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LINK BETWEEN POST COVID INFECTIONS AND SURGE IN DIABETES

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.

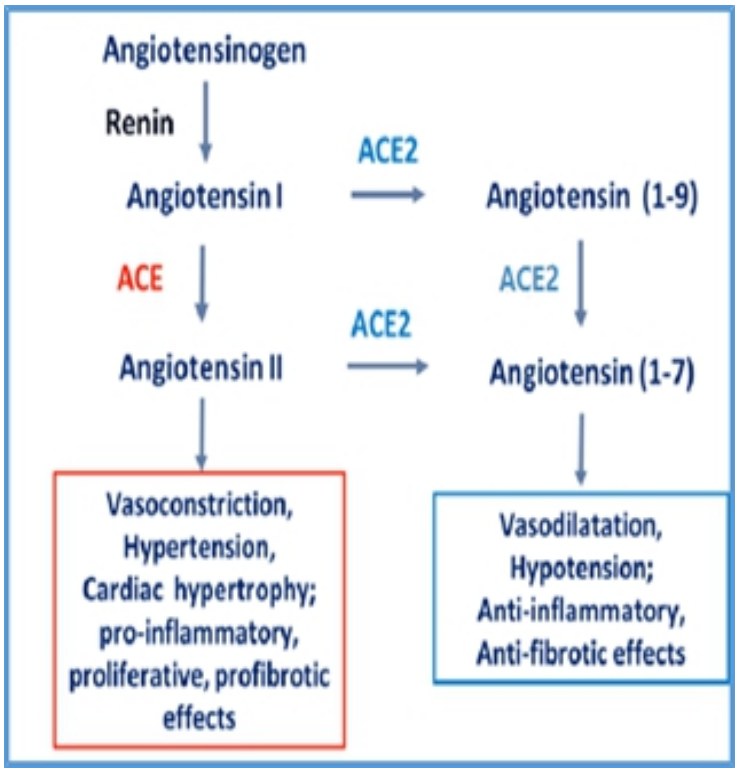
There are various hypothesized mechanisms that contribute to the development of post-Covid diabetes.

ACE2 RECEPTORS

The angiotensin converting enzyme 2 (ACE2), a part of the renin angiotensin aldosterone system (RAAS) has been identified as the receptor for the SARS CoV2 viral binding and entry.

Hence, it is essential to understand the RAAS system and the physiological role of ACE2 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 ACE2 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.

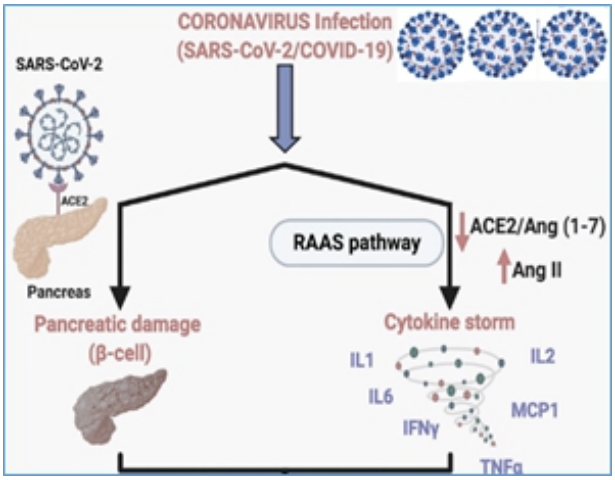
The ACE2 receptors are also present on the beta cells of the pancreas apart from other organs like respiratory tissue, heart, kidney, smooth muscles of GI tract, etc. SARS CoV2 virus enters the body via these ACE2 receptors. Thus, utilizing the pancreatic ACE2 receptors SARS CoV2 cause direct & indirect effects, contributing to the development of new-onset diabetes.

Direct effects

The entry of the SARS CoV2 virus through ACE2 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 ACE2 receptors and ultimately the ACE2 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 GAD65 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:

- ***GAD65:*** It is present in the synaptic like vesicles.
- ***GAD67:*** It is present in the cytosol of the β-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

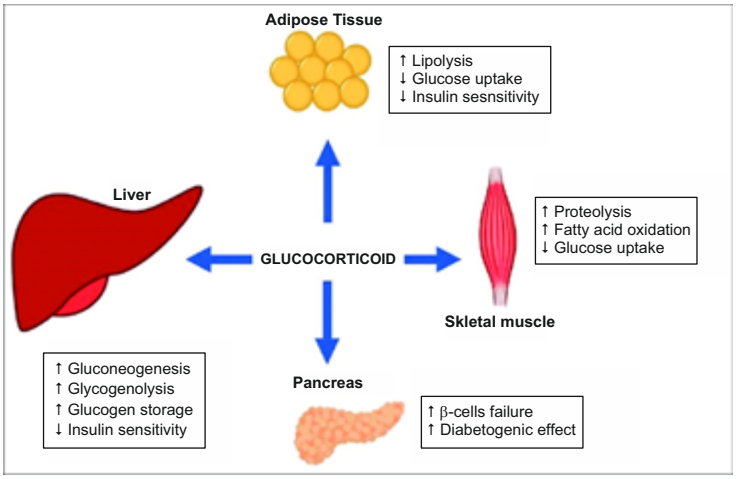
Covid-19 disease presented with a large usage of steroids due to its recommendation in treatment protocol, which is known to affect glucose metabolism and result in hyperglycaemia.

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 of 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).

USE OF MEFENAMIC ACID IN VIRAL INFECTION

One of the fundamental innate immune responses to viral infections includes the processing and release of pro-inflammatory cytokines such as interleukin (IL-1β and IL-18) through the activation of inflammasome. Dengue virus & other viruses stimulates the Nod-like receptor (NLRP3-specific inflammasome) and this is critical for the inflammatory response.

Inflammasomes are multi-molecular complexes that contain many copies of receptors that recognize the molecular structures of cell-damaging factors and pathogenic agents. It is evident from the literature data that the host activates the mechanism of inflammasomes formation as a defense response against the varied viruses, but in turn, some viruses using their virulence factors may antagonize inflammasome pathways and increase their ability to survive in the host and cause disease. The host organism then expresses excessive amounts of inflammasomes to remove harmful factors, which leads to the overproduction of inflammatory cytokines and can cause excessive inflammation.

Only Fenamates group of NSAIDs have the potential to inhibit the NLRP3 inflammasome. Mefenamic acid belonging to the class of NSAIDs and fenamate family, is a versatile agent with an established antipyretic, analgesic and anti-inflammatory actions. Evidence from the literature suggest Mefenamic acid to have the inhibitory action on NLRP3 inflammasome. Mefenamic acid have shown to inhibit NLRP3 inflammasome by reversibly blocking volume-regulated anion

channels, which regulate Cl− transport across plasma membrane and also the volume modulated transient receptor potential (TRP) channels. Thus, the anti-inflammatory action of Mefenamic acid may get augmented with the NLRP3 inhibitory action, which has been evident from the literatures and recent clinical evidences.

Additionally literature also supports in-vitro & preclinical antiviral actions of Mefenamic acid through its serine protease inhibition action. It showed significant anti-dengue activity through their ability to inhibit viral protease activity. The antiviral and anti-inflammatory activities of Mefenamic acid can be utilized in attenuating the clinical symptoms of viral infections.

Source: Front. Cell. Infect. Microbiol. 10:489, 10 September 2020.; Journal of The Association of Physicians of India, Vol. 70 , March 2022.

HOVERING BAN OVER CODEINE...

Codeine is a narcotic which belongs to the opioids class, mostly used to treat cough, cold and pain. Due to high rates of abuse and addiction liability of codeine, its use is closely monitored and controlled across all regulatory authorities globally including US Food and Drug Administration (USFDA), European Medicines Agency (EMA), UK, Therapeutic Goods Administration (TGA)-Australia, Canada, etc.

A study examining codeine-related mortality in a 10-year period from 2000 to 2008 found that deaths with codeine use had more than doubled during this period. Hence, in 2013 codeine use for cough was restricted in children under 12 years.

PRONE TO ABUSE

- Codeine is an **opioid-based** analgesic, mostly used to treat **cough, cold and pain**
- Its use is monitored and controlled in developed markets including the US and Europe due to **high rates of abuse**
- The **US restricted** the use of codeine medicines for children
- Codeine and its preparations are supposed to be dispensed against prescription, but most are **available over the counter**

The USFDA contraindicated codeine use in children under 12 years and in 2018 issued a black box warning for use in children under 18 years.

Codeine is a Schedule H drug which comes under the purview of Narcotics Drugs and Psychotropic Substances Act, 1985 and have been under the government scanner for several years. In March 2016, the Union Health Ministry banned 344 fixed-drug combinations under the section 26A of Drugs and Cosmetics Act, 1940 which was inclusive of commonly used cough syrup solutions.

The government had then decided to prohibit the sale of these drugs as they were found to be irrational. However, a stay order was received for codeine based formulations which is applicable till date. Recently several parliamentarians' raised concerns about codeine based cough syrups which they claim are being misused for recreational purposes. This might lead to a permanent ban of codeine syrups which can create a gap in the antitussive treatment options. However, **Dextromethorphan**, a non-narcotic and reliable antitussive with established efficacy and safety should fill in this gap effectively.

Source: Expert Review of Clinical Pharmacology, 11:11, 1057-1059; https://www.medsafe.govt.nz/profs/datasheet/c/codeine phosphatepsmtab.

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