Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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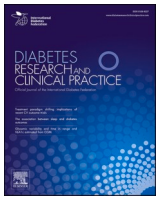

Review

COVID-19 induced Diabetes: A novel presentation

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ABSTRACT

Introduction: The COVID-19 pandemic disproportionately affected patients who had comorbid diabetes mellitus. COVID-19 patients with diabetes experience significantly higher rates of complications and mortality. COVID-induced diabetes is a novel phenomenon observed in critically ill patients. The aims of this review were to explore the literature about COVID-induced diabetes and the pathophysiological mechanisms that could lead to this novel presentation.

Methods: A literature search was performed using PUBMED, Google Scholar, MEDLINE and Embase for original studies (*meta*-analyses, cross-sectional studies, case series, case reports) about new-onset diabetes following COVID infection, and the proposed biochemical pathways behind this presentation. It was assumed that the authors of the studies used the current diagnostic criteria for diagnosis of type 1 and type 2 diabetes.

Results: COVID-19 causes dysregulation of glucose homeostasis leading to new-onset diabetes and hyperglycaemia. This is also seen in patients with no previous risk factors for diabetes mellitus. The atypical glycaemic parameters and increased rates of DKA suggest that COVID-induced diabetes is a novel form of diabetes. A spectrum of COVID-induced diabetes has also been noted. COVID-induced diabetes is associated with remarkably higher mortality rates and worse outcomes compared to COVID-19 patients with pre-existing diabetes. The novel presentation of COVID-induced diabetes could be due to beta cell damage and insulin resistance caused by SARS-CoV-2.

Conclusion: COVID-induced diabetes is essential to detect early, owing to its implications on prognosis. Further studies must include follow-up of these patients to better understand the trajectory of COVID-induced diabetes and the best management plan. It is also important to assess the beta cell function and insulin resistance of COVID-induced diabetes patients over time to better understand the underlying biochemical mechanisms.

1. Introduction

1.1. COVID-19 and diabetes

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that gave rise to the COVID-19 epidemic, which has caused over 5 million deaths globally as of December 2021 [1]. Patients hospitalised with COVID-19 have disproportionately higher rates of comorbidities such as diabetes and cardiovascular disease [2].

The relationship between diabetes and COVID-19 is an enigmatic field of research. Several studies have shown that diabetes is associated with a more severe form of COVID-19 as well as higher mortality [3,4]. The largest COVID-19 related whole-population study in England showed that a third of in-hospital deaths attributed to COVID-19 were in people with diabetes [3]. Alhamar et al developed a mortality-predicting model consisting of 4 risk factors, one of which included blood glucose [5]. Additionally, a *meta*-analysis of 13 studies which included 3027 COVID-19 patients showed that diabetes is associated with an almost 4-fold increase in risk for severe disease and death (OR = 3.68, 95 % CI [2.68–5.03]; P < 0.001) [4].

Many reports during the pandemic have shown that COVID-19 infection is associated with hyperglycaemia in patients without a known diagnosis of diabetes [6]. Hyperglycaemia is commonly seen in critically unwell patients and can be correlated to disease severity [7].

1.2. COVID-induced diabetes

Interestingly, a bidirectional relationship between diabetes and

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COVID-19 has been postulated [8]. The phenomenon of new-onset diabetes and new-onset hyperglycaemia following COVID-19 infection has been documented by numerous studies (see Table 1). Notably, a *meta*-analysis of 8 studies which included more than 3700 patients from 3 countries hospitalised due to COVID-19 infection showed a pooled new-onset diabetes incidence of 14.4 % (95 % CI: [5.9 %-25.8 %]) [9].

In addition, it has been reported that patients with new-onset diabetes have higher mortality rates and more severe COVID-19 outcomes. A *meta*-analysis examining the outcomes of 1,943 patients from 5 countries concluded that patients with COVID-induced diabetes had a mortality rate of 25 %, as compared to 9 % in patients without diabetes [10]. Yang et al performed a retrospective case series of 69 patients which showed that 54 % of patients critically ill with COVID-19 (admitted to intensive care unit or deceased) had new-onset diabetes, which correlated to a significantly increased rate of mortality (HR = 3.75, 95 % CI [1.26–11.15] P = 0.0019) [11]. A *meta*-analysis which included 14,502 patients concluded that each 1 mmol/L increase in fasting blood glucose was associated with a 33 % increase in severe COVID-19 outcomes [12]. Wang et al also corroborated this when they found that fasting blood glucose of $\geq$ 7 mmol/L at admission in COVID-19 patients with no history of diabetes was an independent predictor for 28-day mortality (HR 2.3, 95 % CI [1.49, 3.55]) [13].

COVID-19 patients with new-onset diabetes have been shown to have worse outcomes in comparison to patients with pre-existing diabetes. Li et al found that patients with new-onset diabetes were much more likely to require invasive mechanical ventilation in ICU as compared to patients with pre-existing diabetes [14]. Similarly, Fadini et al found an increased risk of ICU admission or death in patients with new-onset diabetes in comparison to patients with pre-existing diabetes (RR 3.06 vs 1.55, p = 0.004) [15]. Copelli et al showed that COVID-19 patients who were hyperglycaemic on admission had a 30 % higher mortality than the group with known diabetes [16]. Notably, Sathish et al demonstrated that new-onset diabetes could be observed as frequently as pre-existing diabetes observed in hospitalised COVID-19 patients [17]. This highlights that although COVID-induced diabetes is a novel concept, it is not uncommon and hence it is extremely important to recognise due to the poor prognosis seen in previous studies.

1.2.1. A novel form of diabetes?

The significant difference in the outcome of new-onset diabetes patients compared to pre-existing diabetes patients suggests that there may be a difference in the underlying pathological mechanisms. Reports about new-onset diabetes in COVID-19 patients have depicted novel biochemical findings. Li et al conducted a study in Wuhan found that individuals with new-onset diabetes and hyperglycaemia more often had higher levels of inflammatory indicators such as CRP, ESR and white blood cell count compared to those with pre-existing diabetes [14]. Copelli et al also observed a worse inflammatory profile and high D-

Table 1
Studies that have described new-onset diabetes in COVID-19 patients.

Authors	Country	Type of study	Population	Finding
Sathish et al. [9]	China, Italy, US	Meta-analysis	3,711 patients across 8 studies, ethnicity not reported, aged between 47 and 64.9 years	14.4 % of population had new-onset diabetes
Sathish et al. [18]	India	Retrospective study	102 patients, ethnicity not reported	20.6 % of population had new-onset diabetes
Yang et al. [11]	China	Retrospective case series	69 patients, ethnicity not reported, mean age 61 years, 53.3–80 % male	54 % of COVID-19 patients admitted to ICU had new-onset diabetes
Li et al. [14]	China	Retrospective study	453 patients, ethnicity not reported	20.8 % of population had new-onset diabetes
Unsworth et al. [19]	UK	Retrospective study	30 children, 36 % Caucasian European, 68 % male, mean age 10.9 years	80 % increase in new-onset T1D
Trieu et al. [20]	US	Case series	28 children, 36 % Caucasian	16.3 % increase in new-onset T1D and 205.3 % increase in new-onset T2D
Tittel et al. [21]	Germany	Prospective study	Children from 216 paediatric diabetes centres, age of onset between 6 months and 18 years	T1D incidence increased from 16.4 per 100,000 in 2011 to 22.2 per 100,000 in 2019
Salmi et al. [22]	Finland	Retrospective study	Children admitted to PICU due to new-onset diabetes and children registered to the Diabetes Registry in the Helsinki University Hospital from 2016 to 2020. Ethnicity not reported.	Number of children admitted to PICU due to new-onset diabetes increased from 6.25 in 2016 to 20 in 2020.
Al-Abdulrazzaq et al. [23]	Kuwait	Retrospective study	Children under 12 years registered in childhood-onset diabetes registry in Kuwait pre-pandemic and post pandemic. Ethnicity not reported.	A higher proportion of T1D cases presented with DKA during the pandemic when compared to pre-pandemic data (52.2 % vs 37.8 %)
Montefusco et al. [24]	Italy	Retrospective study	551 patients, ethnicity not reported	46 % were hyperglycaemic
Kamrath et al. [25]	Germany	Prospective study	532 newly diagnosed T1D, ethnicity not reported	Frequency of diabetic ketoacidosis was significantly higher during new-onset T1D during the pandemic (44.7 % in 2020 vs 24.5 % in 2019)
Fadini et al. [15]	Italy	Retrospective study	413 patients, ethnicity not reported, mean age 64.9, 59.3 % male	5 % had new-onset diabetes
Wu et al. [26]	Australia	Retrospective study	8 patients, ethnicity not reported	3 patients had new-onset diabetes
Ghosh et al. [27]	India	Retrospective study	555 patients with new-onset diabetes, ethnicity not reported	Patients with new-onset diabetes during the COVID-19 pandemic had worse glycaemic parameters than patients with new-onset diabetes before the pandemic
Heaney et al. [28]	US	Case report	54-year-old male, ethnicity not reported	New-onset type 2 diabetes with BMI 42.56 kg/m^2
Alfishawy et al [29]	Unknown	Case report	17-year-old male, ethnicity not reported	New-onset type 1 diabetes and pancreatitis
Lanca et al. [30]	Portugal	Case report	13-year-old male and 8-year-old male. Ethnicity not reported.	New-onset type 1 diabetes
Motawea et al. [31]	Egypt	Case report	73-year-old female. Ethnicity not reported	New-onset diabetes mellitus. Normal HbA1c
Shrestha et al. [10]	US, China, France, India, Italy	Meta-analysis	1,943 patients across 7 studies included in analysis. Ethnicity not reported.	Mortality rate was 16 % in patients with diabetes, and 25 % in COVID-associated diabetes patients.

dimer [16]. Furthermore, the incidence of DKA in the absence of auto-antibodies appears to be unusually high in COVID patients with new-onset diabetes, which is suggestive of acute viral induced pancreatic damage [32,33]. In a study by Li et al, 42 patients presented COVID-19 and ketoacidosis, and 27 (64 %) of the patients had no prior diagnosis of diabetes [32]. Rubino et al hinted that SARS-CoV-2 produces a ketosis-prone diabetes [34]. In a study looking at patients presenting in DKA without pre-existing diabetes, it was suspected that 45 % of patients had SARS-CoV-2 provoked ketosis-prone diabetes [35]. These patients also showed remarkably poorer glycaemic parameters and increased IL-6 levels in comparison to patients presenting with classical type 1 diabetes features [35].

1.2.2. COVID-19 induces type 1 diabetes

Many studies have also suggested the connection between COVID-19 and an increase in paediatric new-onset type 1 diabetes. Trieu et al. observed a 205.3 % increased rate of new-onset insulin-dependent type 2 diabetes and a 16.3 % increased rate of new-onset type 1 diabetes in the period between April and November 2020, when compared with the same period in 2019 [20]. The study suggested a marked increase in presentation with DKA [20]. Significantly, it suggested that the outcomes and clinical phenotypes of diabetes secondary to COVID-19 infection may be distinct and need to be explored further [20]. A study from the UK reported an 80 % increase in new-onset type 1 diabetes in children during the pandemic compared with previous years [19]. The authors postulated that exposure to COVID-19 infection may have precipitated or accelerated the development of type 1 diabetes [19]. Multiple studies have highlighted that the severity of presentation of type 1 diabetes in children appears to have increased [19,36]. Mastromauro found that a significantly higher percentage of newly diagnosed type 1 diabetes patients were presenting in DKA when compared to the previous 5 years (22.5 % vs 8.4 %, P = 0.01) [36].

Genetics plays a significant role in the aetiology of type 1 diabetes, especially with respect to the permissive HLA class II genotypes [37]. In addition to this, various environmental factors such as viruses have been thought of as triggers for insulitis [38]. In genetically susceptible individuals, this underlying inflammation leads to a complex interplay between *T*-effector and *T*-regulatory cells eventually causing beta cell destruction and autoimmunity [38,39]. DKA implies significant pancreatic beta cell destruction which is associated with greater morbidity and prolonged hospitalization [40]. The significant increase in DKA presentations in new-onset type 1 diabetes during the pandemic may suggest the role of SARS-CoV-2 in triggering the disease process in genetically susceptible individuals. DKA is also correlated with delayed diagnosis, which may have resulted from the overwhelmed healthcare systems in the COVID-19 pandemic [41]. Early diagnosis and management of type 1 diabetes is crucial in the setting as it has been reported to triple the risk of COVID-19 related hospitalisation and severity of illness [42].

1.2.3. A spectrum of COVID-induced diabetes

It is also important to mention the unique spectrum of new-onset diabetes that has been attributed to COVID-19 infection. Most large-scale research studies on the topic have classified this new-onset diabetes into either classical type 1 or type 2 diabetes. However, multiple recent case reports have presented findings of evidently novel forms of COVID-induced diabetes (See Table 2). Omotosho et al reported the case of a 45-year-old female who developed latent autoimmune diabetes of adulthood (LADA) on a background of COVID-19 infection [43]. The patient presented in DKA and was positive for islet cell antibodies and GAD antibodies [43]. A similar case of LADA was seen in a case report by Marchand et al [44].

Some case reports have also described auto-antibody negative insulin-dependent diabetes. A study that followed up 3 patients who developed acute-onset auto-antibody negative diabetes and DKA following COVID-19 infection showed that the patients' insulin requirement greatly diminished 4–6 weeks after discharge [45]. At 14 months, their hyperglycaemia was controlled by oral anti-hyperglycaemic agents [45]. This presentation and follow-up suggest the presence of a spectrum between type 1 and type 2 diabetes.

Another case of auto-antibody negative insulin-dependent diabetes was described in a 19-year-old male following COVID-19 infection [46]. The authors of this report suggested that direct beta cell toxicity caused this presentation of type 1 diabetes [46]. These cases are reminiscent of ketosis-prone diabetes. Ketosis-prone diabetes is an enigmatic form of diabetes in which patients present in DKA or unprovoked ketosis, but do not necessarily have the classical phenotype of autoimmune type 1 diabetes [47].

Furthermore, some case reports have presented lean COVID-19 patients with normal HbA1c results presenting with signs of insulin

Table 2
Case reports depicting novel presentations of diabetes following COVID-19 infection.

Reference	Case details	Parameters reported
Omotosho et al. [43]	45-year-old female diagnosed with LADA	BMI: 25.39 kg/m^2 HbA1c: 13.7 % C-peptide level: 0.49 ng/mL Anti-GAD antibody: 229 IU/mL Insulin autoantibody: 46.9 U/mL
Marchand et al. [44]	29-year-old female diagnosed with LADA	BMI: 21.5 kg/m^2 HbA1c: 11.8 % C-peptide level: 0.43 pmol/mL Anti-GAD antibodies: 93 UI/mL *Tyrosine phosphatase IA2 and zinc transporter 8 antibodies negative* *Note: this patient was obese a year before COVID infection*
Kuchay et al. [45]	Males aged 30, 32 and 60 initially insulin dependent. Follow-up at 14 months: not insulin dependent anymore.	Case 1 BMI: 28.6 kg/m^2 HbA1c: 9.6 % No C-peptide reported Anti-GAD antibody negative Case 2 BMI: 26.2 kg/m^2 HbA1c: 12.6 % No C-peptide reported Anti-GAD antibody negative Case 3 BMI: 27.3 kg/m^2 HbA1c: 12 % No C-peptide reported Anti-GAD antibody negative
Hollstein et al. [46]	19-year-old male with auto-antibody negative insulin-dependent diabetes *Authors suggest type 1B diabetes mellitus subtype*	BMI not reported HbA1c: 16.8 % C-peptide level: 0.62 μg/L Anti-GAD antibody negative *Tyrosine phosphatase IA2 and zinc transporter 8 antibodies negative*
Chee et al. [49]	37-year-old male presenting in DKA with no sign of insulin resistance	BMI: 22.6 kg/m^2 HbA1c: 14.2 % *No C-peptide reported* *No antibody tests reported*
Ghosh et al. [48]	41-year-old male presenting with marked hyperglycaemia and 6 kg weight loss over 1 month	BMI: 21.3 kg/m^2 HbA1c: 14.9 % C-peptide: 1.44 ng/mL *No antibody tests reported*
Alizadeh et al. [51]	16-month-old infant presenting in DKA and new-onset type 1 diabetes	HbA1c: 9.5 % Positive anti-GAD, zinc transporter 8, and islet antigen 2 antibodies
Soliman et al. [50]	8-month-old infant presenting in DKA and new-onset type 1 diabetes	HbA1c: 8.5 % Positive anti-GAD antibodies

resistance [48,49]. Chee et al published a case of a 37-year-old COVID-19 positive male who presented in DKA [49]. The patient had a BMI of 22.6 kg/m^2 and had no evidence of insulin resistance [49]. Ghosh et al presented a similar case about a 41-year-old non-obese man [48]. Autoantibody testing was not reported in both studies [48].

Atypical paediatric presentations of new-onset diabetes following COVID-19 infection have also been reported [50,51]. Alizadeh et al described the case of a 16-month-old infant who presented in DKA [51]. Although the authors hypothesised a genetic predisposition to developing type 1 diabetes, they proposed that COVID-19 infection accelerated the presentation and caused significant insulin resistance during admission [51]. Soliman et al observed a similar presentation in an 8-month-old infant [50].

1.3. The importance of follow-up

Due to the novel nature of COVID-induced diabetes, the literature exploring the follow-up of patients is limited to a few case series. Following up patients after a diagnosis of COVID-induced diabetes is essential to understand if beta regeneration may occur in subjects who were not genetically susceptible to developing diabetes. Gupta et al. followed up 19 patients who developed antibody negative insulin-dependent diabetes provoked by COVID-19 and found that 79 % were able to discontinue insulin completely after 6 months, suggesting beta cell recovery [35]. Kuchay et al found that the insulin requirement of patients who developed new-onset diabetes following COVID-19 infection diminished greatly 4–6 weeks after discharge, suggesting a degree of beta cell regeneration [45].

A study carried out by Montefusco et al illustrated that glycometabolic dysregulation associated with SARS-CoV-2 can persist chronically even after recovery [24]. The study showed that of the patients that displayed new-onset hyperglycaemia following hospital admission with COVID-19, 35 % had persistent hyperglycaemia 6 months after discharge [24]. In addition, patients who had recovered from COVID-19 showed significantly higher fasting insulin and C-peptide levels when compared to healthy controls [24]. Similar findings were also reported in a study by Chen et al [52]. This study showed that C-peptide levels and fasting blood glucose readings were higher at the 6-month follow-up when compared to the 3-month follow-up [52]. The presence of glycometabolic dysregulation 6 months following recovery suggests that SARS-COV-2 can cause significant permanent damage to components of the homeostatic glucose regulation pathways.

Additionally, emerging evidence is showing that new-onset diabetes is also a feature of "long-covid" – a term used to refer to the post-acute phase of the infection [53]. A retrospective cohort study performed in England with 47,780 patients that were discharged post-COVID showed that the incidence of new-onset diabetes was 29 per 1000 person-years, with a mean follow-up period of 4.6 months [54]. Another retrospective cohort study with 193 113 patients aged $\leq$ 65 years showed that new onset diabetes was the 6th most common post-acute infection sequalae [55]. These studies suggest that follow-up after discharge is important for COVID-19 patients that are at risk of developing new-onset diabetes.

2. Mechanisms for new-onset diabetes in COVID-19

The precise mechanisms which lead to new-onset diabetes in COVID-19 are likely to be multifaceted and have yet to be fully comprehended. Fig. 1 outlines the mechanisms discussed in this review.

2.1. Beta cell damage by SARS-CoV-2

SARS-CoV-2 has been known to affect the exocrine pancreas, presenting as pancreatitis in up to 32.5 % of critically ill patients [70]. The virus is also thought to damage the beta cells in the islet of Langerhans following many studies [70]. The increased presentations of DKA during the pandemic suggests that SARS-CoV-2 may have an acute direct or indirect impact on the pancreatic beta cells.

2.1.1. Other viruses and beta cell injury

There have been numerous reports on virus-mediated beta cell injury prior to the SARS-CoV-2 epidemic [71]. Over half a dozen viruses have been reported to be diabetogenic [72]. These include; enteroviruses,

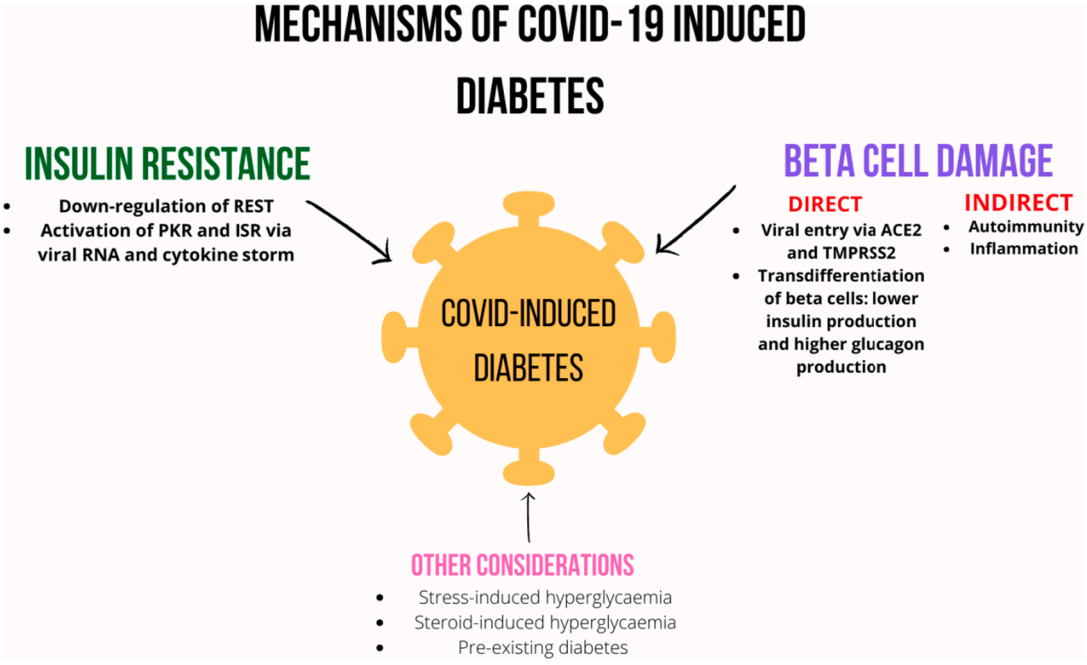

Fig. 1. Mechanisms of COVID-19 induced diabetes. The mechanisms behind new-onset diabetes following COVID-19 infection are likely multifaceted. Insulin resistance and beta cell damage are the two crucial mechanisms that have been proposed by several studies. A multitude of signalling pathways have been postulated to be responsible for the presentation of COVID-induced diabetes. Other considerations not explored in this paper include stress-induced hyperglycaemia, steroid-induced hyperglycaemia, and the unmasking of pre-existing diabetes [56–69].

coxackie virus, rubella and CMV [72]. Coronaviruses in the past have been linked to islet cell damage [72]. For example, the SARS-CoV-1 outbreak between 2002 and 2004 also saw new-onset hyperglycaemia associated with increased mortality. Some studies showed that 10 % of patients with new-onset hyperglycaemia following SARS-CoV-1 infection had diabetes at the 3-year follow-up interval [73]. The shared receptor of SARS-CoV-1 and SARS-CoV-2 (ACE2) and the genetic similarity of the two viruses might predict the diabetogenic effect of COVID-19 [72].

Yang et al. conducted a study investigating the diabetogenic effects of SARS-CoV-1 in 2010. 20 patients who had new-onset diabetes during their hospitalisation were followed up after 3 years. Only 2 patients were found to still have diabetes after follow-up. Furthermore, all these patients were compared to healthy matched siblings during the follow-up and no significant difference was found in post-prandial glucose and insulin levels. This gives the impression that the new-onset diabetes observed in these patients could have been due to transient islet cell injury by the virus [74].

2.1.2. *Direct beta cell damage*

Several studies have also shown increased amylase and lipase levels and focal pancreatic duct enlargement, suggesting that COVID-19 may directly target pancreatic tissues [61]. Recent data has suggested that COVID-19 infection can directly damage the beta cells of the pancreas. SARS-CoV-2 enters tissues via certain receptors expressed on target cells [59,62]. These include transmembrane serine protease 2 (TMPRSS2), angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase-4 (DPP-4) [59,62]. Using single cell RNA sequencing, it has been shown that tissues that express these receptors include pancreatic beta cells, alveolar cells, myocardium, and the small intestine [56,61]. A study which examined autopsy samples of COVID-19 patients demonstrated that several lineages of pancreatic islet cells were prone to viral entry by SARS-CoV-2 [58]. This was further confirmed by a study which used stem-cell derived organoids to show SARS-CoV-2 tropism to pancreatic beta cells [57]. Additional studies confirmed that SARS-CoV-2 can replicate inside the endocrine pancreas [60]. Tang et al. illustrated that SARS-CoV-2 infection of the pancreatic beta cells causes them to transdifferentiate which can lead to lower insulin expression, and higher glucagon and trypsin 1 production (see Fig. 2) [58]. Muller et al. demonstrated that SARS-CoV-2 infected beta cells can become hormone negative [60]. This could help to explain the dysregulation of glucose homeostasis seen in COVID-19 patients, which could potentially trigger new-onset diabetes.

2.1.3. *Indirect beta cell damage: Autoimmunity and inflammation*

2.1.3.1. Autoimmunity. Multiple case reports have suggested a connection between COVID-19 infection and new-onset autoimmune conditions such as SLE, Guillain-Barre syndrome and Graves' disease [65]. A handful of mechanisms have been suggested for the development of SARS-CoV-2 induced islet autoimmunity. These include molecular mimicry and prolonged presentation of beta-cell isotopes because of HLA-1 overexpression [67]. Furthermore, it has also been proposed that COVID-19 leads to the production of neoepitopes via post translationally modified proteins, which can trigger islet cell autoimmunity in genetically susceptible individuals [66]. Another mechanism which may contribute to autoimmunity is the excessive formation of neutrophil extracellular traps (NETs) seen in COVID-19 infection [65]. NETs are composed of chromatin and DNA expelled from the neutrophils and can serve as a reservoir of self-antigens, propagating autoimmunity [65]. Fig. 3 summarises these key mechanisms.

2.1.3.2. Inflammation. Along with being the receptor for SARS-CoV-2 entry, ACE2 also has a critical role in anti-inflammatory pathways through the generation of Ang 1–7 [63]. ACE2 cleaves angiotensin II

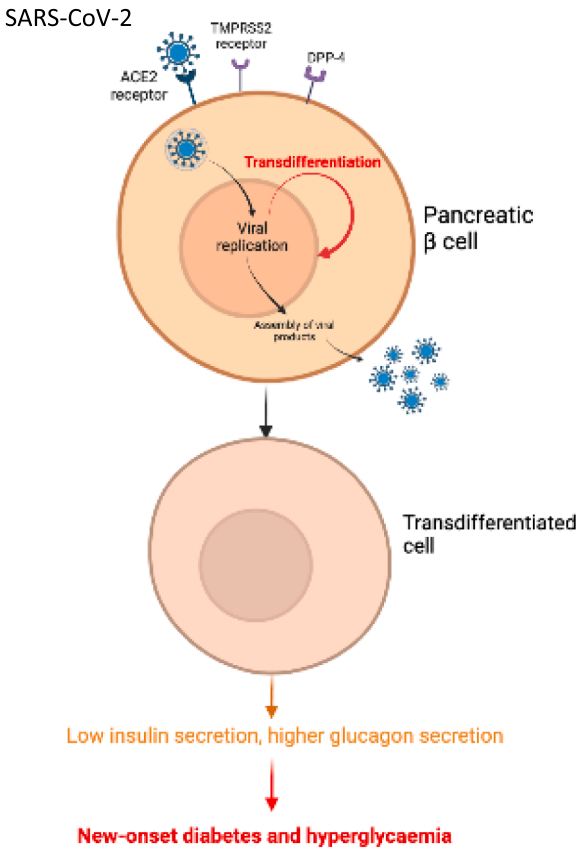

Fig. 2. SARS-COV-2 causes direct beta cell damage. Multiple receptors have been identified with affinity to SARS-CoV-2 in pancreatic beta cells. It has been shown that SARS-CoV-2 can replicate in beta cells and cause them to transdifferentiate [56–62].

into inactive Ang 1–7, the later having anti-fibrotic and vasodilatory properties [63]. In SARS-CoV-2 infection there is a depletion of surface ACE2 with viral entry and replication, through shedding and degradation [69]. Hence, tissues infected with SARS-CoV-2 may have significantly lower levels of Ang 1–7, leading to deleterious effects such as inflammation and a coagulative state [63,69]. A study involving mouse models concluded that a deficiency in ACE2 significantly reduces beta cell mass and proliferation [75]. Furthermore, ACE2 gene therapy in gene knockout mice promoted better beta cell survival and function, as well as improving glucose homeostasis [76]. Chee et al suggested that the depleted levels of ACE2 lead to the unopposed action of angiotensin II which may result in reduced blood flow to the pancreatic islets, as suggested by previous studies [49,68]. Angiotensin II also has well known inflammatory activity, increasing the infiltration of macrophages and monocytes [64]. These mechanisms are likely to lead to the derangement in the functions of the beta cells, leading to glycaemic dysregulation. Fig. 3 summarises this pathway.

2.2. *SARS-CoV-2 causes insulin resistance*

While several studies have postulated that insulin deficiency is responsible for new-onset.

hyperglycaemia in COVID-19, new evidence has suggested that insulin resistance induced by SARS-CoV-2 is a more likely explanation. He et al. studied a cohort of COVID-19 patients without prior history of metabolic disease and found that new-onset insulin resistance was induced by COVID-19 infection [77]. The team found that there was a down-regulation of the transcription factor REST (RE1-silencing transcription factor), which was linked to the altered gene expression of

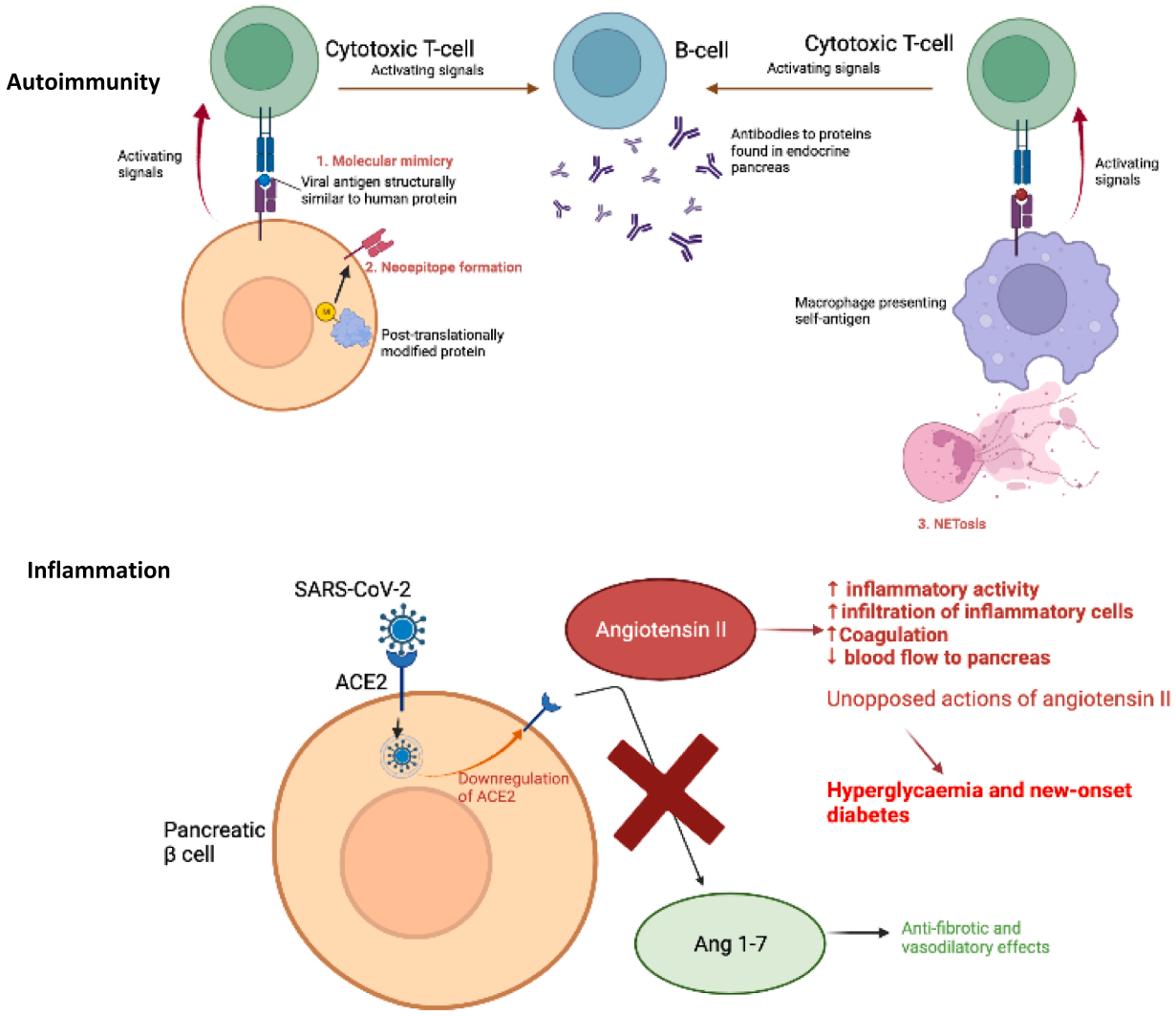

Fig. 3. SARS-COV-2 causes indirect beta cell damage through autoimmunity and inflammation. Several mechanisms have been postulated behind the apparent rise in autoimmune diabetes following COVID-19 infection. These include molecular mimicry, neoisotope formation and NETosis. SARS-CoV-2 also downregulates ACE2, an important enzyme which degrades angiotensin II. Unopposed actions of angiotensin II lead to deleterious effects [63–69].

important factors for glucose and lipid metabolism; myeloperoxidase, apelin and myostatin. Moreover, the analysis of short-chain fatty acids showed an upregulation of propionic acid and isobutyric acid following COVID-19 infection. These fatty acids have been linked to insulin resistance in animal models. Another interesting point from this study was that the BMI range was between 20.5 and 24.6, which shows that lean subjects with COVID-19 infection were also susceptible to developing insulin resistance. This unusual picture strengthens the impression that the insulin resistance observed in COVID-19 patients is independent of pre-existing risk factors such as high BMI [77].

A signalling pathway classified as the integrated stress response (ISR) is initiated when stressors lead to the activation of a family of four serine/threonine kinases. These include double-stranded RNA-dependent protein kinase (PKR) and PKR-like ER kinase (PERK). PKR and PERK have been shown induce serine phosphorylation of insulin receptor substrates (IRS) which leads to downregulation of the insulin signalling pathway. Specifically in the case of SARS-CoV-2, viral RNA fragments can cause activation of PKR resulting in insulin resistance [63].

Additionally, cytokine storm has also been known to activate the family of serine/threonine kinases linked to the ISR, causing insulin resistance [63]. Cytokine storm syndrome is a state of hyperinflammation that has been observed in many COVID-19 patients admitted to hospital [78]. Increased expression of pro-inflammatory cytokines such as IL-6 and TNF-alpha is characteristic of COVID-19 cytokine storm syndrome [79]. Furthermore, Sestan et al showed that viral-induced interferon gamma (IFN) can downregulate insulin receptors in skeletal muscle, leading to insulin resistance [80]. This could also contribute to the insulin resistance syndrome that has been described in COVID-induced diabetes patients.

Fig. 4 summarises the proposed mechanisms by which SARS-CoV-2 may lead to insulin resistance in COVID-19 patients.

3. Future work and conclusion

It is important to carry out prospective cohort studies to follow-up COVID-related diabetes patients over several years to evaluate the course of COVID-related diabetes. This is essential to find out whether the risks associated with new-onset hyperglycaemia on admission and COVID-related diabetes are distinct from conventional diabetes. Studies investigating the effects of SARS-CoV-2 on pancreatic beta cell function and insulin resistance will help to characterise the pathophysiological mechanisms that may be responsible for this novel presentation.

As COVID-induced diabetes remains a novel concept, it is unclear

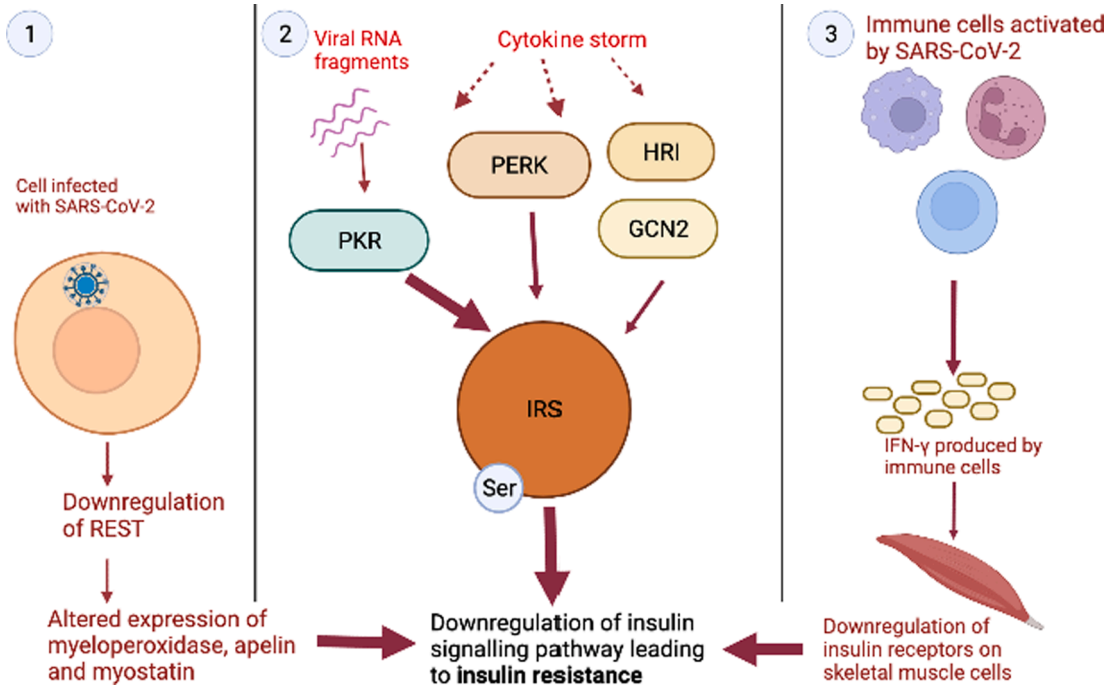

Fig. 4. SARS-COV-2 causes insulin resistance through multiple mechanisms. 1. COVID-19 patients have been shown to have a downregulated REST transcription factor, which has been linked to altered expression of proteins important for the insulin signalling pathway. 2. SARS-COV-2 may cause downregulation of insulin signalling pathway through activation of serine/threonine kinases via RNA fragments and cytokine storm. 3. Viral activation of immune cells causes release of IFN-gamma, which has been shown to downregulate insulin receptors on skeletal muscle cells, exacerbating insulin resistance [63,66,77–80].

whether the new-diabetes can be classified as type 1, type 2 or a more complex subtype. It may therefore be useful to report a full antibody panel for patients in future studies. Results from the coviDIAB study should help to characterise this novel presentation better [81].

Given the significant role of genetics in the development of multiple forms of diabetes, it may be useful to explore factors pre-disposing individuals to COVID-induced diabetes such as ethnicity and family history [37]. Determining the prevalence of long-COVID in patients with COVID-induced diabetes is important to recognise the risks associated with this novel presentation. Conversely, examining the glycaemic parameters of long-COVID patients may better elucidate the risk of long-term metabolic dysregulation resulting from COVID-19 infection.

COVID-induced diabetes is a novel and enigmatic area of research. Multiple studies have demonstrated that it could warrant a classification of its own. It is unclear whether the hyperglycaemia commonly seen in COVID-19 patients and COVID-related diabetes is due to the direct effect of SARS-CoV-2 on beta cells, inflammatory changes causing insulin resistance, or a combination of mechanisms. New-onset diabetes following COVID-19 is related to poor outcomes, hence it is extremely important to recognise and manage patients early. Further work is integral to grasping a better understanding of this novel form of diabetes and optimising management plans to improve patient outcomes.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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