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DO'S and DONT'S with antidiabetic drugs during COVID-19 Infection

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ABSTRACT

patients with diabetes usually are associated with certain comorbid conditions which includes macro vascular as well as micro vascular complications. due to oxidative stress, metabolic derangements, certain proinflammatory conditions patients do suffer from delayed immune response.

ever since the outbreak of COVID-19 virus in December 2019 caused by SARS-COV-2 the most challenging thing was to keep the prevalence rate of covid-19 low in patients with who have preexisting diseases like diabetes, hypertension, bronchial asthma, chronic kidney disease. Diabetes mellitus till date has been most challenging because of its association and existence with various comorbid macro vascular and micro vascular complications. Although the overall mortality rate is low, ranging from 1.4% to 7.2%, people with Diabetes Mellitus (DM) tend to have more severe disease, acute respiratory distress syndrome and increased fatality.

our aim in this study is to determine the uses of various antidiabetic drugs during the covid-19 infection in managing diabetes. . however the broad heterogeneity and complexity of diabetes, with reference to etiologic mechanisms, degree of glycemic derangement and comorbid associations, along with delay in immune responses, can hamper any patient well-being. even more relevant, and irrespective of glucose-lowering activities, dpp4 inhibitors and glp1 receptor agonists may have a favorable impact on the modulation of viral entry and overproduction of inflammatory cytokines during covid-19 infection, although current evidence is limited and not univocal. sglt2 inhibitors may increase the risk of covid-19- related ketoacidosis among patients with severe insulin deficiency.

SPECIAL ASPECTS OF PATHOPHYSIOLOGY OF DIABETES AND RELATIONSHIP OF ANTIDIABETIC DRUGS IN THE CONTEXT OF COVID-19

Apart from usual mechanisms (impaired neutrophil chemo taxis and phagocytosis) by which diabetes predisposes to infections but there are several specific factors also responsible for increased risk and severity of infection with cov2 in diabetes:

1-Increased ace2 expression- diabetic patients have been found to have increased expression of ace-2 which is expressed not only

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in type i and ii alveolar epithelial cells in the lungs but also in heart endothelium, renal tubular epithelium and pancreas, and ace-2 acts as a receptor for entry of coronavirus.

2-Increased Furin which is a type-1 membrane bound protein which is involved in entry of cov-19 into the cell, and increased Furin has been reported in diabetes.

3-Impaired t cell function

4-Increased interleukin-6

Insulin- Insulin is a safe choice under most circumstances and remains the sole therapy for people with type 2 diabetes mellitus and can be considered as a superior alternative in people with type 2 diabetes mellitus (t2dm) having covid-19 infection. although no direct effect on ace2 receptor is reported, insulin treatment has been shown to attenuate renal adam-17 (a disinterring and metalloproteinase-17) expression in diabetic akita mice. in normal physiology, adam-17 cleaves ace2, thereby inactivating the enzyme. Whether the same phenomenon is replicated in human Pneumocytes is not known.Metformin and Sulphonylurea- exhibits no interaction with either ace2 or adam-17 and can be safely continued.

pioglitazone- has been shown to up regulate ace2 in insulin sensitive tissues in rats and reduce adam-17 activity in human skeletal muscles.

Glp1 analogues- due to their claimed protective effects in cardiovascular outcome clinical trials, glp1 ras and sglt2 inhibitors have been recently endorsed by the American diabetes association as the most appropriate second line treatment for t2d patients with established atherosclerotic cardiovascular disease (ascvd) or a high related risk irrespective of glycemic levels. in animal studies, the glp1 ra liraglutide has been associated with the up regulation of ace2 although still unsupported the glp1 ras-induced up regulation of ace2 could ameliorate lung injury during covid-19, antagonizing the reduction of ace2 expression levels that are hallmarks of infection progression [15,27] and preventing the over-activated immune response critical for ards. but it also raised suspicion about the increased risk of cov2 infection when combined with acei/arb's due to over expression of ace2 receptor. Dpp4i- the use of (dpp4i) in the present scenario merits detailed discussion. dpp4i target the enzymatic activity of dpp4, a type ii transmembrane glycoprotein, expressed ubiquitously in many tissues, including immune cells. apart from breaking down circulating glp1, dpp4 activates t-cells, upregulates cd86 expression and nf-κβ pathway, thereby promoting inflammation. hence, inhibition of dpp4 has given rise to concerns regarding a possible increase in the risk of infections. a few meta analyses have identified an increased risk of nasopharyngitis and urinary tract infection. in addition, human dpp4 acts as a functional receptor for mers cov thereby developing a prolonged phase of severe disease and delayed recovery upon infection with mers-cov. although sars cov-2 does not require dpp4, the potential anti-inflammatory role of dpp4i raises questions as to whether dpp4 modulation might help offset the cytokine-mediated acute respiratory complications of covid-19. nonetheless, dpp4i do not alter ace2 expression as shown in diabetic mice.

Hydroxycholroquine- although rarely used, hcq's can be good choice under present circumstances. Hydroxychloroquine, at a dose of 400 mg once a day, is approved by the drug controller general of India (dcgi) as a third line add on anti diabetic drug after metformin and sulfonylurea in people with t2dm. consistent with its Immunomodulator property, Hydroxychloroquine also reduces pro-inflammatory cytokines like tnfα and il6, thereby decreasing insulin resistance. interestingly, Hydroxychloroquine has also been found to be effective against sars-cov-2 and in reducing viral load in covid-19 patients. possible mechanism include impaired binding between host ace2 and sars-cov-2 spike protein and increased intracellular endosomal ph that inhibits antigen-presentation, t-cell activation, cytosolic toll like receptor (tlr)-signaling and transcription of pro-inflammatory cytokines, thereby, averting a cytokine storm. the drug has even been used as a prophylaxis against covid-19 in many countries and the indian council of medical research (icmr) has recently approved the prophylactic use of this drug in high risk groups including healthcare workers at risk of infection.Sglt2 inhibitors- the exceptional risk of dka associated with sglt2i among vulnerable patients such as long standing diabetes with relative insulin deficiency, history of previous ketoacidosis. covid-19 may increase insulin demand and induce fever, nausea and anorexia with consequent Hyperketonemia, which accentuates the gastrointestinal symptoms of infection in a vicious cycle. metabolic decompensation toward dka, either hyperglycemic or Euglycemic, in susceptible diabetic patients on sglt2 inhibitors can be further exacerbated by volume depletion from persistent glycosuria. therefore concomitant use of sglt2i is not recommended in patients with covid19 infection.

ROLE OF STATINS, CCB'S DURING COVID-19

There are several studies which shows the protective effect of statins in pneumonia, statins are known to increase ace2 levels and may protect against viral entry, also statins are known to inhibit nuclear factor kappa b activation and might help in blunting the cytokine storm.

CCB'S have shown to reduce the severity and mortality of disease in pneumonia presumably by inhibiting calcium influx into the cell, but precise role in covid-19 is not well studied right now however it seems safe to use this drug during covid-19 infection.