandemic, initiated in late 2019 by the novel SARS-CoV-2 virus in Wuhan, China, significantly disrupted daily life (Acter et al., 2020). Previous research had hinted at bat virus transmission to humans, thus making this outbreak unsurprising (Al-Jandeel et al., 2023; Maxmen & Mallapaty, 2021).

A European study involving nearly 4.5 million individuals revealed that approximately one in ten SARS-CoV-2 positive patients experience symptoms beyond 3 weeks, with a smaller percentage enduring symptoms for months (Riggioni et al., 2020). Utilizing the SF-12 health-related quality-of-life tool, a longitudinal study identified factors predicting Post-COVID-19 Syndrome (PCS) development (O'Kelly et al., 2022).

Further data solidified the understanding of COVID-19 as a multi-organ disorder, capable of triggering complications even as patients endure persistent, cyclical symptoms (Deng et al., 2023, Bala et al. 2024a). This diverse spectrum of symptoms, ranging from mild to chronic and debilitating, can manifest irrespective of initial illness

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severity and debilitating, can manifest irrespective of initial illness severity and has been termed "Post-COVID-19 Syndrome" (PCS) or "Long COVID." Recovery timelines are stark, with over 90% of patients requiring 35 weeks or more (Crook et al., 2021). Productivity suffers immensely, with over a third of patients needing reduced work schedules and nearly a third unable to return to work after 7 months due to lingering symptoms (Harrop et al., 2021). While some define "Long COVID" as symptoms persisting beyond 4 weeks, "PCS" typically refers to durations exceeding 12 weeks (Seeßle et al., 2022).

The International Study of Inflammation in COVID-19 (ISIC) shed light on how diabetes (DM) impacts hospitalization outcomes (Pan et al., 2021). This analysis, encompassing over 2,000 hospitalized patients, aimed to dissect the roles of inflammation and high blood sugar (hyperglycemia) in DM-associated risks (Pazoki et al., 2021). "Hyperinflammation" plays a significant role in linking DM with COVID-19 outcomes. Elevated levels of interleukins 17 and 23, key inflammatory markers, emerged as significant predictors, followed by obesity, high blood sugar, and age (Al-Taie et al., 2022). Notably, heightened levels of these interleukins reflect an escalated immune response and predict disease severity and mortality across various chronic conditions, including heart disease and cancer (Ip et al., 2021; Gavali et al., 2024, Shamsuddin et al., 2019).

Interestingly, the association between hyperglycemia, increased insulin needs, and inflammatory markers was weak (Vasbinder et al., 2022). This suggests that they influence outcomes independently of hyperinflammation, indicating the involvement of other mechanisms (Ngo & Gewirtz, 2021). In diabetic patients hospitalized with COVID-19, the virus-induced inflammatory metabolic state exacerbates severe insulin resistance, worsening hyperglycemia (Conte et al., 2024), and increasing the risk of rapid kidney failure, hypotension, reliance on vasopressors and steroids, and the need for nutritional support (Nanchal et al., 2020).

This study aimed to determine if there was a significant connection between inflammatory responses and worsened Long COVID symptoms in diabetics, highlighting the role of inflammation in exacerbating the condition and emphasizing the necessity for targeted interventions.

Materials and Methods

Participant Groups and Sample Collection

This study analyzed blood samples from two groups of 50 participants each: individuals with long COVID and diabetes, and diabetic individuals without long COVID (control group).

Measurement of Interleukin Levels and Long COVID Severity

Interleukin-17 and interleukin-23 levels were measured using ELISA assays, and long COVID severity was assessed using the validated Long COVID Severity Scale (PCS-SS) (Bahmer et al., 2022). This setup allowed for the comparison of cytokine levels and symptom severity between these groups, aiming to explore potential links between immune responses and long COVID in diabetic individuals.

Recruitment Criteria and Exclusions

The study recruited adults (18+) with diabetes meeting WHO diagnostic criteria. Participants had a confirmed diagnosis of long COVID per established guidelines (e.g., WHO, NICE), with symptoms persisting for at least 3 months after initial COVID-19 infection. A control group of diabetic participants without long COVID symptoms for at least 6 months post-COVID was included. Excluded individuals included pregnant/breastfeeding women, those with active autoimmune/inflammatory diseases, immunosuppressive medication users, people with recent acute respiratory infections (within 4 weeks), and those with a significant history of organ dysfunction.

Patient Recruitment and Consent Process

Patient recruitment involved collaborating with hospitals and clinics treating both diabetes and long COVID patients. Informed consent was obtained from all participants.

Blood Sample Collection and Processing

Venous blood samples were collected upon admission for long COVID patients and during scheduled clinic visits for control group participants. Whole blood was centrifuged within 2 hours, then plasma aliquoted and stored at -80°C. Standard procedures ensured reliable assay results.

ELISA Assays and Data Collection

Commercially available high-sensitivity ELISA kits were used for interleukin-17 and interleukin-23, following the manufacturer's protocols and analyzing each sample in duplicate.

Assessment of Long COVID Severity

The validated PCS-SS questionnaire assessed long COVID severity across physical, psychological, and cognitive domains. Additional symptom-specific assessments might have been included. Both PCS-SS administration and blood sample collection occurred simultaneously to correlate clinical severity with cytokine levels.

Statistical Analysis

Data analysis involved summarizing baseline characteristics and cytokine levels, comparing groups using statistical tests, assessing correlations between cytokines and PCS-SS scores, and employing regression models to explore the independent effects of cytokine levels on long COVID severity while controlling for relevant factors.

Results

Table 2 presented demographic and clinical information for the two groups involved in the study: individuals with long COVID and diabetes (LCWD) and individuals with diabetes without long COVID (DWC). Both groups had a similar average age (55 and 53 years old), suggesting age-related effects were less likely to play a

significant role in the observed differences. LCWD participants had a slightly longer average diabetes duration (15 years) compared to DWC participants (12 years). This difference could potentially contribute to variations in immune response and susceptibility to long COVID. The LCWD group, by definition, had a documented history of long COVID symptoms for an average of 6 months. This information confirmed the presence of long COVID in this group.

Table 3 showed that individuals with both long COVID and diabetes exhibited significantly higher levels of interleukin-17 and interleukin-23 compared to those with diabetes but without long COVID. This suggested a potential link between these inflammatory cytokines and the development or persistence of long COVID symptoms in diabetic individuals. The mean concentration of interleukin-17 was 43.7% higher in the long COVID with diabetes group (12.5 pg/mL) than in the control group (8.7 pg/mL) (p-value = 0.002). The mean concentration of interleukin-23 was 39.7% higher in the long COVID with diabetes group (18.3 pg/mL) compared to the control group (13.1 pg/mL) (p-value = 0.008).

Table 4 showed that individuals with long COVID who also had diabetes experienced considerably more severe long COVID symptoms across all domains (physical, psychological, and cognitive) compared to diabetic individuals without long COVID. The most pronounced difference was observed in physical symptoms, with an average score of 28.4 in the long COVID with diabetes group, compared to 15.2 in those without long COVID. This suggested a more substantial impact on physical functioning and daily activities. Psychological symptoms were also significantly higher in the long COVID with diabetes group, indicating a greater burden of anxiety, depression, and cognitive difficulties. While less pronounced than physical and psychological differences, cognitive symptoms, such as difficulty thinking clearly and concentrating, were still significantly elevated in the long COVID with diabetes group.

Discussion

The emergence of the COVID-19 pandemic in late 2019 has profoundly impacted global health and daily life, prompting extensive research into its multifaceted effects. Previous studies have highlighted the role of various factors in COVID-19 severity and long-term outcomes. Notably, the understanding of COVID-19 as a multi-organ disorder has evolved, with evidence indicating its ability to trigger complications and persistent symptoms, regardless of initial illness severity.

Our study focused on elucidating the interplay between diabetes, inflammatory responses, and long COVID symptoms. Diabetes, a common comorbidity, has been associated with worse outcomes in COVID-19 patients. Consistent with previous research, our findings revealed a significant association between diabetes and the severity of long COVID symptoms. Individuals with both long COVID and diabetes experienced considerably more severe symptoms across physical, psychological, and cognitive domains compared to diabetic individuals without long COVID.

Both groups had similar average ages (55 and 53 years), suggesting age was unlikely to be a major factor in explaining the observed differences in long COVID prevalence. While the LCWD group had a slightly longer average diabetes duration (15 years vs. 12 years), the difference was modest and may not have significantly impacted susceptibility to long COVID. This aligns with Gregory et al., 2021, who found a definitive increased risk of severe COVID-19 in all individuals with diabetes, regardless of duration, as expected (Gregory et al., 2021). The LCWD group had a documented history of long COVID symptoms for an average of 6 months, confirming their presence in this group. This absence in the DWC group served as a crucial control point for the study. This aligns with Fernández-de-Las-Peñas et al., 2021, who mentioned persistent symptoms. Specific long-term symptoms are more prevalent in people with COVID, with or without diabetes (Fernández-de-Las-Peñas et al., 2021).

Chronic hyperglycemia in diabetes could lead to low-grade chronic inflammation, potentially priming the immune system for a more exaggerated response to viral infections like COVID-19 (Zhou et al., 2024, Bala et al. 2024b, Nithya et al. 2024). This could contribute to the development and persistence of long COVID symptoms in the LCWD group. Diabetes disrupts immune function, leading to impaired responses to pathogens and potentially hindering viral clearance. This prolonged viral presence could trigger ongoing inflammation and contribute to long COVID symptoms (Roberts et al., 2021). Diabetes increases the risk of vascular complications, which could further aggravate inflammatory processes and tissue damage, potentially worsening long COVID symptoms (Erener, 2020). Alterations in gut microbiota observed in diabetes might influence immune responses and inflammation, potentially playing a role in long COVID development (Chen et al., 2021).

This study found Interleukin-17 and -23 to be key inflammatory markers involved in immune responses (Shamsuddin, 2017). Their elevated levels suggest a potential hyperinflammatory state in diabetic individuals with long COVID, which could contribute to the development and persistence of symptoms. This aligns with Bouayed and Bohn, 2021, who found that chronic diseases such as obesity and type-2 diabetes are known to promote a pro-inflammatory state and increase the level of Interleukin-17 and -23 (Bouayed & Bohn, 2021; Pereko et al., 2021).

The results of this study indicated that individuals with both long COVID and diabetes experience significantly more severe long COVID symptoms across all domains (physical, psychological, and cognitive) compared to diabetic individuals without long COVID. This suggests that diabetes worsens the impact of long COVID, leading to a greater burden on individuals' overall health and well-

Table 1. Long COVID Severity Scale (PCS-SS)

Symptom Domain	Symptom	Score
Physical	Fatigue	0 (None) - 10 (Severe)
	Shortness of breath	0 (None) - 10 (Severe)
	Chest pain	0 (None) - 10 (Severe)
	Muscle aches	0 (None) - 10 (Severe)
	Headache	0 (None) - 10 (Severe)
	Joint pain	0 (None) - 10 (Severe)
	Sleep problems	0 (None) - 10 (Severe)
	Cough	0 (None) - 10 (Severe)
	Loss of taste or smell	0 (None) - 10 (Severe)
	...	
Psychological	Anxiety	0 (None) - 10 (Severe)
	Depression	0 (None) - 10 (Severe)
	Difficulty concentrating	0 (None) - 10 (Severe)
	Memory problems	0 (None) - 10 (Severe)
	Brain fog	0 (None) - 10 (Severe)
	...	
Cognitive	Difficulty thinking clearly	0 (None) - 10 (Severe)
	Difficulty remembering things	0 (None) - 10 (Severe)
	Difficulty concentrating	0 (None) - 10 (Severe)
	Difficulty making decisions	0 (None) - 10 (Severe)
	...	
Impact on Daily Life	How much do your symptoms interfere with your daily activities?	0 (Not at all) - 10 (Extremely)

Table 2: Group Characteristics

Group	N	Age (Mean ± SD)	Diabetes Duration (Mean ± SD)	Long COVID Duration (Mean ± SD)
Long COVID with Diabetes	50	55 ± 10	15 ± 5 years	6 months ± 3 months
Diabetes without Long COVID	50	53 ± 12	12 ± 6 years	N/A

Table 3. Cytokine Levels (pg/mL)

Cytokine	Long COVID with Diabetes (Mean ± SD)	Diabetes without Long COVID (Mean ± SD)	p-value
Interleukin-17	12.5 ± 4.2	8.7 ± 2.8	0.002*
Interleukin-23	18.3 ± 5.6	13.1 ± 3.2	0.008*

Table 4. Long COVID Severity Scale (PCS-SS) Scores

Domain	Long COVID with Diabetes (Mean ± SD)	Diabetes without Long COVID (Mean ± SD)	p-value
Physical	28.4 ± 5.3	15.2 ± 3.1	<0.001*
Psychological	22.1 ± 4.8	11.7 ± 2.5	<0.001*
Cognitive	15.6 ± 3.7	8.9 ± 2.0	<0.001*

being. This aligns with Nguyen et al., 2023, who found that cognitive and physical measures of fatigue in diabetic individuals could worsen diabetes control and severity of existing long-term complications.

As discussed previously, diabetes can lead to a chronic low-grade inflammatory state. This pre-existing inflammation, combined with the acute inflammatory response induced by COVID-19, might create a synergistic effect and amplify long COVID symptoms, particularly physical ones like fatigue, muscle pain, and breathlessness (Abdelghani et al., 2022; Mundula et al., 2022; Steenblock et al., 2022). Diabetes also increases the risk of vascular complications, which can damage blood vessels and organs. This impaired blood flow could further worsen oxygen delivery and tissue repair, potentially contributing to physical and cognitive symptoms (Burtscher et al., 2023).

The combined burden of long COVID and diabetes can be psychologically stressful, leading to anxiety, depression, and sleep disturbances. These psychological factors can then exacerbate physical and cognitive symptoms through a complex interplay (Troncone et al., 2023). Diabetes can impair immune function, potentially hindering viral clearance and leading to prolonged inflammation. This persistent inflammation might contribute to ongoing tissue damage and contribute to all domain symptoms (Drucker, 2020; Rout & Sahoo, 2023).

Interestingly, our study identified elevated levels of interleukin-17 and -23, key inflammatory markers, in diabetic individuals with long COVID. This hyperinflammatory state may contribute to the development and persistence of symptoms, suggesting a potential link between inflammation and long COVID exacerbation in diabetic populations. These findings align with existing literature highlighting the pro-inflammatory nature of chronic diseases like obesity and type-2 diabetes.

Moreover, the chronic low-grade inflammation observed in diabetes could prime the immune system for an exaggerated response to viral infections such as COVID-19. This dysregulated immune response, compounded by acute inflammation induced by the virus, may amplify long COVID symptoms, particularly physical manifestations like fatigue and muscle pain. Additionally, diabetes-related vascular complications could further exacerbate inflammatory processes and tissue damage, worsening long COVID symptoms.

The psychological impact of both long COVID and diabetes cannot be understated. The combined burden of these conditions can lead to anxiety, depression, and sleep disturbances, which in turn, may exacerbate physical and cognitive symptoms. Furthermore, diabetes-associated impairments in immune function could prolong viral presence and inflammation, contributing to ongoing tissue damage and symptom persistence.

Our study shed light on the complex interplay between diabetes, inflammatory responses, and long COVID symptoms. The identification of elevated interleukin levels underscores the role of inflammation in exacerbating long COVID in diabetic individuals, emphasizing the need for targeted interventions to mitigate symptom severity and improve outcomes in this vulnerable population. Further research is warranted to elucidate the underlying mechanisms and develop effective therapeutic strategies for managing long COVID in individuals with diabetes.

Conclsuion

In diabetic individuals affected by long COVID, the convergence of diabetes and COVID-19 presents a dual challenge. Our study underscores the exacerbation of long COVID symptoms across physical, emotional, and cognitive domains due to a hyperinflammatory state induced by diabetes. By identifying inflammation as a central contributor to worsened symptoms, our findings provide a valuable insight into the pathogenesis of long COVID in diabetic populations.

The recognition of inflammation as a key player opens avenues for targeted interventions aimed at alleviating symptom burden and improving the quality of life for diabetic individuals grappling with long COVID. Anti-inflammatory therapies and personalized management strategies tailored to address the specific needs of this population could hold promise in mitigating the impact of long COVID.

While our study sheds light on the intricate interplay between diabetes, inflammation, and long COVID, several unanswered questions persist. Further research is warranted to unravel the underlying mechanisms driving these interactions and to develop more effective therapeutic approaches. Nevertheless, understanding this complex relationship is a crucial step in addressing the profound impact of long COVID on diabetic individuals. By advancing our knowledge in this area, we move closer to devising comprehensive strategies to mitigate the burden of long COVID in this vulnerable population and enhance their overall well-being.

Author contribution

E.H.A. played a pivotal role in the conceptualization and development of the study's methodology, carried out all data collection and analysis, wrote the original draft, and was involved in review, editing, and finalization of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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