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# Medical Bulletin

## News You Can Use

## Greater Pressure Drops In Hypertensive Patients Lowers Kidney Function

**Increased reduction in blood pressure in patients undergoing hypertension treatment is associated with an increased risk of kidney dysfunction.**

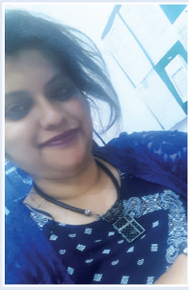
The above study findings were presented at American Society of Nephrology (ASN) Kidney Week at the Ernest N. Morial Convention Center in New Orleans, USA and published in the *Clinical Journal of the American Society of Nephrology (CJASN).*

The SPRINT trial found that in people with high cardiovascular risk, **more intensive BP control (systolic BP <120 mm Hg) reduced the risk of early death; however, intensive treatment was linked with reduced kidney function.**

To further examine this effect on the kidneys, Rita Magriço, MD (Hospital Garcia de Orta, in Portugal) and her colleagues conducted an additional analysis of the study results. **They found that the increased risk to the kidneys was related to greater decreases in mean blood pressure. The benefit-risk balance of intensive treatment was less favourable as the average BP reduction increased.**

If this association is confirmed by prospective studies, **future recommendations for hypertension treatment in this population should integrate personalized/customized targets rather than a fixed cut-off for every patient.**

## Greetings from Blue Cross Laboratories!



*Dear Colleagues,*

*Hope all of you are in the best of health and spirit. It gives me immense pleasure and satisfaction to present you with the third issue of the Blue Cross Medical Bulletin for this current financial year.*

*This issue will have you updated on a few recent medical discoveries/developments, and novel clinical insights involving diverse therapeutic facets. We have also included two short tutorials and a new segment called "Beyond the Pharmacodynamic Frontier", in which we will highlight therapeutic benefits of molecules extending beyond the realm of their current indications. We hope all these topics make for interesting reading !*

*We hope you enjoy reading this edition of the Medical Bulletin as you have been in the past. Please feel free to send in your feedback, so that we can incorporate the same in future editions.*

*Happy Reading!*

*Best wishes & Warm regards,*

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## Atherosclerosis: Skipping Breakfast May Double The Risk

**A study led by researchers in Spain has suggested that skipping breakfast doubles the risk of "*subclinical atherosclerosis.*"** Subclinical atherosclerosis is a latent form of the condition, which does not produce symptoms straight away. Over time, however, this can lead to coronary heart disease, angina, or peripheral artery disease, among other conditions.

Popular wisdom has it that breakfast is the most important meal of the day - and the first set of findings from the Progression and Early Detection of Atherosclerosis study (PESA) suggests that the meal may be even more important than traditionally believed. The study findings were published in the *Journal of American College of Cardiology.*

**The results of this research indicate that those who consume ≤ 5 % of their daily calorie intake for breakfast may have double the risk of subclinical atherosclerosis compared with people who have a high-energy breakfast.** A high-energy breakfast may comprise of good sources of protein (yogurt/ eggs), whole grains, and fruit.

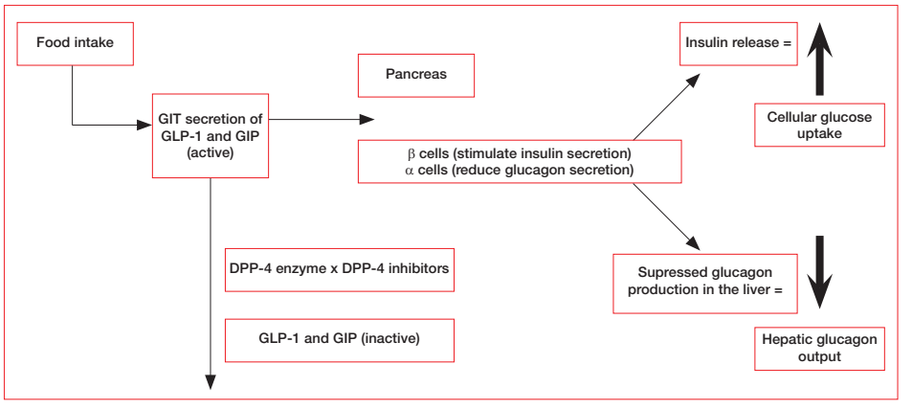
Short Tutorial

# Role Of DPP-4 Inhibitors In Management Of Diabetes

Type 2 diabetes is a progressive disease which may require intensification of therapy over time. Management includes a prudent diet, regular exercise and medicine to reduce blood glucose levels. Current pharmacological options in the management of type 2 diabetes largely include sulphonylureas, insulin, thiazolidinediones, α-glucosidase inhibitors and metformin. These treatment options, although highly effective in reducing blood glucose levels, may be associated with adverse events such as hypoglycemia, gastrointestinal side effects, weight gain, etc. **These unwanted adverse effects may act as barriers to optimal glycemic control. As a result, newer and safer treatment options for optimal glycemic control are continuously being investigated and developed. The dipeptidyl peptidase-4 (DPP-4) inhibitors are examples of such development.**

**Mechanism of Action: DPP-4 inhibitors are a new class of antidiabetic drugs that work to potentiate the effect of incretin hormones.**

- Incretin hormones are secreted from the gastrointestinal tract (the enteroendocrine cells), into the bloodstream in response to food intake. **The two most well-characterised incretin hormones are the glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotopic polypeptide, also known as gastric inhibitory peptide (GIP).**
- **GLP-1, in particular, appears to be responsible for the majority of the incretin effects on the pancreatic β-cell function.** When blood glucose levels are elevated following a meal, GLP-1 is released from the gastrointestinal tract, and it:
  - o Stimulates insulin secretion from the pancreatic β cells.
  - o Reduces glucagon secretion from the pancreatic α cells.
  - o Improves β-cell function.
  - o Slows gastric emptying.




DPP-4: dipeptidyl peptidase-4, GIT: gastrointestinal, GIP: gastric inhibitory peptide, GLP-1: glucagon-like peptide 1

Circulating levels of GLP-1 are low in the fasting state, and rise quickly following a meal. However, **GLP-1 has a very short half-life and is rapidly degraded by the enzyme, DPP-4. DPP-4 inhibitor drugs work by blocking/inhibiting the enzyme DPP-4 which is responsible for degradation of gastrointestinal incretin hormones (such as GLP1). Incretins help stimulate the production of insulin when it is needed (e.g., after eating) and reduce the production of glucagon by the liver when it is not needed (e.g., during digestion). Thus, gliptins regulate hyperglycemia in a glucose-dependent manner (i.e., they lower blood sugar levels only when they are too high).**

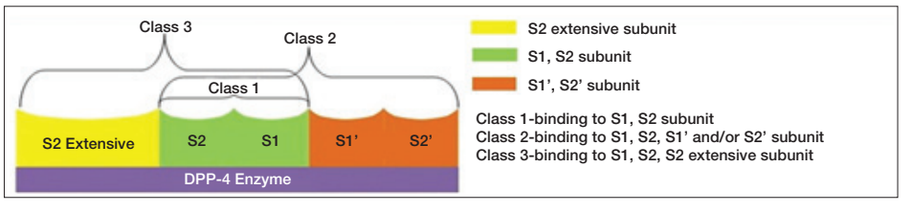
**DPP-4 inhibitors are recommended as monotherapy or in double and triple drug combination** with other oral glucose-lowering agents such as metformin, sulfonylureas, thiazolidinediones, or even with insulin. As a class, DPP-4 inhibitors are considered as a **cornerstone in the management of T2DM due to their efficacy, favourable tolerability profile (low risk of hypoglycemia and weight gain), and compliance due to once-a-day dosage.**

## Are all DPP-4 inhibitors the same?

Comparative studies have determined binding modes of DPP-4 inhibitors with the active site of DPP-4 enzyme. **The DPP-4 enzyme has five binding sites (subsites), namely, S1, S2, S1′, S2′, and S2 extensive. An interaction of DPP-4 inhibitors with S1 and S2 is considered to be the fundamental interaction that is required for DPP-4 inhibition. Additional interaction with S1′, S2′, and S2 extensive site may further increase the DPP-4 inhibition.**

## Classification of DPP-4 inhibitors is based on their selectivity for the enzyme:

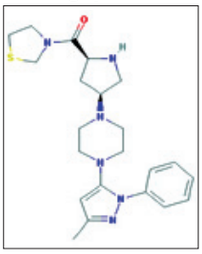
- Class 1 inhibitors (vildagliptin and saxagliptin) bind with S1 and S2 and are considered as fundamental/basic inhibitors.
- Class 2 inhibitors (alogliptin and linagliptin) bind with additional sites of S1′ and S2′ and may produce more DPP-4 inhibition than Class 1.
- Class 3 inhibitors (sitagliptin and teneligliptin) bind additional site of S2 extensive and produce **more extensive DPP-4 inhibition. The binding to this site is tighter than the binding to the other sub sites, and**



**hence provides a more effective and longer duration of DPP-4 inhibition, thus achieving better glycemic control.** Research indicates teneligliptin has a **five-fold higher activity than sitagliptin.**

### TENELIGLIPTIN: One of the Most Potent DPP4 Inhibitors

**Teneligliptin is a recently developed Class 3 oral dipeptidyl peptidase 4 inhibitor indicated for the management of type 2 diabetes mellitus in adults along with diet and exercise.**



**Teneligliptin** has **5-fold higher activity than Sitagliptin** due to the **J-shaped anchor-lock domain, strong covalent bonds with DPP-4 and more extensive S2 extensive binding than Sitagliptin.** This provides a **more potent and long duration of action.**

### OTHER ADVANTAGES OF TENELIGLIPTIN

- Teneligliptin offers pleotropic benefits such as improvement in endothelial function, left ventricular function, and lipid levels.
- Teneligliptin serves as an appropriate add-on to metformin early in therapy to delay exhaustion of pancreatic islet function.
- Teneligliptin offers unique pharmacokinetic advantage with longer half-life allowing convenient once daily administration irrespective of food.
- Teneligliptin is weight neutral and having least chances of hypoglycemia.
- **Teneligliptin has dual mode of elimination via renal and hepatic routes,** and hence can be administered safely in renal impairment patients. Also, dosage adjustment is not required in patients with mild to moderate hepatic impairment.
- Teneligliptin has been systematically evaluated in T2DM as monotherapy with diet and exercise and in combination with metformin, glimepiride, pioglitazone, and insulin in short-term (12 weeks) and long-term (52 weeks) studies. These studies have reported a reduction in HbA1c of 0.8%–0.9% within 12 weeks of therapy. Two 52-week studies reported sustained improvement in glycemic control with teneligliptin. Teneligliptin has been found to be well tolerated, and the safety profile is similar to other DPP-4 inhibitors.

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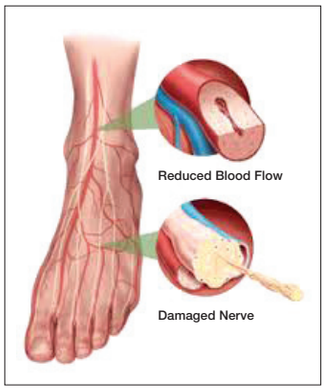
Short Tutorial

# Methylcobalamin & Diabetic Neuropathy

- Diabetic neuropathy is a **common peripheral nervous system dysfunction associated with diabetes.** If left untreated, diabetic neuropathy can be a chronic and a progressive condition. **Almost 50% of individuals affected by diabetes have complained of diabetic neuropathy. Diabetic neuropathy negatively impacts the quality of life of the patient.** It decreases physical activity, increases fatigue, causes sleep disturbances and hampers social interactions.
- **A range of sensory symptoms** such as insensitivity, pricking sensation of pins and needles, tingling, burning, electric shock like feeling, loss of pain sensation or increased sensitivity to pain are experienced in diabetic neuropathy. Initially, sensory symptoms appear in the toes and gradually spread to the upper limbs.
- **A key underlying cause for diabetic neuropathy is deficiency of vitamin B12.** Sometimes the deficiency is drug-induced (e.g., metformin).
- Vitamin B12 has a complex structure and is made up of different analogues. **The primary role of vitamin B12 involves proper functioning of the brain and nervous system and production of blood cells. However, in general, vitamin B12 analogues participate in different essential metabolic functions, including production of energy, fatty acid and DNA synthesis and its regulation. Cyanocobalamin, methylcobalamin and hydroxocobalamin are three therapeutic forms of vitamin B12.**




- **People have often thought that cyanocobalamin and methylcobalamin are synonymous, but they are two different analogues of vitamin B12.** Many people prefer cyanocobalamin formulation because of its low cost. **However, cyanocobalamin cannot produce any health benefits of vitamin B12 until it gets converted to methylcobalamin.** In the human body, the **cyanocobalamin is initially inactive, but it gets converted to methylcobalamin with the help of an enzyme called methylmalonyl CoA mutase in the mitochondria. This enzyme converts cyanocobalamin to methylcobalamin by replacing its cyanide group with a methyl group. Therefore, cyanide is released in this metabolic reaction, which can get accumulated in the body.** This risk is increased in kidney failure patients or smokers. It has been analysed that almost 2% of total cyanocobalamin dose converts to cyanide in the gastrointestinal tract. Therefore, an increased dose of cyanocobalamin has a great risk of increased cyanide concentrations in the body.
- **Methylcobalamin is the most active and effective form of vitamin B12. It is absorbed readily in the human cells and effectively reaches the**

**nervous system.** Therefore, health care experts believe that systemic or local **administration of methylcobalamin can provide a better treatment opportunity for conditions related to the nervous system.**

### Why is methylcobalamin the best option to treat diabetic neuropathy?

- Cyanocobalamin, methylcobalamin and hydroxocobalamin are three therapeutic forms of vitamin B12, but **methylcobalamin is the best in comparison to other generic forms.** Cyanocobalamin is inactive, not readily absorbable in cellular structures and needs to be converted to methylcobalamin. **After oral administration of methylcobalamin, a sufficient amount is available in the blood stream in comparison to cyanocobalamin.** Whereas hydroxocobalamin is a bioactive form, it cannot be given orally and the injections are painful.
- Clinical data trial has suggested that treatment with **methylcobalamin can improve the symptoms of diabetic neuropathy, possibly through regeneration of motor nerve fibres and gradually improving nerve conduction.** In addition, methylcobalamin also inhibits discharge of ectopic nerve impulsions from injured primary sensory neurons. Thus, experts assume that methylcobalamin can alter the pathophysiology of diabetic neuropathy.
- **Methylcobalamin not only helps to regenerate damaged nerves, but also reduce diabetic neuropathy-related pain symptoms.** Methylcobalamin is effective to improve diabetic neuropathy related pain, burning sensation, paraesthesia and heaviness of the limbs. **Methylcobalamin alone or in combination with other drugs has a potent analgesic effect and can effectively reduce diabetic neuropathy pain,** while simultaneously improving nerve conduction. There is a significant reduction in the pain score after using an oral combination of methylcobalamin and pregabalin for 2 weeks. This combination is also well tolerated by the patients.
- **Methylcobalamin is safe and effective in kidney failure patients:** Diabetes is a chronic condition and gradually injures the small blood vessels present in the kidney. Methylcobalamin is a good treatment option for the treatment of diabetic polyneuropathy with a kidney problem. A small scale clinical trial demonstrated that methylcobalamin administered intravenously provided benefits in patients with diabetic neuropathy and on haemodialysis. This study also concluded that methylcobalamin treatment is safe in these patients.

# Beyond The Pharmacodynamic Frontier

## Monotherapy and Dual Combination Therapies Based on Olmesartan: A Comprehensive Strategy to Improve BP Control

Volpe M, *et al. High Blood Press Cardiovasc Prev.* 2017; 24(3): 243-253.

- Olmesartan medoxomil exhibits tighter and more prolonged binding to the angiotensin II type 1 (AT1) receptor compared with other ARBs. These characteristics produce effective and sustained BP reductions in hypertensive patients at different cardiovascular risk profiles.
- Clinical studies have demonstrated that an olmesartan-based antihypertensive strategy provides sustained BP control over the 24-hour period.
- Growing evidence suggests that olmesartan antagonizes the vascular inflammatory process involved in development and progression of atherosclerosis.

## Voglibose can Treat Postprandial Reactive Hypoglycemia, Suppress Oxidative Stress and Prevent Endothelial Dysfunction.

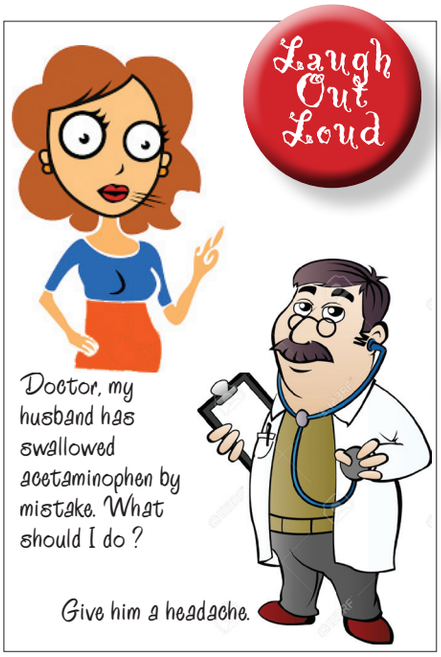
Suzuki K, *et al. Intern Med.* 2016; 55(8): 949-53.

- In postprandial reactive hypoglycaemia, administration of low-dose voglibose (alpha-glucosidase inhibitor), improved the glucose fluctuations and inhibited hypoglycemic symptoms.
- The above may be attributed to its ability to prevent endothelial dysfunction by suppressing oxidative stress.

## Rosuvastatin improves fasting and postprandial endothelial biomarker levels and microvascular reactivity in patients with type 2 diabetes and dyslipidemia.

Kim KM, et al. *Cardiovasc Diabetol.* 2017 Nov 9; 16(1): 146.

- The cardiovascular benefits of statins have been proven, but their effect on circulation in small vessels has not been examined fully.
- Effect of rosuvastatin on biomarkers, including paraoxonase-1 (PON-1) and asymmetric dimethylarginine (ADMA), and on microvascular reactivity was assessed in a 12 week study in 20 dyslipidemic patients with type 2 diabetes.
- Both fasting and postprandial levels of PON-1 increased and those of ADMA decreased after treatment with rosuvastatin for 12 weeks. **The postprandial changes in the endothelial biomarkers were significantly associated with improvement of microvascular reactivity. Therefore, rosuvastatin improves the cardiometabolic milieu in type 2 diabetes and dyslipidemia.**



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