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REVIEW

New-onset type 1 diabetes and severe acute respiratory syndrome coronavirus 2 infection

Roy Anindya[1], Guy A Rutter[2,3,4] & Gargi Meur[5]

1 Department of Biotechnology, Indian Institute of Technology Hyderabad, Sangareddy, Telangana, India
2 Section of Cell Biology and Functional Genomics, Division of Diabetes, Endocrinology and Metabolism, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK
3 Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore City, Singapore
4 Centre of Research of Centre Hospitalier de l'Université de Montréal (CRCHUM), Faculty of Medicine, University of Montréal, Montréal, QC, Canada
5 ICMR-National Institute of Nutrition, Hyderabad, Telangana, India

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Correspondence
Roy Anindya, Department of Biotechnology, Indian Institute of Technology Hyderabad, Kandi, Sangareddy 502284, Telangana, India.
E-mail: anindya@bt.iith.ac.in

Gargi Meur, ICMR-National Institute of Nutrition, Hyderabad-500007, India.
E-mail: gargimeur@icmr.gov.in

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Abstract

Type 1 diabetes (T1D) is a condition characterized by an absolute deficiency of insulin. Loss of insulin-producing pancreatic islet β cells is one of the many causes of T1D. Viral infections have long been associated with new-onset T1D and the balance between virulence and host immunity determines whether the viral infection would lead to T1D. Herein, we detail the dynamic interaction of pancreatic β cells with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host immune system with respect to new-onset T1D. Importantly, β cells express the crucial entry receptors and multiple studies confirmed that β cells are infected by SARS-CoV-2. Innate immune system effectors, such as natural killer cells, can eliminate such infected β cells. Although $CD4^+CD25^+FoxP3^+$ regulatory T (T_{REG}) cells provide immune tolerance to prevent the destruction of the islet β-cell population by autoantigen-specific $CD8^+$ T cells, it can be speculated that SARS-CoV-2 infection may compromise self-tolerance by depleting T_{REG}-cell numbers or diminishing T_{REG}-cell functions by repressing Forkhead box P3 (FoxP3) expression. However, the expansion of β cells by self-duplication, and regeneration from progenitor cells, could effectively replace lost β cells. Appearance of islet autoantibodies following SARS-CoV-2 infection was reported in a few cases, which could imply a breakdown of immune tolerance in the pancreatic islets. However, many of the cases with newly diagnosed autoimmune response following SARS-CoV-2 infection also presented with significantly high HbA_{1c} (glycated hemoglobin) levels that indicated progression of an already set diabetes, rather than new-onset T1D. Here we review the potential underlying mechanisms behind loss of functional β-cell mass as a result of SARS-CoV-2 infection that can trigger new-onset T1D.

INTRODUCTION

Type 1 and type 2 diabetes are considered a comorbidity and risk factor for severe coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); conversely, whether SARS-CoV-2 can *cause* diabetes remains a puzzle.[1] During the pandemic, anecdotal reports of new-onset type 1 diabetes (T1D) in young adults and children raised concerns that SARS-CoV-2 might damage the insulin-producing pancreatic islet β cells. Indeed, some studies reported a higher risk of developing diabetes among patients with COVID-19.[2,3] It was also suggested that one of the long-term consequences of the COVID-19 pandemic is an increase in the new onset of T1D.[4–8] However, population-based studies failed to find

any strong correlation between SARS-CoV-2 infection and new-onset T1D.[9,10]

A proposed link between new-onset T1D following viral infection is not new. Several viral infections, including rotavirus,[11] enterovirus,[12] mumps,[13] measles and rubella virus,[14] Coxsackie virus[15] and cytomegalovirus,[16] have been reported to be the causal agent of T1D. Pancreatic β cells express most of the known SARS-CoV-2 entry receptors, including angiotensin-converting enzyme 2 (ACE2) and neuropilin-1 (NRP1).[17–19] Relatively high expression of NRP1 on β cells makes these cells vulnerable to SARS-CoV-2.[20]

However, the outcome of viral infection might not lead to T1D[21] and could depend on virulence and host immunity. To know whether there is any link between T1D and SARS-CoV-2 infection, it is crucial to understand whether islet β cells were damaged by direct virus-induced cell death, and whether the immune tolerance in the islet milieu could be disrupted following SARS-CoV-2 infection that may evoke an autoimmune response ultimately leading to T1D. With limited direct epidemiological data linking T1D and SARS-CoV-2 infection, this review intends to bring together several laboratory and clinical evidence related to β-cell–specific immune responses following SARS-CoV-2 infection that might help to build a plausible hypothesis.

IMMUNE TOLERANCE MECHANISM PROTECTS AGAINST T1D: COULD SARS-COV-2 INFECTION DISRUPT IMMUNE TOLERANCE LEADING TO THE DEVELOPMENT OF T1D?

T1D is usually caused by β-cell loss accompanied by β-cell dysfunction, and is characterized by impairment in insulin secretion. The development of T1D is frequently associated with insulin-specific autoantibodies, but these autoantibodies are not likely to be the cause of the loss of islet β cells in T1D.[22] Studies with cadaveric pancreatic tissue revealed hyperexpression of major histocompatibility complex class I (MHC-I) on islet β cells and infiltration of effector $CD8^+$ and $CD4^+$ T cells.[23–25] The islet-infiltrated $CD8^+$ T cells can destroy SARS-CoV-2–infected insulin-producing β cells through the recognition of virus-specific proteins presented by MHC-I.[26] Such loss of the β-cell population resulting from direct SARS-CoV-2 infection is transient and may be corrected after recovery from infection. In addition, islet-infiltrated $CD4^+$ T cells secrete cytokines to increase MHC-I expression on β cells resulting in the continuous presentation of β-cell epitopes, thereby increasing the chance of recognition of β-cell–specific proteins presented by MHC-I.[27] Although central tolerance successfully removes the majority of the self-reactive T cells, some self-reactive T cells escape negative thymic selection and give rise to a peripheral T-cell population that still contains some self-reactive T cells (Figure 1a). This repertoire of peripheral self-reactive T cells might subsequently provoke autoimmune diseases, such as T1D, multiple sclerosis and inflammatory bowel disease, unless controlled by "peripheral tolerance."[28] The critical components of peripheral tolerance consist of T cells known as regulatory T (T_{REG}) cells and a specific subpopulation of dendritic cells (DCs) known as plasmacytoid DCs (pDCs).[29] T_{REG} cells are specialized T cells, identified by their expression of CD4 and CD25, and have the ability to regulate immune responses (Figure 1b). These $CD4^+CD25^+$ T cells specifically express the transcription factor Forkhead box P3 (FOXP3), which is crucial for the differentiation and function of T_{REG} cells.[30] The pDCs appear different from conventional DCs (cDCs) and instead have similarities with plasma cells. Unlike cDCs, they are mostly localized in lymphoid organs and display tolerogenic functions under steady-state or resting conditions. They are the primary producers of the antiviral cytokines, such as type I interferons (IFNs). Tolerogenic pDCs secrete a variety of soluble anti-inflammatory cytokines, including interleukin (IL)-10, transforming growth factor β and indoleamine 2,3-dioxygenase.[31] Among the cytokines released by the pDCs, transforming growth factor β triggers FoxP3 and CD25 expression on T_{REG} cells. Indeed, the key tolerogenic function of pDCs involves differentiation of naïve $CD4^+CD25^+$ T cells into $CD4^+CD25^+FoxP3^+$ T_{REG} cells.[32] The tolerogenic pDCs express programmed cell death ligand-1 (PD-L1).[33] Interaction between PD-L1 on pDCs and programmed cell death protein 1 (PD-1) receptor on T_{REG} cells contributes to differentiation and maintenance of the function of T_{REG} cells by sustaining and enhancing FoxP3 expression(Figure 1b).[34] Once mature $CD4^+CD25^+FoxP3^+$ T_{REG} cells are formed, they contribute to peripheral tolerance by functionally suppressing a variety of immune cells, including $CD4^+$ T cells, $CD8^+$ T cells, B cells and natural killer (NK) cells. T_{REG} cells display high surface expression of IL-2 receptor (CD25), and this helps T_{REG} cells to "mop up" extracellular IL-2, thereby suppressing cytokine signaling.[35,36] In fact, the unique presence of high expression of the IL-2 receptor (CD25) was responsible for the discovery of T_{REG} cells.[37] As the $CD4^+$ T and $CD8^+$ T cells are sensitive to the effects of IL-2, their effector function is inhibited by T_{REG} cells by this mechanism. The suppressive function of $CD4^+CD25^+FoxP3^+$ T_{REG} cells is also partially mediated by negative signals to cDCs through contact via the co-inhibitory receptor cytotoxic T-lymphocyte–associated

protein 4 (CTLA-4) of T_{REG} cells.[38] CTLA-4 and CD28 share two ligands of cDCs, namely, CD80 and CD86. T_{REG}-cell CTLA-4 can capture its ligands CD80 and CD86 from DCs by trans-endocytosis and degrade inside T_{REG} cells, depriving CD28-mediated costimulation of effector T cells[39] (Figure 1b). The capture of CD80 and CD86 by the CTLA-4 of T_{REG} cells ensures complete anergy of the self-reactive effector T cells. Many studies have reported that impaired $CD4^+CD25^+FOXP3^+$ T_{REG}-cell function has a causative role in T1D.[40–44]

For successful virus infection of the pancreatic insulin-secreting islet β cells, virus entry is essential. It was reported that SARS-CoV-2 infects human pancreatic β cells in patients as well as islet β cells *in vitro*.[18] The islet β cells are known to express receptor ACE2 and transmembrane serine protease 2 (TMPRSS2), albeit at a lower level, allowing successful virus entry.[19] The SARS-CoV-2 spike protein engages ACE2 as the entry receptor and employs the cellular serine protease TMPRSS2 for spike protein priming.[45] Indeed, ACE2, as well as TMPRSS2 expression, was found to be significantly upregulated in cardiomyocytes from diabetic cadavers, and by favoring the cellular entry of SARS-CoV-2, this could render the diabetic population more susceptible to COVID-19.[46] TMPRSS2 facilitates the entry of viruses, including Middle East respiratory syndrome coronavirus and SARS-CoV-2, into host cells by proteolytically cleaving and thus activating the viral envelope glycoproteins. The bioinformatics analysis suggests that microRNA miR-98-5p could potentially repress TMPRSS2 messenger RNA expression,[47] but the miR-98-5p level was downregulated in diabetes.[48] Islet β cells also display most factors implicated in the entry of SARS-CoV-2, including NRP1, FES upstream region (FURIN), heparan sulfate, transferrin receptor, Ras-associated binding 7A (RAB7A), cathepsin L (CTSL), transmembrane protein 41B and 106B (TMEM41B and 106B).[17,18,49–51]

ELEVATED TYPE I IFN LEVEL IN PATIENTS WITH SARS-COV-2: COULD THIS CONTRIBUTE TO PERIPHERAL TOLERANCE BREAKDOWN?

Several studies measured type I IFN (IFNα and IFNβ) levels in peripheral blood in patients with COVID-19. A meta-analysis of the published literature found that levels of type I IFN in peripheral plasma of mild to moderate

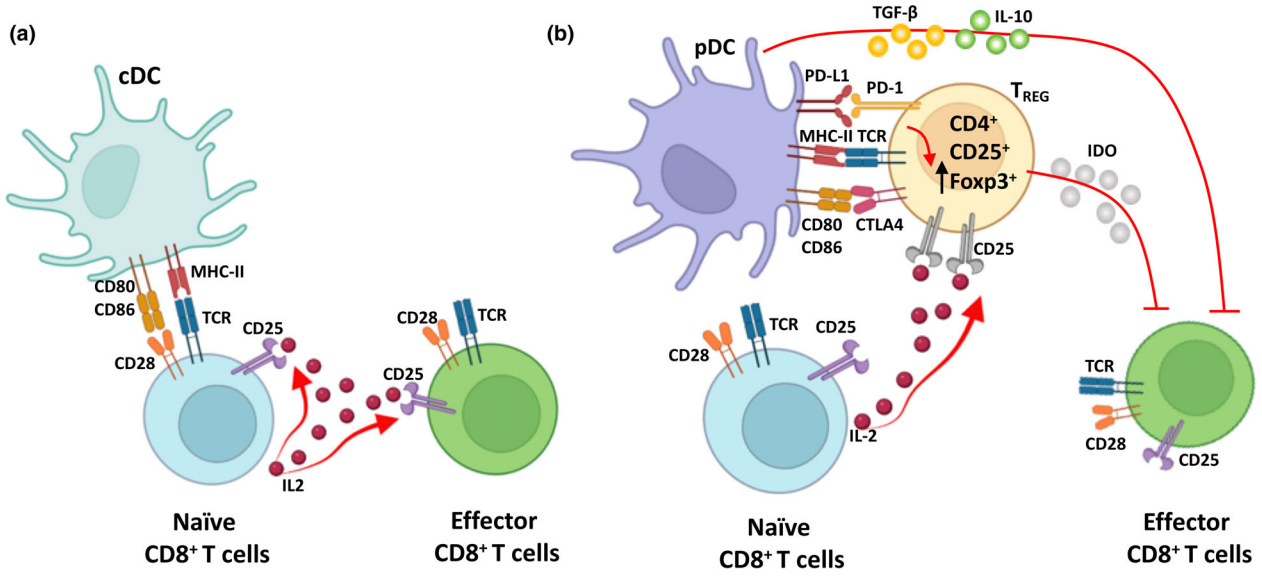

Figure 1. A simplified schematic representation of interactions of dendritic cells (DCs) and T cells. **(a)** Activated, conventional DCs presenting self-antigen can prime differentiation of $CD8^+$ autoreactive killer T cells and $CD4^+$ helper T cells (not shown). **(b)** Tolerogenic plasmacytoid DCs (pDCs) express different coreceptors and cytokines and can interact with regulatory T (T_{REG}) cells. T_{REG} cells and pDCs use multiple mechanisms to inhibit the activation of potentially pathogenic effector T cells. The interaction of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) on T_{REG} cells with its ligand CD80/86 on pDCs, inhibits T-cell activation. The sequestration of T-cell proliferation factor, interleukin-2 (IL-2) by high expression of constitutive IL-2 receptor (CD25) on T_{REG}-cell surface also prevents T-cell activation. T_{REG} cells also upregulate the expression of indoleamine 2,3-dioxygenase, and pDCs secrete anti-inflammatory cytokines, such as IL-10 and transforming growth factor β (TGF-β), which also block T-cell activation. FoxP3, Forkhead box P3; IDO, indoleamine 2,3-dioxygenase; MHC-II, major histocompatibility complex class II; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; TCR, T-cell receptor.

cases of COVID-19 were significantly elevated compared with healthy individuals.[52] This is not unexpected because viral infection is known to induce IFNβ expression in most cell types and IFNα expression in hematopoietic cells. However, the same study did not find any significant difference in plasma levels of type I IFN between mild and severely affected patients.[52] Galani *et al.*[53] observed that proinflammatory cytokines such as tumor necrosis factor and interleukins IL-6 and IL-8 were produced in all patients and persistently, but type I IFN production was both diminished and barely detectable, induced at a high level only in a fraction of patients as they became critically ill. Hadjadj *et al.*[54] also reported a rather low level of type I IFN in patients with COVID-19. It was also observed that the lower serum levels of type I IFN at the initial stage in patients with severe COVID-19 were associated with a higher viral load.[55,56] A longitudinal study that measured IFN levels in the peripheral blood of patients with mild and severe COVID-19 revealed that type I IFN levels in the peripheral blood are elevated during the early infection compared with healthy individuals. However, in mild infection, type I IFN levels gradually declined during the course of the infection, whereas in severe COVID-19 infection it remained unchanged.[57] These data on low type I IFN among patients with COVID-19 are in agreement with those from *in vitro* and animal studies suggesting that SARS-CoV-2 is a poor inducer of type I IFN response.[58] However, the prolonged presence of these IFNs and antiviral cytokines, albeit at a low level, might cause pleiotropic damaging effects.[59]

It is well established that pDCs have a major role in type I IFN secretion following viral infection.[60] Investigation of SARS and Middle East respiratory syndrome coronavirus infections in mouse models[61,62] showed that pDCs migrate to the infection site and are responsible for rapid production of type I IFNs. Postmortem biopsies of the SARS-CoV-2–infected pancreatic cells revealed that pDCs had migrated to the area of infection.[63] By *in vitro* experiment, it was demonstrated that SARS-CoV-2 enters pDC via NRP1/BDCA4 and produces high levels of type I IFN.[64] Interestingly, pDCs display a significant level of NRP1 on the surface[65] and NRP1 is a known SARS-CoV-2 entry receptor.[17] Although SARS-CoV-2 infects pDCs, it does not replicate in pDCs and the viral RNA is recognized by Toll-like receptor-7 (TLR7).[64,66] TLR7 is produced in the endoplasmic reticulum and senses viral RNA in endosomes after virus entry into host cells.[67] The signal from endosomal RNA binding is relayed to the cytoplasm by the myeloid differentiation primary response 88 (MyD88) adaptor which forms a complex with interferon regulatory factor-7 (IRF7) and promotes phosphorylation of IRF7 by interleukin-1 receptor–associated kinase-1.[68] Phosphorylation activates IRF7 and allows its translocation to the nucleus and triggers the expression of hundreds of interferon-stimulated genes[69] required for virus clearance. Detection of the virus by pDCs not only triggers type I IFN production via the TLR7–MyD88–IRF7 pathway, but the TLR7–MyD88 also activates the nuclear factor-kappa B pathway and results in the synthesis of proinflammatory cytokines and chemokines.[70] Large amounts of type I IFNs also induce proliferation and activation of monocytes and macrophages, further increasing the level of proinflammatory cytokines.[71]

SARS-CoV-2–infected pancreatic cells could be the source of type I IFN. Serum levels of type I IFNs, such as IFNα, are elevated in children at diagnosis of T1D.[72] Postmortem biopsies of pancreatic islets obtained from patients with T1D reveal the presence of cytokines and type I IFN.[73–75] Even in animal models, induction of an IFNα response was demonstrated to accelerate T1D development.[76] SARS-CoV-2 has an RNA genome and the viral RNA could be detected by the cytosolic sensors of the islet β cells. Viral RNA could be recognized by TLR7 receptors and recent data with SARS-CoV-2 infection also demonstrated the involvement of the TLR7–MyD88–IRF7 pathway.[66] Thus, SARS-CoV-2 infection of β cells could result in the initial production of type I IFNs and subsequently, a positive feedback loop would be established by the cell surface expression of IFN receptor. IFN binding to the receptor initiates a signaling pathway leading to the expression of IRF7. The newly synthesized IRF7, in turn, leads to the further induction of hundreds of interferon-stimulated genes. Interferon-stimulated genes have diverse functions, ranging from direct inhibition of viral replication to the recruitment and activation of various immune cells.[77] The products of these interferon-stimulated genes collectively establish the antiviral state at the site of viral infection and eventually result in virus clearance.[78] However, a higher level of type I IFN has a trade-off: type I IFN is linked with multiple autoimmune syndromes.[79] It remains to be seen whether type I IFN secretion by SARS-CoV-2–stimulated pDCs can cause substantial disruption in immune tolerance and thereby play a role in the development of T1D.

HIGHER LEVEL OF ANTIVIRAL CYTOKINES IN PATIENTS WITH SARS-COV-2: COULD THIS ACTIVATE CDCS AND CAUSE BREAKDOWN OF IMMUNE TOLERANCE?

Studies in other autoimmune conditions, such as systemic lupus erythematosus,[80] showed that antiviral

cytokines (IFNα and IFNλ) and proinflammatory cytokines (tumor necrosis factor-α and IL-6) could result in a disruption of tolerance. It can be hypothesized that type I IFN produced by pDCs and SARS-CoV-2–infected β cells might immunogenically activate pancreatic cDCs. Immunogenic cDCs would capture viral antigens and islet cell autoantigens more efficiently and enhance $CD8^+$ T-cell activation. The activated $CD8^+$ T cells can directly destroy SARS-CoV-2–infected β cells and also during the process, are likely to recognize β cells MHC-I presenting β-cell–specific antigens, which may potentially increase the risk of T1D (Figure 2a, i). Activation of $CD8^+$ T lymphocytes can also happen independently of T-cell receptor signaling by a high level of type I IFN via a mechanism termed "bystander activation."[81,82] Indeed, enhanced autoantigen presentation and T-cell activation are known to be associated with patients with T1D.[83,84] As the sustained high level of type I IFN enhances the susceptibility to autoimmune diseases, it is possible, but only speculative, that the patients who had long-term elevated type I IFN response as a result of COVID-19 are likely to have more predisposition to develop autoimmune reactions, including T1D.

COULD DIRECT DAMAGE OF ISLET β CELLS BY SARS-COV-2 INFECTION PROMOTE DEVELOPMENT OF T1D?

The death of islet β cells as a result of islet-infiltrating T cells is a common feature of T1D. However, β-cell death could also be mediated by NK cells, which respond rapidly and directly kill virus-infected cells by releasing cytotoxic granules (Figure 2a, ii). Although understanding of the SARS-CoV-2–specific NK cell response remains poorly understood, a quantitative proteomics study showed that SARS-CoV-2 infection provokes limited NK cell responses.[85] However, NK cells can efficiently eliminate SARS-CoV-2–infected cells by antibody-dependent cellular cytotoxicity in the presence of anti-SARS-CoV-2 antibodies in the serum[86] (Figure 2a, ii). Some viruses, such as Coxsackieviruses, establish a chronic infection in β cells. Even when a small percentage of islet β cells are infected,

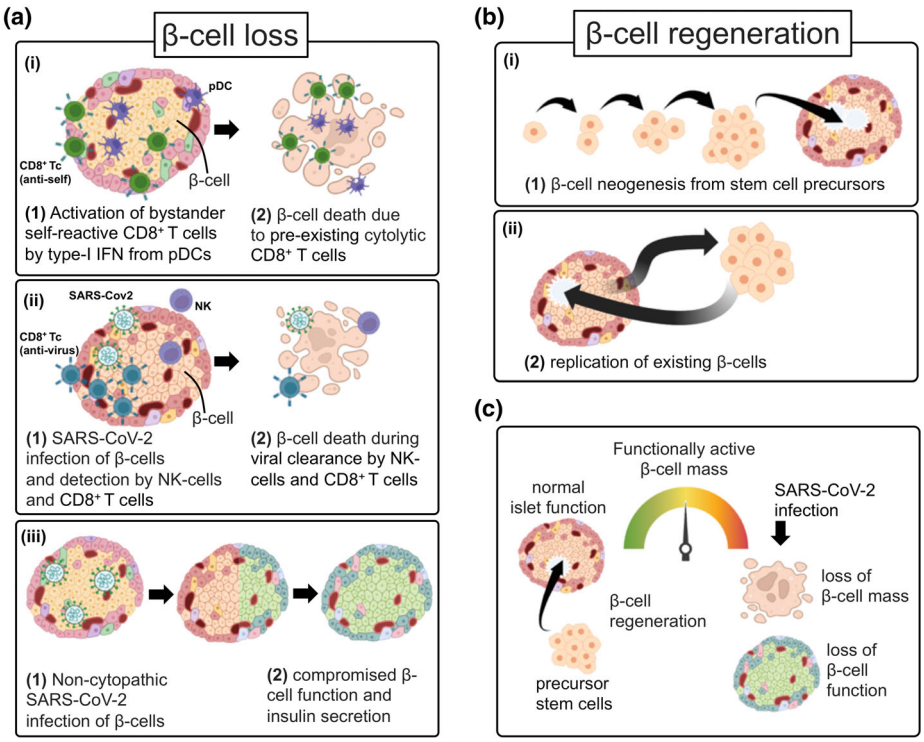

Figure 2. Putative mechanisms affecting the pancreatic β-cell function following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that might lead to new-onset type 1 diabetes. **(a)** Loss of β cells by SARS-CoV-2 infection. **(i)** Bystander activation of $CD8^+$ T cells. An elevated level of type I interferon (IFN) as a result of infection of plasmacytoid dendritic cells (pDCs) by SARS-CoV-2 leads to inactivation of regulatory T cells and β-cell cytolysis **(ii)** When β cells are infected with SARS-CoV-2, they are prone to attack by innate immune cells, including natural killer (NK) cells. **(iii)** Direct infection of β cells by SARS-CoV-2 is mostly cytopathic, eliciting multiple cellular stress responses and diminished expression of insulin. **(b)** Endogenous pathways of β-cell regeneration; **(i)** neogenesis through differentiation from stem cells or progenitor cells and **(ii)** replication of existing pancreatic β cells. **(c)** The balance between the extent of loss of β-cell mass as a result of SARS-CoV-2 infection and the islet regeneration potential of the patient is likely to determine the outcome, including new-onset type 1 diabetes. Tc, cytotoxic T cell.

type I IFN, such as IFNα, triggers overexpression of the MHC-I protein in infected and noninfected cells. The high level of MHC-I molecules contributes to the unabated presentation of β-cell epitopes to the immune system causing an autoimmune response.[87] *Ex vivo* experiments detected the SARS-CoV-2 nucleocapsid protein and spike protein in β cells following infection.[18] Nucleocapsid protein and viral RNA were detected in the autopsy samples of patients with COVID-19.[20] Another study with autopsy samples revealed that SARS-CoV-2 infection was present in most of the pancreatic cells, indicating a systemic infection rather than exclusively β-cell–specific tropism. Further immunohistopathological analysis revealed that a small fraction of pancreatic islet β cells underwent virally induced necroptosis.[88] Two recently published studies showed that direct SARS-CoV-2 infection results in β-cell apoptosis,[18] morphological and functional changes in β cells affecting their insulin-secretion[19] and β-cell trans-differentiation.[20] Experimental evidence from the delivery of a synthetic double-stranded RNA consisting of poly-inosine-cytidine (poly I:C), which mimics an intermediary stage of viral replication, into β cells affected their function[89] and possibly induced dedifferentiation. These different outcomes of β-cell fate are not mutually exclusive and eventually may cause reduced β-cell mass. All of these mechanisms, including destruction by activated $CD8^+$ T cells, are likely to cause transient loss of β cells and are likely to be replenished by regeneration. Contrastingly, β-cell infection by SARS-CoV-2 could also be noncytopathic, characterized by a modest inflammatory response restricted to infected cell subsets.[21] Importantly, the loss of regulatory "hub cells"[90] or "leader cells"[91] may be particularly consequential for overall islet function. This apparent contradiction could arise from the copy number of viral particles used for *in vitro* infection. Indeed, the presence of excess SARS-CoV-2 (high multiplicity of infection) in *ex vivo* experiments promotes interactions via pathogen-associated molecular patterns that may lead to enhanced IFN responses and β-cell death.[92] Therefore, direct loss of β cells by SARS-CoV-2 infection notwithstanding, a noncytopathic infection could also contribute to β-cell destruction by activating the autoimmune response (Figure 2a, iii). One of the mechanisms of type-I IFNs in autoimmune diseases is directly inducing T_{REG}-cell apoptosis.[93,94] Sadeghi *et al.*[95] reported a significant decline in T_{REG}-cell number in intensive care unit patients with COVID-19 when compared with healthy controls. They also observed a decrease in FoxP3 messenger RNA expression levels in patients. Using single-cell RNA-seq analysis Kalfaoglu *et al.*[96] observed that FoxP3 expression was remarkedly reduced in patients with severe COVID-19, although CD25 expression was higher in T cells. Loss of FoxP3 expression in T_{REG} cells can occur as a result of strong T-cell receptor interaction with autoantigens and proinflammatory cytokines.[97] Type I IFNs are also known to limit both T_{REG}-cell number and function in cancer microenvironments.[98–100]

Given the protective nature of T_{REG} cells in blocking hyperactivation of the immune system in patients with severe COVID-19, the depletion of T_{REG} cells as a result of virus infection could be responsible for increased mortality. Mice lacking T_{REG} cells also showed increased mortality when infected with murine coronavirus.[101] It should also be noted that obesity is one of the factors that decrease T_{REG}-cell number in circulation.[102]

The most compelling evidence that SARS-CoV-2 infection may indeed significantly lower SARS-CoV-2–reactive T_{REG} cells in hospitalized patients with COVID-19 compared with nonhospitalized patients came from comprehensive single-cell analysis of viral antigen–reactive $CD4^+$ T cells from patients with COVID-19.[103] Contrastingly, there are reports suggesting that increased T_{REG}-cell numbers and a higher level of FoxP3 expression are correlated with COVID-19 severity.[104,105] Biasi *et al.*[106] showed that SARS-CoV-2 infection resulted in higher proportions, but not absolute numbers, of T_{REG} cells. Although it is still not resolved whether there were changes in the absolute and relative numbers of T_{REG} cells in the circulation in patients with COVID-19, it could be speculated that in the early stage of infection, an increased number of activated T_{REG} cells may reduce antiviral defense by inhibiting the immune responses against SARS-CoV-2. By contrast, a reduction in the number of T_{REG} cells in severe cases or later stages of the disease may contribute to the excessive production of proinflammatory cytokines that lead to acute respiratory distress syndrome.[107] If there is indeed diminished function of T_{REG} cells in patients with severe COVID-19, this might lead to further breakdown of immune tolerance.[108,109] With limited epidemiological data available to support this now, it would be difficult to predict whether the compromised immune tolerance will translate into an increase in the T1D burden in the general population. As the function of T_{REG} cells is known to be impaired in patients with T1D,[110] the likelihood of developing T1D among patients with COVID-19 with prolonged illness, associated with elevated levels of type I IFN, cannot be ruled out.

VARIED ETIOLOGY OF T1D AND CLINICAL EVIDENCE IN PATIENTS WITH COVID-19

As T1D represents the outcome of a constant battle between autoimmune destruction of β cells and self-renewal of β-cell mass (Figure 2b, i–ii), the kinetics of

both events are crucial (Figure 2c).[111] Evidence of dysfunctional β cells accumulating and secreting proinsulin was reported in many cases of T1D,[112–114] where significant β-cell mass was retained at disease onset. Similarly, many reports support the possibilities of a residual population of β-cell mass, islet regeneration and complete recovery from T1D.[115–118] A fundamental understanding that emerged from decades of studies on T1D is that there is an extreme level of heterogeneity between individual patients. The heterogeneity lies in residual β-cell mass at disease onset,[119–122] the severity of presentation unmatched to mass[121,123] and in the distribution of insulitis profile.[25,121,124] Richardson and colleagues[125] found differential insulitic profiles and extent of β-cell destruction based on age at the onset of T1D before age 7 or after teenage years, where the latter retained nearly 40% of the β-cell mass.

Development and progression of autoimmune (type 1A) diabetes, as best understood from the "Eisenbarth model,"[126] follow a series of distinct stages that most often starts with genetic predisposition. A critical pathophysiological event usually triggers the production of one or more islet antibodies in the susceptible individual, which eventually may (or may not) lead to the onset of autoimmunity, progressive loss of β cells and insulin secretion, and overt diabetes. Some of the best characterized autoantigens known in T1D are glutamic acid decarboxylase (GAD65), tyrosine phosphatase (IA-2), insulin and ZnT8[127] and in clinical settings, the presence of two or more autoantibodies has proven to be highly predictive of subsequent development of type I diabetes among relatives.[128,129] Severe diabetic ketoacidosis has frequently been reported in severely ill patients with COVID-19 at hospital admission.[130,131] Transient drug-induced or glucocorticoid-induced hyperglycemia during treatment of COVID-19 usually resolves within 3–6 months.[132,133] Sudden loss of β-cell mass or function can trigger insulin-dependent T1D but without autoimmune etiology.[134] The possibility of post-COVID-19 new-onset autoimmune T1D without genetic susceptibility seemed rather rare from the low number of reported cases. In one study, a 17-year-old male patient who had persistent fever and cough for 4 weeks and pneumonia, SARS-CoV-2 reverse transcriptase-PCR–positive infection, acute pancreatitis, HbA_{1c} (glycated hemoglobin) of 14.7% and severe diabetic ketoacidosis at hospital admission was later diagnosed with new-onset autoimmune T1D.[135] In another case, an 8-year-old boy with an asymptomatic course of SARS-CoV-2 infection of unknown duration presented with symptoms of new-onset T1D and autoantibodies against GAD65, IA-2 and insulin. This patient's laboratory findings, however, showed genetic susceptibility because of the presence of high-risk loci for autoimmune diseases, and additionally, his high HbA_{1c} value (11.6%) led to the authors speculating that his diabetes manifestation was already "on the way," only to be accelerated by COVID-19.[136] Another study reported severe hyperglycemia in two male patients who were diagnosed with autoimmune type 1 diabetes mellitus within 3 months following COVID-19 infection. These patients were positive for autoantibodies and had reduced C-peptide, which are indicative of autoimmune insulitis and β-cell destruction.[137] Although the underlying mechanisms, pathogenesis and incidence remain unclear at present, these pieces of evidence suggest possibilities of autoimmune insulitis and pancreatic beta-cell destruction triggered by COVID-19.

Type 1A diabetes often coexists in patients with other organ-specific autoimmune diseases such as autoimmune thyroid disease.[127] SARS-CoV-2 infection was reported to trigger multiple endocrine dysfunctions apart from hyperglycemia,[138,139] including hypopituitarism, thyroid abnormalities, adrenal insufficiency and male hypogonadism. Thyroid dysfunction was diagnosed in several patients with COVID-19 who were biochemically euthyroid earlier and a majority had euthyroid sick syndrome and atypical thyroiditis.[140,141] In one particular study with 204 patients,[142] it was observed that thyroid function abnormality resolves at a median of 89 days (81.4%), and persistence was rare (1.9%). Interestingly, the authors observed autoimmune antithyroid peroxidase positivity in 5.5% of the patients who were antithyroid peroxidase antibody negative at presentation.[142] The appearance of autoantibodies hints at the breakdown of immune tolerance following SARS-CoV-2 infection.

Considering the existing epidemiological evidence, a systematic review and meta-analysis of 26 qualified articles showed a clear increase in new-onset T1D, diabetic ketoacidosis and severe diabetic ketoacidosis in the pediatric group during the first year of the COVID-19 pandemic by 9.5%, 25% and 19.5%, respectively, when compared with the prevalence before pandemic.[143] Another separate hospital-based study noted an excessive increase in the incidence of T1D between October 2020 and April 2021 when compared with the same period during the previous 5 years. The authors also noted a significantly higher (5.6 times) incidence of COVID-19 in the T1D group compared with the general pediatric population in the region and proposed a plausible causative role of SARS-CoV-2 in triggering the immune response underlying T1D pathology.[144] COVID-19 was equally prevalent across all pediatric age groups, but children, in general, had a milder course of the disease when compared with adults.[145,146] Fewer children became seriously ill after SARS-CoV-2 infection and needed admission to the pediatric intensive care unit, although a

fraction of them developed a multisystem inflammatory syndrome associated with COVID-19 (MIS-C). A multicentric study reported that patients with MIS-C were older than those without MIS-C (P = 0.002): 9.4 years of age (interquartile range 5.5–11.8) *versus* 3.4 years of age (interquartile range 0.4–9.4) in their study population.[147] In another study,[148] younger children (≤ 4 years of age) needed longer time for their lung lesions to disappear compared with 5–14-year-old children when followed up after hospital discharge. The MIS-C in the pediatric group, which usually presented about 4–6 weeks after infection with high fever, organ dysfunction and high inflammation, seemed to have a profile that is different from cytokine storm (discussed earlier). MIS-C shared features of Kawasaki disease and, although the pathogenesis of MIS-C remains unknown, a likely autoimmune etiology was suggested because of the presence of several autoantibodies.[149]

Evidence from across the spectrum of human diseases supports the view that SARS-CoV-2 infection can accelerate the progression of, or exacerbate, an already set disease. For example, one population that was found to be at a higher risk of a poor prognosis was patients with hypertension who were undergoing drug therapy with an ACE inhibitor and/or angiotensin receptor blockers. These data from southern Italy indicated that the patients were at a higher risk of contracting a serious COVID-19 infection.[150] During the pandemic, it became clear that hyperglycemia was a risk factor for worse prognosis in patients with COVID-19.[150–152] Patients with hyperglycemia with moderate-to-severe COVID-19 showed very little response to tocilizumab, which is known to suppress cytokine release by targeting IL-6 receptors.[153] Poor glycemic control was also found to reduce the efficacy of vaccination.[154] In addition, SARS-CoV-2 infection, including asymptomatic infection, could cause endothelium dysfunction and result in myocardial infarction, pericarditis, myocarditis and heart failure.[155] Thus, patients with adverse cardiovascular events could also be included as populations that are at higher risk.

In summary, although the risk of direct virally induced islet β-cell damage among patients with COVID-19 appears to be less, more research is needed to clarify long-term trends in new-onset T1D at a population level among patients with COVID-19. If hyperactivated or sustained for a very long period, a type I IFN response can also lead to a breakdown of immune tolerance and the development of autoimmune diseases, including T1D. However, with limited epidemiological data presently available, it is difficult to suggest whether noncytopathic infection and an autoimmune response would, and if so, to what extent, contribute to an increase in the T1D burden. As autoantibodies were not monitored rigorously as part of routine laboratory investigations in patients with COVID-19, it is also difficult to say whether COVID-19 is a risk factor for new-onset autoimmunity. It may be worth considering the benefits of periodically screening for seroconversion of islet autoantibodies in recovered high-risk group patients, as it may help in the prognosis and management of their condition.

CONCLUSIONS

COVID-19 caused by SARS-CoV-2 was declared a pandemic by the World Health Organization in 2020. Since then, it devastated public health worldwide. COVID-19 is known to cause multiple organ damage as well as metabolic abnormalities. This review aimed to discuss published literature to ascertain whether SARS-CoV-2 infection of pancreatic β cells can promote new-onset T1D associated with impaired pancreatic β-cell function. Based on the available scientific evidence, we can conclude that SARS-CoV-2 infection damages pancreatic β cells. Whether this would cause sufficient cell/tissue damage to induce T1D would depend on the extent of β-cell loss compared with the regeneration potential of endogenous β-cell mass. At present, the epidemiological data do not identify a clear increase in T1D incidence worldwide since the beginning of the pandemic. Whether such a change will be observed over time remains to be determined but, as suggested here, would seem worthy of close monitoring.

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AUTHOR CONTRIBUTIONS

Roy Anindya: Conceptualization; resources; visualization; writing – original draft; writing – review and editing. **Guy A Rutter:** Writing – review and editing. **Gargi Meur:** Writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

GAR has received grant funding from, and is a consultant for, Sun Pharmaceutical Inc. The other authors have declared that no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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