

COVID 19: Diabetes and Obesity API-ICP Recommendations



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BASICS

Novel Human corona virus (SARS-COV2) or Human Corona Virus (HCoV), for the third time in last two decades has threatened to disrupt the planet earth. The earlier two outbreaks were in 2002 originating from china SARS with 8000 people affected and case fatality rate of 10 % and 2012 in Saudi Arabia MERS with 2000 people affected with a case fatality rate of 37%. Both these corona viruses has been virtually conquered successfully. However the hardest evidence related to Diabetes came from Hong Kong during SARS epidemic which showed highest mortality even more than heart disease and cancer in people above 75 years of age. Diabetes clearly emerged in both these epidemics of SARS and MERS a risk factor associated with poorer outcome especially in elderly and vulnerable population. Another interesting experimental work in transgenic mouse of a MERS model showed expression of DPP-4 receptor on the pulmonary alveolar cells. This model showed that MERS coronavirus binds to DPP IV receptor being domain of the pulmonary alveolar cells and may have contributed to the cytokine storm and higher mortality amongst diabetics. Possibly based on this model assumptions were made that diabetic get more pulmonary inflammation & infiltrates, more cytokine damage, weaker immune response and more severe disease. Even more we all know 5 to 15 % of the world population annually suffers from influenza or flu (millions contract it) and it causes in an excess of 300000 to 600000 pulmonary deaths. The current Human Corona virus SARS Cov2 is a zoonotic disease which came via bats possibly using Pangolins into humans. It caused COVID 19 as designated by WHO. Its origin was from Wuhan in China possibly the seafarers market there being the ground zero. It's a beta RNA corona virus with spike glycoprotein which attaches to the ACE2 (Angiotensin Converting Enzyme) found in the pulmonary alveolar cells and possibly also the gut. Clearly the vulnerable groups include Hypertension, Diabetes, Heart Disease, Lung diseases and any other immune compromised state. Our current focus is diabetes and obesity.

DIABETES AND COVID 19

Incidence of infections is usually higher in patients with Diabetes compared to those without it. Diabetics also have more complications, more severe complications and death. Respiratory infections including tuberculosis are common in diabetics. Diabetics have clear cut compromised immune dysfunction. Diabetes and hyperglycemia leads to neutrophil dysfunction, poor chemotaxis, defective macrophage mononuclear function. There is also a deficiency of complement C4 in Diabetics, which is associated with Polymorphonuclear dysfunction and reduced cytokine response. Mononuclear cells and monocytes in Diabetics secrete less IL-1 and IL-6 and glycation would also reduce expression of class 1 MHC on surface of myeloid cells, impairing cell immunity. Decreased mobilization, chemo taxis, and phagocytic activity may occur in hyperglycemia and which may increase the susceptibility to oxidative stress in diabetes. Glycation of immunoglobulins in may be seen with poorer glycemic control (especially if the HbA1c is above 8 %) which harm the biological function of antibodies. In COVID 19 there is over activation of T-cells – leads to severe immune dysfunction. In severe COVID-19 patients had higher concentrations of pro-inflammatory cytokines. Therefore diabetes and hyperglycemic states especially with (a) Elderly above the age of 60 years (b) Hypertension (c) Obesity (d) Chronic heart or lung disease (e) Chronic kidney disease (f) Organ transplant (g) Patients on chronic immunosuppressive therapy (h) Acquired or genetic conditions of immunodeficiency - have a poor clinical as well as mortality outcomes. These vulnerable groups and comorbidities make COVID 19 cases get severe disease, cytokine storm, poorer response and death. Diabetes with complications and poorer glycemic control makes the virus survive longer and makes it more virulent. A new term called “**Sugar-tension**” as a twin epidemic of diabetes and hypertension will adversely alter the outcome possibly by 2 to 4 fold. Diabetic lungs in animal models, often have revealed augmented vascular permeability and collapsed alveolar epithelium.

COVID 19 DYSGLYCEMIA - HYPERGLYCEMIA (STRESS)

COVID 19 can lead to a hyper metabolic state and lead to simple stress hyperglycemia which will alter outcomes. COVID 19 also can unmask latent diabetes especially in pre diabetics as well as predisposed cohorts. This can alter severity of pneumonia, ARDS, weaning of mechanical ventilation, the length of stay in ICU as well as short and early mortality. Often medications can also lead to iatrogenic dysglycemia. Many agents including corticosteroid as well as immune therapies can lead to hyperglycemia states leading to poorer outcomes. Also drugs like chloroquine, hydroxy chlorine can lead to hypoglycemia which can also be severe. Chronic inflammation, pro-coagulant state; increase D dimer, immune dysfunction as well as direct virotrophic effect of human coronavirus on pancreas cannot be ruled out. We will soon have data if a COVID 19 related pancreatopathy exists and autopsy data will give us clues which may also contribute to hyperglycemia or its worsening.

DIABETES AND COVID 19

Types of Diabetes - Type 1, Type 2 or gestational or secondary, do not seem to be directly impacted by COVID 19. However Type 1 Diabetics below the age of 30 years, female gender have better outcomes compared to obese type 2 diabetics, males and elderlies. Glucose control and glycemic variability adversely impact outcomes of COVID 19 diabetics. In asymptomatic or mild COVID diabetics, optimal glycemic control with diabetes specific nutrition (DSN), physical distancing, appropriate exercise with adequate 7 hour sleep and counseling is recommended with self-monitoring of blood glucose frequently to prevent peaks and valleys of glycaemia. Deaddiction from tobacco, smoking, alcohol as well as digital detoxification (zero screen time and mobile phone for 2 hours per day) is recommended. Hydration has to be individualized and optimal nutrition is recommended. Usually ACE inhibitors or Angiotensin Receptor Blockers, Thiazolidinediones, SGLT2 inhibitors may need to be used with extreme caution and pharmacovigilance and it is preferable to avoid starting them afresh. However the ACE inhibitors or ARBs verdict by many global guidelines is that they may be safe and even paradoxically protective. Ibuprofen and other NSAIDs have clearly to be avoided. Chloroquine (CQ) and Hydroxychloroquine (HCQ) can be good anti-inflammatory agents as option. CQ and HCQ are also adjuvants in diabetes but can cause hypoglycemia and need retinal evaluation, QT interval testing. They may have a role for prophylaxis is for healthcare worker and close contact as well a part of treatment regimens. Several Randomized trials are now being conducted on these trials which may answer this in a more definitive way.

MANAGEMENT AND SICK DAY REGIMEN

Management of diabetes - if glucose control is good: then continue same anti diabetic regimen. But if control is suboptimal then intensification with insulin may be needed as per requirement. However, if lockdown situation or access to the medications is an issue, the stricter diet, DSN-MNT, up titration of available drugs is recommended. Obesity can be associated with sleep apnea, reduced ventilatory function and surfactant dysfunction. In obese patients, continue diet, GLP-1 analogs, Orlistat as before unless infected by moderate to severe COVID or hospitalized. It is not wise to initiate aggressive weight losing measures during COVID19 infection. Avoid restrictive diet like keto diet or intermittent or prolonged fasting. No sudden change in pattern of diet or activity is advised. Yoga like Suryanamskar or simple Asana are recommended. Moderation is the key to success. COVID 19 is associated with hyporexia, hyper-catabolism and an overall catabolic state. Sarcopenia can aggravate

RECOMMENDED READING

1. Stoian AP, Banerjee Y, Rizvi AA, Rizzo M. Diabetes and the COVID-19 Pandemic: How Insights from Recent Experience Might Guide Future Management. *Metab Syndr Relat Disord.* 2020 Apr 8. doi: 10.1089/met.2020.0037. [Epub ahead of print]
2. Wang B, Li R, Lu Z, Huang Y, Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY).* 2020 Apr 8;12. doi: 10.18632/aging.103000. [Epub ahead of print]

it. Therefore 25-30 cal/kg/day intake with nutrient dense foods and 1.5-2 g protein/kg/day is recommended. For ICU or ventilated cases, early enteral Nutrition is recommended as early as 12 hours post ventilation and 24-36 hours in the ICU. A formula MNT or enteric formula with peptides may be needed. Disease specific enteral feeds like diabetic specific formulas or renal or hepatic specific diets are also useful. Blood pressure managements should be continued as per usual recommendations. Currently do not stop ACEi or ARB, though this needs individualization. If however, an anti-hypertensive drug has to be initiated or a regimen to be intensified, consider another class of drugs or agent.

When diabetics are ill, counter regulatory hormones like corticosteroids, catecholamines are released to fight the illness as a classical physiological response. These hormones can be triggered by any number of conditions, such as infections, cardiovascular ischaemic events, gastroenteritis, and dehydration causing illnesses etc. This can cause wide fluctuations in the blood glucose levels and increased glycemic variability often leading to life threatening complications like Diabetic ketoacidosis, lactic acidosis and Hyperosmolar hyperglycemic states. Common cold or flu, including COVID-19 apart from Sore throat, Urinary tract infections, Bronchitis or pneumonia, gastroenteritis and diarrhea as well as Skin or genital infections such as abscesses (especially if these conditions are followed by a fever or high temperature) can cause hyperglycemia apart from corticosteroid therapy. Patients should be made aware of target glucose levels during an illness. They must be educated How to adjust medications, more frequent SMBG and ketone testing. They should be told to seek immediate emergency medical help if a) If they are not sure what to do b) If they vomit repeatedly (not able to hold down any food or drink for more than six hours), as they can quickly become very dehydrated c) If their blood glucose stays high (>250 mg /dl) for more than 24 hours or d) If they develop symptoms which could be indicative of developing diabetic ketoacidosis.

General guidelines to manage diabetes during an illness includes frequent blood glucose testing (SMBG). Following steps need to be taken, even if glucose levels are under control. Take diabetes medication as usual. **Insulin treatment should never be stopped.** Test blood glucose every four hours, and keep track of the results. Drink extra (calorie-free) fluid (except cardiac or renal or medical conditions where fluids are restricted), and try to eat as normal. Allow patients to weigh themselves every day. Losing weight while eating normally can be a sign of high blood glucose. Also check body temperature every morning and evening and if fever is present may be a sign of infection. The control diabetes in children during illness should never be ignored though children have better outcomes in COVID 19 due to thymic humoral factors. General sick day diabetes management principles for children with diabetes are more frequent blood glucose and ketone (blood or urine) monitoring. The aim for a blood glucose levels should be between 70-180 mg/dL and blood ketones below 0.6 mmol/L when the child is ill. **NEVER STOP INSULIN.** If there is fever, insulin needs are usually higher. Monitor and maintain hydration with adequate salt and water balance. Treatment of underlying illness and symptoms (fever) is often needed. If, in a child with diabetes, fever or vomiting persists and/or weight loss continues suggesting worsening dehydration and potential circulatory compromise or fruity breath odor (acetone) persists or if there is a worsening or persistent elevated blood ketones >1.5 mmol/L or if urine ketones remain large despite extra insulin and hydration or if the child or adolescent is becoming exhausted, confused, hyperventilating (Kussmaul's breathing), or has severe abdominal pain, urgent emergency medical or if possible specialist help should be taken or urgent hospitalization may be needed. The typical guidelines for T1DM patients remain same. **Remember: Insulin treatment should never be stopped.** The insulin dose may need to be increased and it might be necessary to take additional doses of fast-acting insulin to bring down the blood sugar levels. Blood glucose levels should be checked at least every four hours. Plenty of calorie-free fluids should be taken to avoid dehydration. Ideal blood sugar levels should be between 110-180 mg/dl and should be maintained. Type 1 diabetics on Insulin pumps, if they have availability and access to pump care, should continue pump care or else under expert advice shift to basal bolus regimen with adequate insulin and SMBG supplies.

GLOBAL RECOMMENDATION FOR COVID 19 AND DIABETES

The AACE (American association of Clinical Endocrinologists) recommends to continue to take your prescribed medications. Refill prescriptions and be prepared with medications and testing supplies. Stay home as much as possible to reduce the risk of being exposed. Wash hands with soap and water regularly, for at least 20 seconds, especially before eating or drinking and after using the restroom and blowing nose, coughing or sneezing. Cover nose and mouth while coughing or sneezing with a tissue or a flexed elbow, then dispose the used tissue properly. Avoid touching eyes, mouth or nose if possible. If you get symptoms such as fever, cough, shortness of breath or wheezing, especially if you believe you may have been exposed to COVID-19 positive patient or live in or have recently traveled to an area with ongoing spread, call or see a health care professional immediately.

The Chinese guidelines say for the COVID-19 patients with diabetes, tailored therapeutic strategy and optimal goal of glucose control should be formulated based on clinical classification, coexisting comorbidities, age and other risk factors. Blood glucose should be controlled for all patients during hospitalization to monitor the progress of illness and avoid aggravation. During the 4-week follow-up period after discharge, blood glucose homeostasis should be maintained continuously and patients need to avoid getting exposed to other infectious diseases due to a lower immune response. The IDF (International Diabetes Federation) says older people and people with pre-existing medical conditions (such as diabetes, heart disease and asthma) appear to be more vulnerable to become severely ill with the COVID-19 virus. When people with diabetes develop a viral infection, it can be harder to treat due to fluctuations in blood glucose levels and, possibly, the presence of diabetes complications. There appears to be two reasons for this: Firstly, the **immune system is compromised, making it harder to fight the virus and likely leading to a longer recovery period** secondly, and the **virus may thrive in an environment of elevated blood glucose.** The ADA (American Diabetes Association) is non-committal of the diabetes and COVID-19. People with diabetes do face a higher chance of experiencing serious complications from COVID-19. If diabetes is well-managed, the risk of getting severely sick from COVID-19 is about the same as the general population. COVID-19 is proving to be a more serious illness than seasonal flu, including people with diabetes. The risks are similar for people with type 1 and type 2 diabetes.

KEY MESSAGES

- Diabetes is a condition with significant immune dysfunction
- COVID-19 has also shown a component of immune dysfunction
- Diabetes patient with COVID-19 may have severe immune dysfunction leading to complications
- Diabetes is among the most common comorbidities observed in COVID-19 patients
- Diabetes has also been associated with severity of disease
- Diabetes (along with hypertension and coronary heart disease) needs to be assessed and managed in COVID-19 patients

3. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diabetes Metab Res Rev.* 2020 Mar 31:e33213321. doi: 10.1002/dmrr.3321. [Epub ahead of print]
4. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr.* 2020 Mar 10;14(3):211-212. doi: 10.1016/j.dsx.2020.03.002. [Epub ahead of print] Review.
5. Bloomgarden ZT. Diabetes and COVID-19. *J Diabetes.* 2020 Apr;12(4):347-348. doi: 10.1111/1753-0407.13027.