Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

type 2 diabetes, might have occurred, particularly among younger people. Finally, the sample size was likely to have been underpowered to detect differences between subgroups.

Despite this, our study provides the first estimate of diagnosed type 2 diabetes in First Nations young people across northern Australia, with a higher prevalence than that reported internationally in recent years. The majority of young people had unacceptably high HbA_{1c} values, suggesting a concerning trajectory ahead without intervention. Although participants represented diverse young First Nations people from across a vast Australian area, our findings might not be generalisable to other First Nations peoples globally. However, there are many commonalities of historical experience and socioeconomic inequities.

New approaches to preventing and managing type 2 diabetes in young First Nations people are urgently required. These include culturally, age, and linguistically appropriate engagement of young people and communities, advocacy to eliminate underlying socioeconomic inequities, interventions in pregnancy and early childhood, adequate resourcing, education of health professionals, and openness to reconsidering current models of care. We need to hear the voices of First Nations young people and communities behind these high prevalence rates, working together to reduce risk and improve the health of future generations.

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*Angela Titmuss, Elizabeth A Davis, Vicki O'Donnell, Mark Wenitong, *Louise J Maple-Brown†, Aveni Haynes†, on behalf of the Hot North Diabetes in Youth Collaboration group*

angela.titmuss@menzies.edu.au; louise.maple-brown@menzies.edu.au

†Co-last authors

Wellbeing and Preventable Chronic Diseases Division, Menzies School of Health Research, Charles Darwin University, Darwin, NT 0811, Australia (AT, LJM-B); Department of Paediatrics, Division of Women, Children and Youth (AT) and Endocrinology Department, Division of Medicine (LJM-B), Royal Darwin Hospital, Darwin, NT, Australia (AT); Telethon Kids Institute, University of Western Australia, Perth, WA, Australia (EAD, AH); Kimberley Aboriginal Medical Services, Broome, WA, Australia (VO); Apunipima Cape York Health Council, Cairns, QLD, Australia (MW)

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COVID-19 targets human adrenal glands

COVID-19 develops due to infection with SARS-CoV-2, which particularly in elderly with certain comorbidities (eg, metabolic syndrome)[1] can cause severe pneumonia and acute respiratory distress syndrome. Some patients with severe COVID-19 will develop a life-threatening sepsis with its typical manifestations including disseminated intravascular coagulation and multiorgan dysfunction.[2] Latest evidence suggests that even early treatment with inhaled steroids such as budesonide might prevent clinical deterioration in patients with COVID-19.[3] This evidence underlines the potentially important role for adrenal steroids in coping with COVID-19.

The adrenal gland is an effector organ of the hypothalamic–pituitary–adrenal axis and the main source of glucocorticoids, which are critical to manage and to survive sepsis. Therefore, patients with pre-existing adrenal insufficiency are advised to double their doses of glucocorticoid supplementation after developing moderate to more severe forms of COVID-19.[4]

Adrenal glands are vulnerable to sepsis-induced organ damage and their high vascularisation and blood supply makes them particularly susceptible to endothelial dysfunction and haemorrhage. Accordingly, adrenal endothelial damage, bilateral haemorrhages, and infarctions have been already reported in patients with COVID-19.[5] Adrenal glands contain the highest concentration of antioxidants to compensate enhanced generation of reactive oxygen species, side products of steroidogenesis, which together with elevated intra-adrenal inflammation can contribute to adrenocortical cell death.[6] Furthermore, sepsis-associated critical illness-related corticosteroid insufficiency, which describes coexistence of the hypothalamic–pituitary–adrenal dysfunction, reduced cortisol metabolism, and tissue resistance to glucocorticoids, was reported in critically ill patients with COVID-19.[7] Low cortisol and adrenocorticotropic hormone (ACTH) responses during acute

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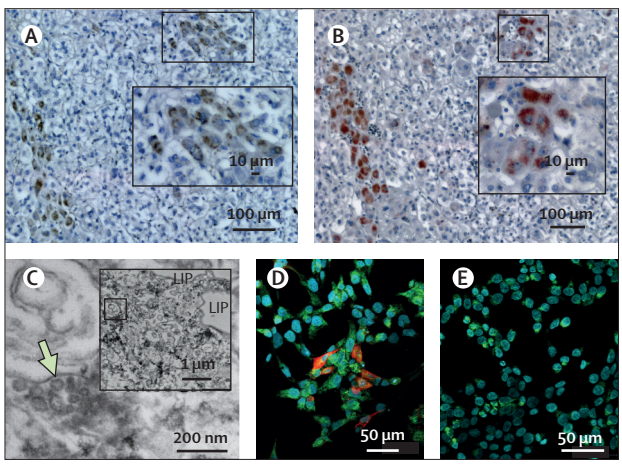

Figure: **Detection of SARS-CoV-2 in human adrenal gland from a patient who died due to COVID-19**

(A) Detection of SARS-CoV-2 RNA by in situ hybridization (ISH; brown DAB staining) and (B) its spike protein by immunohistochemistry (red AEC staining) was found in the same region of two serial 1 µm-thick tissue sections of the adrenal gland. Inserts depict the same regions but were captured at lower magnification showing the chosen area of virus positivity (white squares). Scattered expression of either mRNA or protein can be found in the inner parts of the adrenal gland cortex close to the medulla. Scale bars in pictures from panel A and B represent 100 µm (10 µm in the insert image). (C) Ultrastructural examination of a SARS-CoV-2 triple positive (ISH, immunohistochemistry, and RT-qPCR) adrenal tissue showing numerous viral-like particles in liposome (LIP)-rich adrenocortical cells. A scale bar represents 200 nm. A low magnification picture shown in the insert depicts the region of interest indicated by a green arrow in the enlarged picture. Scale bar in insert indicates 1 µm distance. (D) A positive immunofluorescent red signal (CY3) indicating the expression of spike protein in SARS-CoV-2 infected human adrenocortical cells. (E) Lack of positive signal (CY3) in mock-infected control cells. Adrenocortical cells were additionally stained with an antibody against side-chain cleavage enzyme (CYP11A1), which is a steroidogenic marker (green signal; CY5). Nuclei were counterstained with Hoechst 33342 dye (blue signal). Scale bars in pictures from panel D and E represent 50 µm.

See Online for appendix

phase of infections consistent with critical illness-related corticosteroid insufficiency diagnosis (random plasma cortisol level lower than 10 µg/dL) were reported in one study with patients suffering from mild to moderate COVID-19 manifestations.[8] It is however possible those other factors triggered by COVID-19 such as hypothalamic or pituitary damage, adrenal infarcts, or previously undiagnosed conditions, such as antiphospholipid syndrome, might be responsible for reduced function of adrenal glands. However, contrary to this observation, a study with patients with moderate to severe COVID-19 revealed a very high cortisol response with values exceeding 744 nmol/L, which were positively correlated with severity of disease.[9] In this clinical study,[9] highly elevated cortisol concentrations showed an adequate adrenal cortisol production possibly reflecting the elevated stress level of those severely affected patients.[9] However, since ACTH measurements were not done, it is impossible to verify whether high concentrations of cortisol in those patients resulted from an increment of cortisol, or were confounded by reduced glucocorticoid metabolism.[9]

A critical and yet unsolved major question is whether SARS-CoV-2 infection can contribute either directly or indirectly to adrenal gland dysfunction observed in some patients with COVID-19 or contribute to the slow recovery of some patients with long COVID.

We performed a comprehensive histopathological examination of adrenal tissue sections from autopsies of patients that died due to COVID-19 (40 cases), collected from three different pathology centres in Regensburg, Dresden, and Zurich (appendix pp 1–3). We observed evidence of cellular damage and frequently small vessel vasculitis (endotheliitis) in the periadrenal fat tissue (six cases with low and 13 cases with high density; appendix p 10) and much milder occurrence in adrenal parenchyma (ten cases with low and one case with moderate score; appendix p 10), but no evidence of thrombi formation was found (appendix p 10). Endotheliitis has been scored according to a semi-quantitative immunohistochemistry analysis as described in the appendix (p 4). Additionally, in the majority of cases (38 cases), we noticed enhanced perivascular lymphoplasmacellular infiltration of different density and sporadically a mild extravasation of erythrocytes (appendix p 10). However, no evidence of widespread haemorrhages and degradation of adrenocortical cells were found, which is consistent with histological findings reported previously.[5] In another autopsy study analysing adrenal glands of patients with COVID-19, additional signs of acute fibrinoid necrosis of small vessels in adrenal parenchyma, subendothelial vacuolisation and apoptotic debris were found.[5]

Adrenal gland is frequently targeted by bacteria and viruses, including SARS-CoV,[10] which was responsible for the 2002–04 outbreak of SARS in Asia. Considering that SARS-CoV-2 shares cellular receptors with SARS-CoV, including angiotensin-converting enzyme 2 and transmembrane protease serine subtype 2, its tropism to the adrenal gland is therefore conceivable.

To investigate whether adrenal vascular cells and possibly steroid-producing cells are direct targets of SARS-CoV-2, we examined SARS-CoV-2 presence in adrenal gland tissues obtained from the 40 patients with COVID-19 (appendix pp 1–3). Adrenal tissues from patients who died before the COVID-19 pandemic were used as negative controls to validate antibody specificity. Using a monoclonal antibody (clone 1A9; appendix p 11), we detected SARS-CoV-2 spike protein in adrenocortical cells in 18 (45%) of 40 adrenal gland tissues (figure B; appendix p 12). In the same number of adrenal tissues (18 [45%] of 40), we have detected SARS-CoV-2 mRNA using in situ hybridisation (ISH; figure A; appendix p 12). The concordance rate between immunohistochemistry and ISH methods was 90% (36/40). Scattered and rather focal expression pattern of SARS-CoV-2 spike protein was found in the adrenal cortex (figure A and B; appendix p 12). In addition, SARS-CoV-2 expression was confirmed in 15 out of 30 adrenal gland tissues of patients with COVID-19 by multiplex RT-qPCR (appendix pp 6–7). The concordance between ISH, immunohistochemistry, and RT-qPCR techniques for SARS-CoV-2 positivity was only 23%, which is a technical limitation of our study possibly reflecting the low number of virus-positive cells. However, when considering triple-negative samples,

an overall 53% consensus was found (appendix pp 7–8).

Finally, to confirm the identity of infected cells, we have performed an ultrastructural analysis of adrenal tissue from a triple-positive patient case (by immunohistochemistry, ISH, and RT-qPCR), and found numerous SARS-CoV-2 virus-like particles in cells enriched with liposomes, which are typical markers of adrenocortical cells (figure C). The cortical identity of SARS-CoV-2 spike positive cells was also shown using serial tissue sections, demarcating regions with double positivity for viral protein and StAR RNA (appendix p 12). Furthermore, susceptibility of adrenocortical cells to SARS-CoV-2 infection was confirmed by in-vitro experiments (appendix p 7) showing detection of viral spike protein in adrenocortical carcinoma cells (NCI-H295R) cultured in a medium containing SARS-CoV-2 (figure D), and its absence in mock-treated control cells (figure E). We showed an uptake of viral particles in the adrenocortical cells, by ISH, immunohistochemistry, RT-qPCR and electron microscopy (figure A–C). Mechanistically, an uptake of SARS-CoV-2 like particles might involve expression of ACE2 in vascular cells (appendix p 13) and perhaps of the shorter isoform of ACE2 together with TMPRSS2 and other known or currently unknown virus-entry facilitating factors in adrenocortical cells (appendix p 13). An example of such factor is scavenger receptor type 1, which is highly expressed in adrenocortical cells.[11]

Several forms of regulated cell necrosis were implicated in sepsis-mediated adrenal gland damage.[6] One of the prime examples of regulated necrosis triggered by sepsis-associated tissue inflammation is necroptosis. The necrotic process is characterised by loss of membrane integrity and release of danger-associated molecular patterns, which further promote tissue inflammation (necroinflammation) involving enhanced activation of the complement system and related activation of neutrophils. Whether necroptosis might be involved in COVID-19-associated adrenal damage is currently unknown. In our study, we showed prominent expression of phospho Mixed Lineage Kinase Domain Like Pseudokinase (pMLKL) indicating necroptosis activation in adrenomedullary cells (appendix p 14) in adrenal glands of COVID-19 patients. However, since we have also observed pMLKL expression in adrenal glands obtained from autopsies done before the COVID-19 pandemic (controls), necroptosis activation in medullary cells might be a rather frequent and SARS-CoV-2 independent event. However, contrary to the adrenal medulla, pMLKL positivity in the adrenal cortex was only found in virus-positive regions (appendix p 14). This finding suggests that SARS-CoV-2 infection might have directly triggered activation of necroptosis in infected cells in the adrenal cortex, whereas pMLKL expression in the adrenal medulla seems rather an indirect consequence of systemic inflammation.

In summary, in our study of 40 patients who died from COVID-19, we did not observe widespread degradation of human adrenals that might lead to manifestation of the adrenal crisis. However, our study shows that the adrenal gland is a prominent target for the viral infection and ensuing cellular damage, which could trigger a predisposition for adrenal dysfunction. Whether those changes directly contribute to adrenal insufficiency seen in some patients with COVID-19 or lead to its complications (such as long COVID) remains unclear. Large multicentre clinical studies should address this question.

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*Waldemar Kanczkowski, Katja Evert, Marlena Stadtmüller, Martina Haberecker, Laura Laks, Lan-Sun Chen, Karl Frontzek, Jessica Pablik, Constanze Hantel, Felix Beuschlein, Thomas Kurth, Sven Gruber, Adriano Aguzzi, Zsuzsanna Varga, *Stefan R Bornstein*
stefan.bornstein@uniklinikum-dresden.de

Department of Internal Medicine III (WK, CH, SRB), Institute of Medical Microbiology and Virology (MS, L-SC), and Department of Pathology (JP), University Hospital Carl Gustav Carus, and Center for Molecular and Cellular Bioengineering, Technology Platform (TK), Technische Universität Dresden, 01307 Dresden, Germany; Institute of Pathology, University of Regensburg, Regensburg, Germany (KE); Department of Pathology and Molecular Pathology (MH, ZV) and Department of Endocrinology, Diabetology and Clinical Nutrition (CH, FB, SG), University Hospital Zurich, Zurich Switzerland; Institute of Neuropathology University of Zurich, Zurich, Switzerland (LL, KF, AA, CH, FB, SG); Diabetes and Nutritional Sciences Division, King's College London, London, UK (SRB)

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Access to insulin and diabetes care in the Philippines

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Millions of people from low-income and middle-income countries (LMICs) are unable to access insulin and routine diabetes care.[1] The Philippines, a lower-middle income country in southeast Asia with almost 4 million adults with diabetes,[2] is no stranger to this crisis. Diabetes ranks fourth among the leading causes of death in the Philippines.[3]

Filipino people face substantial barriers to health care, which preclude access to insulin and diabetes care, including inadequate health financing leading to high out-of-pocket expenditure and a fragmented referral system from primary care to specialised care units. During the COVID-19 pandemic, access to diabetes medications became an even greater problem for Filipino people because of financial constraints from the economic recession and substantial supply deficits. Addressing these barriers is instrumental to solving the problem of insulin and diabetes care access in the country.

In 2009, the Philippine Department of Health launched the Insulin Medicine Access Program (InMAP), a public–private partnership to provide affordable insulin.[4] Under InMAP, pharmaceutical companies provide insulin products through consignment with 22 hospitals across the country. However, most of these hospitals are in cities, presenting a challenge for patients living in geographically isolated and disadvantaged areas. Expanding InMAP is crucial to increase accessibility and reduce the out-of-pocket costs of insulin.

The Universal Health Care Act of the Philippines, passed in 2019, created the Health Technology Assessment Council (HTAC), an advisory body mandated to recommend medicines and technologies for government funding.[5] Currently, a single insulin analogue pen is worth 3 days of minimum wage pay. To bring down these costs and leverage government negotiations, HTAC is working to include insulin analogues in the Philippine formulary. As this approach gains momentum, strengthening primary care units and referral systems is imperative to create a robust infrastructure for diabetes care delivery.

We agree with the sentiment expressed in the recent Editorial[1] in *The Lancet Diabetes & Endocrinology* that global collaborative action is needed to tackle the diabetes epidemic. We also support multisectoral discussions among local ministries of health, policy makers, health-care workers, patient advocates, community leaders, and pharmaceutical companies to make insulin more accessible and affordable. Furthermore, we encourage LMICs to come together and share best practice in diabetes care and prevention given limited resources. Not least, we look forward to the fulfillment of the WHO Global Diabetes Compact,[6] which aims to increase treatment access, improve patient outcomes, and promote prevention of diabetes. The Compact's vision can be realised, but only through meaningful engagement, united action, and lifelong commitment among stakeholders around the world.

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*Michelle Ann B Eala, John Jefferson V Besa, Regiel Christian Q Mag-usara, Anna Elvira S Arcellana, *Cecilia A Jimeno*
cajimeno@up.edu.ph

College of Medicine, University of the Philippines, Manila, Philippines (MABE); Department of Medicine, Philippine General Hospital, Manila, Philippines (JJVB, RCQM); Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, Manila, Philippines (AESA, CAJ); Department of Pharmacology and Toxicology, College of Medicine, University of the Philippines, Manila 1000, Philippines (CAJ)

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Diabetes and the WHO Model List of Essential Medicines

The WHO Model List of Essential Medicines was first published in 1977 and includes minimum medicine needs for a basic health-care system, listing the most efficacious, safe, and cost-effective medicines for priority conditions.[1] The goal of this list was to choose the medications that would be crucial to include in a population's formulary, which otherwise would be inaccessible, especially in low-income and middle-income countries.[2] The Model List of Essential Medicines has evolved over the decades and now takes into consideration other