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Medical Bulletin

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XSTAN (TELMISARTAN): BEYOND BLOOD PRESSURE MANAGEMENT

Telmisartan is a selective angiotensin-II type 1 receptor blocker [ARB] which does not affect the other receptor systems involved in cardiovascular regulations. It is considered as a first-line drug in mild-to-moderate hypertension with an excellent safety profile.

Apart from its antihypertensive properties, Telmisartan has been extensively researched for its pleiotropic effects beyond blood pressure management & is also called as Metabosartan.

TELMISARTAN IN DIABETES

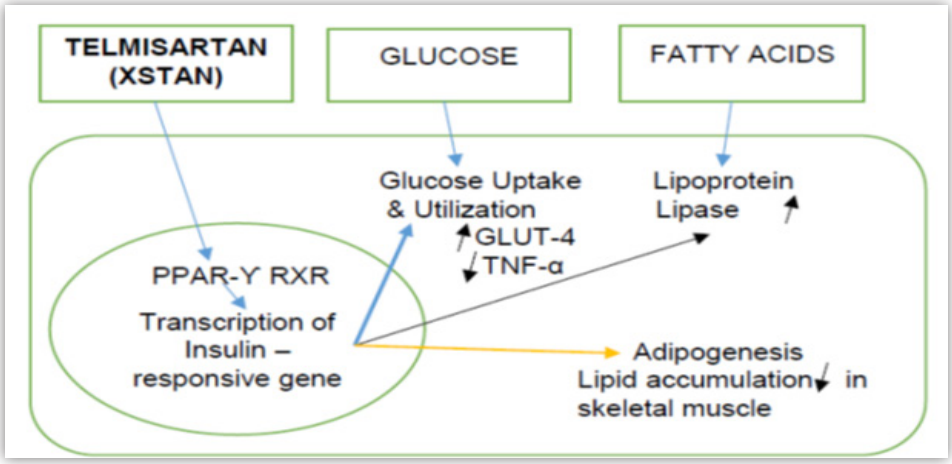
Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors & comprise three subtypes, namely PPARα, PPAR-Y, and PPARβ/δ. Among these, PPAR-Y is the most studied receptor & is involved in the control of energy balance, glucose & lipid homeostasis.

Antidiabetic drugs like thiazolidinedione's act on PPAR-Y and promote insulin sensitization and improve dyslipidaemia in diabetic patients. Full PPAR-Y agonists are associated with a number of side effects, including weight gain, fluid retention and cardiac toxicity. Partial PPAR-Y agonists selectively modify the expression of genes needed only for insulin sensitization without activating the genes responsible for weight gain and oedema, making them preferable over full agonists.

Telmisartan is reported to have partial PPAR-Y agonistic effect, and can regulate glucose and lipid metabolism, and improve insulin resistance. PPAR-Y phosphorylation and its downstream gene expression may be regulated by Telmisartan, promoting glucose uptake and acting as an insulin-sensitizing agent in adipocytes. It also augments glucose transporter-4 protein (GLUT-4) expression and 2-deoxyglucose (2-DG) uptake in the basal and insulin-stimulated states of adipocytes. It further increases GLUT-4 localization to the plasma membrane and enhances glucose uptake in the adipocytes.

In addition, the renin–angiotensin–aldosterone system (RAAS) which is implicated in the development of T2DM gets interrupted & may improve glycaemic control.

Owing to the ability of Telmisartan, partial activation of PPAR-Y and ARB blockade may have additional importance not merely in the management of metabolic syndrome and prevention of T2DM but also in the prevention and treatment of atherosclerotic cardiovascular disease.



Telmisartan and PPAR-Y agonism in glucose and lipid metabolism

TELMISARTAN IN OBESITY

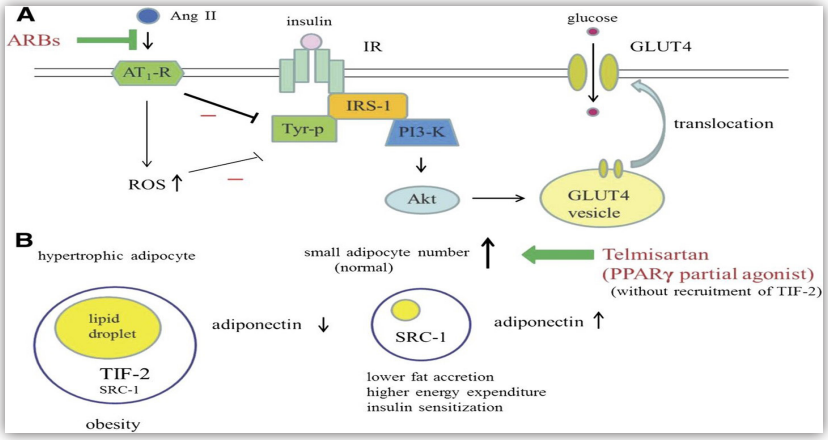
Prevalence of hypertension, obesity and their co-morbidity has increased significantly in recent decades. Adipose tissue synthesizes and secretes hormones (e.g., leptin and adiponectin) and inflammatory mediators (TNF-α & IL-6), and controls insulin sensitivity, while obesity induces adipose tissue dysfunction. Adipose tissue

dysfunction represents tissue remodelling characterized by adipocyte hypertrophy and hyperplasia, increased secretion of pro-inflammatory adipokine, inflammatory cell infiltration, mitochondrial dysfunction, & tissue inflammation.

Obesity dependent hypertension is mainly related to visceral adiposity, which is mostly associated with dysfunction of adipose tissue, dyslipidaemia, & insulin resistance. Several studies suggested that, ARBs could improve adipocytes differentiation, attenuate the inflammatory process in adipose tissues and improve adipocytokine formation.

It has been observed that, Telmisartan opposes obesity induced alterations in serum adipokines and ghrelin levels, thus implying that, Telmisartan preserves much more of the adipose tissue functions beyond the PPAR-Ɣ dependent lipid metabolic effects.

Additionally, several studies have reported the decrease in serum adiponectin level in obesity and interestingly, replenishing adiponectin may be a potential strategy in the treatment of obesity related comorbidities. Telmisartan has shown to improve adiponectin production in hypertensive patients with T2DM.



Telmisartan and partial PPAR-Ɣ agonism in obesity

Overall use of Telmisartan has shown improved altered anthropometric measures and central fat deposition as well as visceral fat deposition.

TELMISARTAN ALTERS CARDIAC FUNCTION AND DYSLIPIDAEMIA

Obesity is an independent risk factor for cardiovascular disease (CVD) and also its related disorders such as hypertension, dyslipidaemia, atherosclerosis and insulin resistance. Obesity related hypertension could be due to multiple mechanisms including endothelial dysfunction, renal affection, stimulation of the renin–angiotensin–aldosterone system (RAAS) and insulin resistance.

Telmisartan exhibits cardio protective effects in terms of decreasing the SBP, normalizing the HR, and reducing the levels of the cardiac enzymes. Telmisartan also helps prevent obesity induced dyslipidaemia by increasing HDL cholesterol levels, decreasing VLDL cholesterol levels as well as reducing triglyceride levels, which are common in obesity related hypertension.

TELMISARTAN AND INFLAMMATION

Hypertensive patients exhibit high levels of CRP and IL-6 as compared to their normotensive counterparts. Telmisartan monotherapy has shown to significantly decrease serum levels of CRP and IL-8 in obese hypertensive patients. Telmisartan has also shown to significantly reduce serum levels of TNF-α and IL-6. This demonstrates the potential effects of Telmisartan on systemic inflammation in obesity related hypertension.

A number of studies have examined the potential mechanisms through which PPAR-Ɣ agonists might act to ameliorate Alzheimer's disease (AD) pathogenesis and progression. AD has a significant inflammatory component which has been linked to β-Amyloid accumulation and neuronal loss. PPAR-Ɣ agonists have been shown to reduce the levels of multiple inflammatory mediators. Several studies suggest that Telmisartan may have additional benefits and be useful for the treatment of elderly hypertensive patients with AD.

CONCLUSION

Hypertension is one of the major risk factors for cardiovascular disease. Angiotensin Receptor Blockers (ARBs) are a class of antihypertensive drugs with established efficacy and favourable safety profile. Telmisartan, a member of the ARB family, holds some additional traits which differentiate it from the rest of the ARBs.

A pivotal role in these characteristics plays its ability to partially activate the PPAR-Y, which in turn controls a number of metabolism-related genes.

Indeed, Telmisartan has shown a number of pleiotropic effects in experimental and clinical studies which include the amelioration of insulin resistance, improvement of lipid profile and favourable fat redistribution. Along with it's effect on metabolic syndrome, it has been associated with other beneficial effects on inflammation, vascular, cardiac and renal functions.

Hence overall, Telmisartan not only qualifies as a safe and effective anti-hypertensive, but also beneficial in many metabolic syndromes like diabetes and obesity, which are often co-morbidities associated with hypertension. Due to its benefit in AD, Telmisartan can be useful in hypertensive patients with AD.

Source: Ayza MA et al. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2020; 13: 3627-3635.; Rizos CV et al. Curr Pharm Des 2009;15(24): 2815-2832.; Kume K et.al; Geriatr Gerontol Int 2012; 12: 207–214.; Naguib YM et al. Cardiovasc Diabetol 2021; 20(70): 1-19.;Kow CS & Hasan SS. Obesity 2020; 28(11): 2035.

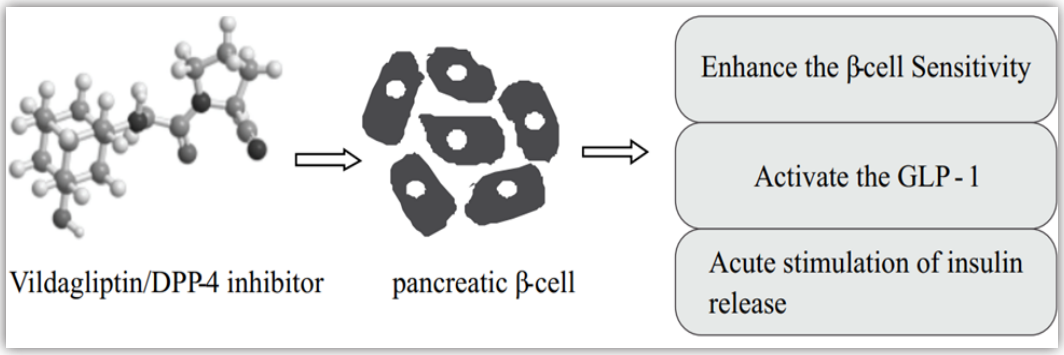
EFFICACY OF BLUGLIP (VILDAGLIPTIN) IN INDIAN PATIENTS

The DPP-4 inhibitor Vildagliptin used for the treatment of type 2 diabetes mellitus (T2DM) is a potent, selective & orally active 2nd generation inhibitor of DPP-4 enzyme, with a reversible & competitive mechanism of action that binds & forms a complex with DPP-4, causing its inhibition.

This results in improved glycemic control as determined by glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels plus an enhancement of pancreatic α and β-cell functions.

Vildagliptin treatment improves beta-cell sensitivity to glucose, producing increased insulin secretory rate relative to glucose in both postprandial and fasting states. Improved alpha-cell function (Interferes with post receptor signalling mechanisms of GLP-1, resulting in an improvement of alpha cell glucose sensing) is shown as restoration of appropriate glucose-related suppression of glucagon and therefore, reduced endogenous glucose production during both postprandial and fasting periods. There is evidence that long-term Vildagliptin treatment may slow underlying deterioration of beta-cell function and also increasing its mass (preclinical studies indicate attenuate oxidative stress and apoptosis, regeneration and neogenesis, for increased mass of β-cells) in T2DM.

There is also a potential synergistic effect of Vildagliptin and Metformin in increasing active GLP-1 levels, and this activity may contribute to the long-term improvements in beta-cell function observed in patients with T2DM who have Vildagliptin added to ongoing metformin therapy. Thus, Vildagliptin monotherapy yielded consistently robust improvement in beta-cell function, measured by HOMA-B & when added to Metformin monotherapy it significantly increased the insulin secretions. who have Vildagliptin added to ongoing Metformin therapy. Thus, Vildagliptin monotherapy yielded consistently robust improvement in beta-cell function, measured by HOMA-B & when added to Metformin monotherapy it significantly increased the insulin secretions.



Action of Vildagliptin on Pancreatic β-cells

India has been labelled as “Diabetic capital of the world” with an estimated 100 million diabetic patients. Indian patients are often diagnosed late and have a high prevalence of microvascular and macrovascular complications at diagnosis. The poor glycemic control, long duration of illness, and the ethnicity of the population contribute to the increased susceptibility to diabetes associated complications. Therefore, early diagnosis of diabetes and improved glycemic control will aid in alleviating the risk factors of these patients. The mean HbA1c is also higher in Indian patients—with epidemiological studies showing the average HbA1c of 9%. *The ADA guidelines suggests that upfront combination therapy should be considered in patients with baseline HbA1c 1.5% above the target range, thus making at least 50% of newly diagnosed Indian patients candidates for upfront combination therapy.*

Targeted glycemic levels may not be achieved by Metformin or another oral antidiabetic drug monotherapy. Hence, considering diabetes as a progressive disease, combination therapies of Metformin with other oral antidiabetic drugs are recommended.

Vildagliptin is a second-generation dipeptidyl peptidase-4 (DPP-4) inhibitor and evidence suggests potential mechanisms of synergy between Metformin and Vildagliptin. The clinical efficacy and safety of Vildagliptin monotherapy or in combination with Metformin have been demonstrated in several studies. Globally, the effectiveness, tolerability and low discontinuation rates of Vildagliptin monotherapy and combination therapy of Vildagliptin and Metformin are reported in several real-world studies.

EFFICACY AND SAFETY OF VILDAGLIPTIN IN INDIAN T2DM PATIENTS

A real-world study documented the clinical characteristics, and treatment patterns including dosage and duration of Vildagliptin monotherapy or Vildagliptin and Metformin combination therapy in adult patients with T2DM across 365 clinical study centres in India.

This study suggested that monotherapy of Vildagliptin or combination therapy with Metformin showed greater improvements in the mean HbA1c (95.3% patients) and greater reduction in the body weight. These observations suggest the clinical effectiveness and tolerability of Vildagliptin / Vildagliptin and Metformin combination in Indian population.

CONCLUSION

The use of Vildagliptin therapy in patients with comorbidities (hypertension and dyslipidaemia), complications (peripheral neuropathy, CAD, nephropathy, and retinopathy), different age groups (younger to elderly patients), and physician acceptance suggests wide use of Vildagliptin for each subgroup of the diabetic continuum in Indian settings.

Source: Iftekar H et al. Indian Journal of Pharmacy Practice 2012; 5(4): 1-8.;Balachandran K. Indian J of Endocrinology & Metabolism 2020; 24(2): 224-226.;Das S et al. Bioinformation 2021; 17(3): 413-423.

PPIs and Glycaemic Index

Patients with type 2 diabetes have decreased pancreatic beta cell mass with an eventual decline in beta cell function. Gastrin is a hormone that has been shown to increase beta cell proliferation.

Due to a negative feedback loop between gastrin and gastric acid, gastrin secretion is inhibited by high gastric acid levels. Because proton pump inhibitors (PPIs) lower gastric acid, subsequently increasing gastrin levels, it is theorized that this may stimulate beta cell proliferation and function and improve glycemic control.

High prevalence of gastro-esophageal reflux disease (GERD) amongst diabetic patients & several mechanisms have been proposed to explicate the association between GERD and diabetes, including the impact of hyperglycemia on the motility of the gastrointestinal tract and neuronal functioning leading to gastroparesis and esophageal motility disorder. Proton pump inhibitors (PPIs) are widely prescribed agents for treating GERD, peptic ulcers, and gastritis with a remarkable safety profile. Several retrospective studies on PPIs have documented its promising role in ameliorating glycemic levels.

POSSIBLE MECHANISM OF PPIS AND GLYCAEMIC CONTROL

Gastrin, a linear peptide hormone which is secreted mostly in the stomach pyloric antrum G cells, secretion of which is stimulated by various factors, as distension of the stomach, vagal stimulation, presence of food (espe-

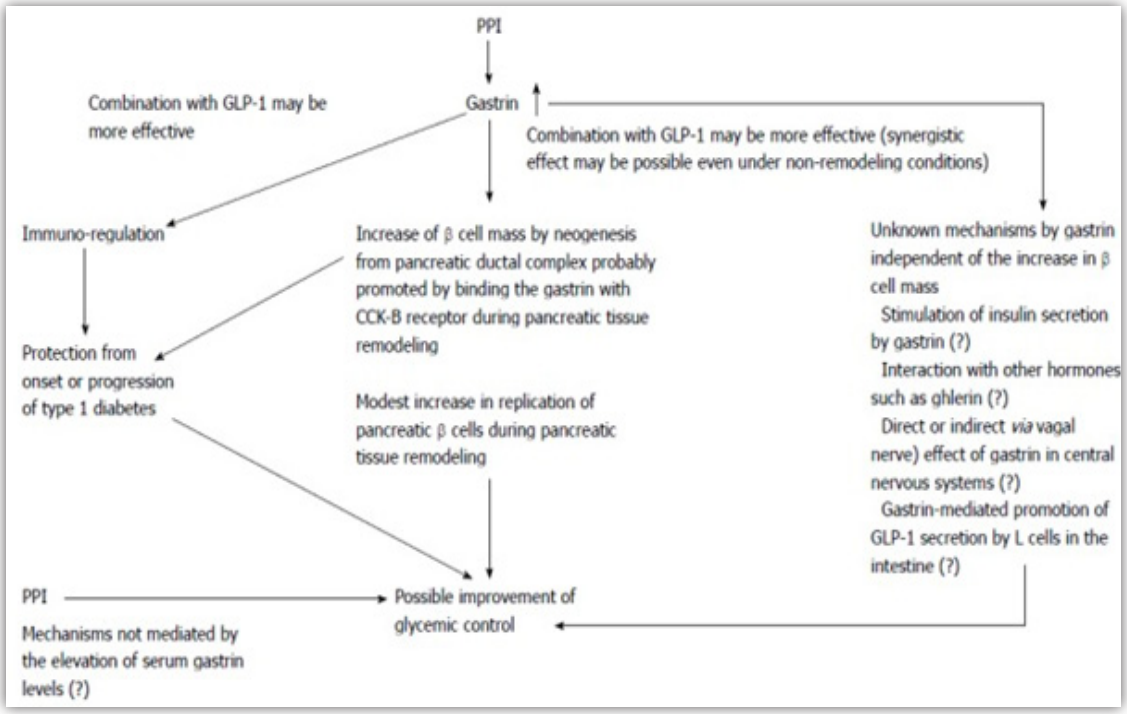
cially protein, peptides, and amino acids) in the stomach, and high pH levels in the stomach cavity. The main role of this hormone is to stimulate gastric acid secretion from the stomach parietal cells.

It is reported that gastrin promotes β cell neogenesis in pancreatic ductal complex, pancreatic β cell replication, and improvement of glucose tolerance. These findings suggest the possibility gastrin has a potential promoting effect for the increase in the pancreatic β cell mass.

PPIs irreversibly block the proton pump and can strongly reduce the secretion of gastric acid promoted by either gastrin, acetylcholine or histamine. It is well known that PPIs indirectly elevate serum gastrin levels via a negative feedback effect and interestingly, in T2DM, it has been reported that PPIs have shown to improve glycaemic control, probably via possible effects on augmenting both serum levels of gastrin and β cell mass.

SUMMARY OF MECHANISM:

- PPIs affect gastric acid secretion, which acts as a physiological regulator of gastrin release increasing its levels.
- Due to its structural similarity to incretin hormone, it can potentiate insulin release.
- Also, Gastrin stimulates beta cell neogenesis, along with a decrease in apoptosis.
- Furthermore, gastrin negatively regulates ghrelin, thus playing a crucial role in suppressing appetite and enabling a better glycaemic control on increased gastrin release.
- The use of PPIs also increases the bioavailability of anti-diabetic medications such as metformin and glimepiride.



Possible mechanism of PPIs and glycaemic control

CONCLUSION

Studies have shown that, PPIs along with oral hypoglycaemic agents and standard care have shown improved glycaemic indices like a significant decrease in the HbA1C levels as well as fasting blood glucose levels, but no decrease in the risk of incidence of diabetes. Hence, this effect of PPIs on glycaemic control should be considered when treating upper gastrointestinal symptoms in patients with diabetes.

Source: Takebayashi K & Inukai T. World J Diabetes 2015; 6(10): 1122-1131.;Peng CC et al. Diabetes 2021; 70(1).; Villegas K et al. Metabolic Syndrome & Related Disorders 2019; 17(4).

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/