

CARDIOVASCULAR COMPLICATIONS IN PATIENTS WHO HAVE HAD COVID ON THE BACKGROUND OF DIABETES MELLITUS 2

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ABSTRACT: Coronavirus disease 2019 (covid-19) has become a major global crisis. preliminary reports have, in general, indicated worse outcomes in diabetes mellitus (dm) patients, but the magnitude of cardiovascular (cv) complications in this subgroup has not been elucidated.

Key words: COVID-19, Al-Wakeel findings , cellular hypoxia , cytokine release,immune system ,dysregulation.

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Introduction

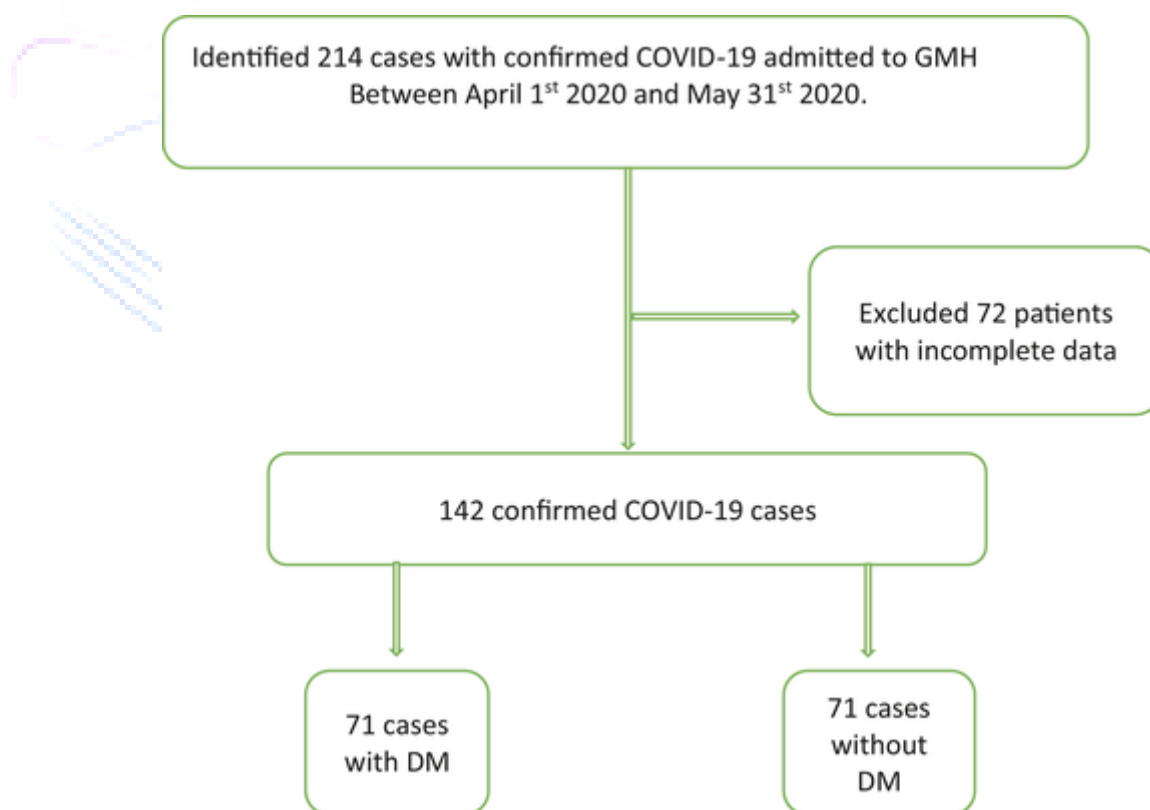
Initial studies found increased severity of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in patients with diabetes mellitus. Furthermore, COVID-19 might also predispose infected individuals to hyperglycaemia. Interacting with other risk factors, hyperglycaemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes. Angiotensin-converting enzyme 2 (ACE2), which is part of the renin–angiotensin–aldosterone system (RAAS), is the main entry receptor for SARS-CoV-2; although dipeptidyl peptidase 4 (DPP4) might also act as a binding target. Preliminary data, however, do not suggest a notable effect of glucose-lowering DPP4 inhibitors on SARS-CoV-2 susceptibility. Owing to their pharmacological characteristics, sodium–glucose cotransporter 2 (SGLT2) inhibitors might cause adverse effects in patients with COVID-19 and so cannot be recommended. Currently, insulin should be the main approach to the control of acute glycaemia. Most available evidence does not distinguish between the major types of diabetes mellitus and is related to type 2 diabetes mellitus owing to its high prevalence. However, some limited evidence

is now available on type 1 diabetes mellitus and COVID-19. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted.

Main part

Coronavirus disease 2019 (COVID-19) has become a major global crisis. Although initially thought to affect only the respiratory system, recent studies have demonstrated gastrointestinal, neurological and cardiovascular sequelae.¹ However, patients with underlying cardiovascular disease (CVD) tend to have worse outcomes compared to those without CVD.¹ Also, COVID-19 is associated with high rates of cardiovascular complications such as acute myocarditis (up to 28%), acute heart failure (23%) and arrhythmias (17%).^{1,2} Finally, those who develop cardiovascular complications like acute myocarditis and acute heart failure are more likely to die.^{1,2} Diabetes mellitus (DM) represents a significant health burden in the United States and is associated with severe illness in patients with COVID-19.³ While preliminary reports have, in general, indicated worse outcomes in diabetics, the magnitude of CVD complications in this subgroup has not been fully elucidated.

This study was conducted at Grady Memorial Hospital, the largest academic centre in Georgia, United States. This study was approved by our institutional review board with a health insurance portability and accountability act (HIPAA) waiver due to minimal risk to the privacy of individuals. We queried the hospital's electronic medical records from April 1st to May 30th 2020, to identify patients with laboratory-confirmed COVID-19 (Figure 1).



In this article, DM was associated with worse cardiovascular outcomes, including composite cardiovascular end-point, acute heart failure and new-onset atrial fibrillation. Cardiovascular complications in COVID-19 is thought to be related to direct myocardial injury, microvascular damage, cellular hypoxia and cytokine release. The role of innate immune system dysregulation in severe

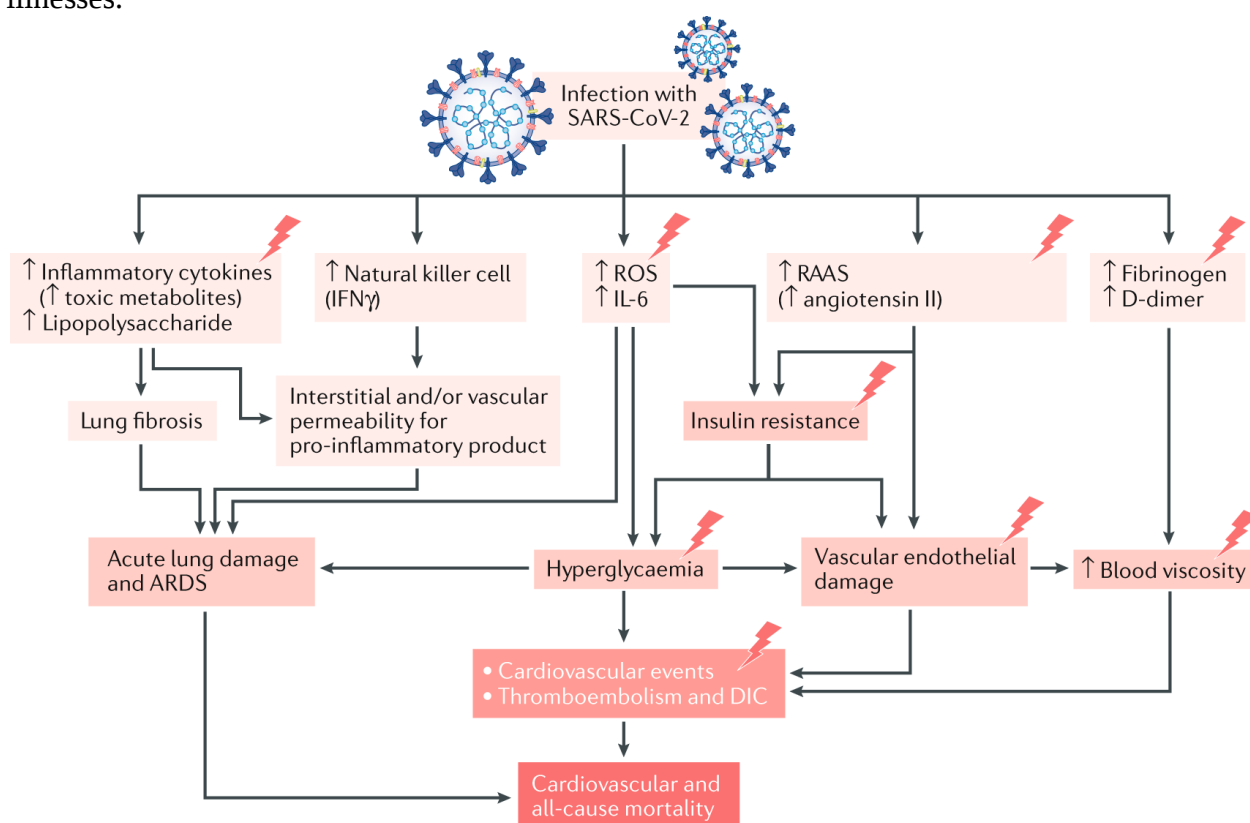
COVID-19 disease in DM patients has yet to be well defined. However, DM patients have been demonstrated to exhibit severe immune response when infected with COVID-19. We speculate that the inflammatory response associated with DM could explain the worse cardiovascular outcomes, among other possible explanations such as increased comorbidities and decreased utilization of life-saving medications, as demonstrated in this study (Table). Further research is needed to understand the disease process's pathophysiologic mechanisms in diabetics and to devise treatment strategies to mitigate complications. The study must be interpreted with caution as over 80% of our study population were African Americans, limiting our study results' generalizability. Also, the study population consisted predominantly of patients with uncontrolled DM, which might impact the study results.

The start of enrollment in our study was the date of diagnosis of type 2 diabetes mellitus. The collected data included the patients' demographics, duration of diabetes, body mass index, blood pressure, low-density lipoprotein, fasting blood glucose, hemoglobin A1c, creatinine, glomerular filtration rate, and urine albumin-creatinine ratio. The diagnosis of cardiovascular complications was based on clinical, electrophysiological, radiological, and biochemical tests. Cardiovascular complications are defined as coronary artery disease, arrhythmia, stroke, peripheral vascular disease, and CV death. The development of diabetic nephropathy was based on developing microalbuminuria (Urine albumin to creatinine ratio (ACR) = 3–30 mg/mmol or 27–265 mg/g), macroalbuminuria (ACR > 30 mg/mmol or > 265 mg/g), chronic kidney disease (ACR > 300 mg/mmol or > 2652 mg/g), or estimated glomerular filtration rate < 60 mL/min/1.73 m²) for three or more months.⁵ Types of treatment the patients received were not available. Also, data on ophthalmological complications and diabetic neuropathy were not available. Patients having prior diagnoses with cardiovascular disease, nephropathy, hypertension, type 1 diabetes, gestational diabetes, and dyslipidemia were excluded from our study.

The earliest diabetic complication was evident as early as 5.5 years from the time of diagnosis, which is longer than what was reported in a hospital-based study. The rate of developing cardiovascular complications and diabetic nephropathy was similar to that in the UKPDS study and the Saudi National Diabetes Registry. However, in a hospital-based setting, Al-Wakeel found that the Saudi population had a high prevalence of diabetic complications. These were more aggressive forms similar to other international secondary and tertiary care settings. The time to develop diabetic nephropathy was almost the same as that in the UKPDS report but was shorter than a local hospital-based study. This may be explained by differences between the primary care and hospital settings in terms of early screening, treatment, and follow-up.

The duration of the development of cardiovascular complications was shorter in our studied population than in local hospital-based study and European reports. Our study showed that males had a high prevalence of cardiovascular and diabetic nephropathy, similar to what was reported in the literature. This may be attributed to men's sedentary lifestyle, more elevated blood sugar levels, higher blood pressure, dyslipidemia, and a lack of understanding about the significance of controlling these

illnesses.



The UKPDS showed no glycemic threshold for a substantial change in risks for any clinical outcomes investigated. A recent meta-analysis showed that randomized controlled trials could not allow us to have a definite conclusion on the suitability of intensively targeting HbA1c to decrease the rate of cardiovascular complications. It advocates a level less than 7%, especially in patients not known to have past cardiovascular events, long life expectancy, and short duration of diagnosis. Similarly, in patients developing diabetic nephropathy, receiving tight control compared to a more relaxed one will only affect developing microalbuminuria and delay progression, but not major renal events. In our study, no statistical significance was observed in the mean of HbA1c between patients who developed diabetic complications and those who did not despite having more controlled diabetes than others reported.

Our research was a retrospective cohort study. The benefit of the electronic health record system enabled us to decrease the risk of potential confounding factors. Although our population size was small, it represents an appropriate sample from the local population who seeks medical advice in a primary care setting. These subjects had access to regular follow-ups with well-trained physicians; therefore, diabetic complications were identified in a timely manner in these individuals. A limitation to our study is that information about types of therapy was not available with the growing evidence that different glucose-lowering drugs are associated with a diverse incidence of complications independently of glycaemic control. However, with the widespread prevalence of this disease in Saudi Arabia and the changes in lifestyle it requires, more extensive studies on it are needed in the community or primary care setting for a better understanding of the progression of this disease, how it can be controlled, and its complications in our unique population.

Conclusion

This can guide us toward introducing more structured screening and follow-up programs in our community. Our study showed that males had a higher prevalence of both cardiovascular complications and diabetic nephropathy. This interesting finding needs further investigation.

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