Quarter 3, 2025 | VOLUME 13 | NUMBER 8

Medical Bulletin

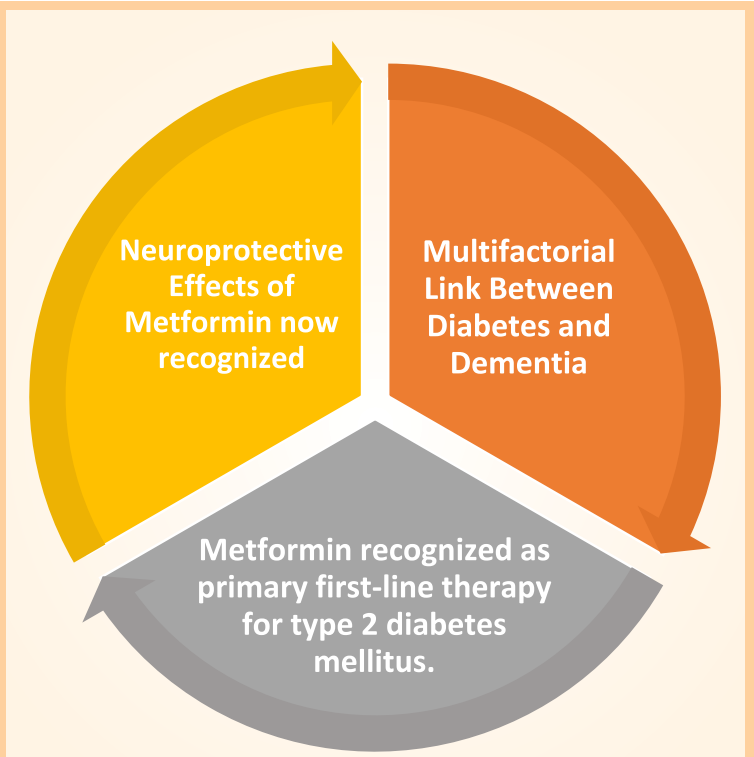
PROTECTIVE EFFECT OF METFORMIN AGAINST DEMENTIA IN PATIENTS WITH OBESITY

Dementia can be caused by vascular etiology or neurodegenerative disease (Alzheimer's disease). It is a syndrome characterized by deterioration in memory and loss of daily self-care ability. It affects mainly the older people but may also happen in the younger generation. The World Health Organization has recognized the growing incidence of dementia in the world population and estimated that the number of people with dementia is currently around 47 million in the world & each year nearly 10 million add up as new cases.

Elevated blood glucose may impair cerebral function and patients with diabetes have an increased risk of dementia. The link between diabetes and dementia is probably multifactorial and mechanisms may involve inflammation, oxidative stress, atherosclerosis, amyloid-β deposition, brain insulin resistance with hyper-insulinemia, advanced glycation end-products (AGEs) and dysregulation of lipid metabolism.

Metformin, the most widely prescribed glucose-lowering treatment reduces blood glucose level by reducing hepatic gluconeogenesis and increasing muscular glucose uptake through activation of the 5'-adenosine monophosphate-activated protein kinase (AMPK). In patients with type 2 diabetes mellitus, in addition to its glucose lowering effect, it has also been shown to reduce the risk of atherosclerotic events and cancers and have an anti-aging effect.

Metformin the gold standard therapy for type 2 diabetes mellitus is linked to a reduced risk for dementia in patients with diabetes; however, its effect on the incidence of dementia among individuals with obesity wasn't established with real-world data. Recently, scientist analyzed data from adults with varying degrees of overweight and obesity from a popular global health research network to investigate the link between metformin and the long-term incidence of dementia and all-cause mortality.



Metformin in dementia risk in type 2 diabetes

The findings of various studies suggested that metformin use in type 2 diabetes patients was associated with a significantly lower risk of dementia, especially when it had been used for more than 2 years.

The exact mechanism of its neuroprotective action is not known however the proposed mechanistic are:- Metformin inhibits gluconeogenesis in the liver and lowers blood glucose by activating the liver kinase B1 (LKB1)/AMPK pathway through inhibiting the mitochondrial respiratory-chain complex 1 & activation of AMPK-dependent pathway in the brain exerts neuroprotective effects. Insulin resistance with impaired insulin signaling and decreased glucose metabolism is observed in patients with dementia. Metformin improves insulin resistance by increasing insulin receptor expression and improving tyrosine kinase activity. Metformin may offer the protective action from oxidative stress and inflammation via AMPK-dependent and -independent pathways.

The more recent studies, corroborated the neuroprotective of metformin against amyloid-β-induced mitochondrial dysfunction in human neuronal stem cells via an AMPK-dependent pathway. Metformin can reduce the formation of AGEs through improving glycemic control and additionally it has been shown that metformin may exert a scavenging effect on AGEs. Dysregulation of lipid metabolism and gut microbiota dysbiosis have also been implicated as potential links between diabetes and dementia. Metformin may reverse insulin resistance, improve insulin signaling and correct lipid dysmetabolism. Recent studies also suggested that metformin may change the composition of gut microbiota with an increase in Akkermansia species leading to improvement in insulin resistance and reduction in tissue inflammation. Metformin may also reduce the risk of dementia through its anti-atherogenic action on the vascular system. Taken together, metformin may exert its beneficial effect on dementia via either vascular protection or neuronal protection.

In a large, multi-centre cohort study, metformin use was associated with reduced risks of dementia and all-cause mortality in obese patients. The protective effect was observed across all BMI groups, with variations noted by population. These findings support the potential of metformin in lowering dementia risk in patients with obesity.

To summarize the present data supports a beneficial effect of metformin on the prevention of dementia in type 2 diabetes patients. These findings give rationale for conducting larger clinical trials to prove this effect. Given that metformin is safe and cheap and would not cause hypoglycemia when used as monotherapy, its usefulness for the prevention of dementia in both the diabetes patients and non-diabetes people is worthy of in-depth investigation.

Source: *Lin YL, Hung YJ, et.al; Diabetes Obes Metab. 2025 Aug; Aderinto, N., et al. Clin Diabetes Endocrinol 10, 10 (2024); Chin-Hsiao T.et.al; Aging Dis. 2019 Feb 1;10(1):37-48.*

CURRENT EVIDENCES AND RECOMMENDATIONS OF VITAMIN D IN CHILDREN

Vitamin D plays an important role in bone growth and remodeling by osteoblasts and osteoclasts and is essential to maintain calcium, phosphate, and magnesium body homeostasis by regulating intestinal absorption, and renal absorption/excretion, alongside the parathyroid hormone (PTH). Plasma calcium and phosphate are mainly influenced by the active form of vitamin D (1α, 25-dihydroxyvitamin D) and PTH.

In the early stages, vitamin D deficiency results in impaired calcium intestinal absorption and consequent low serum calcium levels (hypocalcemia). In turn, hypocalcemia stimulates PTH secretion which acts to normalize serum calcium by reducing renal calcium excretion, increasing renal phosphate excretion, and stimulating renal production of active vitamin D. High levels of PTH (hyperparathyroidism) also boost osteoclast activity which determines bone calcium release. The combination of low serum phosphate levels (hypophosphatasemia) and increased osteoclast activity results in bone demineralization.

Beyond bone health, Vitamin D positive effects on the innate immune system are observed through modulation of monocytes, macrophages, dendritic cell responses, and the production of interleukins.

Autoimmune diseases (ADs) are caused by an erroneous activation of the immune system, with subsequent destruction of tissues by autoreactive immune cells, which can react against self-antigens. Among the causes contributing to the development of ADs, an insufficient vitamin D serum concentration might play a significant role, as proven by epidemiologic findings of higher incidences of ADs among countries with lower sun exposures and high prevalence of vitamin D insufficiency. Recent studies found the vitamin D's involvement in the suppression of T lymphocyte proliferation and adaptive immune system, causing a shift from a Th1 to a Th2 phenotype and a subsequent alteration in the differentiation and maturation of T cells, inducing T regulatory cells function and immune self-tolerance. Moreover, B lymphocytes have been found to express vitamin D receptors, which, when activated, can inhibit the differentiation into plasma cells and modulate immunoglobulin production. All these effects could explain the possible connection between variable vitamin D serum levels and the probability to develop an AD.

Emerging evidence from various meta-analyses supposes a plausible role of low vitamin D levels in many other ADs, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, and vitamin D receptors polymorphisms have been associated with higher incidences of several ADs.

Many studies worldwide have shown high rates of vitamin D deficiency and insufficiency in the pediatric population, with rates ranging on average between 40 and 75%, even in developed countries.

The threshold value about hypovitaminosis should be considered basis upon the cut-off values as given in the below table.

Table 1: Cut-off values for the definition of vitamin D status based on circulating levels of 25(OH)D

	Severe deficiency	Deficiency	Insufficiency	Sufficiency
Serum 25(OH)D	<10 ng/mL	<20 ng/mL	20–29 ng/mL	≥ 30 ng/mL

Risk factor for vitamin D deficiency is related to age, with infants being more at risk of developing hypovitaminosis. Under 12 months of age, the risk is even higher for premature babies, who have less vitamin D deposits, and in children who are breastfed. Indeed, human breast milk is almost lacking in proper amounts of vitamin D, with concentrations that range from 10 to 80 IU/L in healthy lactating women. Considering the first 6 months of age, mothers who are lacking in vitamin D, supply even fewer amounts to their infants.

Most international and national guidelines actually recommend vitamin D prophylaxis to all infants during the first year of life, in order to prevent possible deficiency conditions and in consideration of the frequent, unpredictable, and often insufficient supply typical of the early infancy. Thus, all children during the first year of life should receive an oral supplementation of vitamin D. A daily dose of 400 international units of vitamin D in infants has shown to be effective for preventing rickets. It is well tolerated, and not associated with toxicity. Rickets and vitamin D deficiency should be treated with a daily dosing of (2000 IU below 1 year of age and 3000 IU in older children) for 12 weeks. Serum 25-hydroxy vitamin D level of >20 ng/mL should be maintained in children with conditions at high-risk for vitamin deficiency, like nephrotic syndrome, chronic liver disease, chronic renal failure, and intake of anticonvulsants or glucocorticoids.

The European Society of Pediatric Gastroenterology, Nutrition, and Hepatology (ESPGHAN) & American Academy of Pediatrics (AAP) and Indian academy of Pediatrics (IAP), recommend prophylactic supplementation to all the breastfed and partially breastfed infants, regardless of maternal supplementation & vitamin D status.

Source: *Corsello A, et.al; Front Med (Lausanne). 2023 Mar; Jullien S.et.al; BMC Pediatr. 2021 Sep 8; 21(Suppl 1):319; Gupta et.al; Revised IAP vit.D guidelines, Indian Pediatrics, December 29, 2021.*

Dr. Prabhu Kasture (MD, DPH)
Director Medical Services & Pharmacovigilance
Phone No.: 022-66638043
Email: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt Ltd., Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013.
Website: http://www.bluecrosslabs.com