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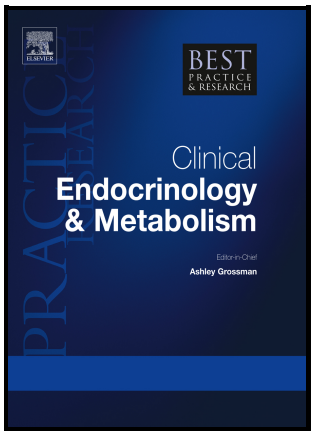

PII: S1521-690X(23)00067-2

DOI: https://doi.org/10.1016/j.beem.2023.101793

Reference: YBEEM101793

To appear in: *Best Practice & Research Clinical Endocrinology & Metabolism*

Please cite this article as: Dhruti Hirani, Victoria Salem, Kamlesh Khunti and Shivani Misra, Newly detected diabetes during the COVID-19 pandemic: what have we learnt?, *Best Practice & Research Clinical Endocrinology & Metabolism,* (2023) doi:https://doi.org/10.1016/j.beem.2023.101793

Newly detected diabetes during the COVID-19 pandemic: what have we learnt?

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Word Count excluding references: 4943
Figures: 2

Abstract

The SARS-CoV-2 pandemic has had an unprecedented effect on global health, mortality and healthcare provision. Diabetes has emerged as a key disease entity over the pandemic period, influencing outcomes from COVID-19 but also a tantalising hypothesis that the virus itself may be inducing diabetes.

An uptick in diabetes cases over the pandemic has been noted for both type 1 diabetes (in children) and type 2 diabetes but understanding how this increase in incidence relates to the pandemic is challenging. It remains unclear whether indirect effects of the pandemic on behaviour, lifestyle and health have contributed to the increase; whether the virus itself has somehow mediated new-onset diabetes or whether other factors such as stress hyperglycaemic of steroid treatment during COVID-19 infection have played a roll.

Within the myriad possibilities are some real challenges in interpreting epidemiological data, assigning diabetes type and understanding what *in vitro* data are telling us.

In this review article we address the issue of newly-diagnosed diabetes during the pandemic, reviewing both epidemiological and basic science data and bringing together both strands of this emerging story.

Introduction

An increase in new presentations of diabetes has been a consistent observation throughout the COVID-19 pandemic (1–3). Though earlier reports of excess diabetes cases were single centre, or smaller cohort studies, there is now better evidence, including systematic reviews, supporting both a rise in type 1 and type 2 diabetes incidence. Whilst the association between a pre-existing diagnosis of both type 1 and type 2 diabetes with increased severity of coronavirus disease-19 (COVID-19) infection has been studied comprehensively (4,5), it is more challenging to unravel the impact of the pandemic on diabetes incidence (6).

The major unanswered question in the field is what is responsible for this rise in diabetes and, whether the virus *itself* is somehow responsible. It is challenging, and indeed may be impossible, to disentangle the direct effect of SARS-CoV-2 viral infection in mediating the development of diabetes from the indirect effects of pandemic measures modifying metabolic risk factors for diabetes. In the midst of this challenge are potential detection biases, including; a) does a new diagnosis of diabetes during the pandemic represent an earlier manifestation due to direct or indirect effects of SARS-CoV-2?; b) Is the new diagnosis unmasking undiagnosed diabetes or does it represent new-onset disease which would not have occurred outside the pandemic? c) does having COVID-19 make it more likely to be screened for diabetes both before, during and after infection - are we detecting the usual missed cases? And d) is this related to high dose steroid treatment given to people with severe COVID-19 infection?

Compounding the issue further is the fact that events by which the virus and or pandemic measures could lead to type 1 or type 2 diabetes are likely to be mechanistically very different. Furthermore, phenotypically separating type 2 diabetes from autoimmune type 1 or insulin deficient diabetes in the pandemic data sets that have been collected and studied to date, has been challenging. Indeed, at the coal face, many hospitalised patients with new onset diabetes, presented with diabetic ketoacidosis (DKA) or warranted insulin treatment for other reasons but these cases may not have been diabetes in the longer term.

In this review article, we first present the evidence of the effect of the pandemic on the epidemiology of type 1 and type 2 diabetes. We then discuss the potential mechanisms for these observations, pulling on a range of evidence, from *in vitro* to population studies.

The rise in incident diabetes during the pandemic

As of February 2023, there have been almost 760 million cases of COVID-19 worldwide and 6.8 million deaths (7). Whilst these large numbers are an epidemiological gold mine it is not straightforward to study associations between COVID-19 and new-onset diabetes due to the plethora of other risk factors, sociocultural differences globally that may impact risk of diabetes and indeed personal differences in diabetes risk.

It is first important to understand that newly diagnosed diabetes and new-onset diabetes may not be the same thing (figure 1). Newly diagnosed diabetes refers to the first-time diabetes has been *detected* in an individual however new onset diabetes refers to the onset of hyperglycaemia. This distinction is usually irrelevant outside of the pandemic, but during the pandemic period first detection vs onset has become an important consideration in deciphering associations between COVID-19 and incident diabetes because newly diagnosed

diabetes may have nothing to do with viral infection per se and may represent better detection of undiagnosed diabetes or delayed diagnoses. From a clinical perspective, however, the distinction is less relevant as numerous studies, including prior to the pandemic, have shown that hyperglycaemia (irrespective of whether there is pre-existing diabetes, stress hyperglycaemia or indeed, newly diagnosed diabetes) is associated with worse outcomes from COVID-19.

The epidemiological evidence showcasing a rise in new diabetes is compelling (3). A random-effects meta-analysis of 3711 COVID-19 patients from 8 studies, showed an estimated pooled prevalence of new-onset diabetes of 14.4% (95% CI 5.9-25.7%) (2). However, the designs of many smaller studies, follow-up period and exposures have been heterogenous, indeed diabetes can develop at any time point after COVID-19 exposure.

Larger cohort studies, with longer follow-up have provided more definitive estimates; in an analysis of over 180,000 people with a positive COVID-19 test, after a median follow-up of 352 days, odds for developing new onset diabetes were 1.40 compared to the control group (95% CI 1.36-1.44) (8).

More recently, a systematic review and meta-analysis of 9 prospective and retrospective cohort studies in 2022 studied almost 40 million patients (1). The exposure was COVID-19 infection based on ICD-10 codes and the main outcome was newly diagnosed diabetes after a diagnosis of SARS-CoV-2 infection. The overall incidence of diabetes after COVID-19 was 15.5 cases per 1000 person-years (95% CI 7.91-25.64) using a random effects metanalysis and compared to those not infected with COVID-19, the relative risk of diabetes was 1.62 (95% CI 1.45-1.80). The study went on to sub-analyse type of diabetes (based on reported definitions in the studies) contributing to this excess risk, finding a relative risk of 1.48 (1.26-1.75) for type 1 diabetes and 1.70 (1.32-1.48) for type 2 diabetes, compared to patients who had not experienced COVID.

Explanations for the rise in type 2 diabetes

There were several possible explanations of the rise in new presentations of type 2 diabetes during the pandemic.

First, it is clear that in the first 6 months of the pandemic the people most at risk of severe COVID-19 infection were older male individuals and people from minority ethnic groups were overrepresented (4,5). These demographics are also associated with type 2 diabetes risk and it is therefore possible that a significant proportion of this group simply had undiagnosed type 2 diabetes, since at any time, 30-50% of people with type 2 diabetes are undiagnosed (9).

It could also be postulated that during active COVID-19 infection with concurrent stress hyperglycaemia or high-dose steroid treatment(10) individuals at risk of type 2 diabetes, were ‘tipped over’ into type 2 diabetes or indeed already had type 2 diabetes that had been undiagnosed to date but was detected either during active COVID-19 infection or in the follow-up period.

The number of new diagnoses of diabetes was reduced below usual trends during the first year of the pandemic as the vast majority of diagnoses are made in general practice (11) and during the first lockdown general practice activity was severely affected(12). Therefore, in the latter years of the pandemic there may have been a “catch up” of those missed type 2 diabetes cases. If true, in years to come, a reduction in type 2 diabetes will be observed.

Another explanation may relate to the indirect effects of the pandemic on cardiometabolic risk factors. A systematic review and metanalysis of 11 studies (with wide geographical coverage) with over 16,895 patients that had type 2 diabetes showed a significant increase in HbA1c, fasting glucose and body mass index (BMI) over the course of lockdowns(13). A rise in body weight has also been observed in people with pre-diabetes i.e. those at risk of developing type 2 diabetes; an analysis of 72,611 people who accessed a remote diabetes prevention programme during year 1 of the pandemic, showed an unadjusted weight increase of 2.4 kg compared to the weight at referral over three preceding years and the difference was most pronounced in those under 40 years (3.9kg increase in weight at referral compared to preceding years)(14).

One final explanation relates to sequelae of COVID-19 infection. If indeed the SARS-CoV-2 virus had a direct effect on pancreatic beta cells it is possible that people with risk factors for type 2 diabetes became hyperglycaemic due to viral effects on pancreatic function (see section below).

Explanations for the rise in type 1 diabetes

The type 1 diabetes story over the course of the pandemic has been controversial. Type 1 diabetes is an autoimmune condition characterised by immune mediated attack of pancreatic beta-cells. There are several phases to its development, which begins with an environmental trigger in a genetically susceptible individual and is followed by sequential loss of beta-cell function resulting in hyperglycaemia and in some cases, diabetic ketoacidosis (15).

There have been two main challenges in deciphering the impact of COVID-19 on incident type 1 diabetes. The first is that type 1 diabetes is phenotypically difficult to identify in adult patients who are acutely unwell patients presenting with DKA or significant hyperglycaemia. These individuals may have underlying type 2 diabetes but present with DKA or may have ketosis prone type 2 diabetes. The diagnosis of type 1 diabetes in adults requires pancreatic autoantibody testing and these results may not be available at diagnosis in all centres. This is a major limitation in epidemiological analysis where type 1 diabetes may be defined on the basis of insulin prescriptions as insulin requirement may not be indicative of type 1 diabetes. The second issue in studies associating COVID-19 with type 1 diabetes, is the follow-up period. It is a complete unknown how quickly type 1 diabetes would develop if COVID-19 was somehow triggering it.

The most informative data therefore has emerged from population-based registries examining incidence of type 1 diabetes in children. One of the most robust analyses came from the German Diabetes Prospective (DPV) follow up registry(16); the registry has nation-wide coverage and using regression models, they calculated the expected number of new type 1 diabetes cases in children between 2020 and 2021 based on known incidence in the preceding 9 years from 2011 to 2019. The study showed that the observed incidence exceeded the predicted based on the known year on year rise pre-pandemic (24.4 cases (95% CI 23.6-25.2) per 100,000 patient years vs expected 21.2 (20.5-21.9). A similar finding was observed in Italy (17) and other studies have shown a similar rise in smaller cohorts (18) and by studying association with new diagnoses of type 1 diabetes with COVID-19 positivity (19).

It is unclear what accounts for this rise in type 1 diabetes incidence in children that exceeds the trend of increasing incidence over the preceding pre-pandemic years. One possibility is that SARS-CoV-2 infection is the environmental trigger precipitating the autoimmune attack that is necessary in the pathogenesis of type 1 diabetes (20). Another explanation maybe that either infection itself or weight gain during the pandemic unmasked type 1 diabetes that was already in development; Whether the infection and weight gain increase insulin resistance and may render someone with insulin deficiency hyperglycaemic earlier than would be expected, is not known. A final explanation is that it is not type 1 diabetes that is increasing in incidence but rather insulin deficient diabetes, that is to say it has been suggested that the virus could itself directly injure pancreatic beta cells inducing insulin deficiency. The potential mechanisms for this are discussed in the next section, however if such injury were to account for the rise in 'type 1 diabetes', the markers of autoimmunity such as pancreatic autoantibodies should be negative in newly presenting cases. In the German DPV study there was no difference in the proportion of antibody negativity in children newly presenting with type 1 diabetes during the pandemic versus preceding years. These studies need to be replicated across age groups and in other populations.

Explanations for the rise in DKA associated with new-onset diabetes

A separate but related phenomenon has been the rise in presentations of DKA during the pandemic. This was initially reported in small case series and cohorts but comprehensively analysed in English national data in 2021. Comparing admissions with DKA in the preceding three years to those during the first 12 months of the pandemic analysis showed the DKA admissions in people with type 2 diabetes. Similarly, DKA admissions increased in people newly presenting with diabetes (not known if type 1 or type 2 diabetes); 57% (48-66) higher during the first wave and 61% (52-70) higher during the second wave. These higher numbers of DKA cases were observed across all age categories.

As mentioned, DKA can occur in type 1 diabetes, type 2 diabetes, and ketosis-prone type 2 diabetes. The characteristics of people newly presenting in DKA are wide-ranging; the excess cases have been observed in children, adults, and older individuals. Therefore, the drivers are likely to be different. A concerning trend towards greater DKA presentations in children has been observed pre-pandemic and was worse over the course of the pandemic (21); a global study of 104,290 children showed a significant increase in the proportion presenting with DKA, in excess of the predicted year on year rise. The interesting observation however was that in multivariable analysis the higher prevalence of DKA at presentation during the pandemic was associated with stringency of lockdown measures. Whilst the explanation of higher DKA risk during the pandemic could just reflect a higher incidence of type one diabetes other explanations must be considered(22). Prompt recognition of the symptoms of new onset type one diabetes are needed to prevent DKA. It is therefore possible that during lockdown delays in people presenting to healthcare providers could explain the excess presentations of DKA(23). However as outlined in the next section it is postulated that SARS-CoV-2 viral infection may trigger beta cell loss either through an autoimmune process (type one diabetes) or through direct injury.

New onset diabetes following vaccination

Isolated case reports have reported on the development of type 1 diabetes post COVID vaccination using mRNA preparations(24–26). However, a more definitive study in 23,709 patients analysed risk of developing diabetes 90 days after COVID-19 infection(27); the study was well-designed and compared the onset of diabetes to other benchmark conditions e.g. urine infections to account for potential bias from healthcare engagement or access to services. The study found that there was an increased risk of new onset diabetes in the 90 days after COVID infection, compared to the 90 days before COVID infection, which was higher than the benchmark conditions (OR 1.58; 95% CI 1.23-2.02). However the most interesting aspect was that COVID vaccination reduced the risk of new onset diabetes; OR 1.78 (95% CI 1.35-2.37) in unvaccinated vs OR 1.07 (95% CI 0.64-1.77) relative to the benchmark conditions.

Mechanistic insights in the pathogenesis of new-onset diabetes

In this next section we consider the evidence base for the major mechanistic hypotheses for these epidemiological observations (summarised in figure 2). We address three key questions; 1) Can SARS-COV-2 virus directly infect beta cells? 2) Does SARS-COV-19 infection triggers autoimmunity resulting in Type 1 diabetes mellitus? and 3) Does the hyperinflammatory response to SARS-COV-19 infection exacerbate features of type 2 diabetes mellitus?

1. **Can SARS-COV-19 virus directly infect beta cells?**

Perhaps one of the most tantalising discussions surrounding the association between COVID-19 and diabetes is the possibility of the SARS CoV-2 virus itself causing direct injury to the pancreatic beta cells. Some groups have found that SARS-COV-2 virus can penetrate human pancreatic islets. SARS-COV-2 spike (S) and nucleocapsid (N) proteins were detected following transduced infection of islets in-vitro (28,29). Muller et al's study infected pancreatic human islets ex-vivo and used transmission electron microscopy to demonstrate the presence of virus-containing secretory vesicles within islet cells, with a greater tendency for islets cells already containing secretory vesicles to be infected (30). Measurements of rising viral titres post-infection suggested productive viral replication, with viral titres and detection of viral proteins being significantly lowered following administration of remdesivir (30). Analysis of autopsy samples from infected subjects confirmed the presence of viral RNA and proteins in pancreatic tissue, with evidence of specificity of localisation to insulin-producing beta cells (28–31).

However, whilst pancreatic islets may be susceptible to SARS-COV-19 infection, the degree of penetration may be relatively low. One study infected human pancreatic islets in-vitro and found a maximum of 3 cells per islet got infected with the virus (28). The overall incidence of islet cells staining positive for both viral proteins and insulin were also relatively low (29,30). Furthermore, whether SARS-COV-19 selectively targets the endocrine cells is also undecided; some report detection of viral RNA and proteins exclusively within endocrine tissue (29) and a tendency for viral proteins to be distributed close to islets (30), but others detected more widespread pancreatic infiltration (28,31).

Entry of SARS-COV-19 into target cells is broadly agreed to primarily occur via the angiotensin converting enzyme-2 (ACE2) receptor (32–34). Consensus on its expression in pancreatic endocrine cells is lacking. Some studies have found significant ACE2 receptor levels in rodent (35,36) and human (28–30,37–39) pancreatic tissue, with one study finding the receptor staining to be strongest in the endocrine pancreatic tissue (37). Within the endocrine tissue, ACE2 receptors most commonly co-localised with insulin or C-peptide (30,35,39), supporting the notion that beta cells are particularly prone to SARS-COV-19 infection. Indeed, the ACE2 receptor itself may also play an important role in normal glucose homeostasis (38). Niu et al showed how ACE2 receptor knockout (ACE2-KO) mice had impaired glucose tolerance with a selective reduction in their first-phase insulin response compared to their wildtype counterparts (40). ACE2 expression has been reported to be higher in diabetic pancreatic islets (38,41), which may be a compensatory response to restore normal glucose homeostasis.

However, other groups using various anti-ACE2 antibodies have been unable to detect significant receptor levels in pancreatic endocrine tissue (42,43), with surrounding pancreatic microvasculature and ductal epithelium harbouring the greatest ACE2 receptor expression instead. The variability in ACE2 receptor expression between studies may be due to differences in exposure to proinflammatory cytokine levels (39). This would be particularly true for studies undertaken on human pancreatic tissue from donors infected with SARS-COV-19, where individual inflammatory responses would differ with age, duration of disease, comorbidities, and other concurrent complications.

Another protein of interest is TMPRSS2, a transmembrane serine protease. As with the SARS-COV virus, TMPRSS2 is thought to facilitate the entry of SARS-COV-19 via ACE2 receptor by priming its spike protein (32). Blockade of TMPRSS2 by a selective protease inhibitor prevented entry of SARS-COV-19 virus into human lung cells in-vitro and inferred therapeutic benefit when administered to mice models of severe COVID-19 infection (44). However, as with ACE2 receptors, the distribution of TMPRSS2 is unclear. Those who found strong ACE2 receptor expression found strong TMPRSS2 expression in pancreatic islets (28,30,38), and those who failed to detect ACE2 reported very low levels or no TMPRSS2 expression in pancreatic endocrine tissue (42,43). It is also likely that TMPRSS2 is not the only protease involved in ACE2-mediated SARS-COV-19 infection. Wruck and Adjaye's RNA-sequencing meta-analysis revealed a particularly strong positive correlation between ACE2 and TMPRSS4 expression (45), which has been corroborated by other primary data studies (46,47), although nothing beta cell specific.

The ACE2 receptor may work alongside other extracellular receptors in order to mediate entry of SARS-COV-19 into host cells. The NRP1 gene, encoding neuropilin-1, has been associated with type 1 diabetes and is highly expressed in pancreatic islets (31,48). Tang et al demonstrated that infected human islets had greatest expression of SARS-COV-19 N protein if islet cells were positive for both ACE2 and NRP-1 (31). Islets from patients with COVID-19 were also found to have greater expression of NRP1 compared to islets from non-COVID-19 donors, and inhibition of NRP1 reduced the ability of SARS-COV-19 to infect beta cells (29). This raises the possibility of targets that may reduce infection risk in patients with diabetes.

Taken together, the studies described so far that the endocrine pancreas in patients with diabetes may have a greater susceptibility to SARS-COV-19 infection, but there is no

conclusive evidence that hyperglycaemia in COVID-19 disease is largely driven by virally induced beta cell death or dysfunction resulting in either acute or long-term insulin deficiency. To recap, post-mortem studies (with low n numbers), have confirmed that the majority of pancreata of people who died from severe COVID were infected with the virus with some evidence for beta cell specificity (28,29). Immunohistopathological analysis of a small number of post-mortem samples of patients that died from severe COVID-19 infection reveal a small fraction of β cells that had undergone virally induced necroptosis (28). However there is an absence of data on pancreatic involvement from patients with less severe COVID-19 and no evidence of widespread beta cell destruction or insulitis.

It is also possible that direct infection of beta cells by the virus could induce acute insulin deficiency via the disruption of insulin production or release. Binding of the virus' S protein to the receptor binding domain (RBD) enables endocytosis, enabling the virus to utilise the host's intracellular machinery to transcript its RNA and facilitate viral replication.
New onset hyperglycaemia with SARS-COV-19 infection might suggest the ability of the virus to successfully enter beta cells, hijack its intracellular machinery and disrupt its insulin output. There is some indirect evidence pointing to the manifestation of hypoinsulinism related to beta cell infection. An increase in peripheral unmethylated INS DNA, a marker of cell death, was evident in a study of ten patients with hyperglycaemia and COVID-19 without islet autoimmunity (49) although it was not possible to link this data with direct histological or molecular evidence of beta cell death or dysfunction. Islets infected in vitro with SARS-CoV2 have been reported to have reduced insulin content and functionally impaired glucose stimulated insulin secretion (29,30). Others have reported that infection triggers human beta cell transdifferentiation with lower insulin transcription (and increased glucagon expression) on immunostaining, although again it was not possible to directly link evidence of cell fate change with clinical measures of glucose homeostasis (31). In an admirable attempt to provide whole body glycaemic measures around SARS-CoV 2 infection, an Italian study by Montefusco et al reported on 551 patients without any pre-existing history or diagnosis of diabetes 2 months after hospitalisation with COVID-19 (50). In this cohort 46% were hyperglycaemic when they were in hospital with COVID, and 63% of those returned to normoglycaemia by 6 months post discharge. In all subgroups studied, fasting insulin, fasting C-peptide, HOMA-B, HOMA-IR and AIR-max were all significantly higher during acute COVID infection compared with the recovery phase, with no groups exhibiting new onset insulin deficiency.

2. Does SARS-COV-19 infection triggers autoimmunity resulting in Type 1 diabetes mellitus?

Interestingly, there is general consensus that in those with pre-existing diagnosis of type 1 diabetes, at least in the UK, there was a decreased incidence of DKA (51). This is generally believed to be the result of behavioural changes enforced by lock down – such as an increased ability to maintain routines or engage with self-care. However, separate to this, as outlined in the above section, there is a signal that the incidence of *newly diagnosed* type 1 diabetes may have increased during the pandemic and the reasons for this remain to be fully elucidated.

In the previous section the evidence for direct virally induced beta cell death or dysfunction was summarised and concluded that there was insufficient evidence to support this as a common or clinically significant cause of hypoinsulinism and hyperglycaemia with COVID-19. Whether SARS-CoV-2 infection that may evoke an autoimmune response that leads to type 1 diabetes is considered in the next section.

Islet auto antibodies are commonly measured as part of the diagnosis of type 1 diabetes but they are not considered the direct cause of beta cell destruction. More broadly, the insulitis and beta cell death that occurs in type 1 diabetes results from an influx of autoreactive CD8+ killer T cells (52). Related to this is the dysfunction of tolerogenic CD4+ regulatory T cells which, via a complex interplay of cytokine signals, normally act to suppress autoreactive killer cells (53). It is feasible that the generalised response to SARS CoV 2 infection, for example the release of antiviral cytokines (IFNα and IFNλ) and proinflammatory cytokines (tumour necrosis factor-α and IL-6) could result in a disruption of the islet tolerogenic niche. It has also been hypothesized that type I IFN produced by SARS-CoV-2–infected β cells themselves might provide the immunogenic trigger for destructive autoimmunity to prevail (29). The interplay between genetic susceptibility and environmental triggers, including a range of possible viral infections, remains incompletely understood with regards the aetiology of type 1 diabetes. As an example, chronic beta cell infection with coxsackieviruses has been established to result in elevated IFNα which triggers overexpression of MHC-I molecules and the unabated presentation of β-cell epitopes to the immune system (54). It remains to be established whether SARS-COV-2 infection can trigger a similar response. It may be difficult to ascertain this by looking at epidemiological data since any effect of COVID-19 triggered autoimmunity may be masked by lower infection rates with other viral triggers due to lockdown measures (55).

3. Does the hyperinflammatory response to SARS-COV-19 infection exacerbate features of type 2 diabetes mellitus?

It is well recognised that COVID-19 severity is closely linked to the systemic hyperinflammatory response that may ensue (56). In the sections above, we have discussed how direct pancreatic infection may cause beta cell death and dysfunction. We also speculate how viral infection may trigger autoimmune type 1 diabetes or how the cytokine storm itself could disrupt the tolerogenic islet niche. However, observational data would suggest that the biggest driver of dysglycaemia and altered presentations of diabetes during the pandemic are related to this hyperinflammatory stress response and the insulin resistance that ensues. Stress hyperglycaemia in the absence of a diagnosis of diabetes is an established independent risk factor for poorer outcomes in patients hospitalised with COVID-19 (57). In a small cohort of paediatric DKA cases studied during the pandemic, those with SARS-COV-2 were more likely to present with indices of higher insulin resistance than those in DKA without SARS-COV-2 infection(58). But during the pandemic, far more people with type 2 than type 1 diabetes died of COVID. Of course, this is largely because type 2 diabetes is itself more prevalent and affects older people. However, in this last section we discuss further some of the ramifications of the COVID-19 with regards new onset or altered presentations of type 2 diabetes.

Type 2 diabetes is much more commonly associated with a long prodrome of non-diabetic hyperglycaemia and insulin resistance. In normal circumstances patients may have had type 2 diabetes for many years before being diagnosed in the community. We now know that due to altered interaction with community medics and reduced screening, the apparent reduction in incidence of type 2 diabetes during the pandemic has been followed by an excess of cases in the aftermath above and beyond a catch up – hinting at an actual real increase in type 2 diabetes incidence (59,60). Whether this is due to changes in behaviours (such as food intake or exercise) resulting in a hastening of type 2 diabetes onset remains to be elucidated, although there was a clear increase in BMI over the years of the pandemic in the UK population (60).

Modern concepts of the aetiology of type 2 diabetes converge on the notion that it is not a single disease state but results from a heterogenous set of metabolic disturbances and genetic risk. For example, some patients may present with severe insulin resistance, gross hyperinsulinism but relatively modest hyperglycaemia whereas others are lean with a phenotype more suggestive of beta cell secretory failure and insulin deficiency (61). Thus, it is possible that the same beta cell toxic mechanisms discussed above could apply to the hastening of the diagnosis of type 2 diabetes in those individuals where a loss of beta cell mass is enough to tip them into frank hyperglycaemia. Many have reported that patients with type 2 diabetes were more likely to present with ketotic crises during the pandemic (51,62,63). This is interesting and remains to be fully elucidated since direct measures of insulin resistance or even insulin doses with these presentations compared with control (non-COVID associated ketosis prone type 2 diabetes) is lacking. There was also a strong intersectionality with ethnicity – ketosis prone diabetes is more common in non-white ethnicities and, largely due to socioeconomic factors, non-white individuals were also more likely to present with severe COVID.

One of the major achievements of the COVID 19 pandemic was the mobilisation and completion of large scale high quality clinical trials to ascertain the benefit of drugs to help improve outcomes in severe infection. By July 2020 the RECOVERY trial was reporting the benefit of dexamethasone in patients admitted with COVID-19 and a supplemental oxygen requirement (64). Steroids reduce the hyperinflammatory sequelae of severe COVID-19, but given their other effects on insulin resistance and hyperglycaemia, it was important to show, as some studies subsequently did, that the benefits of dexamethasone in reducing COVID-19 severity were indeed preserved in patients with diabetes. However, about half of people without diabetes receiving dexamethasone for COVID-19 developed in patient hyperglycaemia (65) and the longevity of steroid induced diabetes or new onset Type 2 diabetes in the face of dexamethasone usage for COVID-19 remains poorly defined. According to a recent meta-analysis (66), it should be a priority to better define and establish evidence-based treatment and follow up strategies for glucocorticoid induced hyperglycaemia.

Conclusions

The cause of the rise in new-onset diabetes during the pandemic remains incompletely resolved. It is likely to be multifactorial and both epidemiological and mechanistic data help

shed light on contributory factors. These factors include direct effects of COVID-19 in an individual (mediated by stress hyperglycaemia and steroid treatment) or indeed possible beta-cell injury and also indirect effects of pandemic measures through effects of lockdown, changes in weight and other environmental factors. Whilst the footprint of SARS-CoV-2 virus is visible in pancreatic cells, from mechanistic studies, the significance remains unclear. Epidemiological and registry-based studies in coming years will help decipher whether the rise in newly diagnosed diabetes will continue and indeed, the type of diabetes accounting for the rise. Until then, resuming diabetes services that have been significantly disrupted during the pandemic, remains a priority.

Practice Points

- It is established that pre-existing diabetes is associated with poor outcomes from COVID-19 infection but the relationship between COVID-19 and new-onset diabetes is less clear.
- During the pandemic there has been a rise in new onset diabetes cases relative to expected year-on-year rises observed pre-pandemic. A similar trend for new onset diabetes presenting with diabetic ketoacidosis has also been observed during the pandemic.
- It is challenging to decipher whether these associations reflect indirect or direct effects of the pandemic.
- For the rise in type 2 diabetes cases, it is possible that there is better case ascertainment following infection or that the lifestyle changes progressed susceptible individuals to type 2 diabetes. For type 1 diabetes, it could be speculated that weight gain unmasked type 1 diabetes earlier in the disease trajectory or that Covid-19 infection was the environmental trigger precipitating autoimmunity.
- Against the backdrop of indirect effects is the possibility that the SARS-CoV-2 virus directly injures pancreatic beta-cells. However evidence is contradictory as to whether SARS-CoV-2 can infect beta cells and induce necroptosis, or whether a hyperinflammatory response or immunomodulatory cytokine storm causes indirect beta cell destruction.
- Whilst the underlying mechanism of new-onset diabetes following COVID-19 infection remains unknown, continuing to optimise glycaemic control and resuming diabetes services are vital in improving outcomes of those with new-onset diabetes durig the pandemic.

Research Agenda

- Phenotyping new-onset diabetes mellitus in adults following COVID-19 infection to help further our understanding of the type of diabetes developed.
- Long term follow-up studies involving cases of new-onset diabetes to determine if there are ongoing insulin requirements and if progression is accelerated in those already established to have diabetes.
- Studies investigating the effect of long COVID on risk of developing type 2 diabetes and progression to insulin dependency.
- In-vitro studies to determine if other islet cells play a role in exacerbating beta cell failure following COVID-19 infection.

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Figure 1: Schematic illustrating the pathways to new-onset diabetes during the pandemic

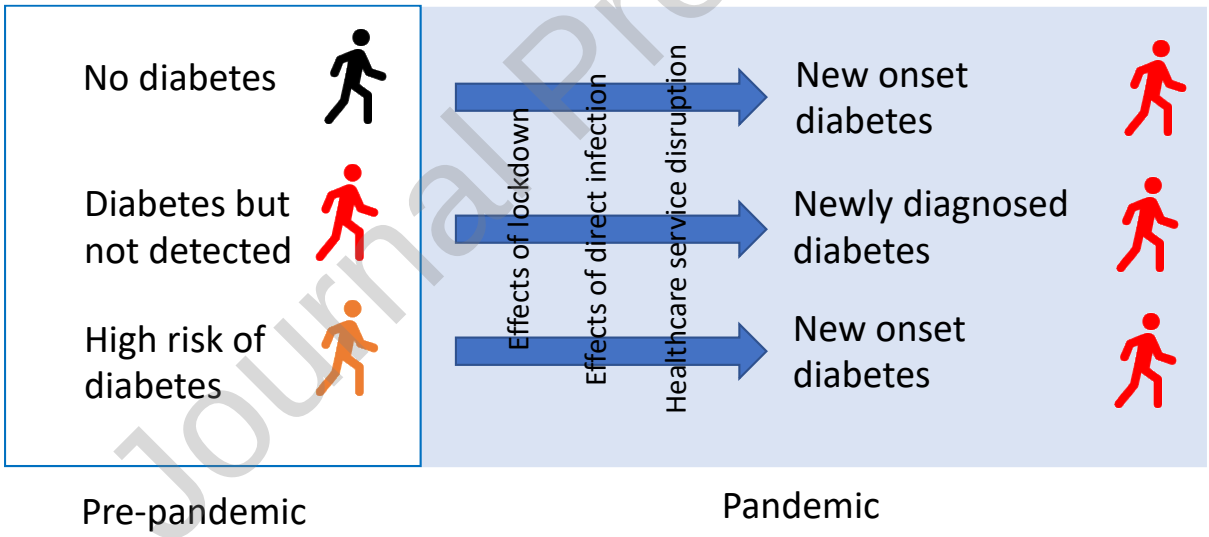

Figure 2: Schematic representation of putative biological mechanisms by which SARS-CoV-2 infection may result in new-onset diabetes.