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Features of Diabetes Mellitus unmasked by COVID-19

Mouna Elleuch[1], Yesmine Elloumi[1], Nadia Moussa [2], Dhouha Ben Salah[1], Hamdi Frikha[1], Khouloud Boujelbene[1], Nadia Charfi[1], Mouna Mnif[1], Faten Hadj Kacem[1], Sami Kammoun[2], Nabila Rekik[1]

[1]Department of Endocrinology Diabetology, Sfax university, Tunisia

[2]pulmonology department, Sfax university, Tunisia

Corresponding author : Mouna Elleuch

Elleuch_mouna@yahoo.fr

ABSTRACT:

INTRODUCTION:

The coronavirus 2019 (COVID-19) pandemic has represented a major global health emergency and It is now recognized as a multisystemic disease, with potential repercussions on various organs. Diabetes mellitus is a common comorbidity associated with COVID-19. Its first-time diagnosis during the course of COVID-19 infection has been frequently reported, often with specific clinical, biological, and prognostic profiles. A better understanding of this association could shed light on the interplay between these two conditions.

PATIENTS AND METHODS :

This retrospective, descriptive, and analytical study included non-diabetic patients hospitalized for COVID-19 between 2021 and 2022 in the Pulmonology Department of the University Hospital of Sfax. Patients who developed newly diagnosed diabetes during hospitalization were identified and formed the basis of our analysis.

RESULTS:

New-onset diabetes was identified in 108 patients (12.9%) during hospitalization for COVID-19 with a mean age of 64.4 years and a male-to-female ratio of 1.34. Hypertension was the most common associated comorbidity, reported in 35.2% of cases. Clinically, the most frequent symptoms were dyspnea (60%), fever (55.6%), and cough (52.8%). On physical examination, hypoxia was observed in 65% of patients at admission. Laboratory findings revealed a mean random blood glucose level of 14.8 mmol/L. Chest CT scans showed extensive pulmonary involvement in 58% of cases. Systemic corticosteroids were prescribed in 70.6%. Diabetic ketoacidosis occurred in 4.6% of cases. Nine percent of patients with newly diagnosed diabetes required transfer to an intensive care unit. The mortality rate in this group was 14.7%.

At a mean follow-up of 24 months, glycemic status was reassessed. Among reachable patients, 60% remained diabetic. Diarrhea and the severity of radiological lung involvement were identified as independent predictors of new-onset diabetes during COVID-19 infection.

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CONCLUSION:
New-onset diabetes during COVID-19 infection is not uncommon. It is associated with distinct clinical and paraclinical features. Early identification of diabetes in this context is essential for timely and appropriate management to prevent complications.
KEYWORDS: New-onset diabetes, COVID-19, Clinical outcomes

INTRODUCTION:

Since January 2020, a new coronavirus variant has caused the COVID-19 pandemic, rapidly evolving into a global crisis responsible for nearly seven million deaths and serious health complications worldwide (1,2). Tunisia has experienced 4 successive waves of COVID-19, resulting in a high number of hospitalizations and a high case-fatality rate (3). This infection is associated with both immediate and prolonged complications, including the emergence of new diabetes and hyperglycemia cases reported in multiple studies globally (4).

Diabetes is a chronic condition associated with significant morbidity and mortality. The International Diabetes Federation (IDF) projects that the global diabetic population will reach 783 million by 2045. However, the COVID-19 pandemic appears likely to disrupt these forecasts, potentially driving an even greater rise in diabetes cases worldwide. A reciprocal relationship between diabetes and COVID-19 infection has now been clearly established (5,6). Diabetic patients infected with this virus have higher rates of hospitalization and mortality compared to non-diabetic individuals (7–9). Moreover, COVID-19 infection has been shown to increase the risk of developing diabetes (10). This study aimed to assess the incidence of newly diagnosed diabetes during COVID-19 infection, describe its associated clinical and biological profiles, and identify predictors of its onset.

PATIENTS AND METHODS

This retrospective, descriptive, and analytical study was conducted in the Department of Pulmonology at Hedi Chaker University Hospital, Sfax, Tunisia. We analyzed data from patients hospitalized for COVID-19 infection between November 2021 and January 2022. The study included non-diabetic patients aged over 18 years with confirmed COVID-19 infection.

We included non-diabetic patients over 18 years of age with COVID-19 infection. The diagnosis of COVID-19 was established by at least one of the following (11) :

- Positive antigen detection rapid diagnostic test (Ag-RDT)
- Positive nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) test
- Chest computed tomography (CT) scan with findings typical of COVID-19 infection

We excluded patients who had negative RT-PCR and Ag-RDT results, those with atypical CT scan findings not consistent with COVID-19, as well as individuals with a history of diabetes, pregnant women, and those with incomplete medical records.

Patients were categorized into two groups based on glycemic status during hospitalization:

- Group 1 (G1): Patients with newly diagnosed diabetes
- Group 2 (G2): Patients with normal glycemic status

Due to the unavailability of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) measurements, the diagnosis of diabetes in G1 was based on the American Diabetes Association (ADA) 2022 criteria (12) : two random blood glucose values >11,1 mmol/l.

A standardized data collection form was used to gather comprehensive information, including demographic and socioeconomic characteristics, personal and family medical history, methods of COVID-19 diagnosis, and clinical presentation.

Data were also collected on treatment approaches, disease progression, and any complications that occurred during hospitalization.

Clinical assessment included a general physical examination, capillary blood glucose testing, blood pressure measurement, heart rate, respiratory rate, and oxygen saturation.

Laboratory evaluations comprised C-reactive protein (CRP), complete blood count (CBC), lactate dehydrogenase (LDH), and random venous blood glucose levels.

Clinical Severity was determined by the required oxygen flow rate:

- Mild : No oxygen therapy needed
- Moderate : Oxygen flow <5 L/min
- Severe : Oxygen flow >10 L/min

Radiological Severity was evaluated based on the extent of lung involvement on initial CT scans:

- Minimal : <10%
- Moderate : 10–25%
- Extensive : 25–50%
- Severe: 50–75%
- Critical : >75%

In November 2023, a follow-up was conducted by telephone to assess the glycemic status of patients in Group 1. Information was obtained regarding whether post-discharge blood glucose testing had been performed, the results of these tests, and the initiation and type of long-term antidiabetic treatment, if applicable.

RESULTS

In this study, 832 patients were included. Among them, 108 (12.9%) were newly diagnosed with diabetes during hospitalization. The mean age of the patients was 64.4 ± 13 years, with a range of 34 to 92 years. Hypertension was the most reported comorbidity (35.2%), followed by dyslipidemia (6.5%). Smoking was reported in 15% of diabetic patients. Dyspnea and cough were present in 60.2% and 52.8% of cases, respectively. The most frequently observed symptoms were fever (55.6%), asthenia (50.9%), and anorexia (11.1%). Digestive symptoms included diarrhea (18.5%) and abdominal pain (3.7%). Anosmia and Ageusia were each reported in 0.9% of cases. Clinical examination findings are summarized in Table 1.

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Table 1. Clinical Examination Data

	Mean ± Standard Deviation	Range
Systolic blood pressure (mmHg)	123.8 ± 21	70 – 220
Diastolic blood pressure (mmHg)	71 ± 13	40 – 120
Heart rate (beats/min)	87 ± 15	40 – 122
Respiratory rate (breaths/min)	22.9 ± 10	15 - 59
Oxygen saturation (%)	87 ± 10	40 - 100
Temperature (°C)	37.7 ± 0.9	37 - 40

The mean random blood glucose at the time of diabetes diagnosis in patients in G1 was 14.8 ± 6.5 mmol/L, with values ranging from 11.22 to 35 mmol/L. Hyperleukocytosis, predominantly neutrophilic, was observed in 40% of cases. Lymphopenia was present in 70.3% of cases. The mean CRP value was 111 ± 83 mg/L, with a range of 3.8 to 324 mg/L. Elevated CRP levels were observed in 88.9% of patients. The average length of inpatient stay in the COVID-19 unit was 9 ± 5 days, with a range of 1 to 27 days. Based on the oxygen flow received, 43% of patients had a mild form, 18% had a moderate form, and 25% had a severe form. Extensive lung damage was noted in 58% cases on CT scan, with 39% showing severe to critical damage and 16% exhibiting minimal to moderate damage.

Fifty-seven percent of G1 patients required oxygen therapy during their hospitalization, with 44% requiring a high flow rate (> 10 liters). Systemic corticosteroids were prescribed to 70.6% of patients for an average duration of 9.9 ± 5.7 days. Fifty-six percent of patients received antibiotic therapy during hospitalization. Anticoagulation therapy was administered to 81% of patients for an average of 10.6 ± 6.5 days. Twelve percent of diabetic patients were treated with insulin during the acute phase. Fourteen percent of patients with newly diagnosed diabetes were treated with diuretics. Five patients (4.6%) experienced diabetic ketoacidosis during hospitalization. The mean time from admission to decompensation was 1.8 ± 3.03 days, with a range from 0 to 7 days. No cases of hyperosmolar hyperglycemic state were observed. Nine percent of patients with newly diagnosed diabetes required transfer to an intensive care unit. All patients were referred to the endocrinology department for diabetes follow-up. The mortality rate among diabetic patients was 14.7%.

The evolution of the glycemic profile in the 92 living patients was assessed by phone calls after an average of 24.5 months between the call and hospitalization. Only 46% of patients could be reached. Six patients died outside the COVID19 context. Among the 36 patients

contacted, persistent diabetes was confirmed in 60% of cases (Figure1). All patients started a healthy diet. In 66.6% of cases, patients initiated oral antidiabetics alone (metformin alone or in combination with hypoglycemic sulfonamides), while 14.2% of them required a combination of insulin therapy and metformin.

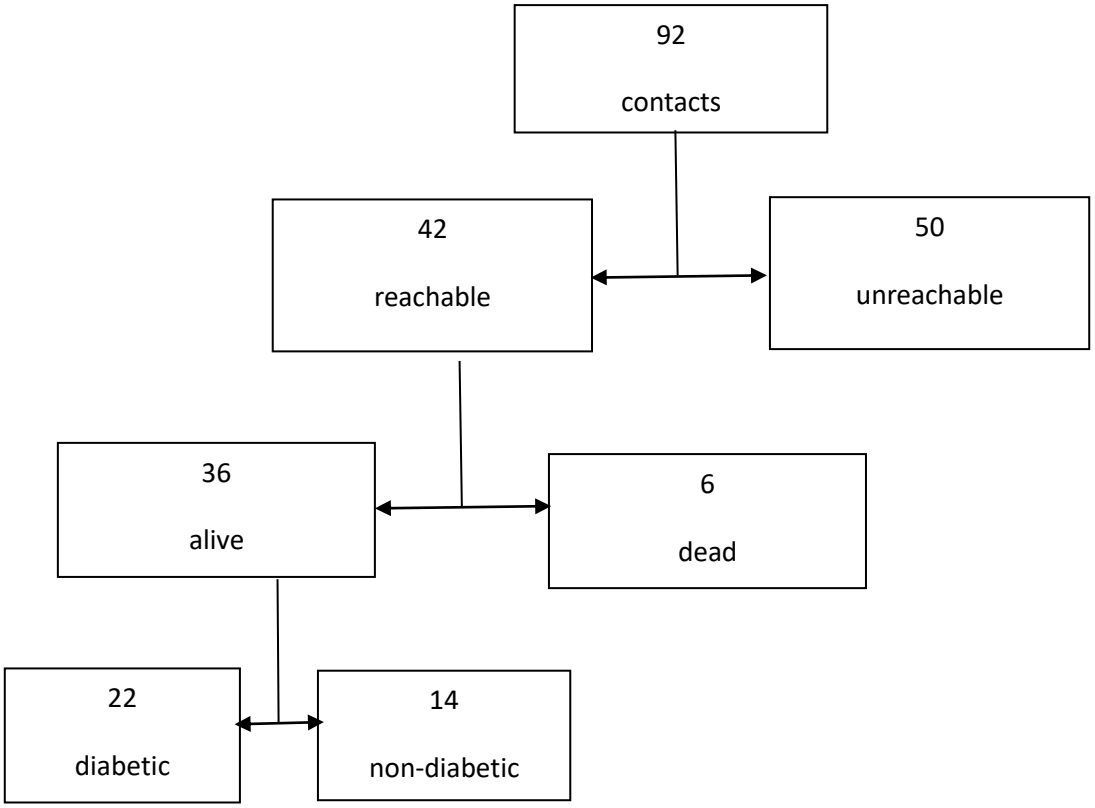

Figure1. Long-term follow-up of diabetic individuals

A comparative analysis was performed between G1 and G2 (Table2).

Table2. Comparative analysis of clinical characteristics between the two groups

Parameters	G1 Patients with newly diagnosed diabetes n=108	G2 Patients with normal glycemic status n=724	p value
Age, mean ± SD (years)	62,9□14	63,02□16	0,798
Male sex (%)	59 (54,6%)	398 (55%)	0,208
Hypertension	38 (35,2%)	185 (25%)	0,037
Dyslipidemia	7 (6,5%)	42 (5,8%)	0,782
Chronic kidney disease	1 (0,9%)	36 (5%)	0,057
Cardiovascular disease	1 (0,9%)	26 (3,6%)	0,144

Stroke	5 (4,6%)	17 (2,4%)	0,169
Asthma	3 (2,8%)	40 (5,5%)	0,228
COPD	5 (4,6%)	29 (4%)	0,762
Hypothyroidism	4 (3,7%)	11 (1,5%)	0,112
Adrenal insufficiency	0	5 (0,7%)	0,386
Dyspnea	65 (60%)	406 (56%)	0,430
Fever	60 (55,6%)	388 (53,7%)	0,713
Cough	57 (53%)	371 (51%)	0,776
Diarrhea	20 (18,5%)	70 (9,7%)	0,006
Chest pain	6 (5,6%)	43 (5,9%)	0,872
Aguesia	1 (0,9%)	15 (2,1%)	0,418
Oxygen Saturation	7,66±10	87,91±9	0,836
Heart rate	87,27±15	90,5±20	0,501
Systolic blood pressure	123,4±56	124,2±57	0.819
Diastolic blood pressure	71±33	70,9±33	0.970
Leucocytes	11036 ± 11644	9718 ± 9940	0,494
Neutrophiles	111 ± 83	112,3 ± 82	0,938
random blood glucose	14,86 ± 6,5	6,5 ± 3	0,000
Corticotherapy use	76 (70%)	489 (67%)	0,570
Antibiotics use	61 (56%)	437 (60%)	0,121
Diuretics use	15 (13,9%)	57 (7,9%)	0,039
Non invasive ventilation use	1 (0,9%)	10 (1,4%)	0,698
Vitamin C	87 (80,5%)	576 (79%)	0,830
Vitamin D	80 (74%)	569 (78,7%)	0,278
Zinc	72 (66%)	524 (72%)	0,211

COPD : *Chronic obstructive pulmonary disease*

Multivariate analysis confirmed that only the radiological severity of lung involvement and diarrhea were predictive factors for diabetes diagnosed during COVID-19 infection (Table3).

Table3. Independant factors associated with new-onset diabetes during COVID-19 infection

Factors	***OR (95%CI)***	***p value***
Arterial hypertension	0,692 (0,444-1,079)	0,105
Diarrhea	2,058 (1,176-3,603)	0,011

Radiological severity	1,153 (0,51-2,606)	0,015
Diuretic administration	1,875 (0,990-3,550)	0,054

DISCUSSION

Literature suggests that the rise in diabetes cases during the pandemic may be linked to recent weight gain caused by lifestyle changes, mainly due to isolation, decreased physical activity, and unhealthy eating habits. These factors promote the onset of insulin resistance (13). COVID-19 might also induce diabetes by promoting pancreatic infiltration via angiotensin-converting enzyme 2 (ACE2), leading to impaired insulin secretion and β-cell apoptosis. This mechanism corresponds to the pancreas's high expression of ACE2, which enables viral entry and targeted tissue damage (14,15). Moreover, severe COVID-19 infections can trigger a cytokine storm that may induce endothelial cell dysfunction and impair insulin secretion (16).

Hypertension has been identified as the most prevalent comorbidity in this group and shows a strong association with newly diagnosed diabetes. Recent findings indicate that certain antihypertensive medications might play a role in the development of iatrogenic diabetes. In particular, Scheen et al. highlighted the diabetogenic effects of thiazide diuretics (17). Furthermore, it increases the risk of diabetes via two main mechanisms: damage to endothelial integrity and the production of oxidative stress, both of which contribute to insulin resistance and impair pancreatic β-cell function (18).

In our study, diabetic patients more frequently exhibited diarrhea. The respiratory and gastrointestinal systems, rich in ACE2 receptors, act as primary sites for human microbiota and are major targets for COVID-19 infection. Increasing evidence indicates that disruption of the microbiota caused by COVID-19 may play a role in triggering cytokine storms. This intense inflammatory reaction, driven by cytokine release syndrome, may contribute to the development of new-onset diabetes (19).

In Zhou et al.'s study, all diabetic patients who underwent chest CT imaging demonstrated radiographic evidence of pneumonia, predominantly exhibiting bilateral ground-glass opacities in most cases (20). The study by Jaccobeli et al. identified acute hyperglycemia as the strongest predictor of extensive ground-glass opacities on chest CT in COVID-19 patients, independent of pre-existing diabetes status (21).

The RECOVERY trial, published on dexamethasone use in 2,104 hospitalized COVID-19 patients in the UK, corroborates the elevated diabetes risk. This risk may stem directly from steroid-induced metabolic disturbances, featuring delayed or impaired recovery of beta-cell dysfunction (22).

Regarding poor clinical outcomes in diabetic patients, hyperglycemia impairs lung volume and induces respiratory deterioration, characterized by reduced PaO_2/FiO_2 ratio, ultimately contributing to worse prognosis (23).

Persistent diabetes in COVID-19 patients may be linked to 'Long COVID' (Post-COVID-19 Syndrome), characterized by symptoms lasting more than three months after the initial infection. This multisystem condition can impact multiple organs, including the pancreas (24). Additionally, the specific viral strain seems to affect the development of chronic diabetes. Rangu et al. showed that the Omicron subvariant induces a milder cytokine response than the Beta and Delta variants, leading to reduced lung inflammation. Importantly, genomic mutations found in the Beta, Gamma, and Delta variants—but absent in Alpha and Omicron—are linked to heightened inflammatory reactions and a greater likelihood of post-acute COVID-19 complications (25).

Li et al. established zinc's multifunctional role, demonstrating antiviral, antioxidant, and anti-inflammatory properties, along with protective effects against diabetes development (26).

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