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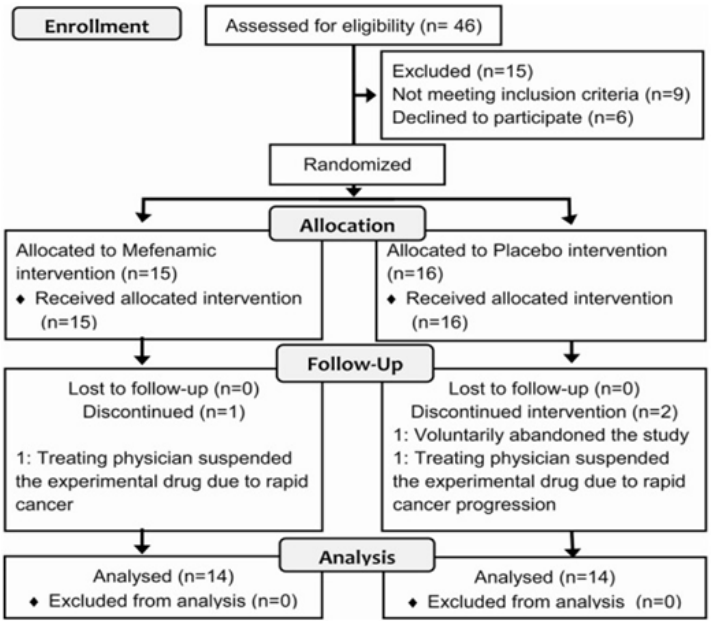
IMPROVED COGNITIVE IMPAIRMENT USING MEFTAL (MEFENAMIC ACID) NON-STEROIDAL ANTI-INFLAMMATORY THERAPY

Mefenamic acid is an established drug exhibiting a potent anti-inflammatory, antipyretic, analgesic and probable antiviral activities.

Clinical trial phase II was conducted to examine the therapeutic potential of mefenamic acid in cognitive impairment. One of the study arm was administered mefenamic acid 500 mg PO every 12hrs for six months & the outcome was evaluated through the Mini-Mental State Examination (MMSE) score at six months. The mefenamic acid group improved its MMSE score after six months compared with the placebo group (27.7±1.8 vs. 25.5±4.2, P=0.037).

Treatment with mefenamic acid significantly increases the probability of maintained or raised cognitive function compared to placebo (92% vs. 42.9%, RR=2.2, 95% CI: 1.16-4.03, NNT=2.0, 95% CI: 1.26-4.81, P=0.014). Furthermore, 42.9% of the placebo group patients had relevant cognitive decline (a 2-point decrease in the MMSE score), while in patients treated with mefenamic acid, cognitive impairment was not present. This study is the first conducted on humans that suggests that mefenamic acid protects against cognitive decline.



Distinct mechanisms of neuroprotection and cognitive function improvement have been proposed for mefenamic acid. It targets the NLRP3 inflammasome pathway, decreasing the free radical production, nitric oxide (NO), and decreases the release of cytochrome C.

There were no serious adverse events with long term regimen of mefenamic acid except few mild gastritis cases reported but none of them discontinued the therapy. This study concluded with mefenamic acid's therapeutic potential could include other diseases that present with cognitive decline.

Source: Melnikov V et al. Am J Transl Res. 2021; 13(5): 4535-4543.

DIABIZ (DAPAGLIFLOZIN) AND ENDOTHELIAL DYSFUNCTION

There is a great heterogeneity in the cardiovascular risk in individuals with type 2 diabetes. Impaired endothelial function is one of the first disorders detected. The endothelium is responsible for maintaining a balance between vasodilation and vasoconstriction, between inhibition and stimulation of smooth muscle cell (SMC) proliferation and migration, and between thrombogenesis and fibrinolysis. When this balance is broken and there is an endothelial dysfunction, damage is caused to the arterial wall.

Endothelial function is often impaired in patients with type 2 diabetes, while insulin resistance augments this association. It contributes to the development of hypertension, thereby promoting cardiovascular and renal damage. Therefore improving endothelial function by restoring NO production may represent an important therapeutic goal in type 2 diabetes.

Recently, sodium-glucose co-transporter-2 (SGLT-2) inhibitors have attracted a significant amount of scientific interest due to their multiple pleiotropic effects beyond glycemic control, mainly in terms of cardio- and reno-protection.

ROLE OF NITRIC OXIDE IN ENDOTHELIAL FUNCTION

Nitric Oxide(NO) has a wide range of biological properties that maintain vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injury from platelets and cells circulating in blood.

Endothelial dysfunction is characterized by diminished release of NO which can be caused due to multiple conditions such as hypertension, hypercholesterolemia, smoking, diabetes mellitus and heart failure. The decreased production of NO in these pathological states causes serious problems in endothelial equilibrium.

DAPAGLIFLOZIN AND ENDOTHELIAL FUNCTION

Among the many protective effects of SGLT-2 inhibitors on cardiovascular function, one of them is modulating vascular endothelial cell activation and improving endothelial cell dysfunction. This role is based on its effect on the nitric oxide (NO) production and alleviating the oxidative stress.

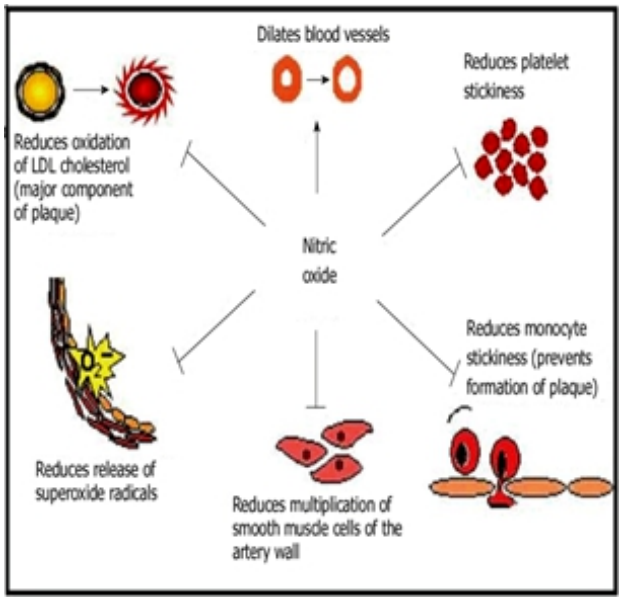
These beneficial effects are likely due to:

1. Its glucose-lowering effects.

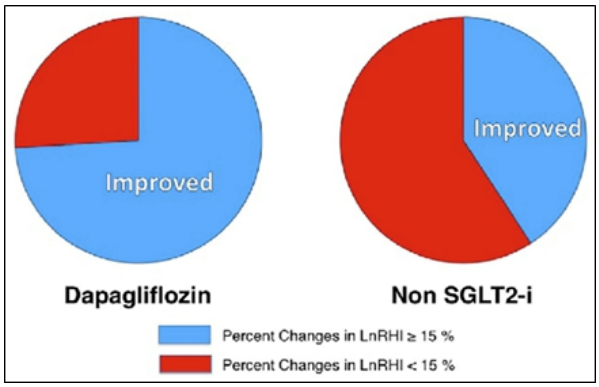
2. Its direct effects on vascular endothelial cells.

Dapagliflozin activate the eNOS and increase NO production which improves the microvascular and macrovascular function. In addition, it favourably regulate the proliferation, migration, differentiation, survival, and senescence of endothelial cells (ECs). Moreover, they exert potent antioxidant and anti-inflammatory effects in ECs. SGLT-2 inhibitors also inhibit the contraction of vascular SMCs and block the proliferation and migration of these cells.

Current studies have shown a significant increase in the nitrite level with dapagliflozin which indicates an overall increase in NO production.



In the normal functioning endothelium, acetylcholine promotes a rapid release of NO and, thus, vasodilation. However, in the dysfunctional endothelium, the effect of acetylcholine that predominates is the contraction of SMCs causing vasoconstriction. Treatment with dapagliflozin showed a decrease in the systolic BP indicating an improvement in arterial constriction and the abnormal arterial response which could be a result of an improvement in the endothelial function.



PROPORTION OF PATIENTS WITH AN IMPROVED ENDOTHELIAL FUNCTION (LnRHI: natural logarithmic transformation of the reactive hyperemia index)

It can be suggested that in addition to its glucose-lowering effect, the improvements in endothelial function from dapagliflozin treatment may contribute to its beneficial impact in cardiovascular morbidity and mortality which makes SGLT2 inhibition with dapagliflozin an attractive antidiabetic therapeutic target with additional cardiovascular benefits.

Source: Solini A et al. Cardiovasc Diabetol 2017; 16(138). Sposito AC et al. Cardiovasc Diabetol 2021; 20(74). Tousoulis D et al. Curr Vasc Pharmacol 2012; 10(1): 4-18. Durante W et al. Int J Mol Sci 2021; 16(22): 8786.

BLUVIT CZ (VITAMIN C AND ZINC) IN INFECTIONS

From past to the present, a considerable understanding has been acquired of both, the physiological role of vitamin C and the impact of vitamin C supplementation on health. Vitamin C plays an important role in the normal functioning of the immune system and its use in preventing and/or treating infections has strongly attracted the interest of physicians.

Zinc along with vitamin C provides a complete approach towards the optimal functioning of the immune system and protection against upper respiratory tract infections as well as viral infections.

Vitamin C and immunity

Besides the extensive range of biochemical pathways in which vitamin C is involved, it participates in the response of the innate and adaptive immune system.

These include:

- Migration of phagocytes (chemotaxis) to the infection site which may be impaired during infections.
- Protecting neutrophils from oxidative stress during the early stages of an immune response.
- Regulating the process of apoptosis once the neutrophils die and help in resolution of inflammation.
- Protecting the lymphocytes from oxidative damage and stimulating differentiation and proliferation from precursors to mature T cells.
- Regulating the inflammatory response by reducing the production of pro inflammatory leucocyte derived cytokines (TNF-α and IL-6).
- Interacting with molecular pathways related to inflammatory stress and immune dysfunction during sepsis.
- Increasing the activity of epigenetic enzymes that cause epigenetic remodelling and immune cell activation.

To maintain adequate body stores, recommended dietary allowance (RDA) for vitamin C has been proposed over the year. The RDA for vitamin C for adults is 80 mg/day for males and 65 mg/day for females.

Oral Supplementation of Vitamin C for the Prevention and Treatment of the Common Cold and Upper Respiratory Tract Infections

The common cold is one of the most widespread viral upper respiratory tract infections (URTI), characterized by coughing, tiredness, fever, sore throat, and muscle pain, which persist for a period ranging from a few days to not more than 3 weeks.

The mechanism for reduction of the incidence and severity of URTIs may be through an improved immune system. Vitamin C has antioxidant properties and protects the immune system against oxidative stress generated during infections.

Studies have shown that high levels of serum vitamin C are associated with enhanced antibody response, neutrophil function, and mitogenic response. Furthermore, in vitro models suggest that vitamin C inhibits rhinoviruses.

The reduction in vitamin C levels observed during infection suggests that supplementing vitamin C could have a positive impact on preventing and treating infections.

Vitamin C and viral infections

A number of observers including Linus Pauling have suggested that vitamin C in high dosages is directly virucidal.

This is based on two concepts:

i) Patients with acute infectious diseases have low circulating vitamin C levels (likely due to metabolic consumption).

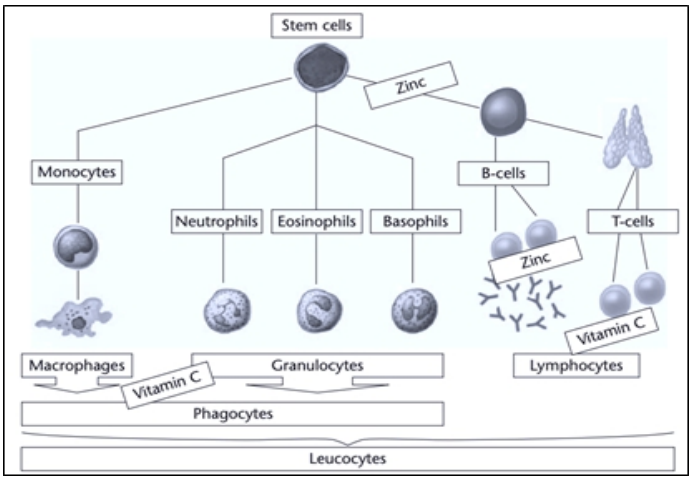
ii) Vitamin C has beneficial immunomodulating properties in patients with viral infections.

Many infections lead to the activation of phagocytes, with the release of ROS which plays a role in the deactivation of viruses. However, many of the ROS are harmful to the host cells and may be involved in the pathogenesis of viral induced host injury. Thus, vitamin C may have a dual effect where it enhances phagocytosis as well as protects hot cell injury from the generated ROS.

Complementary roles of vitamin C and zinc?

Vitamin C and zinc complement each other in their functions as both the nutrients are required to support the functions of innate immunity such as epithelial barriers and cellular components involved in phagocytosis. While vitamin C and zinc both support epithelial barriers, although by different mechanisms, they target different populations of phagocytic cells, thereby complementing each other to ensure an effective phagocytic response.

With regard to adaptive immunity, zinc is the key player. It is essential for the process that causes stem cells in the bone marrow to form lymphocytes, and for the subsequent differentiation into B- and T-lymphocytes. It is also required for the proper functioning of T-lymphocytes, for the production of antibodies by B-lymphocytes, and for efficient interaction between B- and T-lymphocytes.



Finally, both vitamin C and zinc provide complementary antioxidant protection to exogenously derived and endogenously generated ROS.

Apart from this, zinc in different forms (free compared with protein-bound) can stimulate a variety of signalling events, including the antiviral response. In vitro studies have suggested that free zinc may possess potent antiviral effects and moreover, zinc-binding proteins such as the metallothionein may possess antiviral roles.

The role of zinc as an antiviral can be separated into 2 categories:

- Zinc supplementation implementedto improve the antiviral response and systemic immunity in patients with zinc deficiency.
- Zinc treatment performed to specifically inhibit viral replication or infection-related symptoms.

There is, therefore, a good scientific rationale that the combination of vitamin C and zinc support immune functions and reduce the risk of infections.

Recommended daily allowances (RDA) for different age groups

CATEGORY	AGE (Yrs.)	VITAMIN C (mg/d ay)	ZINC (mg/day)
Men		80	17
Women		65	13.2
Infants	0-6 months	-	-
	6-12 months	-	2.0
Children	1 -3	22	2.5
	4-6	27	3.7
	7-9	36	4.9
Boys	10-12	45	7.0
Girls	10-12	44	7.1
Boys	13 -15	60	11.9
Girls	13 -15	55	10.7
Boys	16 -18	69	14.7
Girls	16 -18	57	11.8

The RDA is determined by the rate of turnover and rate of depletion of an initial body pool of 1500 mg vitamin C and an assumed absorption of 85% of the vitamin at usual intakes. The supplementation of vitamin C is based on the addition to the overall intake from daily nutrition in order to augment its effect and prevent or treat infections.

Similarly, the RDA for zinc is calculated to include Average daily level of intake sufficient to meet the nutrient requirements of nearly all healthy individuals, to ensure nutritional adequacy; The supplementation of zinc is also additional to the dietary intake of an individual and based on their dietary choices the amount of supplementation can be altered.

The supplementation for both the nutrients is for the therapeutic effect while the RDA is to prevent deficiencies.

Source: Cerullo G et al. Front Immunol 2020; 11(574029): 1-16. Van Driel ML et al. Cochrane Database Syst Rev 2019; 2019(3): CD013292. Colunga Biancatelli RML et al. Expert Rev of Infective Therapy 2020; 18(2): 99-101. Read SA et al. Adv Nutr 2019; 10(4): 696-710. https://www.im4change.org/upload/files/RDA_short_report%281%29.pdf

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