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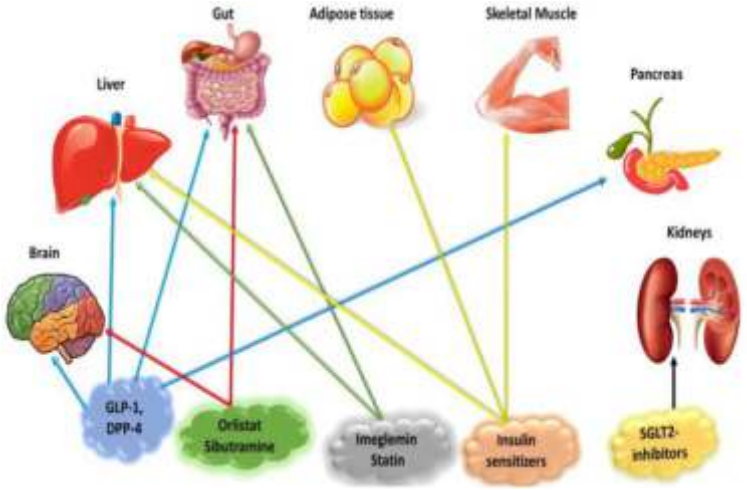
VILDAGLIPTIN IN PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathies among women of reproductive age with a global prevalence of 5.5% to 12.6% and an estimated prevalence in India between 8.2% and 22.5%. It is associated with a broad range of health conditions including hypertension, dyslipidaemia, insulin resistance, hyperandrogenaemia, and type 2 diabetes mellitus (T2DM).

PCOS is one of the primary causes of infertility in women. Overweight and obesity, sedentary lifestyle, and a family history of PCOS may predispose a young girl to PCOS. Women with PCOS have 11-fold increased risk of developing metabolic syndrome and glucose intolerance. However, early diagnosis and management in PCOS can help prevent long-term metabolic abnormalities. PCOS is diagnosed by diverse manifestations including chronic anovulation or oligo-ovulation, hyperandrogenism and polycystic ovaries seen by ultrasound. Overtime different therapeutic interventions have been used to manage PCOS.



Potential target organs for the therapeutic options in managing pcos

INSULIN RESISTANCE IN PCOS

Insulin resistance and its compensatory hyperinsulinemia are thought to play a key role in the pathogenicity of PCOS. The incidence of insulin resistance is a consistent feature of PCOS in both normal and overweight women.

Insulin resistance also appears to play a significant role in the pathogenesis of the hyperandrogenism and infertility of PCOS. Women with anovulation, hyperinsulinemia, and hyperandrogenism are at greater risk of developing diabetes with an age of onset 30 years, earlier than in the general population. Based on this, insulin sensitizers are an alternative therapeutic way to the treatment of PCOS.

Overtime, metformin, a biguanide, which decreases hepatic glucose production, circulating insulin and intestinal glucose absorption, and improving peripheral tissue utilization of glucose has been used. But recent studies have demonstrated the benefit of vildagliptin as an alternative or additional therapy to the standard metformin in the management of PCOS.

VILDAGLIPTIN IN PCOS

Vildagliptin is a selective, reversible, competitive inhibitor of dipeptidyl peptidase-4 (DPP4). DPP4 is involved in the inactivation of

many neuropeptides, cytokines, chemokines, and gastrointestinal hormones. Two important hormones involved in glucose homeostasis that are inactivated by DPP4 are *glucose-dependent insulinotropic polypeptide (GIP) & glucagon like peptide-1 (GLP-1).* GIP and GLP-1 are incretins, which are hormones released from the gut that stimulate insulin secretion in response to food intake.

GLP-1, the most potent insulinotropic hormone, enhances glucose-dependent secretion of insulin from pancreatic β-cells and inhibits glucagon secretion. Inhibition of DPP4 by Vildagliptin, results in increased levels of active GLP-1 and subsequent enhancement of insulin release.

In addition to its insulinotropic effects, GLP-1 expands pancreatic β-cell mass by promoting β-cell growth, differentiation and proliferation by activating the epidermal growth factor receptors. It has also been reported that GLP-1 enhances β-cell survival by reducing apoptosis caused by various cytotoxic stimuli.

A study conducted to study the efficacy of metformin combined with vildagliptin on endocrine, glucose and lipid metabolism in patients with PCOS complicated with abnormal glucose metabolism showed that, combining metformin with vildagliptin resulted in a significant reduction in the testosterone levels, overall blood glucose control and reductions in the lipid parameters, thus demonstrating that metformin combined with vildagliptin effectively safely improved the levels of endocrine, sugar and fat metabolism in patients of PCOS with abnormal glucose metabolism.

Hence, the beneficial efficacy of incretin-based therapies like DPP4 inhibitors such as vildagliptin in the management of T2DM, together with their glucose-dependent mechanism of action, indicates their potential benefits in the management of PCOS and its related metabolic consequences.

Source: Mehreen TS et al. Journal of Diabetology 2021; 12(3): 319-325; El Halwagy A et al. Open Journal of Obstetrics & Gynaecology 2017; 7: 117-128; Abdalla MA et al. Therapeutic Advances in Endocrinology & Metabolism 2021; 12: 1-16;Xiao-lan Z et al. The Chinese Journal of Clinical Pharmacology 2016; 6.

FAVOURABLE BENEFIT–TO-HARM BALANCE OF STATINS

Cardiovascular disease is the leading cause of mortality and morbidity worldwide and statins have been recommended in clinical guidelines as a frontline treatment for prevention of cardiovascular disease.

However, many people are reluctant to take them because of potential of the various adverse events that have been associated with the use of statins like muscle related problems such as stiffness and weakness, liver dysfunction, diabetes, renal insufficiency and eye problems which leads to the underuse of a potentially life-saving treatment.

The last 30 years have seen a large increase in the utilization of statins, which is consistent with changes in recommendations in clinical guidelines. Recent guidelines by *The American Heart Association (AHA),* have recommended a wider use of statins for the primary prevention of cardiovascular disease, making a large population at a low risk of cardiovascular disease eligible for treatment. However, there is an ongoing debate about these changes, as they have expanded the number of people eligible for treatment, particularly in primary prevention.

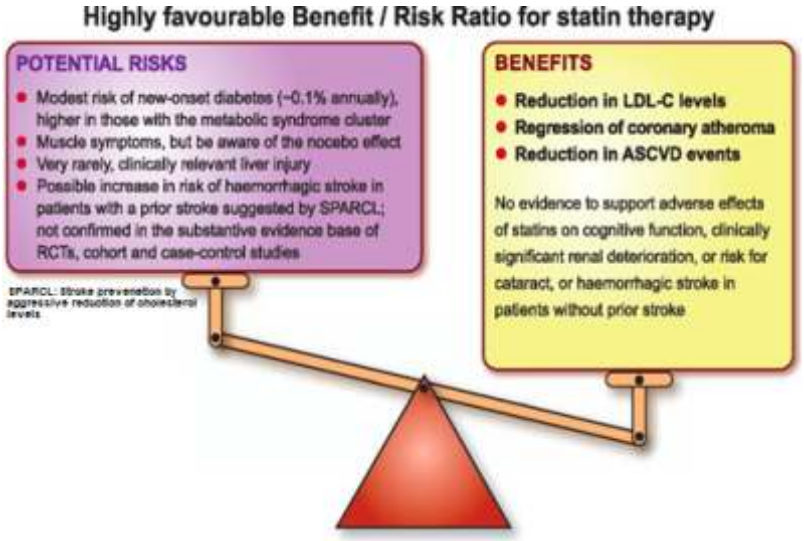
For people with existing heart disease, the benefits of statins far outweigh the risks, but for primary prevention, a better understanding of the risks of adverse effects and evaluation of the benefit versus harm of statins is necessary.

Researchers have analyzed multiple trials in over one lakh people over a period of approximately three and a half years, the results of which concluded that there was a slightly increased risk of self-reported muscle symptoms, mainly myalgia with statins, but no increased risk of clinically confirmed muscle disorders or the progression of diabetes, which also has been considered an adverse effect of statin use.

However, these increased risks did not outweigh the reduction in the risk of major cardiovascular events. Statins were shown to significantly reduce the risks of myocardial infarction, stroke and death from overall cardiovascular disease.

Attributing muscle symptoms to statins was originally identified in various observational studies, but this association has been controversial and analyses of placebo-controlled trials have shown a smaller absolute increased risk of muscle symptoms than

that reported in observational studies, supporting the view that muscle symptoms reported by statin users were nocebo effect and not actually caused by statins.



Potential risks vs benefit of statin use

The low risk of adverse events caused by statins as reported by researchers should reassure patients and physicians that the potential harms of statins are small and should not deter their use for primary prevention of cardiovascular disease.

In particular, given the observed benefits of treatment in preventing major cardiovascular events, the slightly increased risk of self-reported muscle symptoms, which have no confirmed effect on physiological function, should not delay starting treatment with statins.

For patients who do have muscle symptoms after treatment with statins, these data highlight that, in most cases, the symptoms are unlikely to be caused by treatment with statins alone. Physicians should therefore look at the patients' misconceptions of intolerance to statins and perhaps consider providing behavioral interventions, to minimize unnecessary withdrawal of treatment.

Source: Cai T et al. BMJ 2021; 374: n1537.

PPIs IN COPD ASOCIATED WITH GERD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a third leading cause of death worldwide, is characterized by persistent airflow limitation and dyspnea.

Gastroesophageal reflux disease (GERD) is a known frequent co-morbidity of COPD for which studies have shown that the prevalence of GERD is higher in patients with COPD than in the normal population. The prevalence of GERD in people with COPD has been reported to range from 17% to 78%.

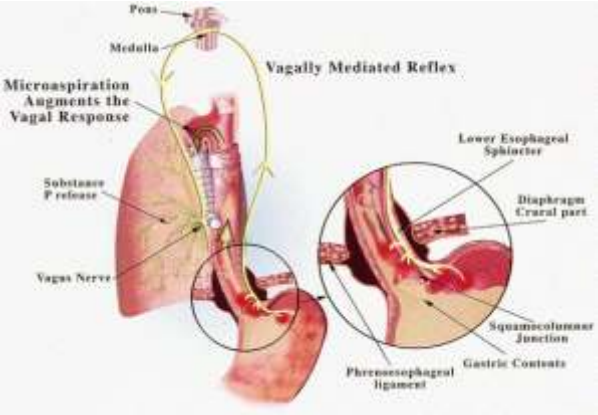
GERD may cause an acute exacerbation of COPD and is considered as an independent risk factor for COPD death. COPD and GERD are mutually casual forming a vicious cycle seriously affecting the quality of life.

HOW DOES GERD CAUSE COPD EXACERBATION?

The mechanism underlying GERD which causes COPD is thought to be related to the pulmonary micro-aspiration of the gastric acid into the airways.

In addition, inflammatory response by GERD, induction of airway contraction by the vagal reflex or stimulation of acid sensitive receptors in the oesophageal wall may also be involved in the exacerbation of COPD. Furthermore, GERD has been reported to increase the risk of bacterial colonization in the lower respiratory tract and thereby increase the risk of acute exacerbations.

Additionally, GERD is considered to be one of the causes of chronic cough, which is a common symptom of COPD.



Effective management of COPD exacerbations that include treatment of related conditions, like GERD in people with COPD has become a considerable clinical necessity.

WHAT IS THE ROLE OF PROTON PUMP INHIBITORS IN COPD?

Usually, proton pump inhibitors (PPIs) reduce gastric acid production by irreversibly blocking the enzymes responsible for hydrogen potassium ATPase (proton pump) in parietal cells & are the most effective medications to reduce gastric acid secretions. Apart from the treatment of peptic ulcer disease, prevention of gastroduodenal ulcers caused due to use of NSAIDs and eradication od *H.Pylori,* PPI therapy for patients with COPD complicated with GERD may reduce the number of acute exacerbations of COPD, thus delaying the progression of the disease and improving clinical outcomes.

The use of PPIs in the exacerbation of COPD related complications can be attributed to the following hypotheses:

- Patients with COPD have long-term hypoxia to which the gastrointestinal tract (GIT) is the most susceptible. The GIT is most sensitive to ischemia and hypoxia which results in varying degree of gastric mucosal damage. PPI has a strong inhibitory effect on the gastric acid secretion and a protective effect on the gastric mucosa thus preventing upper GI bleeding, enhancing immunity and reducing abdominal distension.
- Clinical manifestations of COPD include repeated coughing, sputum expectoration and wheezing. PPIs can reduce the irritation of gastric acid and reflux of gastric contents on the esophagus and bronchi and relieve cough, sputum production and other uncomfortable clinical manifestations.
- PPIs can reduce the incidence of micro-aspiration caused by GERD and avoid the occurrence of aspirational pneumonia.
- Previous studies have found that local or systemic inflammatory infection is an important factor in the pathogenesis of COPD and evidence supports the use of PPIs for inflammation. PPIs can improve neurogenic inflammation, reduce plasma and sputum substance levels, block gastric acid secretion and selectively inhibit the TNF-α and IL-1β secretion, thus reducing the risk of infection in patients with COPD.
- PPIs also have been reported to have an impact on viral infections like rhino virus, herpes virus, etc. which is an important cause of COPD exacerbation. Frequent COPD exacerbations suggests that exacerbators may have high sensitivity for respiratory viral infections or have poor ability to prevent viral replication. Viral infections induce inflammatory mediators, including various cytokines. The anti-inflammatory effect of PPIs is probably due to the effect of inhibiting the production of proinflammatory cytokines.
- Mortality outcomes of patients with COPD is closely related to the frequency of acute exacerbations in COPD patients and thus reducing the exacerbations, PPIs reduce the risk of death in COPD patients.

Thus, increasing evidence suggests that PPIs are highly effective in treating GERD symptoms, and that GERD symptoms are an independent risk factor for acute exacerbation of COPD. Our findings strengthen the evidence for the benefits of PPIs in COPD patients with symptomatic GERD, which might improve the prescription of PPIs in clinical practice.

Source: Yu F et al. Frontiers Medicine 2022; 9(841155): 1-11;Kikuchi S et al. Cochrane Database Sys Rev 2018; 2018(8): Cd013113.

EXCEL
Dr. Prabhu Kasture (MD, DPH)
GM-MEDICAL SERVICES

PHONE NO.: 022-66638043
EMAIL: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt. Ltd. (Peninsula Corporate Park, Peninsula Chambers, Ganpatro Kadam Marg, Lower Parel, Mumbai-400013
http://www.bluecrosslabs.com/