PATIENTS WITH DIABETES (PWD) and COVID 19

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Introduction

• From January, 2020, we have been facing an unprecedented outbreak of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has now become a global catastrophe
Introduction (2)

• Data from the early months of 2020 suggest that most people with COVID-19 have comorbidities, the most prevalent of which are diabetes, cardiovascular disease, and hypertension
COVID-19 death rates ‘four times higher’ among those with diabetes and hyperglycemia

Written by Mike Watts
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Hospital teams are being urged to focus on glycemic management among COVID-19 patients with diabetes and hyperglycemia after a research team found mortality rates are higher in people with diabetes.

An American team from the Emory University School of Medicine in Georgia say...
SARS Cov 2

• It is novel beta corona viruses
• The system that is predominantly affected is respiratory but it also associated with cardiovascular and neurological afflictions.
• Bats are considered the natural reservoirs, interspecies transfers to pangolin may occur.
• It uses the ACE2 receptor as the portal of entry of the affected cells.
SARS COV2  entry and release
Pathophysiology of Type 2 Diabetes: The Ominous Octet

- Multiple drugs in combination may be required to improve glucose homeostasis
- Treatment should target underlying pathophysiology

Dysfunctions outlined in orange are the three core pathophysiology of type 2 diabetes, known as the triumvirate. DeFronzo RA. Diabetes. 2009;58:773-795.
RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

Renin-angiotensin system

Drop in blood pressure
Drop in fluid volume

Renin release from kidney

Renin acts on angiotensinogen to form angiotensin I.

ACE (angiotensin-converting enzyme) release from lungs

ACE acts on angiotensin I to form angiotensin II.

Angiotensin II acts on the adrenal gland to stimulate release of aldosterone.

Angiotensin II also acts directly on blood vessels; stimulating vasoconstriction (narrowing).

Aldosterone acts on the kidneys to stimulate reabsorption of salt (NaCl) and water (H₂O).

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ACE 2 Receptor

• This receptor and its signalling pathway are counter regulatory to the Classic RAAS.

• Its major substrate is Ang II, which it cleaves to Ang 1-7.

• Ang I-7, has a range of anti inflammatory, antioxidant, vasodilator and natriuretic effects.
Questions related to DM and Covid-19

- Are PWD at increased risk of contracting COVID-19?
- Do PWD experience worse outcomes with COVID-19?
- Do treatment options change in PWD with COVID-19?
Are Diabetic patients at risk of Covid 19 infections

• Current data suggests that PWD are not at increased risk of getting Covid 19 infection
Diabetes and risks from COVID-19

April 8, 2020

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Infection causes higher blood glucose levels.

CONCLUSIONS

- There is no evidence on whether people with diabetes (PWD) are more likely to contract COVID-19.
- People with diabetes appear to be at increased risk of having a more severe COVID-19 infection, though evidence quantifying the increased risk is highly uncertain.
- The extent to which clinical and demographic factors moderate the relationship between diabetes and COVID-19 severity is entirely unclear due to a paucity of data.

Disclaimer: the article has not been peer-reviewed; it should not replace individual clinical judgement and the sources cited should be checked. The views expressed in this commentary represent the views of the authors and not necessarily those of the Oxford COVID-19 Evidence Service Team.
Diabetes and coronaviruses

• Diabetes is one of the most important comorbidities linked to the severity of all three known human pathogenic coronavirus infections.

• Patients with diabetes have an increased risk of severe complications including Adult Respiratory Distress Syndrome and multi-organ failure.
Diabetes and Covid 19 (1)

- A significant association with worse outcomes is seen in people with these comorbidities. {HTN, DM}
- Studies have also shown that COVID-19 is associated with hyperglycaemia particularly in the elderly with type 2 diabetes
The potential links between diabetes and COVID-19 infection

• Diabetes is a primary risk factor for the development of severe pneumonia and a septic course due to virus infections and occurs in around 20% of patients

• Studies have shown that the risk of a fatal outcome from COVID-19 is up to 50% higher in patients with diabetes than in those who do not have diabetes
Possible hypotheses

• PWD are at increased risk of infection because of defects in innate immunity affecting phagocytosis, neutrophil chemotaxis, and cell-mediated immunity

• Diabetes in older age is associated with cardiovascular disease, which in itself could help to explain the association with fatal outcomes of COVID-19.
Two specific mechanisms

• The SARS-CoV-2 virus hijacks an endocrine pathway that plays a crucial role in blood pressure regulation, metabolism, and inflammation.

• Angiotensin-converting-enzyme 2 (ACE2) has been identified as the receptor for the coronavirus spike protein. ACE2 has protective effects primarily regarding inflammation.

• COVID-19 infection reduces ACE2 expression inducing cellular damage, hyperinflammation, and respiratory failure.
Mechanism 1 (i)

• Acute hyperglycaemia has been shown to upregulate ACE2 expression on cells which might facilitate viral cell entry.
• However, chronic hyperglycaemia is known to downregulate ACE2 expression making the cells vulnerable to the inflammatory and damaging effect of the virus
• Furthermore, the expression of ACE2 on pancreatic β cells can lead to a direct effect on β cell function
• Cause acute hyperglycemia.
Mechanism 1 (ii)

• Potential β cell damage caused by the virus leading to insulin deficiency and frequent cases of severe diabetic ketoacidosis (DKA) at the time of hospital admission
• PWD affected by **SEVERE COVID-19** have been shown to have tremendous insulin requirements in patients
• To what extent COVID-19 plays a direct role in this high insulin resistance is unclear.
Second potential mechanism

• Dipeptidyl peptidase-4 (DPP-4) enzyme, which is commonly targeted pharmacologically in people with type 2 diabetes.
DDP-4

• It plays a major role in glucose and insulin metabolism but also increases inflammation in type 2 diabetes.
• In cell studies, DPP-4 was identified as a functional receptor for human coronavirus-Erasmus Medical Center (hCoV-EMC), the virus responsible for MERS.
• Antibodies directed against DPP-4 inhibited hCoV-EMC infection of primary cells.
• DPP-4 inhibitors theoretically may play a role covid 19 treatment.
Implications of Covid 19 on diabetes management
Metabolic and glycaemic control

• PWD who have not yet been infected with the SARS-CoV-2 virus should intensify their metabolic control as needed as means of primary prevention of COVID-19 disease
• Continuation and strict abidance with adequate control of blood pressure and lipids.
• Wherever possible, remote consultation
• Follow advice from the government about hand washing and physical distancing.
• All patients without diabetes and particularly when at high risk for metabolic disease who have contracted the viral infection need to be monitored for new onset diabetes
Policy for PWD

• Seven Treasures” policy for diabetes management, including health education, balanced nutrition, physical activity, standardized medication, blood glucose monitoring, regular schedule, and care for mental health
The “Chinese rules"

- Five No” (no going out, no gatherings, no sedentariness, no stop on medications, no anxiety),
- “Five Keep” (keep wearing a face mask when you go out, keep hands clean, keep routine medical check if necessary, keep regular life, keep scientific attitude to COVID-19)
- “Five Refuse” (refuse to visit friends, refuse group dining, refuse to taste wild animals, refuse rumors, refuse to shake hands or hug or kiss)
Management of hyperglycaemia and associated metabolic conditions

• Most patients with type 2 diabetes have other components of the metabolic syndrome including hypertension and dyslipidaemia.

• Therefore, continuation with an appropriate antihypertensive and lipid-lowering regimen in all these patients is of crucial importance.
ACEI and ARBs

• Treatment with ACEI and ARBs could increase the expression of ACE2, which could accelerate the entry of the virus into the cells.

• However, stopping them could impair the protective ACE2/Mas receptor pathway and increase deleterious angiotensin-2 activity.

• Therefore, the use of ACEI and ARBs could protect against severe lung injury following infection.

• On the basis of currently available evidence, it is advised that patients should continue with their antihypertensive regimens including ACEI and ARBs.
Statins

• Statins have been shown to restore the reduction of ACE2 induced by high lipids such as low density lipoprotein or lipoprotein(a).

• The pleiotropic anti-inflammatory effects of statins have been attributed to the upregulation of ACE2.

• Statins should not be discontinued because of the long-term benefits and the potential for tipping the balance towards a cytokine storm by rebound rises in interleukin(IL)-6 and IL-1ß if they were to be discontinued.

• It is recommended control of lipid concentrations in all patients with COVID-19.
Specific Considerations in T1D (1)

• There are certain subgroups of people with diabetes who might require specific consideration.
  • Elevated hemoglobin A\textsubscript{1c} in people with type 1 diabetes compromises immune function rendering them more susceptible to any infectious disease
  • These individuals will need more intense monitoring and supportive therapy to reduce the risk of metabolic decompensation including DKA, in particular for those taking sodium glucose co-transporter 2 inhibitors (SGLT2)
  • Increase in the prevalence of severe DKA in COVID-19 positive patients with established type 1 diabetes has been observed, but this might in part be because of delayed hospital admission.
Specific Considerations in T1D (2)

• In T1D, the following are crucial;
  • Re-educating them about typical symptoms,
  • Home-measurement of urine or blood ketones,
  • Acute behaviour guidelines,
  • Liberal and early inquiry of professional medical advice
  • Sick day rules
PWD with Fatty liver

• The increasing number of patients with type 2 diabetes and concomitant fatty liver disease will probably have an increased risk for a more pronounced inflammatory response including the so-called cytokine storm, and these patients should be considered at increased risk of severe COVID-19 disease.

• Active and early management is important.
PWD and obesity

- Many PWD are overweight or obese.
- They have altered adaptive immune response, characterised by a state of chronic and low-grade inflammation with higher concentrations of the pro-inflammatory leptin and lower anti-inflammatory adiponectin.
- Body mass index is an important determinant of lung volume, respiratory mechanics, and oxygenation during mechanical ventilation, especially in the supine position.
- Patients with obesity and diabetes could be at specific risk of ventilatory failure.
PWD who are healthcare providers

• Given that COVID-19 might be more prevalent among the sick than is currently being diagnosed, health-care professionals with diabetes should be deployed away from front line clinical duties where possible.
Metabolic Surgery

• Provision of elective surgical procedures—including metabolic surgery—is being postponed in many hospitals around the world to increase capacity for in-patient beds and acute care.

• Whether patients with type 2 diabetes who have had metabolic surgery will be protected from adverse outcomes of COVID-19 relative to their peers who have not undergone surgical treatment simply because of better glycaemic control remains unclear.

• Metabolic surgery could induce nutritional deficiencies, including reduced absorption of vitamins and micronutrients, which play important roles in the regulation of the immune and stress response.
Special considerations on use of diabetes drugs

• Aim for optimising glycemic control but remember,
• Lactic acidosis is associated with metformin
• Euglycaemic or moderate hyperglycaemic diabetic ketoacidosis associated with SGLT-2 inhibitors.
• Therefore these drugs should be discontinued for patients with severe symptoms of COVID-19 to reduce the risk of acute metabolic decompensation.
• It is not recommended prophylactically stop them for outpatients with diabetes without any symptoms of infection or in the absence of evidence for a serious course of COVID-19
• Importantly, if drugs are discontinued, the alternative treatment of choice—in cases for which this option is feasible—is insulin
Severe Covid 19 and glycemic control (1)

• Given the multiple stresses associated with COVID-19 including
  • respiratory failure,
  • the defects in insulin secretion and erratic SQ insulin absorption
  • diarrhoea
  • sepsis

• **Majority patients will require insulin** and especially since many cases are reported with very high insulin consumption, this will need to be managed by **intravenous infusion**.
Severe covid 19 and glycemic control (2)

• Care in fluid balance to avoid pulmonary oedema in the severely inflamed lung.
• Potassium balance needs to be considered carefully in the context of insulin treatment as hypokalaemia is a common feature in COVID-19 (possibly associated with hyperaldosteronism induced by high concentrations of angiotensin 2)
## Summary of COVID 19 and Diabetes Care

### Consensus recommendations for COVID-19 and metabolic disease

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<th><strong>In-patient or intensive care unit</strong></th>
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<td><strong>Prevention of infection in diabetes</strong></td>
<td><strong>Monitor for new onset diabetes in infected patients (in-patient care)</strong></td>
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<td></td>
<td><strong>Management of infected patients with diabetes (intensive care unit)</strong></td>
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<tr>
<td>* Sensitisation of patients with diabetes for the importance of optimal metabolic control</td>
<td>* Plasma glucose monitoring, electrolytes, pH, blood ketones, or β-hydroxybutyrate</td>
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<tr>
<td>* Optimisation of current therapy if appropriate</td>
<td>* Liberal indication for early intravenous insulin therapy in severe courses (ARDS, hyperinflammation) for exact titration, avoiding variable subcutaneous resorption, and management of commonly seen very high insulin consumption</td>
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<tr>
<td>* Caution with premature discontinuation of established therapy</td>
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<tr>
<td>* Utilisation of Telemedicine and Connected Health models if possible to maintain maximal self containment</td>
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### Therapeutic aims

- Plasma glucose concentration: 4–8 mmol/L (72–144 mg/dL)*
- HbA₁c: less than 53 mmol/mol (7%)
- CGM/FGM targets
  - TIR (3.9–10 mmol/L): more than 70% (>50% in frail and older people)
  - Hypoglycaemia (<3.9 mmol/L): less than 4% (<1% in frail and older people)
- Plasma glucose concentration: 4–10 mmol/L (72–180 mg/dL)*