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COVID-19 and diabetes — where are we now?

Rüdiger Groß & Alexander Kleger

As emerging clinical analyses suggest an increased risk of new-onset diabetes following COVID-19, a causal link and underlying mechanisms are yet to be established. Persistence of hyperglycaemia after disease regression and the potential infection of non-pancreatic tissue are adding another layer of complexity to the relationship between COVID-19 and diabetes mellitus.

Diabetes mellitus (DM) is a well-established risk factor for severe disease and mortality in COVID-19, but accumulating clinical and laboratory evidence on metabolic dysregulation after infection raises the question whether SARS-CoV-2 itself may trigger or expedite development of DM.

Clinical and epidemiological evidence

After initial reports of new-onset hyperglycaemia coinciding with infection in the early phases of the pandemic, several large cohort studies now suggest an overall increased risk of new-onset diabetes mellitus (DM) for both type 1 diabetes (T1D)[1,2] and type 2 diabetes (T2D)[3–6] following COVID-19 infection. For T1D, however, epidemiological data are controversial — German[2] and Scottish[1] registries noted an increase in T1D diagnosis in children and adolescent shortly after a peak in SARS-CoV-2 infection numbers, whereas a larger population-based, repeated, cross-sectional study from Canada[7] did not. Delayed diagnoses of naturally occurring T1D as an indirect result of the pandemic are likely confounding these results, while the challenge to verify past COVID-19 infection in children with new-onset diabetes further complicates association studies.

At the same time, evidence for a connection of COVID-19 with new-onset T2D appears more robust. Surveys of electronic patient records suggest an overall increased risk of new-onset DM up to 12 weeks post infection[3], an increased likelihood of being prescribed insulin within 91 days of COVID-19 diagnosis[3] and an excess burden of incident diabetes and hyperglycaemia (where >77% were stratified as T2D) at 12-month follow up[4]. If and when glycaemic control is re-established after recovery from COVID-19 in those patients remains unclear. In some cohorts, glucose control had improved in 63–79% of patients 6 months after recovery[5,8] and improved in 41–79% of patients 10 months after recovery[5,6]. Up to 56% of patients remained hyperglycaemic[6]. A separate cohort of hospitalized COVID-19 patients with dysglycaemia during acute infection displayed reversion to physiological glycaemic control in the post-acute phase in a 7 month follow-up[9].

Despite uncertainties regarding prevalence and persistence, dysglycaemia may thus represent a potential aspect of post-acute sequelae of SARS-CoV-2 (PASC), also commonly referred to as 'long COVID' (or 'LC'). However, these findings also do not necessarily imply a direct diabetogenic effect of SARS-CoV-2 infection, as hyperglycaemia is also observed after non-COVID acute respiratory distress syndrome, possibly as a result of systemic inflammation[10]. Nonetheless, occurrence of new-onset T2D[3–6] and insulin resistance[8] post-COVID suggests that SARS-CoV-2 infection may promote β-cell exhaustion in at-risk cohorts.

Notably, breakthrough infection after vaccination was not associated with a significantly lower incidence of DM in the context of PASC, when compared to infections of unvaccinated individuals. However, a decreased risk of insulin use suggests amelioration of the severity of metabolic dysregulation by pre-exisiting immunity[11]. Furthermore, a recent preprint suggests an accumulating risk of new-onset DM with multiple re-infections[12]. Due to ethical reasons, correlative time-resolved data on insulin and glucose levels with degree of β-cell infection in humans will be invariably lacking, which will restrict our experimental knowledge to animal models, including non-human primates. Overall, the long-term risk for and burden of new-onset DM of any type following COVID-19, especially in light of newly emerging,

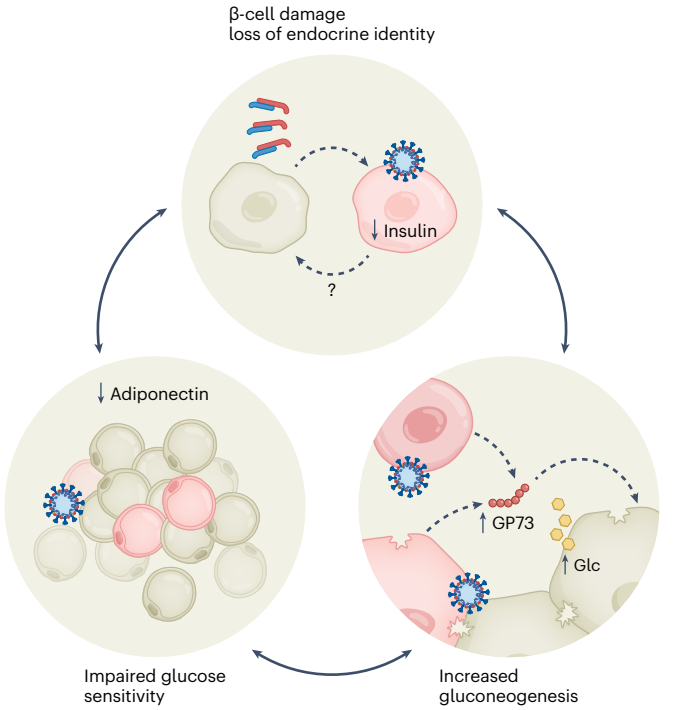

Fig. 1 | Emerging mechanisms underlying hyperglycaemia in COVID-19. Direct infection of pancreatic β cells results in loss of insulin granules and endocrine functionality, as well as in trans- or de-differentiation. Infection of adipocytes reduces release of adiponectin, thus leading to reduced insulin sensitivity. Infection of various tissues including hepatocytes promotes secretion of glucogenic GP73, stimulating gluconeogenesis. In combination, insulin desensitization, increased gluconeogenesis and direct β-cell damage promote β-cell exhaustion. Glc; glucose.

Table 1 | Summary of open and partially answered questions that need to be addressed to gain a deeper understanding on incident diabetes as part of PASC

How persistent is hyperglycaemia after COVID-19?
Can vaccination provide protection against metabolic dysregulation?
What is the frequency and clinical importance of direct β-cell damage?
How do liver and adipose tissue contribute to glycaemic derangement?
Are there persons with a specific risk for glycaemic deterioration through COVID-19?
Are there pharmaceutical interventions that could ameliorate COVID-related dysglycaemia?
Do newly emerging variants exhibit altered tropism, resulting in changed frequency or severity of infection-induced metabolic dysregulation?

immune-evasive variants and multiple subsequent infections, can only be clarified by population-level studies providing long term follow-up data and comprehensive data sets in the coming years.

On SARS-CoV-2 infection of pancreatic β-cells

Whether the SARS-CoV-2 entry receptor ACE2 is expressed in pancreatic tissue, and specifically in β-cells, has been extensively debated[13–15]. This 'ACE2 debate' was fostered by a combination of donor variability, different sample types used (primary islets, stem-cell derived endocrine cells and autopsy samples with different degrees of autolysis) and variable specificity of antibodies, which can interact with either the short or the long isoform of ACE2, or with both[13,15]. However, multiple studies, in some cases even published from groups initially doubting the presence of the two classical entry factors, clearly show expression of ACE2 and TMPRSS2 in β cells[16,17]. Besides, expression of the ACE2-potentiating factor Neuropilin-1 suggests additional viral entry routes in pancreatic β cells, arguing for the susceptibility of β cells for infection by SARS-CoV-2[13,14,18]. Susceptibility of exocrine pancreatic cells and the pancreatic microvasculature to viral infection may aid in dissemination to the endocrine cells of the pancreas, but it can also cause metabolic changes per se due to pancreatic inflammation[19]. A growing body of evidence shows that β cells can be infected in vitro and are infected in patients who died with or as a consequence of COVID-19[13,14,18]. Infection of β cells has been shown to be associated with a loss in endocrine identity, resulting in reduced expression of genes associated with insulin production and release and, subsequently, in altered morphology and diminished functionality. Specifically, infection was associated with degranulation[13], impairment of glucose-stimulated insulin secretion[13,18], de- or transdifferentiation[13,20], or cell death[14,18] (Fig. 1). Although the occurrence and relevance of β-cell transdifferentiation in T2D is still a matter of debate in humans[21], β-cell plasticity with the acquisition of an alpha and acinar cell fate upon SARS-CoV-2 infection was reported in an elegant study employing human islets and autopsies. Of note, the eukaryotic initiation factor 2 (eIF2) signalling pathway was here identified as a 'druggable' mechanism to prevent transdifferentiation[20]. In line with this observation, a recent study revealed that a relevant proportion of islet cells converted into exocrine-like cells during T2D progression, indicating that pathological islet plasticity might be also an underlying cause of β-cell failure in T2D[22]. Accordingly, such findings were recapitulated in non-human primates infected with SARS-CoV-2, in which pancreatic SARS-CoV-2 infection was observed and animals developed a T2D-like phenotype in conjunction with β-cell atrophy and decreased granularity[23]. As in patients, not all animals developed hyperglycaemia (50% developed hyperglycaemia) or displayed elevated serum levels of insulin (37.5% displayed these levels)[23]; the underlying reasons for this variability remain still unclear, although the mentioned interindividual variability of viral entry protein expression might offer a partial explanation[13].

Mechanisms of dysregulated glucose metabolism beyond the pancreas

The extent of β-cell infection[17], together with an intrinsically high insulin reserve in humans, cannot solely explain new-onset DM after COVID-19, suggesting that additional mechanisms exist. Given the broad tissue tropism of SARS-CoV-2, infection of other (endocrine) organs and a contribution to metabolic dysregulation is not surprising. Recently elucidated mechanisms of adipocytic and hepatic SARS-CoV-2 infection provide potential links to increased T2D incidence and its dependence on obesity (Fig. 1): first, mature adipocytes were shown to support viral replication and SARS-CoV-2 proteins were identified in adipose tissue in 56% of males who died from COVID-19. Notably, viral material in adipocytes was only detected in males with overweight or obesity[24], consistent with a male dominance in large-cohort studies reporting increased risk for incident DM[4]. In women, no clear association of BMI and viral RNA levels was present in that study, and not all studies have confirmed this relationship for men[10,24]. Once infected with SARS-CoV-2 in vitro, adipocytes secrete less adiponectin[10]. Adiponectin has insulin-sensitizing properties and its lack could therefore contribute to systemic insulin resistance, as suggested in COVID-19 patients who displayed low adiponectin and high C-peptide concentrations[10].

Insulin resistance may be further exacerbated by hepatic infection — infection of hepatocytes and cells in various other tissues with SARS-CoV-2 enhances secretion of the stress-induced glucogenic factor GP73, which promotes gluconeogenesis in hepatocytes[25]. Consequently, COVID-19 patients display elevated GP73 serum levels, which correlate with blood glucose levels[25]. Together, these findings point towards a mechanistic explanation for (BMI-dependent) incidence of new-onset T2D in some patient cohorts[4]. In addition, these infection-related consequences in non-pancreatic tissue might explain the observed hyperinflammation in the secretome of post-COVID-19 patients, subsequently causing insulin resistance and hyperstimulability of β cells[8].

Although clarification of sex- and obesity-specific differences will require further studies, it is plausible that SARS-CoV-2 infection of cells and organs that are crucial for a healthy glucose metabolism provides a trigger for new onset of DM. Individuals with pre-diabetes might be especially vulnerable, as infection provides a final push towards β-cell exhaustion through a vicious cycle of decreased insulin sensitivity, increased gluconeogenesis and subsequently increased insulin demand, while direct viral damage to β cells leading to pathological plasticity and function further diminishes the regulatory capabilities. Vice versa, uncontrolled and overshooting insulin release, as observed in post-COVID patients, could also be due to both infection and systemic inflammation further accelerating β-cell exhaustion.

Where do we need to go?

Given the bi-directional relationship between COVID-19 and DM, where DM is a comorbidity associated with more severe outcomes but may also be a consequence of infection itself, it will be crucial to thoroughly understand the underlying mechanisms to enable targeted interventions and reduce the likely rising high healthcare burden in the ongoing

pandemic. A number of important questions remain open or have only been partially answered (Table 1). Finding answers to these questions will be a critical task for the metabolic research community in the near future.

These questions can only be addressed by a combination of population-level clinical cohort studies with long-term and comprehensive follow-up data, and detailed mechanistic research in vitro research and in animal models. Current studies are limited by cohort heterogeneity and are largely focused on hospitalized patients, neglecting the vast majority of 'mild' COVID-19 cases still facing PASC. Incomplete data sets, such as those with a lack of proof of infection or a lack of autoantibody determination or DM subtype stratification, further hamper our ability to establish causality of the COVID-19/DM connection.

As randomization in clinical studies is ethically not possible and current rodent models only incompletely recapitulate COVID-19, large animal models with time-resolved access to various DM-relevant tissue, including the pancreas as well as body fluids (for example, blood and also stool to study the microbiome), are highly warranted to close the currently existing mechanistic gap in understanding SARS-CoV-2 pathophysiology. While rates of infection remain perpetually high and the risk of re-infection is increased, which is a result of eased public health measures and vigilance due to lower mortality associated with new variants and high immunization rates, it will be crucial to clarify the incidence and burden of new-onset diabetes and other aspects of PACS.

DM is already one of the most common non-communicable diseases worldwide. Even when assuming a low incidence and transience, the 600 million current cases of COVID-19 worldwide may add a substantial figure to the number of DM diagnoses, further jeopardizing the goals set by the WHO and the UN on reducing the rise of disease burden caused by non-communicable diseases, which were set as part of the 2030 Agenda for Sustainable Development. As a consequence, policymakers may need to re-think their strategy of basing the stringency of public health measures primarily on mortality and hospital occupancy to prevent an excessive burden on the population, the economy and already strained healthcare systems.

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