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BLUE CROSS

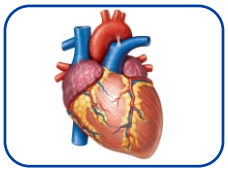
Medical Bulletin

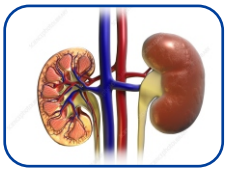
REASSESSING SITAGLIPTIN: CARDIORENAL SAFETY AND EFFICACY IN TYPE 2 DIABETES MANAGEMENT

Cardiovascular disease (CVD) and Chronic kidney disease (CKD) are well-recognized complications of long-standing diabetes, and are a major factor contributing to the morbidity & mortality. Hospitalization, low quality of life, & high mortality rate are inevitable in patients with this dual burden. Thus, the emphasis in diabetes care should be glycemic control, as well as optimal management of cardiorenal risk factors and comorbidities. Despite advances in preventive treatment strategies, such as dietary protein restriction, intensified glycemic control, improved blood pressure management and modulation of the renin-angiotensin system, CVD & CKD both remain common comorbidity for patients with type 2 diabetes mellitus.

Type 2 diabetes mellitus

- Oxidative stress (ROS)↑
- Sympathetic activity↑
- Activation of RAAS
- Inflammatory cytokines (IL-1, TNF-α, IL-6)↑
- Fibrinogen↑
- Arginine vasopressin↑
- Angiotensin II production↑
- NK cells (IFN-γ)↑
- Lipopolysaccharide↑





Cardiac dysfunction

- Arterial and endothelial calcification
- Cardiac pump capacity↓
- Cardiac output↓
- Venous resistance and pressure ↑

Renal dysfunction

- Kidney hypoperfusion
- Glomerular filtration rate↓
- Sodium secretion↓
- Electrolyte imbalance
- Fluid retention
- Anemia
- Hypertension

Treatment guidelines for the management of hyperglycemia in type 2 diabetes mellitus continue to emphasize personalized therapy, balancing the benefits of improved glycemic control with the risks related to adverse effects of glucose-lowering medications. These considerations are particularly relevant for patients with CVD & CKD, who may be at greater risk for, or more susceptible to, severe consequences from such adverse effects.

Sitagliptin is a highly efficient and selective dipeptidyl peptidase-4 inhibitor (DPP-4i) that improves glycemic control by prolonging the action of the incretin hormones glucagon-like peptide-1 (GLP-1) & glucose-dependent insulinotropic peptide (GIP), while having a low risk of hypoglycemia. It has neutral effects on body weight, low proclivity for pharmacokinetic interactions, and a favorable safety profile. Numerous clinical trials have proven that Sitagliptin is CV and renal safe in T2DM patients, even in those with obesity, old age, renal impairment (RI), and preexisting CVD. It also corrects hyperglycemia induced osmotic diuresis and excessive filtration. In people with T2DM who are at high CV risk or moderate-to-severe renal insufficiency, Sitagliptin is documented as a well-tolerated treatment that does not augment the risk of CV and renal complications.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin **(TECOS)** assessed the impact of Sitagliptin on cardiovascular outcomes in patients with T2DM and cardiovascular disease. The improvements in glucose insulin homeostasis and a reduction in low-grade inflammation in diabetic subjects with high CV risk may be attributed to Sitagliptin therapy.

In a randomized study, unaltered risk of major adverse CV events (MACE), adverse events, or hospitalization for HF (hHF) was observed with Sitagliptin.

Taiwan National Health Insurance Research Database (NHIRD) demonstrated that Sitagliptin lowers the rate of total CVDs, ischemic stroke, peripheral artery occlusive disease, the risk of hospitalization, and all-cause mortality.

In a retrospective cohort (PERsistent Sitagliptin treatment & Outcomes or PERS&O) study involving “real-world” data, persistent Sitagliptin treatment [12 months to 48 months] showed substantial effects on metabolic control (measured by HbA1c) as well as a reduction in CV risk at 12 months & 48 months.

A meta-analysis of randomized 52-week studies & 25 clinical studies data showed a significantly reduced risk of all-cause mortality with Sitagliptin in comparison to active controls(OR 0.39) / SUs, as well as lower risks of unstable angina, HF, MI, & CV mortality.

Another systematic review and meta-analysis of 14 studies on Sitagliptin, as monotherapy or adjunct therapy, demonstrated effective lowering of total cholesterol & low-density lipoprotein cholesterol, thereby lowering the risk of CV illnesses.

A prospective observational study reported, Urine albumin-creatinine ratio (UACR) at 3 months was significantly decreased in patients with baseline eGFR of ≥45 to <60 mL/minute/1.73 m2 & ≥30 to <45 mL/minute/1.73 m2.The probable reason for the decrease in albuminuria by Sitagliptin without lowering the eGFR was the reduction in blood sugar, blood pressure, & inflammation. Another 12-week, RCT showed that Sitagliptin delayed the development of albuminuria & reduced urinary albumin excretion besides reducing blood glucose levels in patients with T2DM, indicating the benefits of Sitagliptin treatment in the initial stage of diabetic nephropathy. In the *TECOS* trial no clinically significant increase in CKD outcomes with Sitagliptin was recorded irrespective of the stages. The CompoSIT-R & REAL trails have established the effectiveness of Sitagliptin in providing glycemic control and was well-tolerated in moderate-to-severe renal insufficiency, including dialysis-requiring patients with ESRD.

A systematic review & meta-analysis from 10 clinical studies indicated a decrease in albuminuria, a small decline in eGFR, and no difference in the risk of ESRD with Sitagliptin.

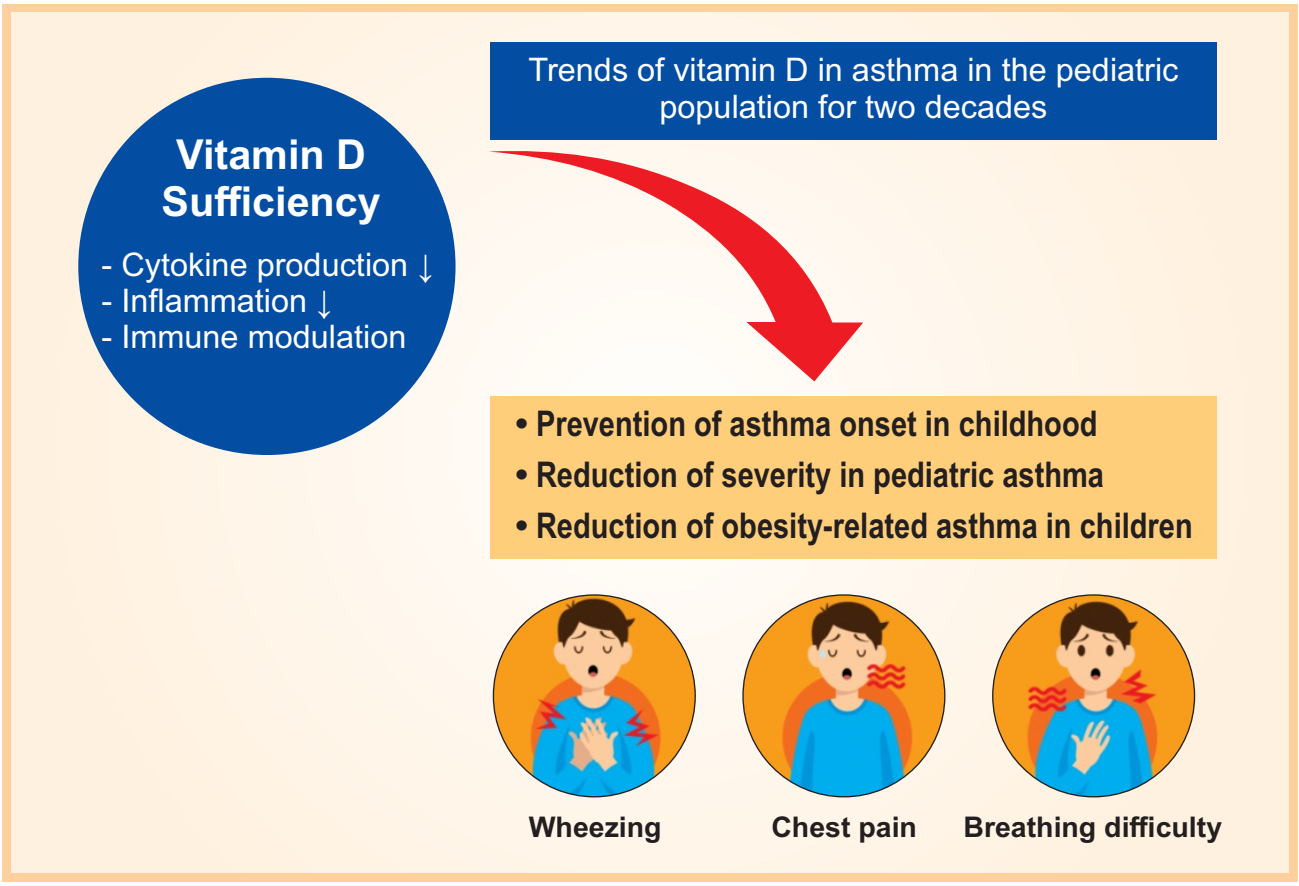
A favorable safety profile of Sitagliptin in patients with CVD & renal insufficiency is established with reference to findings of various studies. Sitagliptin is well-tolerated in patients with T2DM and moderate-to severe renal

insufficiency. Therefore, Sitagliptin could be a good therapeutic option for people with diabetes and cardiorenal impairment.

Source: *J Assoc Physicians India. 2025 Apr; 73(4):e19-e25.*

VITAMIN D DEFICIENCY IN CHILDREN: A HIDDEN TRIGGER FOR ASTHMA

Vitamin D exhibits anti-inflammatory properties through multiple mechanisms. Vitamin D deficiency is associated with increased inflammation, exacerbations, and overall worse outcomes in pediatric asthma and is observed in asthmatic children with obesity. In addition, given the increase in the prevalence of asthma over the last few decades, there has been enormous interest in vitamin D supplementation as a potential therapeutic option.



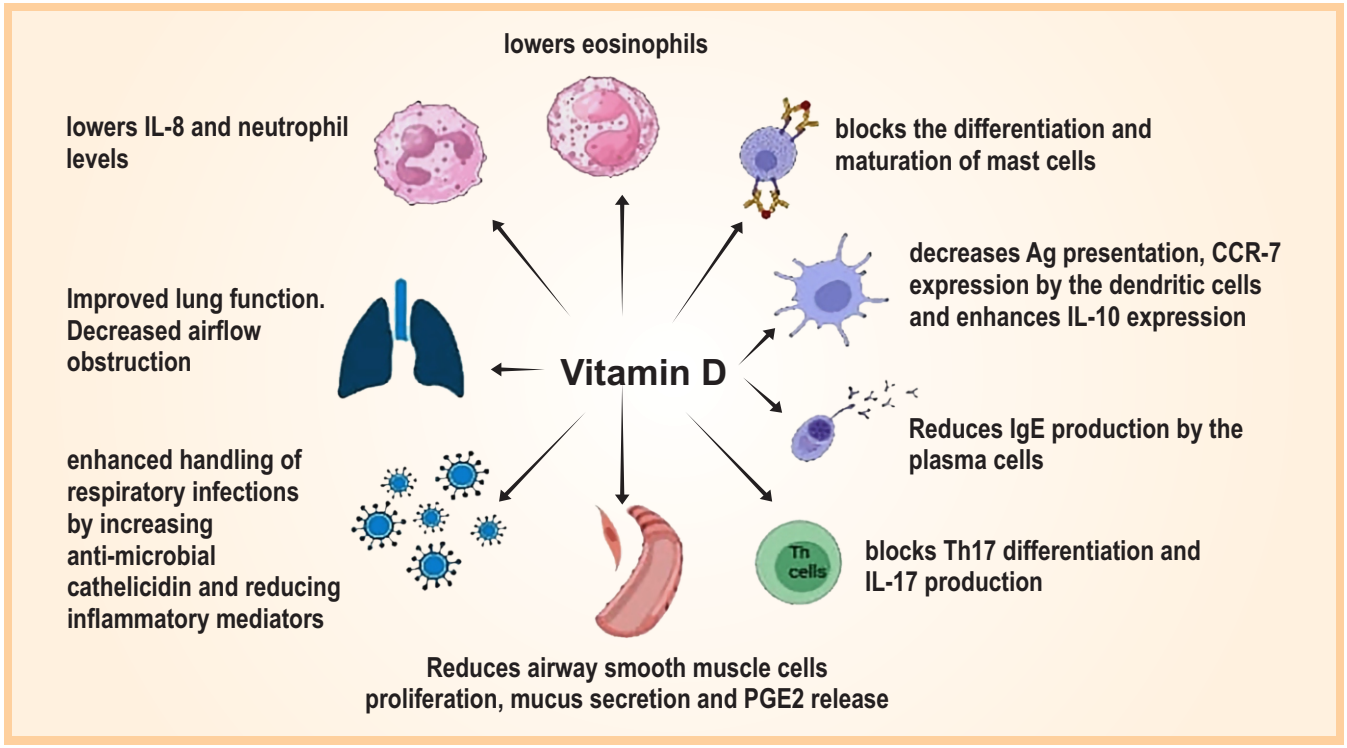
The effects of vitamin D as a hormone have gained increasing attention. Besides its numerous classical functions (calcium absorption, bone mineralization, and neuromuscular function regulation) and non-classical actions (cellular differentiation, insulin secretion, and blood pressure regulation), vitamin D is also believed to be a potent immune-system regulator, having a potential role in various allergic diseases. Furthermore, vitamin D has been reported to enhance lung development in infants when taken during pregnancy, and to have prophylactic effects on wheezing & asthma, which may occur later due to insuffiency of vit D.

Several studies measured the vitamin D level in asthmatic patients during periods of asthma exacerbation and found that most of those patients had low levels of vitamin D.

In one of the recently conducted prospective study with more than 500 children was conducted to examine the association between serum 25(OH)D levels and the risk for the onset of eosinophilic asthma. Serum 25(OH)D levels were tested and categorized as < 20, 20-39.9, and ≥ 40 ng/mL, whereas eosinophil counts were tested at infancy (aged less than 1 year) and at 3 and 6 years old, to evaluate the association between vitamin D status and asthma/eosinophilia.

Of the children included in the study, 58.2% and 28.8% of children developed eosinophilia and asthma, respectively, by the age of 6 years in the group having <20 ng/mL of serum 25(OH)D levels during the early childhood days. Thus, among children with a history of severe bronchiolitis during infancy, low serum 25-hydroxyvitamin D (25(OH)D) levels (< 20 ng/mL) at 3 years were associated with an increased risk for eosinophilic asthma and eosinophilia without asthma by the age of 6 years.

Supplementing VitD3 resulted in amelioration of clinical asthma manifestations in human studies as well as in experimental allergic asthma, indicating that VitD3 shifts proinflammatory immune responses to anti-inflammatory immune responses via upregulating the B lymphocyte–induced maturation protein 1 (Blimp-1) in lung innate lymphoid cells and tissue-resident memory cells.



Thus there seems to be potential role of early-life vitamin D supplementation among children with a history of severe bronchiolitis and eosinophilia for preventing childhood asthma and therefore supplementation of vitamin D to both mother during pregnancy and the child after birth may be helpful in its prevention.

Source: *Doumat G, et al Thorax 2025; 80:180-183. Cureus 15(7): e41956 ;July 16, 2023; J Int Med Res. 2020 Dec 7; 48(12):0300060520974242.*

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