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Newly Diagnosed Diabetes Mellitus During COVID-19: The New Pandemic – A Literature Review

Nicole Knebusch Toriello[1] · Natalia María Prato Alterio[1] · Lourdes María Ramírez Villeda[1]

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Abstract

Purpose of Review Coronavirus disease 2019 (COVID-19) has caused a spike in newly diagnosed diabetes mellitus (NDDM). NDDM and COVID-19 infection are not well established as a cause-and-effect relationship; hence, the present review aims to define the underlying causes and consequences of COVID-19 infection in relation to the condition.

Recent Findings β-Cells are infiltrated by SARS-CoV-2, causing glycometabolic dysfunction and insulin dysregulation. The disease causes systemic inflammation and pro-inflammatory cytokines, as well as hormonal changes that lead to insulin resistance and hyperglycemia that are difficult to manage. As a result of NDDM, complications related to COVID-19 infection become more severe.

Summary NDDM related to COVID-19 infection complicates hospitalization outcomes and adversely affects quality of life in patients. There are many possible causes and consequences associated with NDDM, but for establishing preventive measures and treatments for NDDM, more evidence regarding its epidemiology, physiopathology, etiology, and nutritional aspects is required.

Keywords Newly diagnosed diabetes mellitus · COVID-19 · New-onset diabetes · SARS-CoV-2 · Hyperglycemia

Introduction

Coronavirus disease 2019 (COVID-19) has affected the world in a variety of ways, ranging from the disease itself to lockdowns and changes in lifestyle and behavior. Approximately 565,207,160 cases of COVID-19 have been confirmed as of mid-July of 2022, according to the World Health Organization (WHO) [1]. While the disease has been thoroughly studied, evidence of post-acute sequelae is still being analyzed [2]. These post-acute sequelae are often referred to as "long COVID" which is defined by the National Institute for Health and Care Excellence (NICE) as "signs and symptoms that emerge during or after an infection consistent with COVID-19, persist for more than 12 weeks, and are not explained by an alternative diagnosis" [3]. There are multiple manifestations of long COVID, including pulmonary and multiorganic signs and symptoms that can impair the quality of life of patients who have recovered from the illness [2, 4].

Several studies have reported a link between diabetes mellitus (DM) and COVID-19, ranging from and increased risk of poor prognosis and increased mortality to newly diagnosed diabetes mellitus (NDDM) precipitated by COVID-19 [5–7]. NDDM causes are still being debated among researchers, as it could be caused by direct viral entry into β-cells, resulting in dysfunction, systemic inflammation resulting in insulin resistance, or endocrine changes triggering this response [5, 6, 8••]. Also, glucocorticoids are usually prescribed for moderate and severe COVID-19, which are reported to cause hyperglycemia and insulin resistance, which could exacerbate the incidence of NDDM [6].

In comparison with previously diagnosed DM, NDDM is known to increase the odds of being admitted to the intensive care unit (ICU), having a longer length of stay and a higher mortality from SARS-CoV-2 infection [9•, 10]. The purpose of this review is to evaluate the existing evidence surrounding the causes and consequences of NDDM. It is imperative that we have a better understanding of the

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✉ Nicole Knebusch Toriello
Nknebusch@ufm.edu

[1] Baccalaureus Scientiae in Clinical Nutrition, Guatemala, Guatemala

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findings of NDDM due to the pandemic's ongoing spread and the increase in NDDM cases that are occurring.

COVID-19: A Nightmare for Glycemic Management

Glycemic levels can fluctuate for many reasons when the body goes through a state of stress caused by an infectious and inflammatory process. The immune and endocrine systems interact closely to keep glucose metabolism in homeostasis [11]. As a result of metabolic stress induced by a pathogen, an inflammatory response leads to hormonal changes as the overproduction of counterregulatory hormones such as glucagon and catecholamines, as well as an adrenocortical response, resulting in insulin resistance and contributing to the blood sugar imbalance [12•] (Table 1). Hyperglycemia with or without a history of DM is a strong predictor of adverse outcomes, increasing the risk of mortality [9•, 13]. According to Huang Y et al., patients with abnormal fasting plasma glucose levels without having DM had a crude mortality of COVID-19 of 3.54 times higher than those with normal glycemic levels ($OR = 3.54$; $p = 0.018$) [13]. A meta-analysis conducted by Sathish T et al. showed that 14.4% of hospitalized patients with COVID-19 developed NDDM, even though it is important to consider that some of the patients could have not been diagnosed before infection [14]. There are many mechanisms that may contribute to COVID-19's ability to cause glycemic imbalance and cause the development of NDDM.

It is well known that SARS-CoV-2 is a respiratory tract infection; despite this, growing evidence has allowed the emergence of a different hypothesis that suggests that other cells can be infected, leading to extrapulmonary pathological changes and complications [15, 16]. As a result of the acute inflammatory process involving C-reactive protein (CRP) and interleukin-6 (IL-6), damage may occur to β-cells, resulting in dysfunction of these pancreatic cells [17] (Fig. 1). This was demonstrated by Yavropoulou A. et al.'s study, which assessed levels of IL-6, salivary cortisol, and CRP levels in COVID-19 patients, finding that CRP and IL-6 levels were 6 times higher in infected patients ($p < 0.001$). Related to cortisol levels, evidence showed that nocturnal salivary cortisol was higher compared to the control group [17]. This metabolic response during a period of COVID-19 infection can result in hyperglycemia secondary to insulin resistance [6, 18].

Adipose tissue plays an important endocrine role by secreting hormones; dysfunction of this carefully controlled system can be associated with insulin resistance [18]. Adiponectin is an anabolic hormone secreted by the adipose tissue, which during metabolic stress related to infection tends to decrease, as there is a significant correlation between the severity of the inflammatory process and adiponectin levels [19, 20]. Reiterer M et al. found that adiponectin level was 50–60% decreased in patients with COVID-19 and ARDS, compared with ICU patients without ARDS ($p = 0.003$) [18]. These results can be compared with those obtained by Filippo et al., where the adiponectin/leptin ratio was evaluated in patients with COVID-19 as a marker of survival and inflammatory load. The results showed that patients with a higher adiponectin/leptin ratio tended to have more cardiometabolic disturbances (NDDM, HTA, obesity, etc.), more death, and ICU admission ($p = 0.010$) [20]. Also, it showed that patients with severe COVID-19 had significantly higher CRP serum levels ($p < 0.001$) and that this ratio was significantly associated with CRP serum levels ($p = 0.023$) [20, 21].

In addition to the previously described metabolic and endocrine alterations, it is important to consider that the COVID-19 treatment guidelines recommend the use of systemic corticosteroids for some nonhospitalized and all hospitalized patients since it has been seen that this therapy improves clinical outcomes by mitigating the

Table 1 Hormones involved in glucose regulation

Function	Hormone
Cortisol	It is a catabolic hormone produced by adrenal glands in response to stress; its role is to induce gluconeogenesis and glycogenolysis, increasing blood glucose levels
Glucagon	Produced by the pancreas, this catabolic hormone promotes gluconeogenesis and protein catabolism, an increase in glucagon secretion leads to hyperglycemia
Leptin	A hormone secreted by adipose tissue, it increases during acute exacerbations and promotes inflammation, feeding back cortisol, glucagon, and IL-6 response
IL-6	A cytokine secreted by adipose tissue that promotes inflammation and insulin resistance
Insulin	It is an anabolic hormone produced by the pancreas; its effect is to control blood glucose levels by promoting glucose uptake into cells
Adiponectin	It is involved in glucose regulation; it has an anti-inflammatory and antidiabetic effect as it increases insulin sensitivity

[a]Adapted from Krause's Food & The Nutrition Care Process, by Mahan K, Escott-Stump S, Raymond J, Krause M. page. 386. Copyright 2017, Elsevier Inc

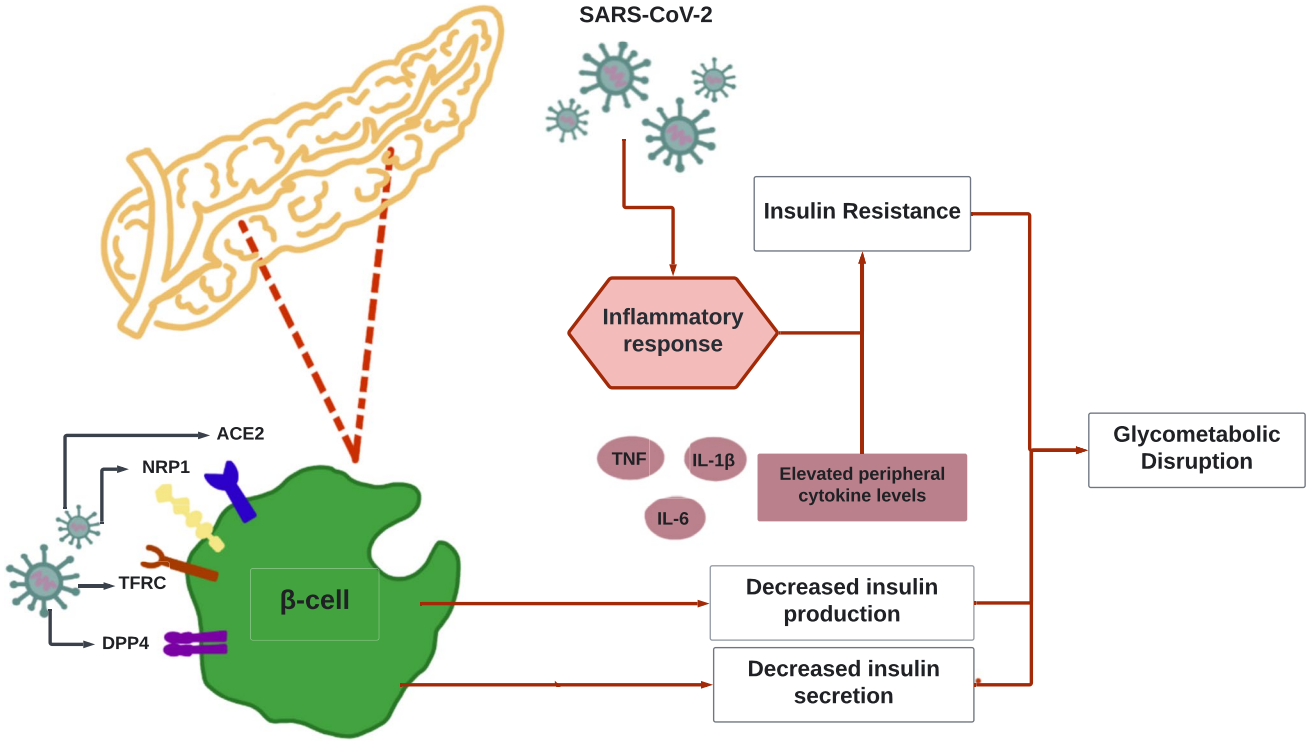

Fig. 1 Causes of glycometabolic disruptions during COVID-19 infection. Interactions of SARS-CoV-2 and pancreatic β-cells and molecular components needed for viral infiltration in the cells and systemic inflammation and its effects on increasing cytokine levels as the cause glycometabolic disruption. Adapted from: Steenblock C, Richter S, Berger I, et al. [5] Montefusco, L, Ben Nasr, M, D'Addio, F. et al. [8••], Wu CT, Lidsky PV, Xiao Y. et al. [26••], and Müller, J.A., Groß, R., Conzelmann, C. et al. [28]

inflammatory response [22]. It is worth considering that it helps in reducing inflammation, and the use of glucocorticosteroids has a key effect on NDDM on COVID-19 patients [23]. Significant levels of glucose variation were found in patients who used corticosteroids for COVID-19 treatment ($p < 0.026$), basal glucose increased by 23.9 mg/dl ($p = 0.010$), and postprandial blood sugar increased by 46.5 mg/dl ($p < 0.001$) [24]. These results can be compared to the meta-analysis by Chaudhuri et al. who found that there was an increase in glycemic levels with corticosteroid use (RR 1.11, CI 95% 1.01–1.23); however, the results are not certain there is variability in definitions for hyperglycemia used across studies [25].

How Does COVID-19 Affect the Pancreas?

There are different ways in which the pancreas could be affected by SARS-CoV-2 infection. There is evidence that the pancreatic islet endocrine cells, specially β-cells, can be harmed by viral infections, such as SARS-CoV-2 [5, 26••]. Moreover, β-cell dysfunction can happen when there is an inflammatory state, which is the case in COVID-19 patients [8••]. There is still a debate regarding whether infection or inflammation is the primary cause of β-cell dysfunction.

SARS-CoV-2 is capable of infecting pancreatic cells through multiple entry factors besides angiotensin-converting enzyme 2 (ACE2). In endocrine pancreatic cells, ACE2 expression has been reported to be low, but when compared to α-cells, β-cells express higher levels of ACE2 (colocalization rate: ACE2-INS 57.6 ± 19.3% vs. ACE2-GCG 6.8 ± 5.4%; $p < 0. \pm 0001$ [27, 28]. The entry of viruses into insulin-producing cells might be facilitated by a number of receptors and factors. It was evidenced by Wu CT et al. that β-cells, obtained from isolated human islets from healthy pancreatic donors ex vivo, express a large amount of neuropilin 1 (NRP1) and the transferrin receptor (TFRC) proteins, a small number of ACE2, and transmembrane serine protease 2 (TMPRSS2). Furthermore, NRP1 expression in patients positive for COVID-19 was significantly higher than in controls ($p < 0.05$) [26••]. These results compared to the ones obtained by Steenblock C et al. which evaluated SARS-CoV-2 entry factors in pancreatic islets obtained from 18 pancreatic donors, 11 who passed from COVID-19 and 6 from other causes. In this study, it was evidenced that human islets expressed NRP1, which could

facilitate virus uptake. They also evaluated the MERS-CoV receptor dipeptidyl-peptidase 4 (DPP4), which is expressed by cells of the endocrine and exocrine pancreas, and that it could work as a receptor for SARS-CoV-2 in β-cells [5]. The S protein of the virus can also invade other cells by binding through the same receptor DPP4 [29]. Consequently, these findings demonstrate that these cells are specifically equipped with the molecular components that permit SARS-CoV-2 to infect β-cells in the pancreas and that ACE2 is not the only factor in determining whether these cells become infected with this virus.

Based on RT-PCR and SARS-CoV-2 spike transcripts, there is evidence of SARS-CoV-2 viral positivity in the pancreas of patients who died from COVID-19–related complications [26••]. Steenblock C et al. stained the pancreas of all deceased patients with SARS-CoV-2 viral antigens, which were detected in endocrine and exocrine pancreas of patients who died from COVID-19 and negative in the control group [5]. Concerning endocrine function and insulin secretion, there is evidence that cells infected with SARS-CoV-2 lack hormone expression [28]. Wu CT et al. quantified the insulin content and glucose-stimulated insulin secretion in β-cells ex vivo, and the results showed a decrease in insulin and glucose-stimulated insulin secretion in SARS-CoV-2–infected human islets when compared to the control ($p < 0.05$) [26••]. A similar finding was reported by Müller JA et al. demonstrating that infected cells had a lower response to glucose-stimulated insulin secretion when compared to control cells ($p = 0.006$) [28]. Additionally, Steenblock C et al. suggested that this metabolic dysfunction might be caused by necrosis mediated by MLKL protein, which was detected in a small percentage of islets in all COVID-19 patient samples [5]. The data presented here shows that β-cells are infected by SARS-CoV-2 via various mechanisms and that it might lead to dysfunction of insulin secretion and production. β-Cell infection or apoptosis could cause this dysfunction, leading to hyperglycemia or NDDM.

NDDM: What Evidence Do We Have Until Now?

At the beginning of SARS-CoV-2 pandemic, DM was called as one of the comorbidities with worse outcomes and highest mortality rates. However, researchers have discovered and are gathering up information about NDDM and how these patients may have a worse outcome than patients who had already been diagnosed with DM before the infection with COVID-19 [9•, 17]. A retrospective study found that 4.0% of the patients ($n = 1902$) had NDDM, and they reported that 42.9% of them had evidence of prediabetes prior to hospital admission. Additionally, they reported that NDDM was more common in younger patients and less common in non-Hispanic white patients and that inflammatory parameters were higher in these patients, longer ICU stay, but not in deaths [10]. The CORONADO study found that 2.8% (80 patients)

Table 2 Characteristics of newly diagnosed diabetes mellitus compared to previously diagnosed diabetes mellitus

Characteristics		NDDM	Previously diagnosed DM
Baseline characteristics			
	Age	Younger (54–60 years)	Older (64–70 years)
	Sex	-	-
	BMI (kg/m2)	-	-
Comorbidities			
	Hypertension	+	+ +
	Dyslipidemia	+	+ +
	Cardiovascular disease	+	+ +
Short-term outcomes			
	COVID-19 mortality rate	+ +	+
	Inflammatory markers during COVID-19 infection	+ +	+
	Risk of ICU admission	+ +	+
	Length of stay	Longer	Shorter

+ + = higher risk or incidence; + = lower risk or incidence; — = no difference

NDDM, newly diagnosed diabetes mellitus; DM, diabetes mellitus; BMI, body mass index; ICU, intensive care unit

Adapted from: Cariou B, Pichelin M, Goronflot T et al. [9•] and Cromer S, Colling C, Schatoff D et al. [10]

of the patients they analyzed had NDDM and that these patients were younger than those who had already been diagnosed (60.2 ± 12.5 vs 70.5 ± 12.3 years, $p < 0.001$), and the majority were of African or Caribbean origin (31.1 vs 16.7%, $p = 0.0055$) (Table 2). The interesting fact is that NDDM patients did not have as many comorbidities as the previously diagnosed patients, but still had a more severe infection [9•]. In another study, they analyzed retrospectively 453 patients from Wuhan China with severe acute respiratory syndrome caused by COVID-19. They classified patients into groups based on glucose levels and separated patients with an existing DM diagnosis. The results showed that NDDM patients had the highest probability of admission to the ICU (11.7%) [7]. These results can be compared to the ones obtained by Fadini G et al. in a study that included 437 patients who tested positive for COVID-19 in Italy, including 107 who had DM, of which 21 had NDDM; NDDM had a stronger association with ICU admission or death compared to patients with pre-existing DM (RR 1.55, 95% C.I. 1.06–2.27; $p = 0.004$) [30]. A discrepancy still exists between the results, as some indicate that NDDM patients have a poorer prognosis than previously diagnosed patients, while others do not.

Long-term NDDM-related outcomes are still being investigated; according to a meta-analysis, patients post-acute COVID-19 have a 59% higher risk of developing NDDM than healthy controls (HR:1.59; 95% CI:1.40–1.81, $p < 0.001$, I2 = 94%, random-effects model) [31]. Maestre-Muñiz M et al. evaluated patients one year after hospitalization due to complications of the infection, in order to analyze the long-term effects caused by COVID-19. Regarding NDDM, they found out that 1.3% of the patients ($n = 543$) had been diagnosed with the condition during 1 year of recovery, that patients with a previous diagnosis required higher doses of oral antidiabetic drugs and insulin, and that some had developed DM complications like diabetic retinopathy or peripheral neuropathy [32]. According to another study, 56.3% of NDDM patients continue to have DM and that 40.6% had glycemic parameters back to normal range or prediabetes [10].

Could Lifestyle Changes During COVID-19 Lockdown Have an Effect on NDDM?

It has been well established that the pandemic has caused multiple changes in the lifestyle of people. The quality of diet changed according to a study performed in North India, reporting an increase in carbohydrate and fat intake during the pandemic compared to before (21% and 13% increased intake, respectively) [33]. These results can be compared to the ones obtained by Ammar A et al. which performed an international online survey of 1047 subjects. The surveys showed that when compared to before lockdown, unhealthy food consumption and "eating out of control" were significantly higher during lockdown ($t = -3.46$, $p < 0.001$; $t = -9.44$, $p < 0.001$, respectively) [34].

In terms of physical activity during the pandemic, it was found that minutes/day of general physical activity, vigorous activity, and moderate activity decreased by 33.5%, 33.1%, and 33.4%, respectively ($p < 0.001$) [34]. Furthermore, 87% of subjects reported high psychological stress during lockdown in Ghosh A et al. study [33]. The combination of these results with the fact that there is an association between physical inactivity, changes in dietary habits, and insulin resistance could provide a potential explanation for the changes in NDDM [35, 36]. As evidenced by Ghosh A et al., the NDDM patients diagnosed during pandemic had a higher fasting blood glucose, postprandial blood glucose, glycated hemoglobin, and fasting C-peptide when compared patients diagnosed with DM before the pandemic [37]. All of these changes during the pandemic, even though necessary in order to flatten the curve, may have negatively impacted patients, increasing the risk of NDDM and the differences seen between NDDM during COVID-19 pandemic and before the pandemic started.

Conclusion

There are many theories surrounding the causes of NDDM, including β-cell dysfunction, systemic inflammation, medication use, and metabolic and hormonal disturbances. It is possible that NDDM is caused by a combination of all of these systemic effects as well as lifestyle changes. There is still a lack of definitive evidence regarding the definition, duration, and etiology of NDDM. There are a number of challenges in studying NDDM, including a lack of reports on prediabetes and other conditions that may predispose to the condition. To better understand how to prevent and treat this long-term sequela of COVID-19, as well as future treatment options, more evidence is needed.

Author Contribution All authors contributed to the study conception and design. Material preparation and analysis were performed by Nicole Knebusch Toriello, Natalia María Prato Alterio, and Lourdes María Ramirez Villeda. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interest.

Human and Animal Rights Statement This article does not contain any studies with human or animal subjects performed by any of the authors.

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