COVID-19-associated new-onset hyperglycaemia: a reversible entity or persistent risk?

New-onset hyperglycaemia (NOH) in COVID-19 is a clinically and biochemically heterogeneous entity. While the clinical variations range from a predominant pattern of insulin resistance (IR) and β-cell overstimulation to a depleted β-cell reserve phenotype, differences in working definition make NOH biochemically diverse. The American diabetes association (ADA) defines NOH as fasting plasma glucose (FPG) values 100–125 mg/dL and/or glycated hemoglobin (HbA1c) 5.7%–6.4%, without prior evidence of dysglycaemia. However, studies have used FPG ≥126 mg/dL or two FPG 100–125 mg/dL and/or single plasma glucose 100–199 mg/dL.

Over half a dozen viruses are known to be diabetogenic, including enteroviruses, Coxsackie virus, rubella, cytomegalovirus (CMV) and hepatitis C virus (HCV). The basis of this dysglycaemia is either cytolyis or molecular mimicry, resulting in insulinopenic diabetes. Interestingly, certain infections (CMV, HCV) portend a higher risk of T2DM, by exaggerating IR. Its contribution has also been suggested in COVID-19 induced NOH. Stress hyperglycaemia is an integrated neuroendocrine response, mediated by catecholamines, the persistence of overt diabetes in 10% of patients at 3 years follow-up. Genetic similarity and common receptor (ACE2) between SARS-CoV-1 and SARS-CoV-2 suggest that a proportion of patients with NOH in COVID-19 will have persistent hyperglycaemia.

IR has been suggested as the central pathogenic mechanism of NOH, backed by observations of reduced adiponectin and improved glycaemic profile with the use of tocilizumab. Higher levels of insulin and C-peptide in NOH during COVID-19 as compared with NOH pre-COVID, also indirectly favours this hypothesis. In a study, the biochemical signature of β-cell hyperstimulation (high insulin, C-peptide, proinsulin, homoeostatic model assessment (HOMA-β, HOMA-IR)) was observed, with a good correlation of HOMA-IR with inflammatory scores. This suggests a synergistic IR on a background of already high IR in patients predisposed to severe COVID-19. High in-hospital insulin requirements (>2 units/kg/day) lend further credence to the role of IR. A cytokine-mediated IR rather than stress hyperglycaemia (due to counter-regulatory hormones including cortisol) is also suggested by our observation of a relative hypocortisolism in severe COVID-19.

Direct viral infiltration of the islets is reported using immunofluorescence and electron microscopy techniques. Interestingly, ACE2 expression is more common in the endothelial vasculature than in β-cells. In cells that did not express ACE2, dipeptidyl peptidase type 4 was found to mediate viral entry. The role of depleted β-cell reserve is suggested by reports of autoantibody-negative, fulminant diabetes after COVID-19. Pancreatitis due to exocrine ACE2 expression has been suggested, but the real risk of this complication is, in fact, minimal (<1%).

Interestingly, a high glycaemic variability (GV) has been documented in patients with COVID-19 using continuous glucose monitoring. GV is a marker of depleted β-cell reserve akin to an insulinopenic milieu in patients with T1DM as the physiological cascade requires sensing of the delta fall in insulin by the α-cells to release glucagon. Further, it can also be envisaged that the β-cell hyperstimulation seen in acute stages in response to a high IR, will ultimately result in exhaustion of reserves and persistent hyperglycaemia.

Dysregulated immune response in COVID-19 may lead to the formation of anti-insulin autoantibodies, suggested by reports of type 1 diabetes mellitus (T1DM) following COVID-19 and molecular mimicry (figure 1). Oxidative stress mediates hyperglycaemia-induced endothelial injury, thrombosis and inflammation, especially in acute hyperglycaemia. Its contribution has also been suggested in COVID-19 induced NOH. Stress hyperglycaemia is an integrated neuroendocrine response, mediated by catecholamines.

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**Figure 1** Schematic representation of the factors contributing to new-onset hyperglycaemia in COVID-19 and analysis of the persistence or remission of hyperglycaemia during follow-up as an integrated outcome of multiple dysregulated pathways. DM- Diabetes mellitus; DPPIV, dipeptidyl peptidase type IV; GAD-65, glutamic acid decarboxylase-65; IR, insulin resistance; PSC, pancreatic stellate cells.
cortisol and cytokines. Prior experience suggests the non-reversibility of stress hyperglycaemia in a fraction of patients (5%) and a doubled risk for the future development of DM over a median follow-up of 5.3 years. Similarly, glucocorticoid-induced hyperglycaemia has been found to increase the future risk of T2DM (30-fold), 1 year after hospitalisation. These premorbid conditions may herald permanent hyperglycaemia in NOH. Severe COVID-19 manifests as hypoxia and non-remitting hyperglycaemia. Hypoxia can cause islet-cell death by activation of pancreatic stellate cells. This may be an underlying mechanism by which patients with hypoxia in COVID-19 sustain islet injury.

Interestingly, hyperinsulinaemic-euglycaemic clamp studies suggest persistence of IR even 3 months after respiratory infections, as a direct result of increased cytokines tumour necrosis factor α, interferon γ and interleukin-6. In COVID-19, persisting high IR has been seen both in euglycaemia and NOH. In fact, lower FPG levels at 3 months, followed by a higher rate of 6 months in non-diabetic individuals, suggest the sequence of events as acute IR, β-cell hyperstimulation, and ultimately, reduced β-cell reserve. Evidence on persistent hyperglycaemia is still nascent. In one study, persistent hyperglycaemia or diabetes was present in 35% of patients at 6 months follow-up. NOH has long-term implications in terms of adverse glycaemic and metabolic outcomes. Gauging the burden of persisting hyperglycaemia will not only expand the existing pool of diabetes but will aid policymakers in targeting high-risk individuals. It remains to be determined whether NOH in COVID-19 is equivalent to the risk of future development of DM seen in stress-induced/glucocorticoid-induced hyperglycaemia or more.

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