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Covid-19: A new cause of "provoked" A-β+ Ketosis-Prone Diabetes☆

From the early days of the SARS-CoV2 pandemic, clinical and epidemiologic evidence has revealed a bi-directional relationship between Covid-19 disease and diabetes.[1] Pre-existing diabetes is associated with worse outcomes for those hospitalized with Covid-19; conversely, SARS-CoV2 infection is associated with acute worsening of metabolic control in patients with pre-existing diabetes. An important possibility – which remains conjectural but for which evidence is accumulating – is whether SARS-CoV2 infection can cause or induce diabetes in persons without pre-existing diabetes. Epidemiologic data support this possibility, with reports of increasing incidence of new-onset diabetes with metabolic decompensation among hospitalized patients admitted for Covid-19.[2,3] For example, in a large, retrospective study of hospitalized adult Covid-19 patients in New York City, 6.6% developed DKA and 5.7% had no prior diagnosis of diabetes.[4] A retrospective study from China noted 6.4% of patients admitted with Covid-19 had ketosis, of whom two-thirds had no prior diagnosis of diabetes.[5] In a U.K. study, among 35 patients with Covid-19 who presented with DKA, hyperosmolar state or both, over 80% carried a diagnosis of type 2 diabetes (T2D) and 5.7% were newly diagnosed.[6] Among children, there are numerous reports of increased numbers of new admissions of patients with DKA and phenotypes of both type 1 diabetes (T1D) and T2D. For example, a multicenter study from the U.K. reported 30 children aged 23 months to 17 years with new-onset T1D - 70% presented with DKA and 15% of these had COVID-19.[7] Although many of these cases might represent the effect of prolonged lockdown with decreased monitoring and poor access to health care rather than a direct effect of Covid-19,[8,9] a very recent report from the CDC indicates children with Covid-19 are more likely to be diagnosed >30 days after infection than those without Covid-19 and those with pre-pandemic acute respiratory infections.[10]

Mechanisms supporting a direct role for SARS-CoV2 or its acute systemic inflammatory consequences in the causation of new-onset diabetes are intriguing but mainly speculative. The inflammatory effects of the Covid-19 immune response on insulin-sensitive tissues could heighten insulin resistance.[11–13] Islet beta cell expression of the SARS-CoV2 receptor ACE-2 could facilitate virus entry, leading to cellular dysfunction and decreased insulin secretion.[10–12] A notable exception to the sparseness of compelling mechanistic data is a recent report by Wu et al.[14] In this study of pancreatic tissues at autopsy from patients with and without Covid-19, a range of molecules required for SARS-CoV2 entry (ACE2, TMPRSS2, TFRC and especially neuropilin-1) were found to be highly expressed in beta cells. SARS-CoV2 preferentially infected beta cells in the islets and induced apoptosis, decreased insulin content and diminished glucose-stimulated insulin secretion.

Another approach to investigate a causal role for Covid-19 in new-onset diabetes is through careful clinical phenotyping and longitudinal follow-up of patients presenting with both diabetes and Covid-19 infection. In this regard, it is useful to identify among these patients those with atypical forms of diabetes, especially those with acute or "fulminant" presentations with DKA but lacking the characteristic biomarkers and clinical features of autoimmune T1D. This is the approach taken by the study of Das Gupta et al reported in the current issue of the journal. They investigated the coincidence of Ketosis-Prone Diabetes (KPD) with Covid-19 infection in a large cohort from East India, and through careful analysis and detailed follow-up show strong evidence for a role of Covid-19 in one characteristic subgroup of this syndrome. The authors selected 42 adult, previously non-diabetic patients who presented with new-onset DKA and Covid-19. They diagnosed A-β+ KPD (without T1D autoantibodies and with preserved beta cell functional reserve) in 22 of these patients and autoimmune T1D in the remainder, and followed them with serial clinical, biochemical and autoantibody assessments. Fifteen of the 19 KPD patients (79%) reassessed 6–10 months later had robust beta cell recovery and were able to come off insulin completely with good glycemic control. Hence, Covid-19 – either via direct SARS-CoV2 infection of beta cells or indirectly via inflammatory mechanisms – is likely a novel cause of new-onset "provoked" A-β+ KPD. The physical and clinical characteristics of the KPD patients in this cohort are consistent with those of previous reports of A-β+ KPD. Of note, the Covid-19 associated KPD patients had significantly elevated serum levels of the inflammatory cytokines interleukin-6 and C-reactive protein, suggesting that components of the exaggerated systemic inflammatory response to SARS-CoV2[15] rather than permanent destruction of beta cells might be a dominant mechanism underlying both the acute presentation with DKA and beta cell functional recovery within months of the acute infection.

KPD comprises four subgroups classified by presence or absence of islet cell autoantibodies ("A+" or "A−") and quantitative differences in β cell functional reserve ("β+" or "β−").[16,17] A-β+ KPD patients resemble T2D patients (adult-onset, overweight/obese, absent islet autoantibodies) and have substantial β cell functional reserve. Over 70% of these patients achieve near-normoglycemia within 2–3 months after the index DKA and can discontinue insulin therapy with good glycemic control on oral medications.[18] A-β+ KPD includes two distinct phenotypes.[19] Approximately 50% of the patients initially present with DKA without a clinically evident precipitating factor at first diagnosis of diabetes ("unprovoked" A-β+ KPD). They display male predominance, low

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frequency of HLA Class II susceptibility alleles for T1D, no T cell reactivity to islet autoantigens,[20] and sustained preservation of β cell function following recovery from the index DKA with excellent glycemic control off insulin.[21] The other 50%, have "provoked" A-β+ KPD, i.e., they develop DKA in association with a clinically evident precipitating factor such as acute illness. They have high frequencies of HLA class II T1D susceptibility alleles or T cell reactivity to islet autoantigens, and over 2–3 years after the index DKA suffer progressive loss of beta cell function and often relapse to insulin treatment.[20,21] It will be most interesting to follow the patients in this East Indian cohort longitudinally to determine whether their beta cell function is sustained over 2–3 years or declines within this period to the point of requiring exogenous insulin for metabolic control.

Viral infections (cytomegalovirus, Epstein–Barr, mumps, rotavirus, rubella, and, in particular, enteroviruses and Coxsackie) have long been implicated in the development of T1D.[22,23] Hepatitis C infection and chronic HIV infection are known risk factors for T2D with beta cell dysfunction.[24,25] A patient with new-onset fulminant diabetes has been reported following infection by human herpesvirus 6,[26] and other cases of fulminant diabetes in Japanese patients have evidence for antecedent viral infection.[27,28] Syndromes suggestive of provoked A-β+ KPD have been associated with H1N1 influenza and human herpesvirus-8 infection.[29] SARS-CoV2 may now be added to this list.

"Long Covid" syndrome is likely to loom large as a chronic sequel to the current pandemic. Its components will include diabetes that originated with the initial infection. Careful phenotyping and close follow-up of these patients will be critical, both to understand the pathophysiology (is it primarily insulin resistance, or permanent beta cell destruction, or a KPD-like reversible form of beta cell dysfunction despite initial metabolic decompensation?) and for optimal long-term therapy (lifelong insulin, or short term insulin followed by non-insulin agents?). These are important questions to ask in diagnosing and treating the heterogeneous forms of diabetes induced by Covid-19, and the study of Das Gupta et al provides a salutary approach and useful data to answer them.

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