

Long-Term Recovery From Post-COVID-19 Hyperglycemia: A Three-Years Follow-Up Study in Iraq

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Abstract- The COVID-19 pandemic has caused several health problems, including newly diagnosed diabetes mellitus (DM) and new-onset hyperglycemia. Research indicates that some individuals with COVID-19 recover from hyperglycemia. To examine the long-term outcomes and factors that may predict recovery from new-onset hyperglycemia following COVID-19 infection over a three-year follow-up period. A prospective longitudinal cohort study was conducted involving 50 patients recently diagnosed with COVID-19 infection based on a positive RT-PCR test and a lung CT scan. All patients developed new-onset hyperglycemia upon admission, had no previous history of DM, had a normal recent HbA1c level, and had not used steroids before diagnosis. All patients were treated with insulin and/or an oral hypoglycemic drug during the periods of COVID-19 infection and hyperglycemia. The study included 50 patients with COVID-19 and new-onset hyperglycemia, of whom 62% were male, 50% were young, 52% were overweight, and 36% had CT lung severity scores between 20 and 30. After 6 months, 54% of the patients had recovered from hyperglycemia; this proportion increased to 60% after 1 year and 64% after 3 years. A higher likelihood of recovery from DM was observed among younger patients ($P=0.003$), those without a family history of DM ($P=0.008$), and those with lower CT lung severity scores ($P<0.001$). Most patients with new-onset hyperglycemia following COVID-19 infection recovered from DM, and the recovery rate progressively increased over the three-year follow-up period.

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Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020, and has since affected millions of individuals worldwide (1). Diabetes mellitus (DM) emerged early in the pandemic as a significant risk factor for severe COVID-19 outcomes (2). Due to impaired immune function, individuals with DM are more vulnerable to infections from various pathogens, including bacteria, viruses, and

fungi (3-5). This vulnerability is compounded by the pro-inflammatory state inherent to diabetes and the systemic hyperinflammatory response triggered by COVID-19, as reflected by elevated inflammatory markers such as C-reactive protein (CRP) and serum ferritin (6). Several studies have demonstrated that both pre-existing diabetes and acute hyperglycemia can significantly worsen the prognosis of COVID-19 by increasing disease severity and mortality risk (7-9). One proposed mechanism is that elevated glucose levels may enhance viral replication; indeed, in vitro studies have shown that hyperglycemia can directly promote SARS-

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CoV-2 proliferation in human monocytes (10). The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020, and has since affected millions of individuals worldwide (1). Diabetes mellitus (DM) emerged early in the pandemic as a significant risk factor for severe COVID-19 outcomes (2). Individuals with DM are more vulnerable to infections from various pathogens—including bacteria, viruses, and fungi—due to impaired immune function (3-5). This vulnerability is compounded by the pro-inflammatory state inherent to diabetes and the systemic hyperinflammatory response triggered by COVID-19, which is reflected by elevated inflammatory markers such as C-reactive protein (CRP) and serum ferritin (6). Several studies have demonstrated that both pre-existing diabetes and acute hyperglycemia can significantly worsen the prognosis of COVID-19 by increasing disease severity and mortality risk (7-9). One proposed mechanism is that elevated glucose levels may enhance viral replication. *In vitro* studies have shown that hyperglycemia can directly promote SARS-CoV-2 proliferation in human monocytes (10).

Additionally, the dysregulated immune responses and impaired inflammatory mechanisms common in diabetic patients may further exacerbate susceptibility to, and disease progression in, COVID-19 (11,12). A growing body of literature has documented the emergence of newly diagnosed diabetes mellitus (NDDM) or transient hyperglycemia in patients without a known history of diabetes, particularly during hospital admission or in the post-acute phase of COVID-19 (1-5). This condition, often referred to as “new-onset diabetes,” remains poorly defined due to limited pre-infection glycemic data. It is unclear whether such cases reflect unmasked prediabetes, stress-induced hyperglycemia, or a distinct phenotype of dysglycemia associated with SARS-CoV-2. Emerging evidence also suggests a bidirectional relationship between COVID-19 and diabetes. COVID-19 has been implicated in triggering both new-onset diabetes and acute complications of existing diabetes, including diabetic ketoacidosis and hyperosmolar states (13-16). Notably, some patients without prior diabetes have developed hyperglycemia during COVID-19 treatment, despite having normal HbA1c levels on admission (17). Furthermore, patients with new-onset diabetes appear to experience more severe disease and poorer outcomes, including higher rates of ICU admission, respiratory failure, multi-organ complications, and mortality,

compared to those with pre-existing diabetes or normoglycemia (15,18,19). These findings underscore the clinical and economic burden associated with COVID-19-induced hyperglycemia (20). Although the exact mechanisms remain unclear, several interrelated factors, such as impaired insulin secretion, insulin resistance, steroid therapy, stress responses, and preclinical diabetes, are believed to contribute to new-onset hyperglycemia in COVID-19 patients (21). This study aims to assess the long-term outcomes of these patients and to identify factors associated with the resolution or persistence of hyperglycemia over a three-year follow-up period.

Materials and Methods

A prospective longitudinal cohort study was conducted on 50 patients recently diagnosed with COVID-19 infection based on a positive reverse transcription polymerase chain reaction (RT-PCR) test and lung CT scan, who were admitted to Merjan Medical City in Babylon Governorate from March 2021 to October 2021. All patients developed new-onset hyperglycemia on admission, with no previous history of DM, a normal recent HbA1c level, and no prior steroid use before diagnosis. All patients received appropriate treatment for their COVID-19 infection and hyperglycemia with insulin therapy and/or oral hypoglycemic drugs and were followed for 3 years regarding their glycemic status using HbA1c and random blood sugar measurements. A full history was taken from the patients, and a clinical examination was performed, along with appropriate investigations to obtain data regarding name, age, sex, past medical history of DM, family history of DM, smoking status, BMI, chest CT scan findings to determine the percentage of lung involvement, and HbA1c before diagnosis, with repeated fasting and random blood sugar measurements during hospitalization, followed by post-discharge follow-up after they continued their medication to control the elevated blood sugar, including insulin, oral hypoglycemic drugs, and dietary advice. The first follow-up was conducted at 6 months, the second at 1 year, and the third at 3 years. During each visit, a medical history was obtained from the patient, and assessments for HbA1c and random blood sugar were performed. The diagnosis of, and recovery from, diabetes mellitus (DM) were based on the American Diabetes Association (ADA) criteria for non-pregnant individuals (22); recovery was defined as an HbA1c level of less than 6.5% sustained for at least

three months without the use of glucose-lowering agents. Body mass index (BMI) was classified according to the World Health Organization (WHO) criteria for adults (23). Regarding the chest CT scan assessment, the scans for all patients were evaluated by two consultant radiologists. The CT severity score was determined based on the anatomical structure of the 18 lung segments, which were further divided into 20 regions. Specifically, the apicoposterior segment of the left upper lobe was divided into apical and posterior regions, while the anteromedial basal segment of the left lower lobe was divided into anterior and medial basal regions. The radiologists subjectively scored each of the 20 regions as 0, 1, or 2, depending on whether parenchymal opacification was absent, involved less than 50%, or involved 50% or more of the region. The CT severity score was calculated as the sum of the scores from all 20 regions of both lungs, with a possible total score ranging from 0 to 40 points (24).

The inclusion criteria were:

- 1- Any age between 18- 60 years old.
- 2- Patient admitted with COVID-19 infection and develops hyperglycemia with no previous history of DM, and normal HbA1c, and before use of steroid.
- 3- Patient who survive and complete their follow-up.

The exclusion criteria were:

- 1- Previous history of DM.
- 2- Long use of steroid medications.
- 3- Use of immune suppresser treatment.
- 4- Patients use thiazide drugs.
- 5- Patient with malignant disease with or without use of chemotherapy.
- 6- Patients with connective tissue diseases or vasculitis.
- 7- Pregnancy.
- 8- Patients who not complete the follow up.
- 9- Patients who had normal blood sugar after recovery from COVID-19 infection (stress hyperglycemia).

Data analysis

Statistical analysis was conducted using SPSS version 27. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean $\pm$ SD. The Student's t-test was used to compare means between two groups. To determine associations between categorical variables, the Pearson Chi-Square test and Fisher's Exact test were utilized. A *P* of 0.05 or less was considered statistically

significant.

Sampling technique

A convenience sample of 50 patients recently diagnosed with COVID-19, who were admitted to Merjan Medical City in the Babylon Governorate between March 2021 and October 2021, was included in this study. All participants developed new-onset hyperglycemia upon admission, with no prior history of DM, normal baseline HbA1c levels, and no steroid use prior to diagnosis. All patients received appropriate treatment for COVID-19 and hyperglycemia, utilizing insulin therapy and/or oral hypoglycemic agents, and were followed for three years to monitor their glycemic status via HbA1c and random blood sugar measurements. All 50 recruited patients completed the required follow-up assessments at 6 months, 1 year, and 3 years. Patients who did not complete the follow-up were excluded based on pre-established criteria. A complete-case analysis was performed as there were no missing data for the primary outcome.

Results

Table 1 presents the distribution of COVID-19 patients according to sociodemographic characteristics, including age, sex, smoking habit, and body mass index (BMI). The mean age of the patients was 43.38 $\pm$ 14.48 years, with ages ranging from 22 to 72 years. Half of the patients (N=25, 50.0%) were in the younger age group. More than half of the patients (N=31, 62.0%) were male. Current smokers accounted for 12 patients (24.0%), while obese patients represented 38.0% of the sample (N=19).

Figure 1 shows the distribution of COVID-19 patients according to family history of diabetes mellitus (DM), categorized as present or absent. Patients with a positive family history of DM represented 21 cases (42.0%), while those with a negative family history represented 29 cases (58.0%).

Table 3 shows the distribution of COVID-19 patients according to CT lung severity score (SS) categories: <10%, 10-20%, 20-30%, and 30-40%. Patients with a lung score of <10% represented 9 cases (18.0%). Those with a lung score of 10-20% represented 12 cases (24.0%). Patients with a lung score of 20-30% represented 18 cases (36.0%), while those with a lung score of 30-40% represented 11 cases (22.0%).

Table 4 shows the distribution of COVID-19 patients according to diabetes mellitus status after three follow-up periods, including DM after 6 months, after 1 year,

and after 3 years. After 6 months of follow-up, 23 patients (46.0%) still had DM. After 1 year of follow-up, 20 patients (40.0%) still had DM.

After 3 years of follow-up, 18 patients (36.0%) still had DM. Table 5 shows the association between diabetes mellitus after 3 years of follow-up and sociodemographic characteristics, including age, sex, smoking habit, body mass index, and family history of DM, among COVID-19 patients. There was a significant association between patient age and the persistence of diabetes after 3 years of follow-up ($P=0.003$). There was also a significant association between family history of DM and the persistence of diabetes after 3 years of follow-up ($P=0.008$).

Table 6 shows the association between diabetes mellitus after 3 years of follow-up and CT lung severity score (SS) categories, including <10, 10-20, 20-30, and 30-40. There was a significant association between CT lung SS score and the persistence of diabetes after 3 years of follow-up ($P<0.001$).

Tables 7 and 8 shows the mean differences in fasting blood sugar (FBS) (mg/dL), random blood sugar (RBS) (mg/dL), and HbA1c (%) among COVID-19 patients at the time of presentation according to diabetes mellitus status after 3 years of follow-up. There were no significant differences in the mean values of the study variables according to diabetes mellitus status after 3 years of follow-up.

Table 1. Distribution of COVID-19 patients according to sociodemographic characteristics (N=50)

Sociodemographic characteristics	Number	%
Age (years)		
Young age group	25	50.0%
Middle age group	16	32.0%
Elderly age group	9	18.0%
Total	50	100.0%
Sex		
Male	31	62.0%
Female	19	38.0%
Total	50	100.0%
Smoking habit		
Current smokers	12	24.0%
X-smokers	5	10.0%
Non smokers	33	66.0%
Total	50	100.0%
Body mass index (Kg/m2)		
Normal (18.5-24.9)	5	10.0%
Overweight (25-29.9)	26	52.0%
Class I obesity (30-34.9)	16	32.0%
Class II obesity (35-39.9)	3	6.0%
Total	50	100.0%

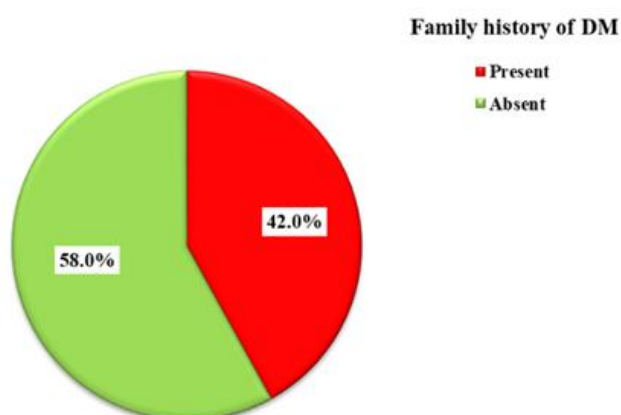


Figure 1. Distribution of COVID-19 patients according to family history of diabetes mellitus (N=50)

Table 2. Mean±SD and range of FBS (mg/dl), RBS (mg/dl) and HbA1C (%) of COVID-19 patients at time of presentation (N=50)

Study variables	Mean±SD	Range
FBS (mg/dl)	156.28 ± 24.45	110-240
RBS (mg/dl)	334.28 ± 99.28	190-582
HbA1C (%)	5.77 ± 0.36	5.0-6.4

FBS (mg/dl): Fasting blood sugar (mg/dl), RBS (mg/dl): Random blood sugar (mg/dl), HbA1C (%): Hemoglobin A1C test (%)

Table 3. Distribution of COVID-19 patients according to CT lung SS score (N=50)

CT lung SS score	Number	%
<10	9	18.0%
10-20	12	24.0%
20-30	18	36.0%
30-40	11	22.0%
Total	50	100.0%

SS score: Severity Score

Table 4. Distribution of COVID-19 patients according to diabetes mellitus after three periods of assessment (N=50)

DM after three periods of assessment	Number	%
DM after 6 months of follow up		
Yes	23	46.0%
No	27	54.0%
Total	50	100.0%
DM after 1 year of follow up		
Yes	20	40.0%
No	30	60.0%
Total	50	100.0%
DM after 3 years of follow up		
Yes	18	36.0%
No	32	64.0%
Total	50	100.0%

Table 5. The association between diabetes mellitus after 3 years of follow up and sociodemographic characteristics (N=50)

Sociodemographic characteristics	DM after 3 years of follow up		Total (N=50)	P
	Yes (N=18)	No (N=32)		
Age (years)				
Young age group	4 (22.2)	21 (65.6)	25 (50.0)	0.003*
Middle age group	7 (38.9)	9 (28.1)	16 (32.0)	
Elderly age group	7 (38.9)	2 (6.3)	9 (18.0)	
Total	18 (100.0)	32 (100.0)	50 (100.0)	
Sex				
Male	12 (66.7)	19 (59.4)	31 (62.0)	0.61
Female	6 (33.3)	13 (40.6)	19 (38.0)	
Total	18 (100.0)	32 (100.0)	50 (100.0)	
Smoking habit				
Current smokers	12 (66.7)	21 (65.6)	33 (66.0)	0.392
X-smokers	3 (16.7)	2 (6.3)	5 (10.0)	
Non smokers	3 (16.7)	9 (28.1)	12 (24.0)	
Total	18 (100.0)	32 (100.0)	50 (100.0)	
Body mass index (Kg/m ²)				
Normal (18.5-24.9)	1 (5.6)	4 (12.5)	5 (10.0)	0.825
Overweight (25-29.9)	11 (61.1)	15 (46.9)	26 (52.0)	
Class I obesity (30-34.9)	5 (27.7)	11 (34.4)	16 (32.0)	
Class II obesity (35-39.9)	1 (5.6)	2 (6.2)	3 (6.0)	
Total	18 (100.0)	32 (100.0)	50 (100.0)	
Family history of DM				
Yes	12 (66.7)	9 (28.1)	21 (42.0)	0.008*
No	6 (33.3)	23 (71.9)	29 (58.0)	
Total	18 (100.0)	32 (100.0)	50 (100.0)	

Table 6. The association between diabetes mellitus after 3 years of follow up and CT lung SS score (%) (N=50)

CT lung SS score points	DM after 3 years of follow up		Total (N=50)	P
	Yes (N=18)	No (N=32)		
<10	0 (0.0)	9 (28.1)	9 (18.0)	<0.001*
10-20	3 (16.7)	9 (28.1)	12 (24.0)	
20-30	6 (33.3)	12 (37.5)	18 (36.0)	
30-40	9 (50.0)	2 (6.3)	11 (22.0)	
Total	18 (100.0)	32 (100.0)	50 (100.0)	

SS score: Severity score

Table 7. The mean differences of FBS (mg/dl), RBS (mg/dl) and HbA1C (%) among COVID-19 patients at time of presentation according to DM after 3 years of follow up

Study variables	DM after 3years	N	Mean±SD	P
FBS (mg/dl)	Yes	18	163.33 ± 25.85	0.127
	No	32	152.31 ± 23.08	
RBS (mg/dl)	Yes	18	315.72 ± 96.39	0.327
	No	32	344.72 ± 100.86	
HbA1C (%)	Yes	18	5.82 ± 0.39	0.495
	No	32	5.74 ± 0.34	

FBS (mg/dl): Fasting blood sugar (mg/dl), RBS (mg/dl) : Random blood sugar (mg/dl), HbA1C (%): Hemoglobin A1C test (%)

Table 8. Multivariable analysis including age, family history and CT lung SS score points as independent predictors for DM after 3 years of follow up

Study variables	B	S.E.	Wald	df	P	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Young age group			4.50	2	0.105			
Middle age group	2.434	1.15	4.47	1	0.034*	11.40	1.195	108.77
Elderly age group	1.763	1.14	2.41	1	0.120	5.83	.630	53.91
FH	-1.741	0.89	3.85	1	0.050*	0.175	.031	0.999
SS score points <10			3.12	3	0.371			
SS score points 10-20	-19.55	12639.9	0.00	1	0.999	0.00	0.00	.
SS score points 20-30	-20.29	12639.9	0.00	1	0.999	0.00	0.00	.
SS score points 30-40	-21.57	12639.9	0.00	1	0.999	0.00	0.00	.

Discussion

COVID-19 viral infection causes numerous complications, one of which is the new onset of hyperglycemia. While many studies have demonstrated the risks associated with hyperglycemia in these patients, the long-term prognosis after full recovery remains poorly understood. In this study, we followed these patients and monitored their glycemic status over a three-year period. Hyperglycemia occurring during COVID-19 infection may represent stress-induced hyperglycemia, unmasked pre-diabetes, or true diabetes mellitus (DM) following the infection. To differentiate between these conditions, a detailed history was obtained from all patients regarding any prior diagnosis of DM or the use of glucose-lowering medications; such individuals were excluded from the study. Additionally, HbA1c was measured upon admission, and patients with levels within the diabetic range were also excluded. Stress-induced hyperglycemia is characterized by a

transient elevation of blood glucose during acute illness, often driven by stress hormones and medications such as corticosteroids. We sought to minimize this confounding factor by confirming hyperglycemia before the initiation of steroid therapy. Furthermore, patients whose blood glucose returned to normal following recovery were analyzed to ensure an accurate assessment of persistent versus transient dysglycemia. Although the exact mechanisms by which COVID-19 induces hyperglycemia remain unclear, several factors have been implicated, including impaired insulin secretion due to direct beta-cell damage, insulin resistance secondary to cytokine-mediated inflammation, steroid therapy, stress responses, and preclinical diabetes (21).

Regarding the age and sex of the patients, half were in the younger age group, and most were male. Half of the patients with COVID-19 infection and hyperglycemia were young. Although this may seem unusual, it should be noted that infectious diseases, including COVID-19, tend to affect the most socially

and physically active individuals, which may explain why half of the affected patients belonged to this age group. In a cross-sectional study by Abu Taiub M. *et al.*, more than 50% of patients were also within the younger age group (25). Regarding the persistence of DM after recovery from COVID-19 infection among patients who continued to have hyperglycemia following hospital discharge, follow-up began after 6 months, and we found that 46% of patients continued to have DM and still required treatment for hyperglycemia. The explanation for this may be that some patients had previously undiagnosed DM or pre-diabetes, while others may have had viral-induced pancreatitis causing damage to the pancreatic beta cells that required time for recovery. In addition, poor adherence to diet and/or medication may have affected recovery in some patients. The second follow-up was conducted at 1 year to assess their diabetic status and the need for treatment modification. We found that the percentage of patients who still had DM slightly decreased to 40%, as three additional patients recovered. This delayed recovery may be explained by the gradual restoration of beta-cell function. In the study by Das RG *et al.*, C-peptide levels gradually increased over time from baseline, with follow-up at 6 months and again at 10 months. In that study, 67% of patients without autoantibodies were maintained on lifestyle measures alone without medications after 10 months (26), and this result is close to that of our study, in which 60% of patients no longer required medications after 1 year. In the study by Corbin SJ *et al.*, at a median follow-up of 323 days, 56.3% of patients with newly diagnosed DM continued to show evidence of DM (27). The follow-up in our study was further extended to 3 years. During this period, two additional patients were able to discontinue medication and achieved normal HbA1c levels, while the percentage of patients who continued to have hyperglycemia declined to 36%. This improvement may be explained by the gradual recovery of beta-cell function over time. The second aim of this study was to identify the factors associated with improvement in hyperglycemia after COVID-19 infection. The first factor was age, which showed a significant association, as most patients in the younger age group recovered from hyperglycemia, whereas most elderly patients continued to have persistent DM. This finding highlights the importance of age in the improvement of hyperglycemia and possibly in beta-cell recovery. A 6-month prospective study by Mochuan Chen *et al.*, showed that patients with COVID-19 may be at increased risk of insulin resistance even without prior

DM, and that elderly patients are more likely to develop such resistance during the first 3 months of follow-up (28). The second significant factor was family history of DM, which indicated that the risk of persistent DM was higher among patients with a positive family history. This may imply that COVID-19 either unmasks pre-existing susceptibility or accelerates the diabetic process, and that patients who carry a genetic predisposition are less likely to recover from hyperglycemia. The third significant factor was the lung CT severity score, as all patients with mild lung CT involvement recovered from DM, whereas most patients with severe CT scores (30-40 points of involvement) continued to have DM. The CT severity score may reflect the severity of COVID-19 infection; therefore, greater lung involvement may be associated with a lower likelihood of recovery from DM. This suggests that the severity of infection and inflammation, which increases with greater lung involvement, may influence future recovery from DM. The factors that did not show significant associations included sex, as being male or female did not appear to affect recovery from DM. Smoking habit was another factor that did not significantly influence recovery from DM. BMI showed some effect, but the result was not statistically significant; this may have been influenced by the small sample size, and a larger sample with a longer follow-up period might yield significant findings. The glycemic parameters assessed at presentation, including fasting blood sugar, random blood sugar, and HbA1c, also showed no significant associations. Regarding HbA1c, it showed a tendency to be higher in non-recovered patients, but this finding was not statistically significant and may require a larger sample size for confirmation. The same applies to fasting blood sugar. In contrast, random blood sugar was even higher in recovered patients, although this result was also not significant, which may suggest that random blood sugar at presentation does not affect the eventual outcome of DM.

Limitations

- 1- Small sample size.
- 2- Single-center design.
- 3- No autoimmune markers (GAD, C-peptide).
- 4- Absence of pre-COVID glycemic status documentation.
- 5- Lack of multivariate modeling.

Most patients with new-onset hyperglycemia

following COVID-19 infection recovered from DM, and the recovery rate progressively increased over the three-year follow-up period. Younger patients showed a higher likelihood of recovery from DM. Patients with a family history of DM were less likely to recover from DM. The severity of lung involvement due to COVID-19 infection also affected the recovery status of DM. Factors such as sex, smoking, body mass index, and glycemic parameters at presentation showed no significant associations.

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