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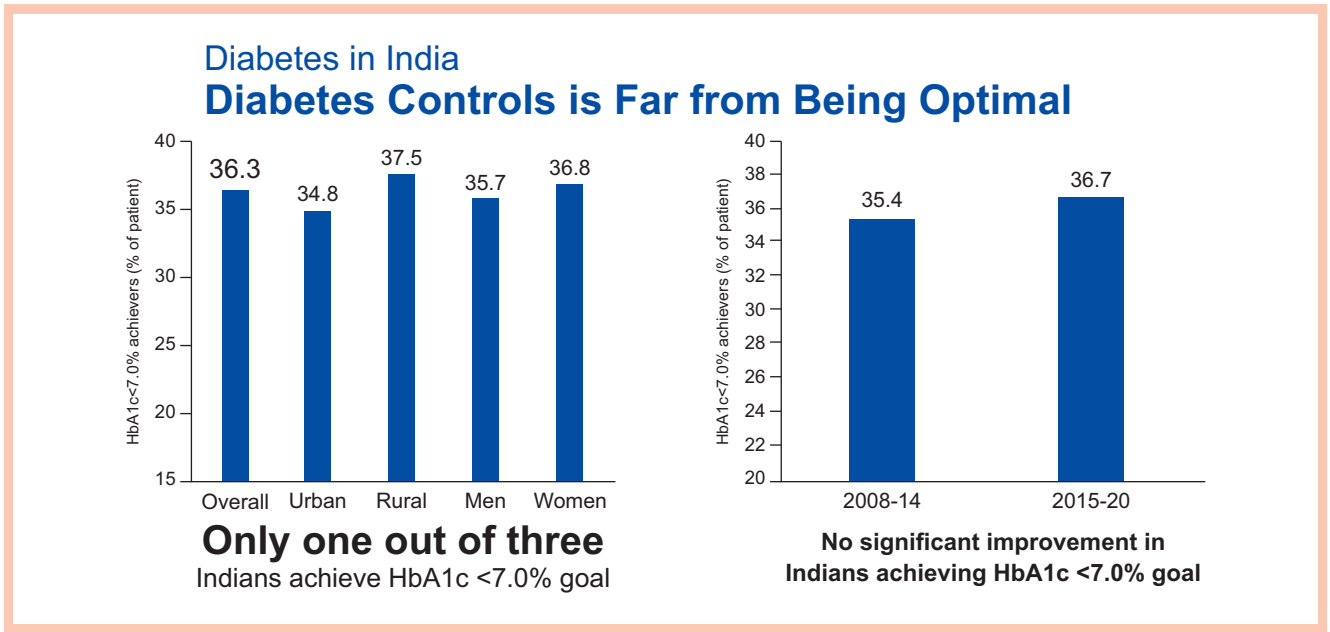
Medical Bulletin

OPTIMUM CLINICAL APPROACH TO COMBINATION USE OF SGLT2I + DPP4I + METFORMIN IN THE INDIAN DIABETES SETTING

The Asian-Indian phenotype of type 2 diabetes mellitus is uniquely characterized for cardio-metabolic risk. In emerging nations such as India, the burden of diabetes mellitus (DM) is large and rising, mostly due to soaring rates of overweight/obese individuals and poor lifestyle choices. In India, 101 million people were estimated to have DM and 136 million with pre-diabetes in 2021. Of the Indian population with DM, 76.6% has poor glycemic control. Type 2 DM (T2DM) which makes up most cases, can cause microvascular and macrovascular problems that can affect several organ systems. Additionally, insulin resistance associated with obesity contributes to the development of other cardiovascular (CV) risk factors, including dyslipidemia, hypertension. These problems play a significant role in the rise in early morbidity and death among the patients with diabetes, which results in a reduction of life expectancy and a huge financial load on the Indian healthcare system as complications of DM increase the total cost.



Treatment of diabetes must be personalized according to the factors of the patient such as atherosclerotic cardiovascular disease (ASCVD), indicators of high CV risk, heart failure (HF), chronic kidney disease (CKD), weight and glycemic levels. Criteria to consider while selecting a suitable agent include glycated hemoglobin (HbA1c) decrease, alteration in body weight, change in blood pressure (BP) and risk of hypoglycaemia.

Maintaining glycemic control & variability is difficult in the context of insulin resistance and typically requires adjunct medications because cell function diminishes. Due to metformin's ability to increase insulin sensitivity, the

addition of a medication that uses an insulin-independent mechanism may be beneficial. The latest American Diabetes Association (ADA) 2023 guidelines mention that for achieving the glycemic goals in a patient with DM, metformin can be combined with other OAD agent with adequate efficacy. Sodium glucose co-transporter-2 (SGLT2) inhibitors have been categorized under “high” glucose lowering capacity and thus become a potential option for combination therapy with metformin. Additionally, in DM cases with HF, CKD or CVD, SGLT2 inhibitors with proven benefit can be chosen, independent of the background use of metformin. SGLT2 inhibitors have been noted to have CV as well as renal benefits which extends to elderly population.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used in various individuals with T2DM from the young to the elderly because of their good glucose-lowering effect and safety including low risk of hypoglycaemia. DPP-4 inhibitors promote insulin secretion and suppress glucagon secretion by inhibiting the degradation of glucagon-like peptide-1.

SGLT2 inhibitors, improve glycemic control by reducing filtered renal glucose reabsorption from the proximal tubule and promoting excretion of excess glucose, which is a totally different mechanism compared with DPP-4 inhibitors. SGLT2i's as add-on therapy to teneligliptin exerted beneficial effects on metabolic parameters such as body weight, HbA1c, and uric acid without any severe adverse events.

DPP-4 inhibitors have a blood glucose-lowering effect induced via blood glucose-dependent secretion of insulin and suppression of glucagon, and they also suppress glycaemic fluctuation well and are associated with a lower risk of hypoglycaemia. Additionally, SGLT2 inhibitors have a blood glucose-lowering effect with a low risk of hypoglycaemia via kidney function and blood glucose-dependent urinary glucose excretion. Thus the triple-combination treatment with DPP4 inhibitors added to metformin plus SGLT2 inhibitors may exhibit synergism with complementary actions, thereby offering an effective therapeutic option reducing the glycemic levels rapidly with greater reduction & lesser glycemic variability.

Source: *Sethi, B, et al. Drugs - Real World Outcomes. 2024; 11: 81–90; Kim HJ, et.al, Journal of Diabetes Research. 2024: 8915591.*

VITAMIN D & OBSTRUCTIVE SLEEP APNEA: AN EMERGING LINK

Obstructive sleep apnea (OSA), a common sleep disorder associated with considerable morbidity, is defined by recurrent episodes of upper airway occlusion (partial or complete) leading to recurrent arterial hypoxemia and sleep fragmentation. Based on findings on the prevalence of OSA in Indian adults, it was estimated that approximately 104 million Indians of working age suffer from this condition, of whom 47 million have moderate-to-severe OSA. Data has also emphasized the association between OSA and a number of disorders, such as cardiovascular disease (CVD), impaired glucose metabolism and other endocrinopathies. In addition to this, current treatment options are not universally effective or well tolerated.

- One potential agent that has gained attention with respect to OSA is Vitamin D. OSA presence has been linked to lower serum Vitamin D levels, especially as the severity of OSA progresses. Several studies have consistently found a significantly higher prevalence of vitamin D insufficiency/deficiency in individuals with OSA, regardless of their geographical location or exposure to sunlight, suggesting a possible connection.
- A meta-analysis (29 studies comprising of 6717 participants) found that Vitamin D level was lower in OSA patients. Moreover, with increasing OSA severity, the serum Vitamin D level decreased more obviously, suggesting low levels as risk factor for OSA.

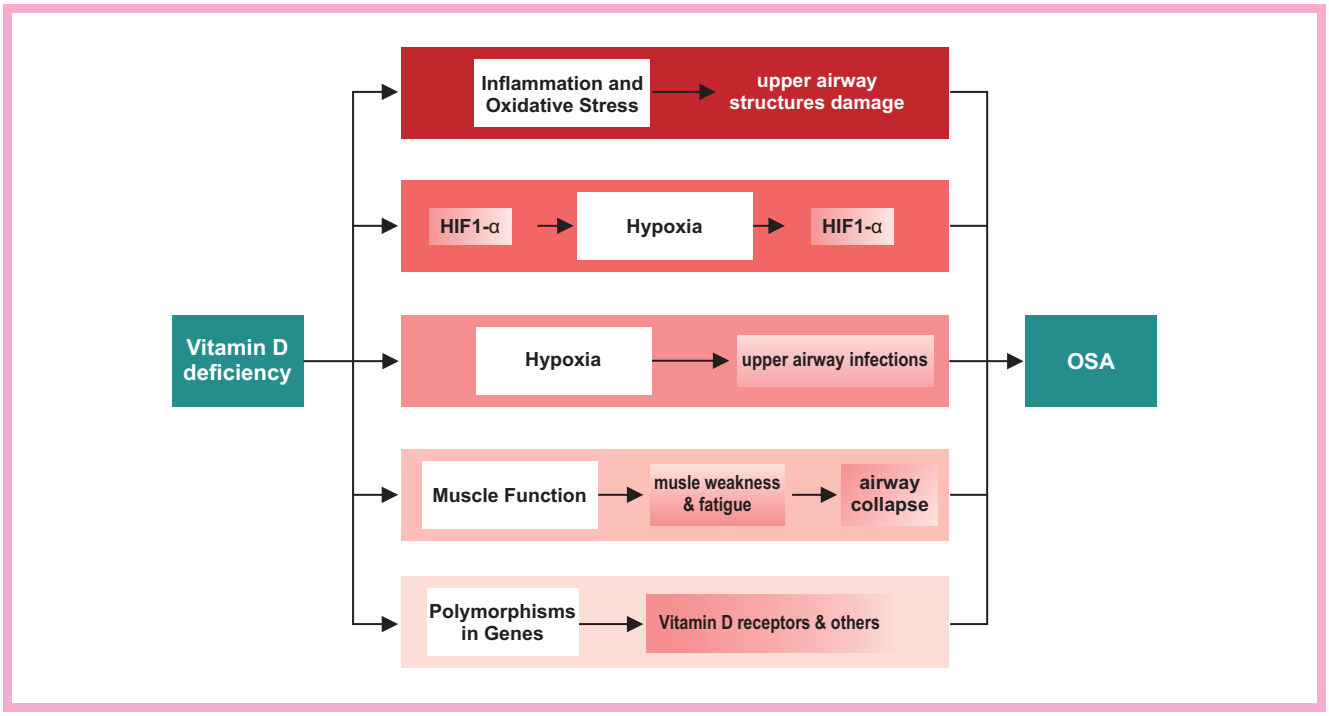
- A meta-analysis (9 studies, 9397 participants) has also demonstrated that inadequate levels of vitamin D, particularly those below 50 nmol/L, are linked to a heightened risk of sleep disorders. These disorders can manifest as poor sleep quality, shorter sleep duration and excessive daytime sleepiness, all of which may contribute to the deterioration of OSA symptoms.
- Furthermore, comorbid conditions commonly associated with OSA, such as obesity, diabetes and CVD can further complicate the interplay between vitamin D levels & OSA.

- Obesity is often linked with lower vitamin D levels due to the sequestration of vitamin D in adipose tissues.
- The presence of diabetes and CVD in patients with OSA can influence their vitamin D status, thereby potentially exacerbating the severity of sleep apnea.

✤ Potential Mechanisms Underlying Association between Vitamin D deficiency & OSA:

Several theories that have been suggested for the association are explained below:-

i Inflammation and Oxidative Stress: Vitamin D is known to have anti-inflammatory property, and a deficiency in it has been linked to heightened levels of inflammatory indicators. In OSA, intermittent hypoxia and sleep fragmentation can lead to systemic inflammation and oxidative stress, which can cause damage to the upper airway structures and contribute to the pathogenesis of the disease. Therefore, vitamin D deficiency may exacerbate this inflammatory process, thereby contributing to the severity of OSA.



ii. Hypoxia: The link between vitamin D deficiency and OSA has been suggested to involve hypoxia through the mediation of hypoxia-inducible factor 1-α (HIF1-α). HIF1-α is a key regulator of oxygen metabolism homeostasis and its expression has been shown to increase in OSA. Studies have demonstrated that vitamin D3 supplementation can reduce the protein expression, transcriptional activity and target genes of HIF1-α in various human cancer cells, thus affirming the relationship between vitamin D deficiency and hypoxia.

iii. Immune Function: Vitamin D modulates both the innate and adaptive immune responses and a lack of it has been linked to a heightened vulnerability to infections. In OSA, recurrent upper airway infections can lead to inflammation and swelling of the upper airway tissues, which can contribute to the development and progression of the disease. Therefore, Vitamin D deficiency can increase the risk of upper airway infections and contribute to the development of OSA by impairing immune function.

iv. Muscle Function: Vitamin D is recognized for its significant role in muscle functionality, and its deficiency has been linked to muscle weakness and fatigue. Dysfunction of the upper airway muscles in OSA can lead to collapse of the airway during sleep, which is a key feature of the disease. Therefore, vitamin D deficiency, by impairing muscle function, may contribute to the pathogenesis of OSA.

v. Gene Polymorphisms: The VDR gene, exhibits polymorphisms such as the VDR FokI variant. High prevalence of VDR FokI CC genotype has been found in patients with OSA correlating with reduced vitamin D levels. This polymorphism not only influences susceptibility to OSA but also appears to affect the severity of OSA symptoms, particularly daytime somnolence.

Besides, polymorphisms in genes encoding enzymes for vitamin D metabolism, such as CYP2R1 and CYP27B1 have been implicated- a) CYP2R converts vitamin D to its active form, and variations in this gene may affect vitamin D availability and function. b) CYP27B1, which also plays a role in vitamin D activation, has been linked to OSA severity.

These genetic variations can modulate the effectiveness of vitamin D in the body and potentially influence the pathophysiology of OSA.

The above underscore the intricate interactions between low Vitamin D levels and OSA.

✤ Clinical Evidence on the influence of Vitamin D Supplementation for OSA

i. One found that vitamin D supplementation may have a positive effect on the prognosis of mild OSA. Besides increase in Vitamin D levels, the patients showed a significant decrease in the number of obstructive apneas, hypopneas, apnea index, hypopnea index and apnea–hypopnea index after vitamin D supplementation (50000 IU/week for 8 weeks).

ii. Another placebo-controlled trial found significant increase in vitamin D levels and improvement in metabolic parameters (decrease in low density lipoprotein, lipoprotein associated phospholipase A2 and fasting glucose) in OSA patients with supplementation of vitamin D3.

The emerging evidence of the role of vitamin D in OSA may thus offer a new therapeutic possibility with consideration for optimal dosing, personalized treatment approach based on OSA severity, baseline Vitamin D status, response to standard treatment for OSA and further clinical exploration.

Source: *Yao, et al. J Sleep Res. 2024;33:e14166, Li X, et al. Respir Res. 2020; 21: 294, Kostas A, et al. Breathe (Sheff).2018; 14(3): 206–215, Suri TM, et al. Sleep Medicine Reviews. 2023: 101829.*

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