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Medical Bulletin

Blue Cross Division

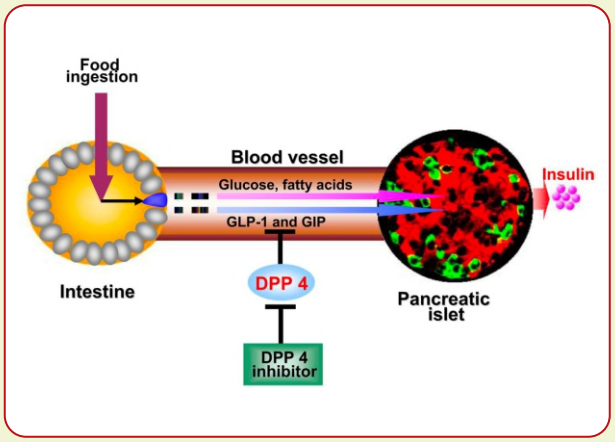
GLIPTINS AND INCRETIN HORMONES

Incretins are hormones released from the gut in response to ingestion of food, which then modulate the insulin secretion. This response of incretins is called the **incretin effect**, and accounts for at least 50% of the total insulin secreted after oral glucose ingestion.

There are two incretins, known as glucose-dependent insulinotropic peptide (GIP), released by the **'K' cells** of the duodenum and glucagon-like peptide-1 (GLP-1), released by the **'L' cells** of the distal ileum.

These incretin hormones achieve their insulinotropic effects by binding to its specific receptors and stimulate insulin biosynthesis as well as secretion.

In addition to being insulinotropic, GIP affects fat metabolism in adipocytes by enhancing insulin-stimulated incorporation of fatty acids into triglycerides. It also stimulates lipoprotein lipase activity, modulates fatty acid synthesis, and promotes β-cell proliferation and β-cell survival.



Similarly, GLP-1 also inhibits gastric emptying, decreases food intake, inhibits glucagon secretion, and slows the rate of endogenous glucose production, all of which together helps glycemic control.

These incretin hormones are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) and hence, inhibitors for this enzyme (DPP-4 inhibitors) help maintain adequate levels of the incretin hormones and are often used as therapy for blood glucose management in T2DM.

DPP-4 INHIBITORS

Gliptins are of DPP-4 inhibitors used for glycaemic control in T2DM patients. There have been various gliptins developed over time through extensive research, with sitagliptin being the first of its class approved, followed by Vildagliptin, Saxagliptin,Linagliptin, Alogliptin and Teneligliptin.

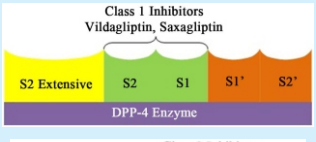
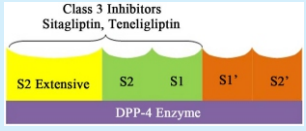
All DPP-4 inhibitors have the same mechanism of action, but there are some characteristics that define the potency of DPP-4 enzyme inhibition.

DPP-4 enzyme has five binding sites (subsites), namely, S_1, S_2, S_1', S_2', and S_2 extensive. An interaction of DPP-4 inhibitors with S_1 and S_2 is considered to be the fundamental interaction that is required for DPP-4 inhibition. Additional interaction with S_1', S_2', and S_2 extensive site may further increase the DPP-4 inhibition.

Teneligliptin appears to possess a different chemical structure when compared to other DPP-4 inhibitors exhibiting an "anchor lock domain" of **S_2 extensive subsite** along with the S_1 and S_2 subsites thus boosting its potency, duration of action as well as its selectivity as compared to vildagliptin which binds to only the S_1 and S_2 subsites of the enzyme.

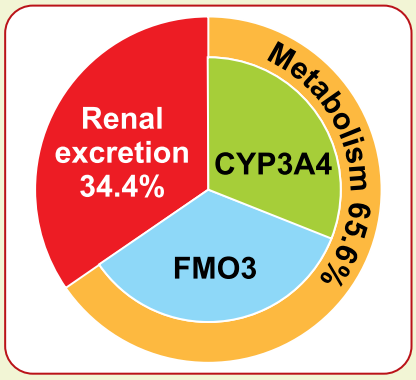
Teneligliptin is thus, a potent, selective, and long-lasting DPP-4 inhibitor and has approximately **700- to 1500-fold greater affinity for DPP-4 than other DPP enzymes, such as DPP-8 and DPP-9**, which are other intracellular proteases responsible for T-cell activation and therefore off-target inhibition can cause undesirable and serious side-effects such as immune dysfunction, impaired healing, reticulocytopenias and skin manifestations, thus making teneligliptin a safer DPP-4 inhibitor.

As far as the pharmacokinetic properties are concerned, the **half-life of teneligliptin is 24h** which as compared to vildagliptin. is only 2.8h, giving a longer duration of action - **once a day** dosing as against BID dosing of vildagliptin. Which in turn becomes beneficial for patient compliance, especially since diabetic treatment is usually for long duration.

Class	DPP-4 inhibitors	Binding at DPP-4	Interaction with DPP-4 at various sites	Details
1	Vildagliptin & Saxagliptin	S_1 & S_2 subsites		• Fundamental/basic interaction required for DPP-4 inhibition • Cyanopyrrolidine moieties bind to S_1 • Hydroxyadamantyl groups bind to S_2 • Saxagliptin has 5-fold higher activity than Vildagliptin
2	Alogliptin & Linagliptin	S_1, S_2, S_1' & S_2' subsites		• Alogliptin binds to S_1, S_2 & S_1' • Linagliptin binds to S_1, S_2, S_1' & S_2' • Linagliptin has 8-fold higher activity than Alogliptin
3	Teneligliptin & Sitagliptin	S_1,S_2 & S_2 extensive subsites		• **Teneligliptin has 5 fold higher activity than Sitagliptin due to J-shaped anchor-lock domain, strong covalent bonds with DPP-4 & more extensive S_2 extensive binding than Sitagliptin**

Teneligliptin is known to show no drug interactions as compared to other gliptins, making it safer and more effective to be used in monotherapy as well as in combination with other diabetic medications as well as an adjunct to other drugs that are commonly a part of the polypharmacy amongst patients with T2DM .

The elimination of teneligliptin from the body is 50% through urine and 50% through faeces and hence as compared to Vildagliptin, it can be safely used in patients with mild to moderate hepatic impaired cases or any renal impaired cases.



In conclusion, Teneligliptin demonstrates potent, selective and sustained effects on glycaemic control in patients with T2DM, both in monotherapy and in combination with other antidiabetic drugs, can be effectively used in patients with renal or hepatic impairment, thus making Teneligliptin a particularly viable consideration for a diverse range of T2DM patients, including those with renal impairment or elderly subjects.

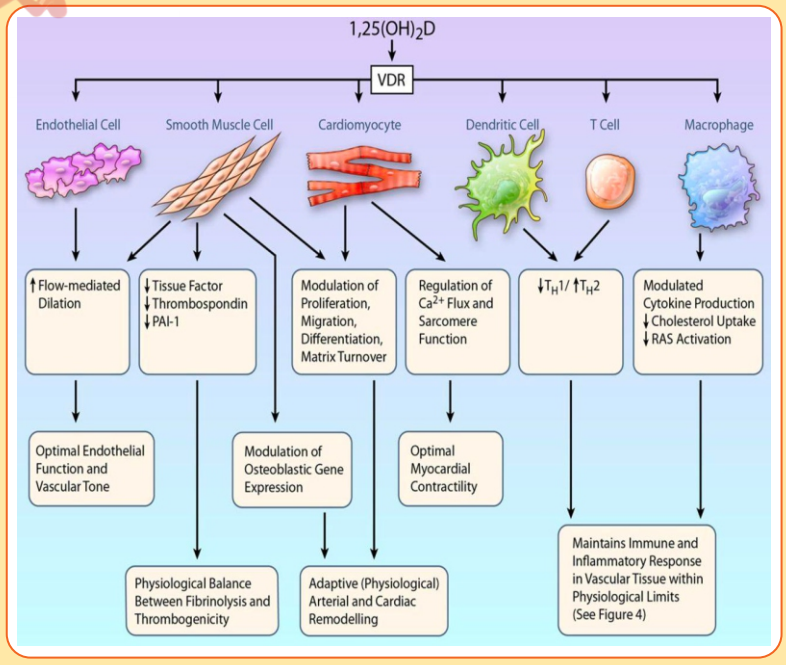
Source: *Kim W & Egan JM. Pharmacol Rev 2008; 60(4): 470-512. Girard J. Diabetes & Amp; Metabolism 2008; 34(6): 550-559. Omar B & Ahren B. Diabetes 2014; 63(7): 2196-2202. Kushwaha RN et al. Chemistry & Biology Interface 2014; 4(3): 137-162. Sharma SK et al. Dovepress 2016; 2016(9): 251-260. Samraj GP. Therapy 2011; 8(6): 703-719. Gupta V & Kalra S. Indian J Endocrin Metab 2011; 15(4): 298-308. Ceriello A et al. Drugs 2019; 79(7): 733-750. Singh AK. Indian J Endocrine Metab 2017; 21(1): 11-17. Maideen NMP. World J Meta-Anal 2019; 7(4): 156-161.*

VITAMIN D AND ATHEROSCLEROSIS

The role of vitamin D beyond bone health has been extensively researched. There has been increasing evidence associating deficiency of vitamin D with development of atherosclerosis and other cardiovascular diseases (CVD) through several potential mechanisms.

VITAMIN D AND ATHEROGENESIS

At the cellular level, Vitamin D acts through the binding of its active form to the Vitamin D Receptors (VDRs), which are found in virtually all tissues of the body, including CV tissues such as cardiomyocytes and endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). Impairment of VDR activation has been implicated in the dysfunction of vascular smooth muscle and endothelium, and in accelerated atherosclerosis, calcification and cardiac hypertrophy.



It has been observed that, VDR deficiency not only promotes the development of atherosclerosis, but also decreases the stability of atherosclerotic plaques. This happens through mechanisms that include cell proliferation & differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, and cell adhesion.

Additionally, it has been suggested that VDRs up-regulate the endothelial nitric oxide synthase (eNOS) protein expression, an important enzyme that stimulates NO production, which is reduced and reactive oxygen species (ROS) increased, as the primary alterations of endothelial dysfunctions.

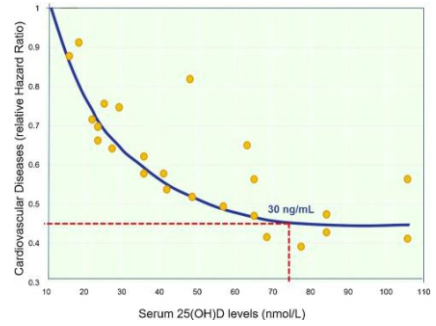
The presence of VDRs on VSMCs highlights the biological importance of vitamin D in the VSMC homeostasis and function. Vitamin D inhibits VSMC migration and proliferation by reducing the effect of vitamin D binding protein as well as affects the macrophages by lowering the oxidized LDL uptake, thus reducing the foam cell formation.

They also exert some morphological effects like increased elastogenesis and stabilization of muscluo-elastic multilayer of VSMCs via regulation of the production of proteins related to the vascular wall.

Along with these effects, vitamin D regulates the expression of profibrotic and antifibrotic factors through VDR mediated effects as well as upregulates the expression of Gla proteins and osteopontin by VSMCs, both of which are potent inhibitors of vascular calcification, thus overall inhibiting the process of atherogenesis.

VDR AND ATHEROSCLEROSIS

The process of atherosclerosis also involves innate as well as adaptive immune responses, where a subset of T cells called T_{h1} primarily drives the inflammatory response whereas, T_{h2} drives the anti-atherogenic cytokines, thus neutralising the effect of T_{h1}. Vitamin D shifts the immune response away from T_{h1} towards T_{h2}, thus promoting an antiatherogenic immune profile.



Vitamin D Levels and CV Disease

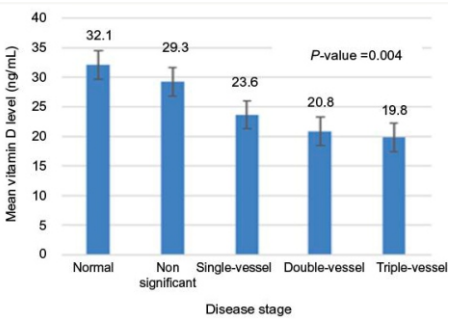
VITAMIN D DEFICIENCY AND RISK OF ATHEROSCLEROSIS

Vitamin D deficiency is a common public health problem, very often unrecognized and untreated and affects almost 50% of the population worldwide, with a prevalence of 70-90% among Indians contributing to an increased incidence of CVDs.

Large epidemiological studies have highlighted vitamin D deficiency as a marker of CV risk, promoting accelerated atherosclerosis and subsequent CV events.

Most experts define vitamin D deficiency as a level of <20 ng/mL and insufficiency as 21-29 ng/mL. Vitamin D is sufficient if the levels are >30 ng/mL, and vitamin D intoxication is considered if levels are >150 ng/mL.

Maintaining an optimal vitamin D serum level seems important not only for calcium homeostasis but also for CV risk. Observational data support the link between vitamin D status and cardiovascular diseases, and vitamin D deficiency can be considered a CV risk marker. This is very important for public health, considering the high prevalence of vitamin D deficiency, the aging population, and the indoor oriented lifestyle.



Vitamin Deficiency and Progression of Atherosclerosis

In conclusion, vitamin D deficiency is treatable and supplementation can be considered as a simple, inexpensive, and important prophylactic method in order to prevent CV morbidity and mortality.

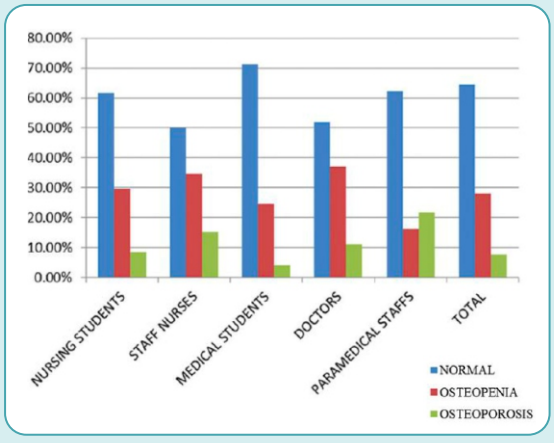
Source: *Lavie CJ et al. Circulation 2013; 128(22): 2404-2406. Talwalkar PG et al. Endocrine Abstracts 2018; 56: P218. Kassi E et al. Circulation 2013; 128: 2517-2531. Oberoi D et al. Annals of Cardiac Anasthesia 2019; 22(1): 47-50. Perez-Hernandez N et al. Korean J Int Med 2016; 31(6): 1018-1029. Mozos I & Marginean O. Biomed Res Int 2015; 109275: 1-12.*

PREVALENCE OF OSTEOPOROSIS AMONG MEDICAL AND PARAMEDICAL STAFF IN INDIA

Osteoporosis is a silent, underdiagnosed disease, which is characterized by low bone mass leading to increased susceptibility to fractures. Screening for osteoporosis is not routinely done despite growing awareness of this condition and its complications.

Although osteoporosis occurs among all populations, not all are at equal risk. Studies have reported that Asians have a higher predisposition for osteoporosis and it is estimated that by 2050, half of the world's fractures will occur in Asia. It is estimated that currently, 50 million Indians are living with osteoporosis or osteopenia.

The considerably high prevalence of osteopenia and osteoporosis among medical professionals could be viewed as a tip of an iceberg as bone mineral density (BMD) screening is not routinely done and there are no such recognizable signs and symptoms of low BMD unless the individuals turn up with fractures.



A study conducted on various health care professionals showed a significantly high prevalence of osteoporosis and osteopenia. Among doctors, the prevalence of osteoporosis was 11.32% in males, whereas in female doctors, it was 10.9%, with 48.1% of the doctors, irrespective of the gender, having significantly low BMD levels. Among staff nurses, the prevalence of osteopenia was seen in 40.9% and that of osteoporosis in 9.09%.

Conclusion: With the high occurrence of osteoporosis, the need of the hour for the medical professionals is to diagnose the problem at the earliest, so that optimal preventive measures can be initiated.

Source: *Sengodan VC et al, J Nat SC Biol Med, 2019; 10:29-33.*

WHAT'S NEW!!!

CORONAVIRUS: THE VIRAL OUTBREAK IN CHINA

China has been recently affected by a new strain of a pathogen as the cause of the recent pneumonia outbreak called "Corona virus", which has affected about 75,748 cases world wide people along with deaths of 2121 in 26 countries.*

The identified coronavirus is a new strain of virus, that has not been previously identified in humans. They are a broad family of viruses, but only 6, and now 7, are known to infect people, with an animal source to be the most likely "primary source".

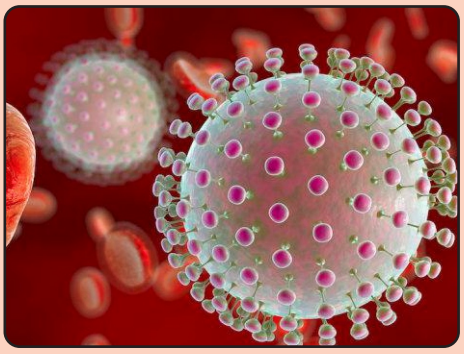
The virus is however, likely to spread via air by coughing and sneezing, close personal contact or by touching an object or surface with the virus on it and then touching the mouth, eyes or nose.

The signs of infection include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.

Taking precautions and following healthy guidelines will reduce the risk of getting an infection as well as spreading it.

***Source:** Coronavirus Disease-19 (COVID-19) Situation Report 31, World Health Organisation, 20th February 2020.*

ZIKA VIRUS VACCINE



Zika is a 'flavivirus', similar to dengue fever and yellow fever, transmitted through infected Aedes aegypti mosquito bites, sexually & through intrauterine infections.

Zika can cross through the placental barrier and affect the foetus, resulting in foetal microcephaly and other neurologic abnormalities.

The introduction of an effective vaccine for Zika will prevent infection of pregnant women and the resultant congenital effects in the unborn child.

The virology team, based at the Basil Hetzel Institute for Translational Health Research has developed a vaccine that prevents Zika infection in pre-clinical models of the disease.

It has been quoted "It is the first vaccine study that shows that a T cell-based vaccine can confer protection against a systemic Zika infection, and the vaccine offers an advantage over other vaccines in development by eliminating the ongoing concerns in the field about enhancement of infection following exposure to dengue virus. This finding demonstrates that protective T cell vaccines against Zika are achievable."

With progress on this work, women who are of reproductive age and most at risk can be immunised, and the devastating effects of Zika infection in pregnancy can be controlled.

ALZHEIMERS DETECTION EYE SCAN

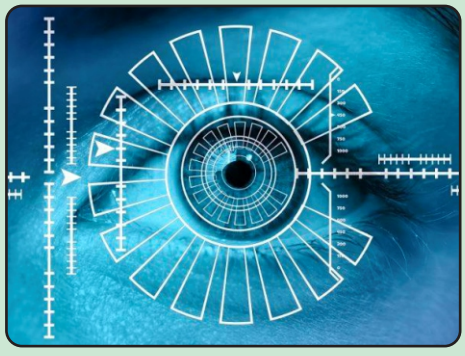
Alzheimer's disease and other forms of dementia affect an estimated 50 million patients in the world. Globally, India houses the second highest number of individuals suffering from dementia with an estimated 4.1 million people suffering from it as per the 'Dementia India' report published by the Alzheimer's and Related Disorders Society of India. This is expected to double by 2035.

Even though this is a commonly seen disease mainly in elderly people, the awareness about Alzheimer's disease is not much which affects its early detection.

While some treatments have been developed, there remain challenges to its detection and fast and accurate diagnosis, especially in the early stages. Up until now, patients had to undergo memory testing and/or PET scan or spinal tap-tests that are not always cheap or accessible.

The technology of the eye scan, developed in Canada, simply scans the retina to detect the presence of specific hormones developed in the brain by Alzheimer's disease. What is new is the technology: a high definition camera connected to specific software able to detect the presence of Alzheimer's biomarkers years before the emergence of clinical symptoms.

This technology has already been tested in a clinic in Toronto, in order to validate if the retina scan tests can diagnose Alzheimer's disease using a hypersensitive eye scan. The validation test is comparing the accuracy of diagnosis on patients that have already passed other detection tests. This makes detection simple, cheap, light, accessible, quick and harmless and helps the patient to know the exact diagnosis in order to cope with it and start the necessary treatment as early as possible.



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