QUARTER 1, 2021 | VOLUME 9 | NUMBER 2

EXCEL Medical Bulletin

EXCEL Division of Blue Cross Laboratories

VILDAGLIPTIN (BLUGLIP): A VERSATILE GLIPTIN

The burden of diabetes has been increasing in our country over the years. In fact, India is deemed as the **"Diabetes Capital of the World"** with its diabetic population being close to hitting the alarming mark of 69.9 million by 2025 and 80 million by 2030.

Diabetes affects the regulation of insulin, resulting in high levels of blood sugar. While there are some similarities in symptoms, the two main types of diabetes develop in different ways.

Type 1 diabetes is an autoimmune disease that destroys insulin producing beta-pancreatic cells.

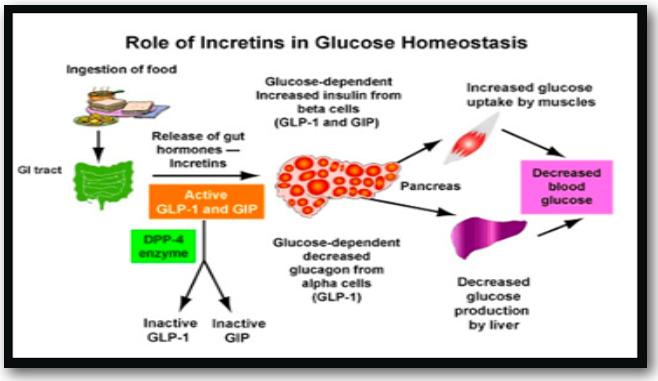
In contrast, patients with type 2 diabetes develop insulin resistance, meaning that it has less and less effect on reducing the blood sugar.

ROLE OF INCRETIN HORMONES

Incretins are hormones that are released from the gut into the bloodstream in response to ingestion of food, and they then modulate the insulin secretory response to the products within the nutrients in the food.

This incretin effect accounts for at least 50% of the total insulin secreted after oral glucose.

Therefore, by definition, **incretin hormones are insulinotropic (i.e., they induce insulin secretion) at usual physiological concentrations seen in the plasma after ingestion of food.**



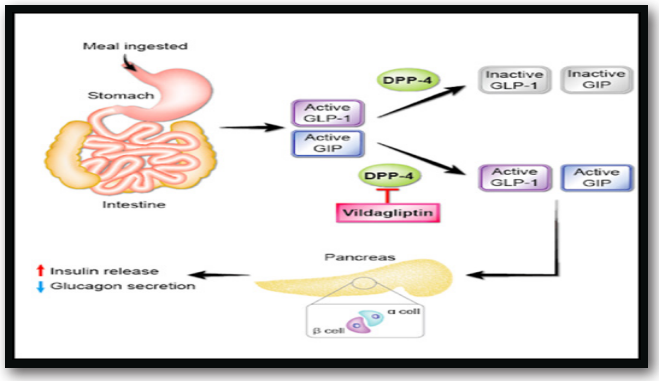
There are two incretins, known as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), that share many common actions in the pancreas but have distinct actions outside of the pancreas. Both incretins are rapidly deactivated by an enzyme called dipeptidyl peptidase-4 (DPP4).

A lack of secretion of incretins or an increase in their clearance are not pathogenic factors in diabetes. However, in type 2 diabetes, GIP no longer modulates glucose-dependent insulin secretion, even at supra physiological plasma levels, and therefore GIP incompetence is detrimental to ß-cell function, especially after eating. GLP-1, on the other hand, is still insulinotropic in type 2 diabetes.

VILDAGLIPTIN

Vildagliptin is a potent and selective inhibitor of DPP-4, the enzyme responsible for the rapid degradation of the incretin hormones GLP-1 and GIP.

This activity increases levels of active incretins and enhances pancreatic islet α- and ß-cell responsiveness to glucose, thus improving insulin secretion and reducing inappropriate glucagon production, improving insulin sensitivity, improving postprandial lipid and lipoprotein metabolism, and reducing fasting and prandial glucose and glycosylated haemoglobin (HbA1c).



Most DPP-4 inhibitors are well tolerated owing to their glucose-dependent mechanism of action, they are generally associated with a low risk of hypoglycaemia and are an attractive treatment option for difficult-to-treat patients.

There are differences in the mechanisms of action of DPP-4 inhibitors, in particular their catalytic

binding kinetics, which may translate into clinical differences. For example, vildagliptin blocks DPP-4 through substrate-like binding to the active site of the enzyme for an extended time.

While vildagliptin is covalently bound to the DPP-4 catalytic site, the enzyme cannot act on any other substrate. Following dissociation of vildagliptin from the catalytic side, within a fraction of a second, another vildagliptin molecule will interact with the catalytic site. This leads to complete blocking of DPP-4 activity over the entire time & that vildagliptin drug levels are adequate to effectively associate with the catalytic site unlike the other competitive inhibitors of DPP-4 enzyme.

Apart from this, vildagliptin has shown to have various beneficial effects in the overall management of hyperglycaemia and its associated co-morbidities.

- **Only vildagliptin has been shown to block the inactivation of GLP-1 and GIP between meals and overnight.**

Competitive DPP-4 inhibitors, such as sitagliptin, which achieve 90-95% inhibition of DPP-4 can maintain GLP-1 and GIP levels above the threshold required for their actions in the pancreas over the course of each meal, falling below this threshold between meals and overnight. Vildagliptin is a slow substrate for DPP-4 which blocks GLP-1 and GIP inactivation over 24 hours resulting in maintenance of GLP-1 and GIP levels above the threshold for their actions in the pancreas over the entire 24 hours of each day.

- Vildagliptin improves **α-cell sensitivity to glucose in the hyperglycaemic range of glucose which reduces the glucagon levels** in hyperglycaemia.
- Vildagliptin has also been shown to **improve the ß-cell sensitivity to glucose leading to increased insulin secretion** when glucose levels are above normal.
- Vildagliptin **inhibits fasting lipolysis leading to enhanced insulin sensitivity** via reduced lipo-toxicity and it has been observed that vildagliptin treatment leads to the redistribution fat out of muscle/liver and ß-cells into adipocytes.
- Vildagliptin also **decreases postprandial lipidaemia by the GLP-1 mechanism** independent of the pancreatic islets, which presumably results in less postprandial lipid extraction from the gut.
- It has been observed that vildagliptin **improves ß-cell mass** by stimulating replication and inhibiting apoptosis of ß-cell turnover.
- Vildagliptin is not metabolised by CYP 450 enzymes and hence **exhibit minimal drug interactions.**

COMBINING VILDAGLIPTIN WITH METFORMIN

The most interesting combination in which to use vildagliptin is with metformin, for two different reasons. First, from a pathogenic perspective, combining an agent primarily targeting insulin resistance, like metformin, with an agent primarily targeting the α-cell, like vildagliptin, is a logical approach. In addition, the choice of vildagliptin gives the added value of also targeting the ß-cell dysfunction that is clearly present in T2DM patients, with insufficient suppression of glucagon secretion leading to postprandial hyperglycemia.

Secondly, additive effects have been observed with this combination as metformin has been found to increase GLP-1 levels, presumably through increasing GLP-1 synthesis rather than DPP-4 inhibition.

CONCLUSION

Administration of vildagliptin in patients with type 2 diabetes has been suggested as a safe and effective treatment with the potential to achieve long-term glycaemic control.

Studies have shown that the levels of haemoglobin A1c (HbA1c), fasting plasma glucose, mean prandial glucose and peak prandial glucose were reduced to a significantly greater effect after 12 weeks of additional treatment with vildagliptin compared with continued therapy with metformin alone.

Long-term treatment with vildagliptin has also been shown to be well-tolerated as reflected by low rates of study discontinuation for adverse events in clinical trials and is not associated with weight gain which is a common problem associated with type 2 diabetes.

To conclude, DPP-IV inhibitors are one of several new classes of anti-diabetic medications for type 2 diabetes. The ability to achieve sustainable reductions in HbA1c, the primary measure of blood glucose control, with an orally administered, well-tolerated agent is seen as one of the most important advantages of this new class of drugs.

Source:https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(19)31230-6/fulltext. ;Pandey SK & Sharma V. Indian J Ophthalmol. 2018 Nov; 66(11): 1652–1653; Kim W & Egan JM. Pharmacol Rev 2008; 60(4): 470-512;Mathieu C & Degrande E. Vasc Health Risk Manag 2008; 4(6): 1349-1360.; Kothny W et al. Diabetologia. 2015; 58(9): 2020-2026; Foley JE. Med Chem 2014; 4(5): 439-440.

B VITAMINS (MEGO-XL) AND IMMUNITY

B group vitamins represent essential micronutrients for myriad metabolic and regulatory processes required for human health, serving as co-factors used by hundreds of enzymes that carry out essential functions such as energy metabolism, DNA and protein synthesis and other critical functions.

B vitamins and their corresponding vitamers are universally essential for all cellular life forms, from bacteria to humans. Humans are unable to synthesize most B vitamins and are therefore dependent on their diet for these essential micronutrients.

These micronutrients have gained much importance during the current pandemic because of their anti-inflammatory and immune supporting properties. There is a need to highlight the importance of B vitamins because it plays a pivotal role in cell functioning, energy metabolism, and proper immune function. B vitamins assists in proper activation of both the innate and adaptive immune responses, reduces pro-inflammatory cytokine levels, improves respiratory function, maintains endothelial integrity and prevents hypercoagulability.

Severe cases of Covid-19 infection have presented with a hyper immune response or the **"cytokine storm"** leading to increased mortality among patients and thus the importance of maintaining normal levels of these B vitamins is of utmost importance.

Some of the B vitamins that play an essential role in the immune functions are:

VITAMIN B12 (METHYCOBALAMIN)

Vitamin B12 is a water-soluble vitamin and an important micronutrient with critical role in DNA, protein, and lipid synthesis. Apart from these functions, Vitamin B12 plays a crucial role in the proper functioning of immune system.

Methionine synthase, which uses methylcobalamin as a co-factor, is essential for the synthesis of purines and pyrimidines in all cells, including fast-dividing immune cells.

Vitamin B12 is also known to play an important role in cellular immunity, especially relating to CD8+ cells and the NK cell system, which suggests effects on cytotoxic cells and acts as an immunomodulator for cellular immunity.

Studies have shown that vitamin B12 treatment leads to an increase in the number of lymphocytes, including CD8+ cells, not only in patients but also in control subjects, and to a significant increase of NK cell activity in patients. Hence, vitamin B 12 plays a crucial role in the healthy balance of the immune system.

VITAMIN B9 (FOLIC ACID)

Folic acid plays a crucial role in immunity. It plays a role in DNA and protein synthesis, suggesting that every mechanism in which cell proliferation intervenes may be altered.

Cell-mediated immunity is especially affected by folate deficiency: the blastogenic response of T lymphocytes to certain mitogens is decreased in folate-deficient humans, and the thymus is preferentially altered. The effects of folic acid deficiency upon humoral immunity have been more thoroughly investigated, and the antibody responses to several antigens have been shown to decrease. It is also associated with lower levels of proteins involved in activation and regulation of immune function while an adequate concentration supports a Th-1 cytokine-mediated immune response with sufficient production of pro-inflammatory cytokines, which maintains an effective immune response.

Hence, alterations in immune system functions could lead to decreased resistance to infections, as commonly observed in folate-deficient humans.

VITAMIN B6 (PYRIDOXINE)

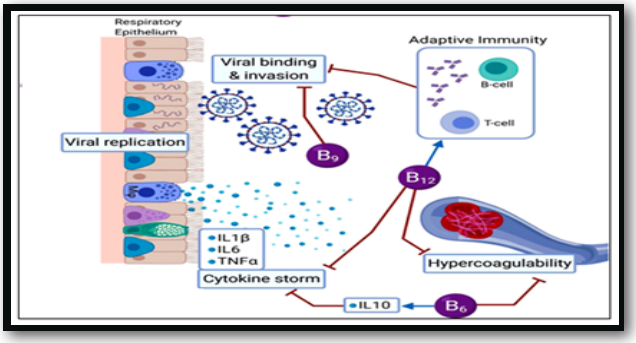
Vitamin B6 acts as co-enzyme for many metabolic reactions and is essential in nucleic acid and protein biosynthesis. Hence, its effect on immune function is logical, since antibodies and cytokines build up from amino acids and require vitamin B6 as co-enzyme in their metabolism.

Vitamin B6 deficiency is shown to affect the development and function of lymphoid organs and is involved in lymphoid organ atrophy.Studies have also shown that, vitamin B6 supplementation in arthritis patients resulted in a reduction in plasma IL-6 and TNF-alpha levels in response to a 12-week supplementation of vitamin B6.

Lymphocyte differentiation and maturation are altered by deficiency, delayed-type hypersensitivity responses are reduced and antibody production may be indirectly impaired.

Some studies have shown that the lymphocyte

mutagenic response is impaired by dietary vitamin B6 depletion in elderly subjects and restored by administration of vitamin B6.
Effects of deficiency were seen in a decreased antibody DTH response, IL-1beta, IL-2, IL-2 receptor, NK cell activity, and in lymphocyte proliferation, and insufficient levels of B6 inhibit the immune system's ability to respond to a pathogenic challenge
Total lymphocyte count, T-helper and T-suppressor cell numbers and the percentage of T-lymphocyte cells and T-suppressors significantly increase in the B6 supplemented groups.
These findings reveal that Vitamin B6 is necessary for the body's immune function and its deficiency affects both humoral and cell-mediated immune responses.

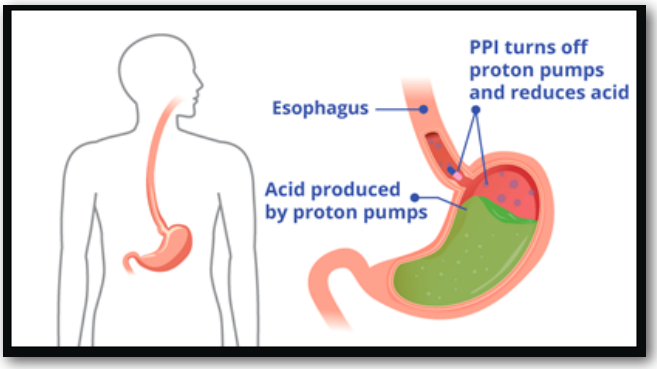


Apart from the B vitamins, immune modulation is taken care of in the body by other molecules like **ALA or Alpha-Lipoic Acid.**
Research has indicated that alpha-lipoic acid has an effect on both, adaptive and innate immunity.

Source: Shakoor H et al. Maturitas 2021; 144: 108-111;Peterson CT et al. Nutrients 2020; 12 (3380): 1-23;Tamura J et al. Clin Exp Immunol 1999; 116(1): 28-32;Dhur A et al. Prog Food Nutr Sci 1991;15(1-2): 43-60;Saeed F et al. Food & Agricultural Immunology 2016; 27 (2): 205-229;Liu W et al. Med Research International 2019; (1):1-11.

PROTON PUMP INHIBITOR & LONG TERM SAFETY

Proton Pump Inhibitors (PPis) are one of the most widely used drugs across the world and most effective in the treatment of Gastro-oesophageal Reflux Disease (GERD).



PPIs are also recommended in many other acid-related conditions, such as the management of dyspepsia, as part of Helicobacter pylori eradication therapy, and for prevention of peptic ulcer bleeding in high-risk patients on aspirin and/or non-steroidal anti-inflammatory drugs.

PPIs are often used long term, particularly in patients with GERD and other acid secretion related disease, since the acid secretion returns to normal after 12-24 hours of treatment.
Given how commonly acid suppressive medications are used, it is important to ensure that this class of drugs is safe. However, concerns have been raised regarding potential harms of long-term PPI therapy. Observational studies have suggested an association between PPI therapy and risk of pneumonia, fracture, enteric infection, Clostridium difficile–associated diarrhea, cerebrovascular events, chronic renal failure, dementia, and all-cause mortality.
There needs to be a balance between concerns regarding the long-term safety of PPI therapy vs their efficacy in treating acid-related diseases.
There have been large randomized trials evaluating the many long-term safety concerns related to PPI therapy.
A trial that included 17,598 patients assigned to groups that were given the PPI pantoprazole or placebo. The data was collected on development of pneumonia, Clostridium difficile infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every six months.
The results of this trial showed that pantoprazole was not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections.

Hence, although PPIs are considered safe overall, as with all drugs, PPI therapy should only be used when the benefits are expected to outweigh the risks and should be used according to recommended dose and duration of treatment. However, this new research suggests that limiting prescriptions of PPI therapy because of concerns of long-term harm is not appropriate.

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

PHONE NO.: 022-666638043
EMAIL: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt. Ltd. (Peninsula Corporate Park, Peninsula Chambers, Ganpatro Kadam Marg, Lower Parel, Mumbai-400013