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BCG and Covid

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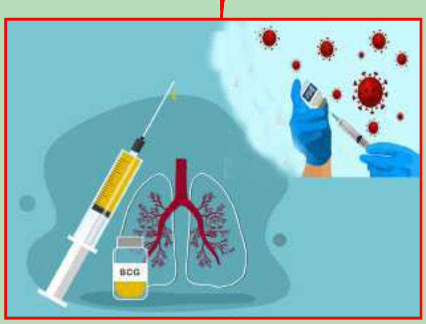

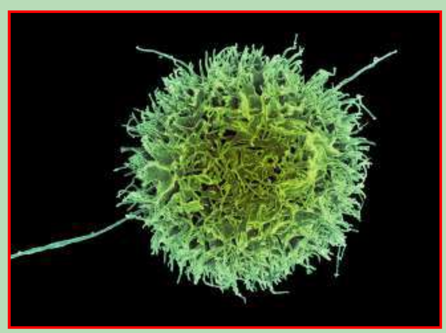

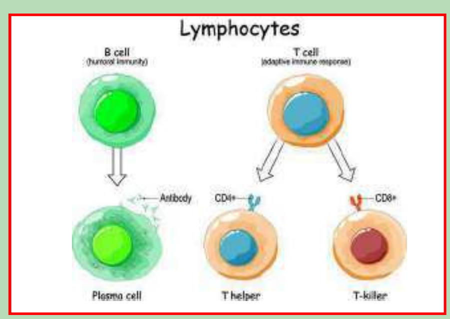

GENERAL

Omega - 3 - Fatty Acids and its Role in Hypertension and Diabetes

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Omega−3 fatty acids (FA), also called Omega-3 oils, ω−3 fatty acids or n−3 fatty acids, are polyunsaturated fatty acids (PUFAs) characterized by the presence of a double bond, three atoms away from the terminal methyl group in their chemical structure. The three types of omega-3 fatty acids involved in human physiology are α-linolenic acid (ALA) (found in seeds, plant oils, green leafy vegetables, nuts, beans), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (both commonly found in fish oil that originally come from microalgae that is further consumed by phytoplankton, a source of diet for fish, mainly fatty fish)(Covington, 2004). EPA and DHA are 20, 22-carbon molecules with five and six double bonds respectively. Omega -3 FA cannot be synthesised by mammals and has to be provided through diet. Omega-3 fatty acids are found in foods, such as fish and flaxseed, and in dietary supplements, such as fish oil. Salmon, mackerel, albacore tuna, herring, and sardines are high-fat seafood that are great providers of EPA and DHA.Oils containing these fatty acids originate in plant sources and can be found in fish, fish products, seeds, nuts, green leafy vegetables, and beans (Harris, 2004).

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Omega-3 FA are a part of human diet for thousands of years and have caused no harm in amounts approved by US-FDA. 3g/day is the daily allowance limit of marine omega-3 FA as given by FDA as GRAS (Generally Recognized as Safe). They play a vital role in cardiovascular diseases, asthma, diabetes, inflammatory disorders, arthritis, cancer and various cognitive, behavioural and visual pathways(Harris, 2004).They play a critical role in metabolism and cellular function and they are available as daily supplements.EPA and DHA mediate important cellular functions such as inhibition of platelet function, prolongation of bleeding time, anti-inflammatory effects and reduction of plasma fibrinogen.DHA tends to exist in high concentrations in the retina, brain (via uptake by Mfsd2a as a transporter), and sperm.PUFAs are components of the phospholipids that form the structures of the cell membranes and also serve as energy source. They form eicosanoids which are important signalling molecules with wide-ranging functions in the body's cardiovascular, pulmonary, immune and endocrine systems.

Mechanism of action

Omega-3 fatty acids mediate anti-inflammatory effects through increased levels of EPA or DHA, which has shown decreased levels of PGE2 and 4 series-LT. EPA compete with arachidonic acid in cell membranes for the same desaturation enzymes and produce 3-series prostaglandins (PGs), thromboxanes, and 5-series Leukotrienes (LT) which have low pro-inflammatory potential. The alteration in leukotriene biosynthesis due to higher concentration of omega-3 fatty acids compared to arachidonic acid underlies the anti-inflammatory effects. EPA and DHA also give rise to Resolvins and related lipid signalling molecules such as protectins via cyclooxygenase and lipoxygenase pathways, which have anti-inflammatory effects. They inhibit transendothelial migration of neutrophils and inhibit Tumor Necrosis Factor (TNF) and interleukins (IL)-1β production. Omega-3 fatty acids also decrease adhesion molecule expression on leukocytes and endothelial cells and decrease intercellular adhesive interactions. Omega-3 and their metabolites are natural ligands for peroxisome proliferator-activated receptor (PPAR) gamma that regulates inflammatory gene expression and NF-κB activation. The role of EPA and DHA in reducing triglyceride levels include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal-beta-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. They also may reduce triglyceride synthesis because they are poor substrates for the enzymes responsible for TG synthesis. Also, EPA and DHA inhibit esterification of other fatty acids(https://go.drugbank.com/drugs/DB11133).

Role in hypertension

Hypertension is a chronic medical condition characterised by higher pressure exerted by blood against the walls of the arteries. According to the American Heart Association guidelines hypertension is mainly classified into two stages. Stage 1 and stage 2 is characterised by systolic blood pressure 130-139mmHg and ≥140mmHg, diastolic pressure 80-89mmHg and ≥90mmHgrespectively (https://www.cdc.gov/bloodpressure/facts.htm). Physiological mechanisms which govern the development of hypertension include cardiac output and peripheral vascular resistance, renin-angiotensin-aldosterone system, autonomic nervous system, endothelial dysfunction and the release of vasodilators like nitric oxide, bradykinin, hypercoagulability, insulin sensitivity, intrauterine factors, diastolic dysfunction and genetic factors (Beevers et al., 2001).

Through their positive effects on blood pressure, a high consumption of omega-3 PUFAs has been linked to cardiovascular protective benefits, enhancing endothelial function, and lowering atherosclerosis. In addition, they also have effect on their lipid profile, platelet aggregation, and characteristics that reduce inflammation.α-linolenic acid (ALA) undergoes desaturation in the presence of 6-desaturase, 5-desaturase and elongation in the presence of elongase to form eicosapentaenoic acid (EPA), a precursor of 3 series of prostaglandins, 5 series of leukotrienes and thromboxanes. These 3 series PGs are less potent when compared to series 2 obtained through arachidonic acid and hence they have antagonistic effects on vascular tone, platelet aggregation, and inflammation. EPA further undergoes desaturation and elongation in the presence of 4-desaturase and elongase respectively resulting in the formation of docosahexaenoic acid (DHA). EPA and DHA are precursors for lipoxins, resolvins and protectins which are involved in mediating inflammation, vascular tone and blood pressure as given in Figure 1. But these desaturation and elongation reactions are slow in human body which attribute to its lesser efficacy and in addition to this, metabolic pathway of omega-6 FA interfere with EPA and DHA formation, thereby affecting peripheral vascular resistance and blood pressure. Also, omega-3 FA suppress the aldosterone secretion and enhance nitric oxide production controlling hypertension. Various studies have proved the cardioprotective action of omega-3 FA in lowering systemic vascular resistance, reducing heart rate and improving cardiac diastole thereby lowering risk of cardiac death and possibly ischaemic stroke, heart failure, and non-fatal coronary events(Cabo et al., 2012).

Mori et al have reported a significant effect of EPA and DHA in lowering blood pressure via improving endothelial and smooth muscle functions. Incorporation of DHA into the endothelial membranes increased membrane fluidity, calcium influx, synthesis and release of NO, enhanced release of vasodilatory prostanoids and endothelial derived hyperpolarising factor. They also reported the a reduction in leptin levels thereby causing weight loss in hypertensive patients, reducing ambulatory blood pressure and heart rate(Mori, 2006). Hence it can be concluded that omega-3 fatty acids play a vital role in the treatment of hypertension and in turn cardio protection.

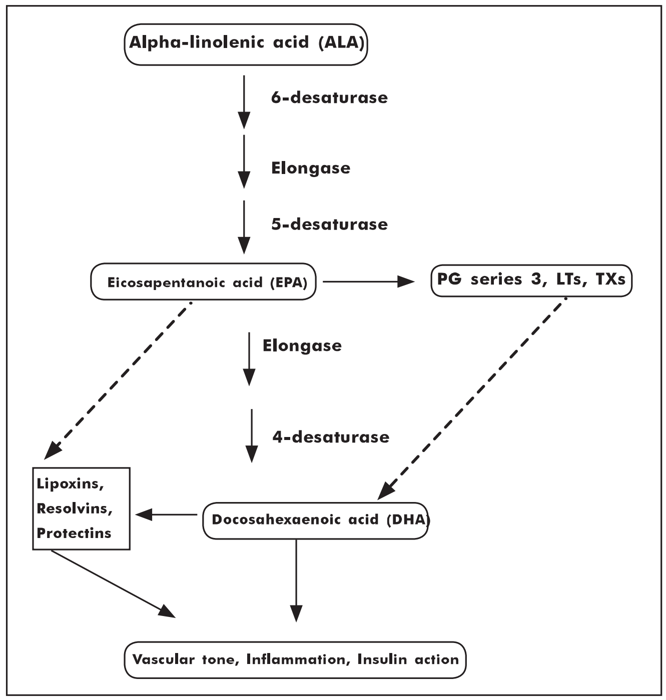

Figure1. Metabolic pathway of omega-3 FA

Role in diabetes

Diabetes mellitus is a chronic health condition characterised by high blood glucose level. They are mainly classified into type 1, type 2 and gestational diabetes. Type 1 diabetes is a result of autoimmune destruction of pancreatic β cells producing insulin and type 2 diabetes occurs due to the impaired insulin secretion from the β cells or impaired insulin action as a result of insulin resistance. Pathogenesis of type 1 diabetes is mediated via the action of interleukins, TNF-α, T-lymphocytes causing destruction of pancreatic β cells whereas in type 2 diabetes through mutations in genes or lifestyle factors(Ozougwu et al., 2013).

Effect of omega-3 FA in causing diabetes and its associated risk factors still remains unclear. Various studied were conducted to determine its effect on diabetes and many are still under progress. According to the study conducted by Kaushik et al, consumption of fish and omega-3 FA in higher amounts didn't help in lowering blood glucose level whereas it modestly increased chances of developing type II diabetes mellitus. They also reported an increase in the level of glycated haemoglobin (Hb A1C) and fasting blood glucose level in people who consumed omega-3 FA(Kaushik et al., 2009). Based on the results obtained from the study conducted by chewcharat et al omega-3 FA was effective in reducing proteinuria thereby decreasing the chances of diabetic nephropathy. Even though the mechanism underlying this function is not yet clear it is believed to be due to its anti-inflammatory and oxidative stress effects.Due to the formation of advanced glycation end-products (AGE), activation of protein kinase C (PKC), and production of reactive oxygen species, hyperglycaemia in diabetic patients causes podocyte injury as well as endothelial cell and tubulointerstitial injury. This process is crucial for the beginning and progression of proteinuria and diabetic nephropathy.Omega-3 fatty acids aid in lowering adipose tissue's pro-inflammatory reactions and insulin resistance. When compared to people with type 1 diabetes, whose proteinuria is mostly caused by the polyol, hexosamine, advanced glycation end product, and protein kinase C (PKC) pathway, this action may result in lesser proteinuria(Chewcharat et al., 2020). Wu et al have also reported heterogenic effects on the risk of diabetes mellitus (DM), where upon EPA/DHA and sea food/fish consumption by people in Asia have resulted in lesser risk of DM and increased risk in North America/Europe which may be attributable to the type of fish consumed or different method of preparations(Wu et al., 2012). Type 1 diabetes mellitus which is an autoimmunity disorder characterised by the generation of islet autoantibodies (IA) was developed mainly due to genetic and environmental factors including dietary factors. Norris et al have studied on the effects of omega-3 supplements in the onset of IA and they concluded from their studies that it had reduced the risk of IA in children more prone to type I diabetes through genetic factors(Norris et al., 2007).

Behl, T. et al have studied on the beneficial effects of omega-3 FA in diabetic retinopathy. Due to their extensive spectrum of protective qualities, which include anti-inflammatory, antiangiogenic, and antioxidant, among many others, they have a significant potential to prevent the advancement of diabetic retinopathy. They block a variety of inflammatory mediators involved in the pathogenesis of diabetic retinopathy, in addition to reducing free radical production and increasing the expression of endogenous antioxidant enzymes. Further, they significantly suppress retinal angiogenesis from initiating by reducing the levels of different angiogenic gene expression substances like VEGF (Vascular Endothelial Growth Factor), MMPs (Metalloproteinases), and COX-2 (Cyclooxygenase-2)(Behl and Kotwani, 2017).

Yee, P. et al have studied the effect of change in lipid metabolism as a consequence of retinal damage in diabetes patients and concluded that a balanced diet intake of omega-3 FA can maintain lipid membranes of retina in diabetes patients and improve rod dysfunction.The cone or glial response did not show dietary alteration, however the greater photoreceptor output is probably what caused the partial improvement in the OPs (oscillatory potential, which measures the activity of retinal neurons)(Yee et al., 2010).Hence various studies help us to conclude that there is not much evidence in supporting that omega-3 FAs can reduce the risk of type I and II diabetes but they can be a factor in reducing certain complications due to diabetes like diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, IA production etc.

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