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New onset diabetes, type 1 diabetes and COVID-19

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Abstract
Background and aims: New data has emerged regarding higher risk of coronavirus disease 2019 (COVID-19), and its severity and complications in patients with type 2 diabetes mellitus (T2DM). However, there is a dearth of evidence regarding type 1 diabetes mellitus (T1DM). This article explores the possibility of COVID-19 induced diabetes and highlights a potential bidirectional link between COVID-19 and T1DM.

Methods: A literature search was performed with Medline (PubMed), Scopus, and Google Scholar electronic databases till October 2020, using relevant keywords (COVID-19 induced diabetes; COVID-19 and type 1 diabetes; COVID-19 induced DKA; new-onset diabetes after SARS-CoV-2 infection) to extract relevant studies describing relationship between COVID-19 and T1DM.

Results: Past lessons and new data teach us that severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2) can enter islet cells via angiotensin converting enzyme-2 (ACE-2) receptors and cause reversible β-cell damage and transient hyperglycemia. There have been postulations regarding the potential new-onset T1DM triggered by COVID-19. This article reviews the available evidence regarding the impact and interlink between COVID-19 and T1DM. We also explore the mechanisms behind the viral etiology of T1DM.

Conclusions: SARS-CoV-2 can trigger severe diabetic ketoacidosis at presentation in individuals with new-onset diabetes. However, at present, there is no hard evidence that SARS-CoV-2 induces T1DM on its own accord. Long term follow-up of children and adults presenting with new-onset diabetes during this pandemic is required to fully understand the type of diabetes induced by COVID-19.

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1. Introduction

Since the onset of COVID 19 pandemic, a great deal of evidence has emerged regarding its relationship with T2DM. However, reports on effects of SARS-CoV-2 infection on people with T1DM have been more recent and relatively sparse. T1DM constitutes about 5% of all diagnosed cases of diabetes and its global incidence is increasing at an alarming rate of about 3% every year [1]. Pre-existing diabetes mellitus is purported to be one of the high-risk factors for developing COVID-19 and related complications [2]. Indeed, there have been reports of COVID-19 induced severe metabolic decompensation of pre-existing or new-onset diabetes such as diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) [3–7]. More characteristically, SARS-CoV-2 has been suggested as a potential inducer of new-onset T1DM [8].

Coronavirus mediated islet cell damage does not seem to be a novel phenomenon, as evidenced by the experience from previous coronavirus (SARS and MERS) epidemics [9]. However, in this review, we explore the mechanisms of hyperglycemia particularly in relation to COVID 19 illness and also examine the Covid-19 related morbidity and mortality in people with T1DM.

2. Etiology of T1DM – the viral paradigm

T1DM is a genetic autoimmune condition where β-cells are destroyed by the auto-reactive CD4+ and CD8+ T cells. Although >50 candidate genes were identified, poor concordance of T1DM (<50%) in monozygotic twins suggests players beyond genetics. Regional differences in prevalence with incidence in migrants conforming to the incidence of the region of destination, and the North-South gradient with higher figures in northern latitudes indicate non-genetic environmental influences. Well established seasonality of new-onset T1DM led to exploration of viral etiology [10]. The relationship between viral infections and T1DM is
complex. Mouse models have demonstrated that while certain viruses could be detrimental to the β-cells and initiate autoimmunity, others can be protective and have preventive effects. However, one needs to exercise caution when extrapolating these findings to human subjects [11].

2.1. Pathogenesis of viral induced β-cell damage: acute vs chronic

Conceptually, virus induced β-cell damage is due to either 1) direct lytic effects of viral replication and/or 2) host inflammatory response mediated damage by autoreactive CD+ T cells, leading to autoimmunity (Fig. 1). While destruction of >90% of β-cells by direct viral mediated damage leads to non-autoimmune diabetes, limited lysis releases islet cell antigens, which in conjunction with enhanced immune response paves way for autoimmunity. Evidence for the earlier instance is most notable from the cases of fulminant T1DM, reported almost exclusively from Japan and predominantly for the earlier instance is most notable from the cases of fulminant T1DM. In children with recently diagnosed diabetes, hyperglycemia is characterized by acute onset of hyperglycemic lysis releases islet cell antigens, and a HbA1c less than 8.5% on the first visit [12–17]. Nevertheless, it is the limited β-cell destruction with release of sequestered islet cell antigens and activation of autoreactive T-cells that result in long-term autoimmune damage and subsequent T1DM. In children with recently diagnosed diabetes, hyper-expression of major histocompatibility complex –1 (MHC-1) and interferon-α was observed within the islets that are otherwise completely devoid of these markers [18]. These markers characteristically increase antigen mediated activation of CD8+ T Cells, and it is most likely that their enhanced production is viral mediated.

2.2. Mediators of chronic β-cell destruction

The pathological processes mediating chronic β-cell damage are varied. The foremost contender is molecular mimicry, where viral epitope shares a resemblance with host islet protein causing cross-reactivity and autoimmune T cell response against host tissue in susceptible individuals. However, studies aiming to demonstrate molecular mimicry are inconclusive. It is likely that molecular mimicry can accelerate the autoimmune process once it is already started, rather than initiate it on its own [18]. Other proposed mechanisms are bystander T-cell activation, the activation of a T cell independent of an antigen specific T-cell receptor stimulation, and bystander damage, where destruction of β-cells is accelerated by the proinflammatory cytokines released due to infection of adjacent pancreatic cells like alpha, exocrine, endothelial and neuronal cells [19–21]. In addition to the decreased insulin release due to β-cell loss, proinflammatory mediators can result in functional defects like defective glucose mediated insulin release and delay in the conversion of proinsulin to insulin.

Another crucial element is the seeming inability of β-cells to clear viral infections, when compared with alpha cells. Chronicity of β-cell infection was apparent from postmortem studies where expression of viral capsid protein VP1 was detected in the islets of >60% T1DM organ donors while only 8% of non-T1DM samples showed its presence [21]. Chronic β-cell infection results in persistent overexpression of MHC-I leading to continuous presentation of beta cell epitopes to the immune system, facilitating autoimmunity.

2.3. Putative viruses causing β-cell damage

Though many viruses came to be associated with T1DM, namely, enteroviruses (especially Coxackie B1, B4, mumps, rubella and CMV; so far the most robust evidence for viral induced T1DM is seen with enterovirus, an ssRNA virus of picornavirus family, when enteroviral RNA was detected in the blood of recently diagnosed patients with T1DM (Table 1). A systematic review and meta-analysis showed a significant association between enterovirus infection and T1DM-related autoimmunity (OR: 3.7, 95%CI: 2.1–6.8) and clinical T1DM (OR: 9.8, 95%CI: 5.5–17.4) [33]. The Epidemiological Determinants of Diabetes in Young (TEDDY) study that followed 8676 newborn babies with increased genetic risk for T1DM, conferred by a specific HLA genotype, over 15 years, observed that number of respiratory infections occurring in a 9-month period was associated with the subsequent risk of autoimmunity (p < 0.001). For each 1/year increase in infections, the hazard of islet autoimmunity increased by 5.6%. Autoantibodies were more commonly detected in patients with severe respiratory disease, and interestingly, coronaviruses were identified among the different pathogens involved [34]. In the latest update of the TEDDY study, persistent presence of enterovirus B species in a child’s stool appears to predict development of islet autoimmunity, especially antibodies against Insulin [35]. Nonetheless, there is substantial epidemiological data contradicting the viral origins of β-cell autoimmunity. Viral data from non-obese diabetic (NOD) mice has shown that coxackie B3 (CB3) and lymphocytic choriomeningitic virus (LCMV) can offer protection from T1DM by promoting immune tolerance. Early exposure to infections was also deemed to educate the immune system leading to reduced incidence of autoimmune diseases like T1DM as seen in countries with low SES where the incidence of infections is high [33].

2.4. SARS-CoV-1 and diabetes — lessons from the past

Angiotensin converting enzyme (ACE) is the key enzyme in mediating the effects of renin angiotensin aldosterone system (RAAS) by converting angiotensin-I to II. The more recently identified ACE2, a novel homolog of ACE that degrades angiotensin-II to
### Table 1
Recent evidence on role of virus in islet cell autoimmunity and T1D.

| Author & year (reference) | Type of study (case/control) | Test and Sample | Virus | Findings |
|--------------------------|-----------------------------|-----------------|-------|----------|
| Schulte BM et al. 2010 [21] | Case control (10/20) | RT PCR/plasma, PBMC, throat, stool | Enterovirus (EV) | All controls are negative. 4/10 PBMC samples, only 1/10 stool samples positive for EV PCR. None of the throat samples are positive, which argues against acute infection, but probably delayed clearance of EV infection. |
| Laitinen OH et al. 2013 [22] | Nested case control study samples from the DIPP cohort (183/366) | Antibodies | Coxsackie B1 (CB1) | CB1 is associated with increased risk of beta cell autoimmunity, strongest when infection occurred few months before islet AA appeared (OR: 1.5, 95% CI: 1.0–2.2). CB3, CB6 appear to reduce risk of autoimmunity. |
| Oikarinen S et al. 2013 [23] | Case control (249/249) | Antibodies | Coxsackie B1 (CB1) | CB1 antibodies are more frequently seen in those with T1D (OR: 1.7, 95% CI: 1.0–2.9). |
| Stene LC et al. 2010 [24] | Prospective study in 140 cases seroconverted for IAA from DAISY cohort | RT PCR Blood, rectal swab Antibodies, RT PCR stool & serum | EV | Risk of progression from islet cell autoimmunity to clinical T1D is significantly higher following detection of EV RNA. 83% cases had at least one EV infection before developing islet AA, while only 42% controls had EV by the same age (p = 0.006). |
| Salminen RK et al. 2004 [25] | Case control From DIPP cohort (12/53) | Antibodies, RT PCR stool & serum | EV | Early (fetal, neonatal) EV infection may play a role in T1D pathogenesis (OR: 1.98, 95% CI: 1.04–3.77). No difference seen with CMV, Parvo-B19. |
| Dahlquist GG et al. 2004 [26] | Case control (542/542) | RT PCR of postnatal Day2–4 blood spot samples | EV | AA-positive children had more enterovirus infections than AA-negative children before the appearance of AA (0.83 versus 0.29 infection per child, P = 0.01). |
| Sadeharju K et al. 2003 [27] | Case control (19/84) From TRIGR cohort | Antibodies and RT PCR | EV | GAR-65 specific T-cells cross-react with a peptide of hCMV major DNA binding protein, resulting in possible loss of T cell tolerance to GAR-65. |
| Hiemstra HS et al. 2001 [28] | Clonal CD4+ T cells reactive to GAD65 - from a prediabetic stiff-man syndrome patient. | Synthetic peptide libraries that bind to HLA-DR3, are screened | Cytomegalovirus (CMV) | Peptides in VP7, immunogenic protein of RV have significant similarity to T cell epitope peptides in IA2 and GAD65. Molecular mimicry with RV could promote autoimmunity to islet antigens. |
| Honeyman MC et al. 2010 [29] | Comparative | Antibodies | Rotavirus (RV) | Peptides in VP7, immunogenic protein of RV have significant similarity to T cell epitope peptides in IA2 and GAD65. Molecular mimicry with RV could promote autoimmunity to islet antigens. |
| Blom K et al. 2016 [30] | Case control; control: 42/42 | Antibodies | Epstein-Barr virus (EBV) | Positive EBV antibody response is associated with significantly higher cases of T1D (OR: 6.6, 95% CI: 2.0–25.7). |
| Nilsson AL et al. 2015 [31] | Case control; control: 69/294 | Antibodies | Parechovirus (PV) | Ljungan virus antibodies correlated with insulin AA, especially in young HLA-DQ8 subjects, suggesting a possible role in T1D. |
| Tapia G et al. 2011 [32] | Nested case control | PCR Fecal samples | Parechovirus (PV) | Weak association, if PV infection in 3 months prior to development of autoimmunity, warranting further investigation. |

DIPP: Diabetes Prediction and Prevention; DAISY: Diabetes and Autoimmunity Study in the Young; TRIGR: Trial to Reduce IDDm in Genetically at Risk; MIDIA: Norwegian acronym for “Environmental Triggers of Type 1 Diabetes” study; AA: Autoantibodies; GAD65: Glutamic acid decarboxylase 65; IA2: Tyrosine phosphatase-like insulinoma Ag 2; PBMC: Peripheral blood mononuclear cells.
angiotensin-I–VII, was found to be the functional receptor for SARS-CoV-1 and -2 [36]. ACE2 is abundantly present in humans in the epithelia of the lung and small intestine, which might provide possible routes of entry for the SARS-CoV-1, and -2 [37]. Study of 72 human tissues confirmed ACE2 mRNA expression in tissues other than the lung and gastrointestinal system, like tests, cardiovascular, renal, and pancreas [38,39]. Studies from 2003 SARS-CoV-1 epidemic evidenced that even milder SARS pneumonitis cases who did not receive glucocorticoid medications, had higher fasting blood glucose; and hyperglycemia in turn was an independent predictor of higher mortality and morbidity [40]. A follow up study in 2010 of the same cohort, investigating pathogenesis of pancreatic lesions, also found that pancreatic islets are strongly immune-positive for ACE2 while exocrine tissues are only weakly positive.

Insulin dependent diabetes occurred during the hospitalization in 20 of the 39 patients (age: 47.2 ± 2.2 years) who received no corticosteroids during the course of SARS disease. Out of these, six had diabetes at discharge. But after 3 years of follow-up, only two had persistent diabetes, suggesting that the damage incurred by islet cells is acute and mostly transient [9].

3. COVID-19 and T1DM: bidirectional link

Earlier reports from Italy and China noticed a curious lack of people with T1DM in hospitalized cohorts of SARS-CoV-2, that made the authors wonder if the immunological attributes of T1DM are in some way protective [41,42]. However, it is more plausible that lock-down measures with special directives of caution to people with pre-existing conditions like diabetes, fear of infection, more parental supervision while staying at home encouraged young people to avoid crowded places as well as take better care of their diabetes. Nonetheless, as we try to comprehend this unfolding pandemic, new evidence is emerging that COVID-19 not only increases the risk of DKA and mortality in those with T1DM & T2DM, but also could potentially induce new-onset T1DM.

3.1. Does COVID-19 increase mortality/morbidity in T1DM?

Diabetes has long been associated with increased susceptibility to and severity of infections. Hyperglycemia, by altering immune response and causing cytokine dysregulation, is an inherently proinflammatory and procoagulant state [43–47]. In an observational study on 59 hospitalized adult COVID-19 patients, patients with hyperglycemia had higher IL-6 and D-dimer levels, which reduced significantly with optimal glucose control, supporting the permissive role hyperglycemia plays in enhancing inflammation and creating procoagulant state independent of viral mediation [4]. Hence T1DM and T2DM, especially with poor glycomic control become high-risk pre-existing conditions for many bacterial and viral infections including SARS-CoV-2.

Multiple centers reported that COVID-19 induces DKA and increases the length of hospital stay in those with diabetes [5]. Even as evidence mounts on the increased COVID-19 related mortality and morbidity in those with pre-existing diabetes, most of these observations were in relation to people with T2DM, who typically have a range of co-morbidities like hypertension, obesity, cardiovascular disease etc., unlike the relatively younger and otherwise fit T1DM community [6,48].

In a preliminary report from a multicenter USA study, out of 64 adults with T1DM who have confirmed or suspected COVID-19, more than 50% reported hyperglycemia, and nearly one-third had DKA [49]. In a nationwide analysis in England, adjusted for age, sex, deprivation, ethnicity, and geographical region, compared with people without diabetes, the odds ratios for in-hospital COVID-19-related death were 3.51 (95% CI 3.16–3.90) in people with T1DM and 2.03 (1.97–2.09) in people with T2DM. These effects were attenuated to ORs of 2.86 for T1DM and 1.80 for T2DM when also adjusted for underlying cardio/cerebrovascular disease, though other potential confounders like BMI, hypertension, kidney disease, and tobacco smoking were not adjusted for [50]. Moreover, people younger than 40 years with either type of diabetes were at very low absolute risk of in-hospital death with COVID-19, further indicating that comorbidities might have contributed significantly to the increased mortality. Moreover, evidence hitherto points towards a milder covid-19 in children with better prognosis when compared with adults [51].

In a population-based cohort study of all the people with T1DM and T2DM who were registered to general practice in England, COVID-19 related mortality is higher (Hazard ratio 2.23 in T1DM, 1.61 in T2DM) in those with prior higher HbA1c of 10% (86 mmol/mol) versus those with a HbA1c of 6.5–7.0% (48–53 mmol/mol). In addition, older age (>70 years), non-white ethnicity, co-morbidities like previous stroke or cardiac failure or renal compromise and socio-economic deprivation are associated with increased mortality, in both T1DM and T2DM [52]. These studies indicate that COVID-19 increases mortality even in people with T1DM, especially in older age groups with co-existing renal or cardiac disease. In patients with diabetes, it is important to maintain optimal glycemic control by frequent blood glucose and ketone measurements, and adjusting insulin regime accordingly.

3.2. Challenges in the management of individuals with T1DM

As it is becoming more evident that the length of hospital-stay, risk of complications and overall mortality from COVID-19 are higher with poor glycemic control, this could be partly due to the adverse effects of certain therapies currently under trials to treat severe cOVID-19 [52,53].

Hydroxychloroquine, an immunomodulatory agent that was extensively used during the initial phases of the pandemic, can decrease insulin degradation at the cellular level and stimulate insulin-mediated glucose transport, resulting in potential hyperglycemia [54,55]. On the other hand, antiviral drugs such as lopinavir and ritonavir could lead to hyperglycemia and worsen glycemic control [56]. Glucocorticoids, which were seen to improve outcomes in COVID-19 related severe acute respiratory distress syndrome and hence became an integral part of treatment regime for hospitalized patients, can lead to marked hyperglycemia by reducing insulin sensitivity as well as by interfering with the actions of glucagon like peptide-1 and stimulating production of glucagon [57]. Some of the challenges in managing individuals with T1DM during COVID-19 pandemic are given in Table 2.

3.3. COVID-19, pancreatitis, and new onset diabetes

Recent virologic data from Germany (Hoffmann et al.) and China (Zhou et al.) reveal important commonalities between SARS-CoV-2 and SARS-CoV-1 infections, and demonstrate that SARS-CoV-2 uses the same ACE2 receptor as SARS-CoV-1 for host cell entry [58,59]. As the substantially high transmissibility of SARS-CoV-2 relative to SARS-CoV-1 is becoming evident, one may speculate that the new virus might exploit cellular attachment factors with higher efficiency than SARS-CoV-1, causing more robust infection of ACE2+ cells.

3.3.1. COVID-19 and pancreatitis

Despite the findings of islet cell infection, new onset hyperglycemia and diabetes, there have been no reports of acute pancreatitis with the SARS-CoV-1 epidemic of 2003. However, the effects of SARS-CoV-2 seem to differ in this perspective, with many cases of
COVID-19 related acute pancreatitis being reported during the last few months [60–64]. In a case series of 52 patients with acute COVID-19, eight patients experienced pancreatic injury in the form of abnormal elevation in lipase or amylase [65]. Whether this pancreatic injury is due to the direct cytopathic effect of the virus, or the indirect result of severe systemic inflammatory response and multiorgan dysfunction in the context of severe COVID-19 illness is yet to be established.

A distinct subset of moderate pancreatitis with a benign course was described by researchers at Liverpool, UK. Out of 35 patients presenting with acute pancreatitis over a period of 6 weeks during March/April 2020, 10 were positive for SARS-CoV-2, and 5 of these were excluded as they had a clearly defined etiology. The remaining five patients were male, overweight or obese, had abdominal pain, mildly elevated amylase, and pancreatic-duodenal inflammation with hepatic steatosis on CT scan. Though all had persistently elevated inflammatory markers, none had either transient or persistent multiorgan failure. Three of them had new onset diabetes requiring Insulin, with two going home on Insulin [66]. Though none of these reports prove causality, the role of direct viral cytopathic damage of pancreas can not be discounted, and it seems that endocrine islet cells are particularly more vulnerable to the viral insult.

3.3.2. COVID-19 and new onset diabetes

New-onset hyperglycemia is being increasingly described with COVID-19 in adults without a previous history of diabetes, albeit with significant mortality and morbidity. While infection induced inflammation and cytokine activation and resultant insulin resistance could lead to stress hyperglycemia, it is uncertain as to what extent the direct viral destruction of islet cells with decreased insulin production and release might be contributing [67] (Fig. 2). COVID-19 can also act as an infectious trigger that could decompensate and precipitate DKA in patients with new-onset T1DM and T2DM. During early months of pandemic in Italy, 23% fewer annual cases of new childhood diabetes were reported, though the ones presenting had more severe DKA in 2020 than in 2019 (44.3% vs. 36%, respectively) [68]. A two-fold increase in DKA and severe ketoacidosis at diabetes diagnosis in children and adolescents during the COVID-19 pandemic was reported from Germany, while an increase in referral of children with DKA was reported from the UK when compared with previous years. However, the underlying reasons for this phenomenon may be multifactorial and reflect reduced access to primary care services, parental fear of approaching the health care system during the pandemic period resulting in delayed diagnosis of new cases of T1DM [69–71]. A more recent multicenter study from the UK describes an apparent increase in new-onset T1DM in children, with evidence of SARS-CoV-2 infection or exposure in some of these. Seventy per cent (21/30) children presented with DKA and 52% (11/21) had severe DKA (pH 6.82–7.05). Of the five children with positive results (2 of 21 tested were SARS-CoV-2 PCR positive and 3 of 16 tested were SARS-CoV-2 IgG positive), three presented with severe DKA and refractory hypokalemia, and one PCR positive child suffered a hypokalemia-related cardiac arrest but recovered fully. Interestingly, majority had only a short duration of preceding symptoms of diabetes, refuting the previous notion of delayed presentation as the reason for increase in incidence of DKA at disease onset [8]. SARS-CoV-2 reduces ACE2 expression, leading to decreased degradation of angiotensin II, which can cause increased secretion of aldosterone and renal potassium loss. Whether this phenomenon was the basis for severe hypokalemia seen in the PCR positive child, needs further evidence. There are a few case reports of COVID-19 inducing acute onset diabetes and DKA in several individuals, mimicking T1DM. However, on follow-up there was reduced need for insulin and ultimately insulin could be discontinued in all the three patients. At last follow-up, these patients had normoglycemia on oral antihyperglycemic medication [7,72].

4. Future directions

At this point, it would be mostly conjectural to say that SARS-CoV-2 exposure contributed to the rise in DKA by precipitating or accelerating onset of T1DM. Our understanding so far is uncertain if this new-onset diabetes is classic T1DM or some new form of diabetes. Whether the severe COVID-19 induced hyperglycemia noticed in some individuals would remit on a long run as seen with SARS-CoV-1 induced diabetes is also unclear. How COVID-19 changes the natural history of disease in those with pre-existing diabetes is difficult to surmise.

To address some of these issues, an international group of diabetes researchers have established a global registry of patients with COVID-19–related diabetes (covidien.e-dendrite.com), as part of CoviDIAB Project. The goal of the registry is to establish the extent and phenotype of new-onset diabetes that is defined by
hyperglycemia, confirmed COVID-19, a negative history of diabetes, and a history of a normal glyced hemoglobin level [73].

5. Conclusion

COVID-19 is an indiscriminate disease with unequal vulnerability. While hyperglycemia is seen to increase mortality and morbidity related to COVID-19, the virus itself can induce/worsen hyperglycemia, culminating in a vicious cycle. While we comprehend the intriguing mechanism of COVID-19 inducing diabetes or worsening the existing disease, we are still left with some unanswered questions. Is COVID-19 induced β-cell damage transient or permanent? Can COVID-19 linger on in the beta-β-cells, causing chronic infection and new-onset T1DM? As this pandemic evolves, coordinated global efforts might throw some light upon these important concerns. Until that time, it is prudent to keep a diligent vigil on the patients with new-onset diabetes during this pandemic and also those with hyperglycemia induced by severe COVID-19.

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