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EXCEL Medical Bulletin

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POST-COVID RISE OF DIABETES IN INDIA

Emerging literature points towards an increasing burden of incident diabetes during the post-Covid period. New onset hyperglycemia and insulin resistance have been reported in patients with Covid-19 disease without the history of diabetes.

Recent Indian data based on OPD cases from an Indian hospital have suggested that, at least 25% of newly reported diabetes cases had a confirmed history of Covid-19.

PATHOPHYSIOLOGY OF POST-COVID DIABETES

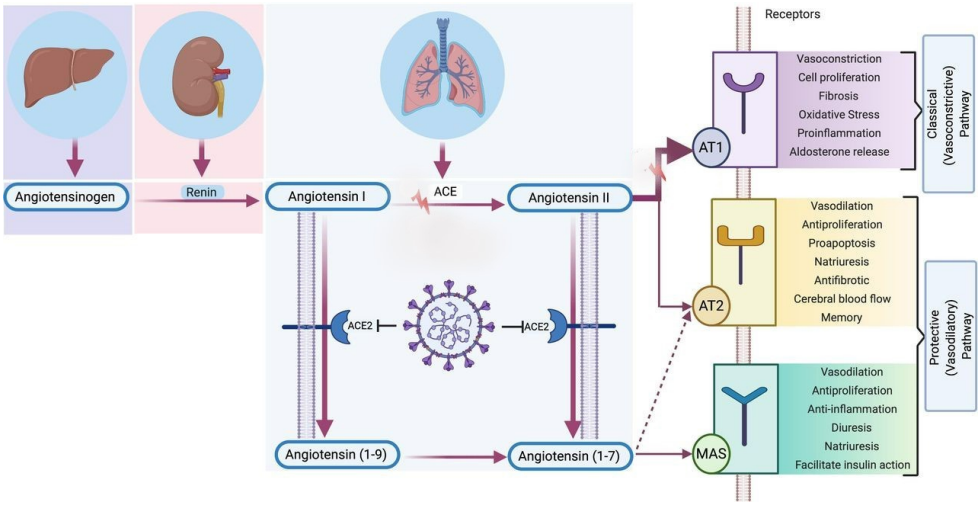
The relationship between diabetes and Covid-19 is bidirectional. Not only does diabetes increase the risk of developing a severe Covid-19 disease, but growing evidence also shows that Covid-19 may be an attributable factor for new-onset diabetes.

There are various hypothesized mechanisms that contribute to the development of post-Covid diabetes.

ACE-2 RECEPTORS

The angiotensin converting enzyme 2 (ACE-2), a part of the renin angiotensin aldosterone system (RAAS) has been identified as the receptor for the SARS-CoV-2 viral binding and entry.

Hence, it is essential to understand the RAAS system and the physiological role of ACE-2 receptors in the same. It has been observed that the RAAS system comprises of two pathways that act as counter regulatory mechanisms to each other.



As per the classic RAAS system, the renin converts the angiotensinogen to angiotensin I which is then converted to angiotensin II that binds with the AT1 receptors to cause vasoconstriction.

However, recent evidences suggest ACE-2 enzyme converts angiotensin I to angiotensin (1-9) and further to angiotensin (1-7). It also converts angiotensin II to angiotensin (1-7).

The angiotensin (1-7) has counter regulatory beneficial effects as vasodilation and anti-inflammatory effects.

The ACE-2 receptors are also present on the β-cells of the pancreas apart from other organs like respiratory tissue, heart, kidney, smooth muscles of GI tract, etc. SARS-CoV-2 virus enters the body via these ACE-2 receptors. Thus utilizing the pancreatic ACE-2 receptors SARS-CoV-2 cause direct & indirect effects, contributing to the development

of new onset diabetes.

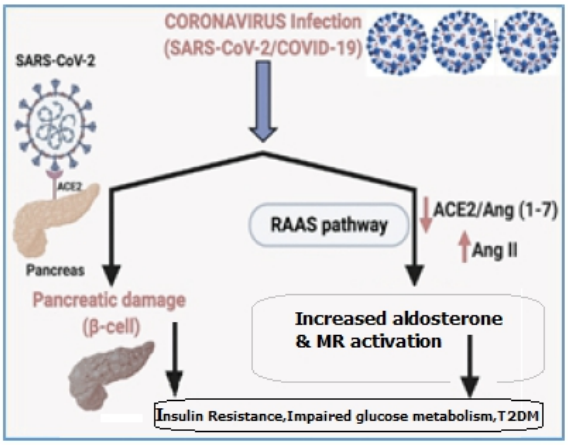
Direct effects

The entry of the SARS-CoV-2 virus through ACE-2 receptors on the β-cells in the pancreas directly results in infection of the β-cells resulting in apoptosis and directly inducing programmed β-cell death.

Indirect effects

The binding of the virus to these receptors results in the down regulation of the ACE-2 receptors and ultimately the ACE-2 enzyme resulting in reduced conversion of the angiotensin II to the protective angiotensin (1-7).

This results in the increased levels of free angiotensin II which activates the aldosterone which in turn activates the mineralocorticoid receptors (MR) thus interfering with the insulin signalling mechanism, reducing adiponectin (enhances the response of cells to insulin) production, increase oxidative stress and inflammation and ultimately lead to the development of insulin resistance.



GLUTAMATE DECARBOXYLASE (GAD 65)

Another finding regarding the development of post-Covid diabetes was seen in the presence of certain antibodies like the GAD 65 antibody.

Glutamate decarboxylase (GAD) is an enzyme that is distributed in the neuroendocrine tissues and is needed for the synthesis of GABA, a potent neurotransmitter. This enzyme, apart from being present in the GABA-ergic nerve cells, is also found in non-neuronal cells and organs like the pancreas.

The GAD has two protein isoforms:

- GAD 65: It is present in the synaptic like vesicles.
- GAD 67: It is present in the cytosol of the beta cells.

GAD antibodies belong to a group of diabetes associated antibodies along with anti-islet antibodies, the presence of which instructs the immune system to destroy insulin producing pancreatic cells.

STEROID INDUCED DIABETES

Covid-19 disease presented with a large usage of steroids due to its recommendation in treatment protocol, which is known to affect glucose metabolism and result in hyperglycaemia.

Glucocorticoids have an effect on glucose metabolism in various ways:

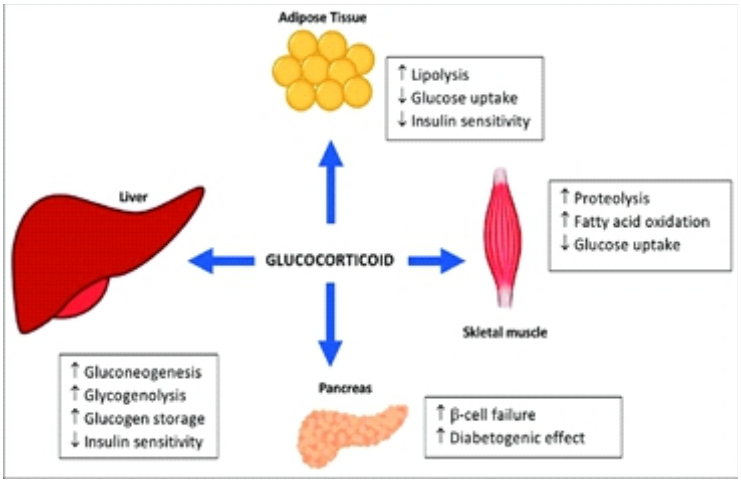
- Inhibit gluconeogenesis: This affects the liver and the adipose tissue and increase the levels of fatty acids in the blood, interferes with glucose utilization and results in insulin resistance.
- The insulin mediated pathways of glycogen synthesis and protein degradation and synthesis are also directly influenced by glucocorticoids.

The glucocorticoids impair the insulin mediated glucose uptake by directly interfering with the components of insulin signalling, increase the oxidative stress and reduce adiponectin levels via the MR receptors.

This activation of MR receptors by the glucocorticoids leads to actions in various organs that ultimately lead to insulin resistance.

People who get COVID-19 have a greater risk of developing diabetes up to a year later, even after a mild SARS-CoV-2 infection, compared with those who never had the disease.

Epidemiological data on a large population has shown that people who had COVID-19 were about 40% more likely to develop diabetes up to a year later than the control groups. That meant that for every 1,000 people studied in each group, roughly 13 more individuals in the COVID-19 group were diagnosed with diabetes. Almost all cases detected were type 2 diabetes, in which the body becomes resistant to or doesn't produce enough insulin.



Given the extraordinary number of COVID-19 cases globally, 480 million confirmed cases and counting, the modest increase in diabetes risk could correspond to a drastic rise in the number of people diagnosed with the disease worldwide.

Source: Banerjee M et al. Primary Care Diabetes, https://doi.org/10/1016/j.pcd.2022.05.009.;Birabaharan M et al. Diabetes, Obesity & Metabolism 2022; 24(6): 1176-1179.; Rathmann W et al. Diabetologia 2022; 65: 949-954.;Xie Y &Al-Aly Z 2022; 10(5): P311-321.; Ajmera KM. Arch Med Case Rep 2021; 5(6): 855-861.; Shreshtha DB et al. World J Virol 2021; 10(5): 275-281.;Alessi J et al. Diabetology & Metabolic Syndrome 2020; 12(80).

AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG) GUIDELINES ON PPI SAFETY

The American College of Gastroenterology (ACG) guidelines define gastroesophageal reflux disease (GERD) as "symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung."

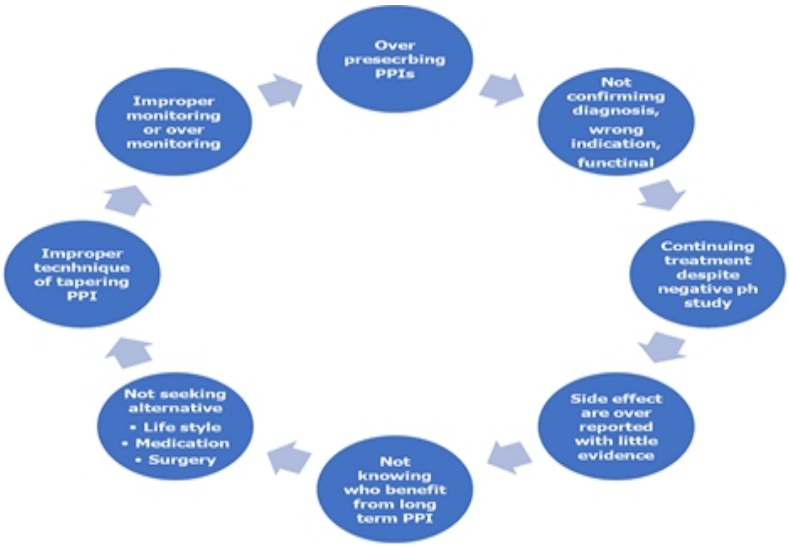
GERD is a common disease with its prevalence in India ranging from 7.6% to 30%. Increase in consumption of unhealthy diets, sedentary work culture, increased obesity and increase in geriatric population are attributable factors for increasing incidences of GERD.

PPI has been the gold standard for the treatment of GERD and its long term use has been rising and therefore concerns about their possible adverse effects specifically related to the long-term use of PPI have been intensely investigated. However, there is no consensus on how to define long-term use of PPIs and an appropriate definition of the same seems relevant in clinical practice.

Position statements or guidelines have provided comprehensive and rational clinical advice concerning long-term use but have not provided a clear definition of what long-term use is.

Based on a review of multiple studies involving patients with GERD, long-term use could be defined as 4-8 weeks of PPI use in clinical context depending on the indication of PPI therapy and resolution of symptoms and more than 6 months of PPI use as a possible definition for long-term use in pharmacoepidemiologic studies and for studies of adverse effects.

PPIs stimulate the body's feedback loop that tries to reactivate acid secretion, and higher initial doses are more likely to activate this feedback response. If the drug is removed, there is a potential risk of rebound hyper secretion, creating a sort of dependency on the drug because the body is acclimated to having acid suppressed. Hence, it becomes imperative to evaluate irrational prescription of PPI to patients not presenting with valid indications warranting PPI use. If rightly prescribed, PPIs are well tolerated in patients with a frequency of adverse effects being <5%, the most common being headache diarrhea, abdominal pain and nausea.



Preventable chain of events in improper PPI use

The American Gastroenterological Association (AGA) has outlined an evidence of potential adverse events some of them being kidney disease, myocardial infarction, pneumonia, micronutrient deficiencies and GI malignancies. However, the quality of evidence is low to very low which is most likely attributed to a bias which predisposes to these conditions, independent of PPI exposure.

Based on these considerations the updated guidelines released in November 2021 by the American College of Gastroenterology (ACG) focuses on appropriate use of PPIs along with a review of lifestyle modifications.

SAFETY OF PPIs

PPIs remain the treatment choice for GERD and ACG recommend its use over H2 receptor antagonists. If the patient responds to the 8 week trial, then an attempt to discontinue the PPI should be made. For the maintenance therapy patients could be treated with the lowest effective PPI dose that controls the symptoms and maintains healing of reflux esophagitis and discontinue once the symptoms resolve over time. On-demand or intermittent use of PPIs can also be a treatment option for heartburn symptom control in patients with non-erosive reflux disease.

- Some studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. These studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions.
- High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections.
- Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions.

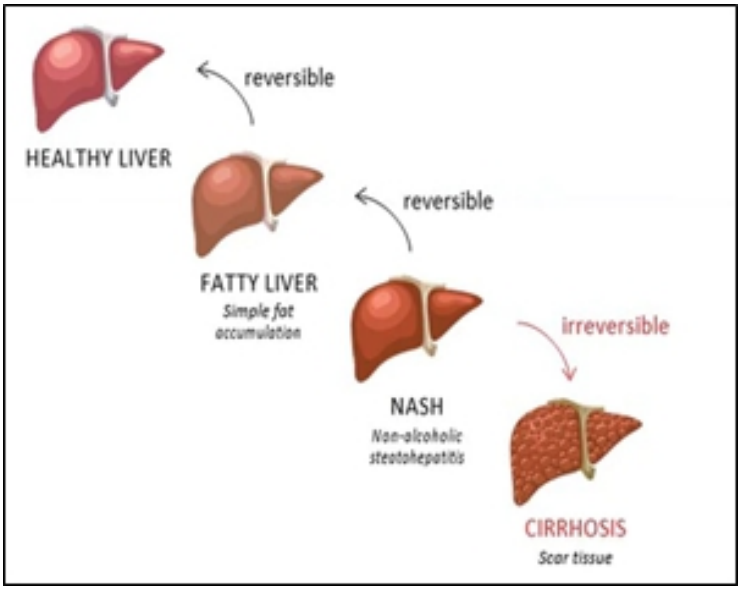
Data provided by ACG is reassuring, PPI therapy should still be utilized according to evidence-based practice knowing more about which patients are more likely to benefit from this therapy.

Source: Bhatia S et al. Indian J of Gastroenterology 2019; 38(5).; Haastrup PF et al. BMJ Open Gastroenterology 2021; 8: e000563.;Metz DC. Gastroenterol Hepatol (NY) 2008; 4(5): 322-325.

BENEFIT OF B-VITAMINS (MEGO-XL+) IN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide and is a term used for a range of conditions caused by a buildup of fat in the liver.

Unrelated to alcohol consumption, NAFLD is caused by other factors such as obesity, type 2 diabetes, high cholesterol and triglyceride levels and high blood pressure.



NAFLD ranges from a benign condition of a non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), which is the more severe end of the spectrum.

NASH which is an aggressive form of fatty liver disease can cause severe liver damage and impact overall health.

A recent study that has examined the mechanism of NASH has discovered a specific protein called syntaxin 17 which was critical in the process of autophagy (removal of damaged cells from the body) as well as transporting and digesting fat in fatty acid metabolism, mitochondrial turnover and inflammation prevention. It has been observed that increased homocysteine levels, associated with NASH attaches to the various liver proteins including syntaxin 17 and blocks the protein from performing its function of autophagy and digestion and transport of fats inducing the development and progression of fatty liver disease to its more aggressive form, NASH.

Preclinical studies have shown that supplementing the diet with B12 and folic acid increases the syntaxin 17 levels in the liver and restores its role in autophagy and fat transport and digestion, thus slowing the NASH progression and reverse liver inflammation and fibrosis.

These findings are promising suggesting that a relatively inexpensive therapy with vitamin B12 and folic acid could be used to prevent and/or delay the progression of NASH and that the serum and hepatic homocysteine levels could serve as a biomarker for NASH severity.

These findings demonstrate that a simple, affordable and accessible intervention could potentially halt or reverse the damage to the liver, bringing new hope to those suffering from fatty liver diseases.

Source: Pouwels et al. BMC Endocrine Disorders 2022; 22(63).

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