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Project: Glucose and lipid metabolism in severe acute respiratory distress syndrome (SARS-CoV-2)

INTRODUCTION

Diabetes mellitus (DM) is a leading cause of mortality among non-communicable diseases.[1] DM and cardiovascular disease (CVD) are risk factors for severe COVID-19. Local and international data show that SARS-CoV-2 induces hyperglycaemia (HG) even in those without DM. This entity of "new-onset" HG has been associated with worse outcomes compared with normoglycaemic individuals or pre-existing DM, with significantly higher in-hospital complications, intensive care unit (ICU) admissions and all-cause mortality.[4-6]

Preliminary data from our retrospective, single-centre, observational study evaluating patients hospitalised with PCR confirmed COVID-19 infection, between 6 March and 31 August 2020, confirmed DM in 37% (n=258) of patients and 63% (n=432) were classified as non-DM. After exclusion of incomplete records, the diabetics constituted 58% of the cohort. When looking at the distribution of known DM and new onset DM, of the 258 diabetics, 41% (n=106) were newly diagnosed. 96% pf patients were T2DM (n=247) and 4 % were T1DM (n=11). The study showed that in patients classified with HG in the absence of DM, despite having a lower mean admission fasting plasma glucose (FPG) and mean blood glucose (BG) than those with DM, the mortality rate was significantly higher than in those with known DM.[7] Those with HG had worse outcomes, including a 3-fold higher mortality and need for ventilation and a 3.5-fold greater chance for ICU admission compared to those with euglycaemia.[7] In addition to uncontrolled HG, in patients older than 70 years, elevated lactate dehydrogenase (LDH) and

c-reactive protein (CRP) were independent predictors of mortality in COVID 19 and admission HG was also found to be an independent predictor for ICU admission.[7]

This study has led to me pursuing my PhD. Despite this evidence, an important question that remains is whether COVID-19 induced DM has a different pathogenesis and whether SARS-CoV-2 is precipitating a "new form" of DM. Considering the current social and economic burden of DM in South Africa, further research is necessary to identify the pathophysiological phenotype of COVID-19 associated DM.

OBJECTIVES & OUTCOME MEASURES:

The main objectives of my project are focused on glucose and lipid metabolism in COVID 19 as well as an analysis of the rate and resolution of new-onset DM in COVID-19. Secondary objectives will focus on the role of biomarkers to understand the pathogenesis of hyperglycaemia in COVID-19. These include, biomarkers of β cell function, inflammation, lipid profiling, myocardial function, and genetic determinants associated with severe COVID in various glycaemic states. Outcome measures in both the retrospective and prospective component of the project include primary endpoints, specifically, in-hospital mortality, the need for invasive mechanical ventilation and admission to an ICU according to glycaemic status. Secondary endpoints include the need for non-mechanical ventilatory support (non-rebreather mask, high- flow nasal cannula, non invasive ventilation and length of stay.

HYPOTHESIS: We hypothesize that the pathogenesis of COVID-19 mediated new onset DM is complex and is characterized by a combination of direct and indirect virally mediated insulin deficiency and insulin resistance associated with the pro-inflammatory milieu.

METHODS

Study Design: The study design includes a retrospective (n=445) and prospective component (n=164). Recruitment for the prospective component, includes hospitalised, COVID-19 positive patients to diabetic and healthy controls without COVID-19, assigned in a 2:1:1 ratio for analysis, with a three-month post discharge follow-up of all surviving patients.

Laboratory analysis: In addition to *anthropometry*, including body mass index and waist circumference, the methods of laboratory analysis will be directed at achieving these objectives. *Standard of care bloods* are directed at assessing disease severity and classifying glycaemic status on admission. *β cell function* and antibody assessment will include a fasting insulin, c-peptide, anti-GAD antibody and anti-IA2 antibody as these are more sensitive and specific. Viral infections have previously been shown to trigger islet autoimmunity and type 1 DM (T1DM).[8] Therefore, the potential cytotoxic effects of COVID-19 on the β cell mediating a form of T1DM, requires further investigation. *Inflammatory markers* including but not limited to TH1/TH2 cytokines (Interleukin [IL]-I-2, IL-4, IL-6, IL-10, TNF-α, Interferon level), and *pro-fibrotic markers* (ILGFBP70, PICP and CITP: MMP-1 ratio and VCAM-1) in the serum will be determined with the multianalyte immunoassay (Luminex). *Lipoprotein(a)* (Lp(a)) levels will be determined using the Randox immunoturbidimetric assay, which detects the complete Lp(a) molecule, allowing more accurate results. The LPA gene encodes for Lp(a) and contains an interleukin-6 (IL-6) response element that may induce an "acute phase" increase in Lp(a) levels following a "cytokine storm" from COVID-19. COVID-19 is characterized by a pro inflammatory state and associated with thrombotic complications and the role of Lp(a) in various glycaemic states in relation to severity of COVID-19 and thrombosis is important to assess.[9-11] *DNA extraction, SNP genotyping* (ACE, TMPRSS2) *and microRNA profiling* (beta-cell function- miRNA375, 192; cardiac fibrosis- miRNA 19b,31 and 133; inflammation- miRNA 146a, 155) will be assessed. These genetic markers will potentially identify genetic variants that influence the

severity of COVID-19 and the miRNA could be a potential biomarker of severity as well as provide insight into the cellular pathways and the underlying pathogenesis of the disease. CV risk measures and outcomes include *echocardiography and carotid ultrasound*, to measure the carotid intima media thickness. ***ETHICS***: Approved (M2008110, M210566)

COLLABORATION AND TRANSFORMATION: The multi-faceted nature of this cardiometabolic project has created numerous collaborative networks between the department of physiology, chemical pathology, genetics, immunology, endocrinology, and infectious diseases. The retrospective study has created an opportunity for transformation whereby I have mentored 6 junior researchers on sub studies. Further MMED's and a post-doctoral opportunity will follow.

SCIENTIFIC & COMMUNITY CONTRIBUTION: Retrospective data is published, and 6 sub-studies are due for publication. A minimum of 7 publications will arise from the prospective work. Changes to the standard operating procedure of the local hospital were made based on retrospective data. Data will be relevant to the diagnosis and follow-up of this new form of DM and is critical for policy change.

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