Review Article

A review on role of vitamin supplements on the lipid profile.

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Abstract

Hyperlipidemia can be defined as a medical condition characterized by an increase in plasma lipids and plasma lipoproteins. This higher level of plasma lipids could be a major risk factor associated with various cardiovascular diseases. Over the years, statins and fibrates evolved to become the foremost widely prescribed agents for the elevated lipid profile even with their side effects.
The current review focuses mainly on the "role of vitamins within the lipid profile of hyperlipidemic patients, different classes of hyperlipidemia, pharmacological treatment and also the influence of the vitamin supplements with respect to the lipid metabolism". This review suggests that a hyperlipidemic treatment regimen along with vitamins may help reduce the high serum lipid levels and thereby reduce the risk in the development of cardiovascular diseases.

Keywords: Hyperlipidemia, Hyperlipidemic drugs, Vitamin supplements, Lipid profile.

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Introduction

Hyperlipidemia is the most common form of disorder, during this condition the blood cholesterol and the lipid parameters gets elevated from the normal value. It's also referred to as Hypercholesterolemia and hyperlipoprotenemia.

It's considered to be the most common risk factor for the development of cardio vascular diseases [1]. Hyperlipidemia is mostly classified by patterns of lipids and lipoproteins (Fredrickson Phenotypes - Lipoprotein Patterns) and causing factors [2].(Table 1)

Table 1. *Fredrickson Phenotypes and Lipoprotein Patterns.*

Lipoprotein patterns (Fredrickson phenotypes)		
Phenotype	**Elevated plasma lipoprotein(s)**	**Elevated lipid fraction**
1	Chylomicrons	Tgs
2a	Ldl	Cholesterol
2b	Ldl and vldl	Tgs and cholesterol
3	Vldl and chylomicron remnants	Tgs and cholesterol
4	Vldl	Tgs
5	Chylomicrons and vldl	Tgs and cholesterol

Causing factors

Certain monogenic disorders are determined that results in a unique sort of dyslipidemia, especially primary hyperlipidemia except for many cases, the cause is polygenic. It will affect plasma lipoprotein levels by the decreased clearance and/or over generation of lipoproteins.

The common familial (genetic) disorders can be divided as:

- Familial hypercholesterolemia which may be a congenital metabolic disease that differs from family to family, in genes, and eliminates LDL-C from the blood due to mutations.
- Familial combined hyperlipidemia is related to over synthesis of VLDL-C. In extension to the present elevated level of triglycerides and LDL-C, patients also mostly have high levels of apo B and better levels of small and dense LDL particles.
- Familial type III hyperlipoproteinemia is defined by the aggregation of chylomicron and VLDL remnants.
- Familial lipoprotein lipase deficiency is characterized by chylomicronaemia and hypertriglyceridemia.
  It's due to lack of extrahepatic enzyme lipoprotein lipase, which results in failure of lipolysis and also the chylomicrons aggregation in plasma.
- Familial apolipoprotein C-II deficiency is correlated with decreased levels of the activator of lipoprotein lipase, apo C-II.
- Beyond these, diabetes mellitus (DM), hypothyroidism, hepatocellular disease, chronic renal disorder, and obesity are prone to lead to hyperlipidemia [3].

Treatment regimen for hyperlipidemia

Non-pharmacological therapy for hyperlipidemia may include dietary therapy, weight reduction, and an increase physical activity. Advise overweight patients to lose bodyweight of 10%. The most common objectives of dietary therapy are progressively reducing the intake of total fat and saturated fat [4].

Instigation of several drugs mainly statins, fibrates, and other classes have shown a radical achievement in lipid-lowering.

The statins are the foremost dominant LDL lowering agents so they are considered as the initial choice for hyperlipidemia. Atorvastatin, rosuvastatin, simvastatin, fluvastatin are the members of this class. The mechanism of action is by inhibiting HMG CoA Reductase and also the formation of mevalonic acid. Statins help to cut back TC, LDL-C, VLDL-C, and TG with an elevation in HDL-C [5].

In the history of liver disease and inactive liver disease patients' statin should be used with caution. Other side effects include rhabdomyolysis, sleep disturbances, dizziness, depression, peripheral neuropathy [6].

Fibrates, another widely used class which includes Bezafibrates, Ciprofibrates, Fenofibrate, Gemfibrozil, act by binding to peroxisomes proliferator activator receptor α (PRAR-α) on hepatocytes. The gene expression for the lipoprotein metabolism gets altered which in turn raises the HDL-C levels and reduce the LDL-C and TG [7].

In bile acid-binding agents, it includes cholestyramine, colestipol, and colesevelam. They are used in the management of hypercholesterolemia where they diminish TC and increase TG levels. They unite bile acids in the intestine, inhibit re-absorption, and develop an insoluble complex that is eliminated in the feces. The hepatic enzyme 7-α-hydroxylase gets upregulated by the depletion of hepatic cholesterol, thereby enhances the transformation of cholesterol to bile acids. This rise LDL receptor activity in the liver and clears away LDL-C from the blood [8].

This prevent the cholesterol uptake from the small intestine, thus lowering the lipid profile levels is found to be the main action of cholesterol absorption inhibitors. By limiting the cholesterol uptake they reduce the binding of chylomicron particles with cholesterol esters. The high hepatic LDL receptor action will increase the clearance of circulating LDL due to diminished cholesterol distribution to the liver, finally reducing the circulating LDL particles [9].

The influence of vitamins on the lipid metabolism

Vitamins are crucial for the general well-being and maintenance of our body [10]. Recent studies have shown that vitamins play a serious role in reducing atherosclerosis due to their strong antioxidant properties [11].

Generally, 13 essential vitamins i.e., four fat-soluble vitamins (Vitamin A, Vitamin D, Vitamin E, and Vitamin K) and nine water-soluble vitamins (Vitamin B_1, Vitamin B_2, Vitamin B_3, Vitamin B_5, Vitamin B_6, Vitamin B_7, Vitamin B_9, Vitamin B_{12} complex, and Vitamin C) are found to be important for the conventional growth and development of our body [12]. These vitamins individually play a characteristic role in the total physiological activity of our body [13].

Vitamin-A: Vitamin A is a fat soluble vitamin which is well known for its anti-infective properties and its role in regulating the immune system [14]. Vitamin A is abundant in foods of animal origin like in meat, dairy products, Cod liver oil, and in green leafy vegetables and in fruits like mango, watermelon, and papaya, and other beta carotene-rich foods [15]. A deficiency in Vitamin A or antiophthalmic factor deficiency may result in hypovitaminosis, reduced immunity, hematopoiesis, anemia, and rashes [16]. Vitamin A derivatives are widely used to treat nyctalopia, hyper and parakeratotic skin diseases, autoimmune diseases, maintain the structural integrity of the skin, lipid metabolism, and in reproduction [17,18].

Vitamin-B: Vitamin B is generally a group of water-soluble vitamins which are further grouped into eight and are commonly termed as B-complex vitamins. The eight B vitamins are Vitamin-B_1 [Thamine], Vitamin B_2 [Riboflavin], Vitamin B_3 [Niacin], Vitamin B_5 [Panthothenic acid], B vitamin [Pyridoxine], Vitamin B_7 [Biotin], Vitamin B_9 [Folate] and Vitamin B_{12} [Cyanocobalamin] respectively [19,20]. It's rich in foods like milk, meat, eggs, legumes, whole grains, dark green vegetables, and fruits. A diet low in Vitamin B complex may put an individual at a high risk of developing various disorders like Beriberi, pernicious anemia, impaired cognitive function, Lupus or Graves ' disease, and intestinal disorders such as colitis and an abnormal lipid levels in the body [21]. Further B-complex vitamins, specifically the B_{12}, and folate have shown to decrease the homocysteine levels in the body [22]. Vitamin-B Promote and maintain cell growth, regulate cell metabolic and catabolic activity, improve brain functions, prevent infections,promote synthesis of fatty acids and amino acids [23].

Vitamin-C: Vitamin C, which is a water-soluble vitamin, is predominantly found in citrus fruits like oranges, lemons, grapes, papaya, mango, pineapple, cherries, red peppers, and in green leafy vegetables. A deficiency in Vitamin C may cause Scurvy, fatigue, and impaired wound healing [24,25]. Vitamin C has Antioxidant properties, anti-atherogenic effect and anti-carcinogenic effect, maintain bones and teeth and also aid in the absorption of iron in the body [26].

Vitamin-D: Vitamin D, a group of fat-soluble secosteroids which is often divided into two major groups, vitamin D2 (Ergocalciferol) and Vitamin D3 (Cholecalciferol) [27]. Cholecalciferol is produced naturally by the body through a chemical process on exposure to the sunlight. Vitamin D3 is found in fatty fish, egg yolks, and in meat. Ergocalciferol is produced by the irradiation of ergosterol, which is found within the ergot fungus.

Cholecarciferol deficiency is related to vascular dysfunction, Diabetes, hypertension, Hyperlipidemia, and Osteomalacia [28]. Vitamin D increase the intestinal absorption of Calcium, Phosphate, Magnesium,

regulates the renin-angiotensin-aldosterone system, and manages the pancreatic cell activity. Calciferol also controls the lipid metabolism and helps to lower the oxidative stress markers [29,30].

Vitamin-E: Vitamin-E is a fat soluble nutrient and is abundantly found within the green leafy vegetables and oils and in fortified cereals. A deficiency in vitamin E may result in an impaired fat metabolism, muscle weakness, monogenic disease, bowel syndrome, and various other hepatobiliary diseases [31]. The antioxidant property of this vitamin helps in various cellular activities, protects and keeps the system efficient enough to fight infections, reduces cardiovascular complications, improves cognitive functions, and promotes muscle homeostasis [32].

Vitamin-K: Vitamin - K is a fat soluble nutrient. Phylloquinone (Vit-K_1) and Menaquinone (Vit-K_2) are the two primary subclass of Vitamin K known. Vitamin K_1 is rich in the dark green leafy vegetables whereas Vitamin-K_2 is mainly found in animal products such as liver and in fermented foods. Vitamin –K deficiency may lead to excessive bleeding and bruising and also may increase the risk of bone diseases [33,34]. Vitamin K helps in the regulation of the blood coagulation cascade, bone strength, improve cardiac functions, support endothelial integrity and cell growth [35].

Association between vitamins and the lipid metabolism

Vitamin-A, as retinyl esters enter the bloodstream together with the lymph lipoprotein particles through our diet. During its circulation, the triglycerides are removed but retinyl esters remain attached to the chylomicron particles.

After the uptake, hydrolysis and re-esterification of the chylomicron retinyl esters occur within the liver. Thus, the pathway of lipid metabolism and vitamin A are interlinked together [36].

A study conducted which aims to analyze the association between the plasma cholesterol level and fat soluble vitamin A in healthy obese. Pearson's coefficient of correlation was employed to measure the association between vitamin A and HDL cholesterol levels. The study concluded that there's a major direct correlation between vitamin A and HDL cholesterol levels [15].

A deficiency in vitamin B complex eventually may lead to an accumulation of the MM – CoA (Methylmalonyl CoA). This process inhibits the rate-limiting enzyme of carboxylic acid oxidation and promotes lipogenesis increasing the likelihood in the development of cardiovascular disorders [37]. A study conducted to assess and compare the level of serum vitamin B_{12} and its correlation with the lipid profile in type 2 diabetes mellitus. Serum Vitamin B_{12}, Serum lipid profile, and HbA1c, Fasting plasma glucose, were measured in all the groups. The study concluded that there is an decrease in serum Vitamin B_{12} level with increase in HbA1c, Cholesterol and triglyceride levels [38]. A non- randomized 8 week trail conducted on effects of folic acid supplementation on serum homocysteine levels, lipid profiles, and vascular parameters of type 2 diabetic patients. The study results showed a significant decrease in the low-density lipoprotein cholesterol levels as well as the ratios of low-density lipoproteincholesterol to high density lipoprotein cholesterol in the patients [39]. A retrospective observational study conducted to estimate the lipid parameters in patients receiving Vitamin B_{12} therapy. The serum glucose, lipid and vitamin B_{12} were estimated and it was found that the mean cholesterol and triglyceride levels was decreased after the treatment. So the study concluded that vitamin B_{12} had a positive effect on lowering the lipid parameters, especially on serum triglycerides [19].

A randomized placebo conducted controlled clinical trial, the aim was to identify the effect of vitamin B_6, lysine and carnitine supplementation on lipid profile of the hypertriglyceridemic patients. The study results showed that vitamin B_6 supplementation was associated with significant reduction in the lipid profile of the triglyceridemicpatients [40]. A study conducted which aims to evaluate the association between the vitamin B, vitamin B_{12}, and homocysteine levels with cardiac risk factors in subjects. The results showed that the B vitamin levels were significantly lower in patients with hyperlipidemia; the vitamin B_{12} was inversely related to the TG and VLDL concentrations and positively related to the HDL. Thus a vitamin B_{12} deficiency may increase the cardiovascular risk factors [41]. A study conducted to analyze whether vitamin B_{12} deficiency in type II DM patients is related to cardiovascular riskfactors. The study concluded that the prevalence of cobalamin deficiency is common in type 2 diabetes patients and is related to adverse lipid parameters [38].

A study conducted which aims to evaluate the connection of homocysteine , folate, B complex with lipids and obesity parameters. The conclusion was that vitamin B_{12} deficiency was significantly related to both low HDL and hyper-homocysteinemia. Folate was found to significantly reduce the high TC and HDL [42].

Vitamin C helps in reducing the monocyte adherence to the endothelial memberane and improves the endothelium-dependent formation of nitric oxide and relaxation of the arteries. It also prevents vascular smooth-muscle-cell apoptosis. This process prevents the plaque instability in atherosclerosis and helps reduce the cardiovascular risk [43]. A study conducted meta-analysis of 13 randomized controlled trials in patients with hypercholesterolemia. These patients were administered with atleast 500 mg/d of Vit C for 3 to 24 weeks. Here, Vitamin C supplementation resulted in reduced LDL and triglycerides but did not show a significant increase in HDL. One such explanation for this is that Vitamin C levels were not elevated enough to produce a positive effect on HDL Cholesterolin the patients. The Artherosclerosis Risk in Communities study showed that an decrease of LDL of -7.9 mg/dl and triglycerides of -20% mg/dl may lead to a 6.6 % and 2.4% reduction in coronary heart disease respectively. In conclusion atleast 500 mg/d of Vit C for a minimum of 4 weeks can result in a significant decrease in serum LDL and triglycerides. The Helsinki Heart study determined that the

LDL/HDL ratio was the best single predictor of cardiac events [44].

Another study states that it's the antioxidant property of Vitamin C that slows down plaque aggregation in artherosclerosis and provides cardioprotection. Antioxidants neutralize free radicals by donating one of their own electrons, helping to prevent cell/tissue damage. These antioxidant nutrients do not become free radicals by donating electrons because they are stable in both forms. Vitamin C also protects Vitamin A and Vitamin E from oxidation and also helps to remove toxic substances from the body [24].

Vitamin D aid in the reduction of the serum PTH (Parathyroid hormone) Concentrations in the body. This suppression further promotes the peripheral removal of triglycerides. In addition a scarcity of fat-soluble vitaminD receptors (VDR) may also increase the cardiovascular risk [45].

A cross sectional study conducted on the association between Vitamin-D concentrations, lipid levels and C-reactive protein in familial combined hyperlipidemic patients. From the study it was found that familial combined dyslipidemic patients had lower 25 (OH)D concentrations when compared to the control group. Decreased Vitamin-D concentrations found in these patients were found to be an risk factor for the development of artherosclerosis [28]. Another cross sectional study showed a Vitamin-D deficiency of 58.34% and Vitamin-D sufficiency and insufficiency of 41.66% in type 2 Diabetes patients. The study revealed a negative but non-significant relationship between serum levels of 25(OH)D and that of triglycerides in diabetes patients. In general, the mean levels of triglycerides, fasting blood sugar were significantly higher and calcium was lower in type 2 diabetes patients with vitamin D deficiency compared to patients with sufficient and insufficient levels of Vitamin-D [27]. A study conducted which was aimed to investigate the effects of active Vitamin-D on serum lipids and oxidative stress markers in T2-DM patients. The results showed a significant reduction in total cholesterol, LDL, triglycerides and also in oxidative stress markers in both treatment and in control group. This may help in the prevention of cardiovascular complications in CAD Patients [45].

Vitamin E (Gamma tocopherol) increases the activity of gas synthase nitric oxide and produce a vessel relaxing effect. It helps to enhance the endothelial function and further aids in reducing the cardiac risk factors and complications [46]. A study conducted on the effect of Magnesium and Vitamin E co – supplementation on parameter of glucose homeostasis and lipid profile in patients with Gestational Diabetes. 60 subjects were randomly divided into two groups to receive 250 mg/day magnesium oxide plus and 400 Iu/day of vitamin E supplementation and placebo for 6 weeks and they concluded that Magnesium and vitamin E has significantly improved glycemic contol and lipid profile except HDL cholesterol levels. So the author supported our study stating that vitamin E has an effect on the lipid profile [47]. A study conducted to estimate the effect of vitamin E on cholesterol level of hypercholesterolemic patients receiving statins. Totally 44 patients were involved in the study and treated with 400 IU/day of vitamin E for 8 weeks and the result showed that Vitamin E has an effect on HDL but no significant changes on Total Cholesterol and LDL [48].

The Carboxylated matrix Gla protein prevents the deposition of mineral substances in the vascular system whereas the Vitamin K-dependent matrix Gla proteins reduce vascular calcification and age-related degenerations on the arteries and protects the arteries from mineral overload. This process aid in the protection of the myocardium and bones. Thus a diet low in vitamin K and presence of Uncarboxylated MGP is an independent risk factor for cardiovascular complications [49].

A Double Blind Placebo controlled trial was carried out to assess the effect of Phylloquione (vitamin K) supplementation on the lipid profile in women with Rheumatoid Arthritis. 58 patients identified with Rheumatoid Arthritis were randomly allocated into two groups to receive vitamin k (10 mg/day)or placebo for 8 weeks. By comparing the result of two groups after 8 weeks the author concluded that there was no significant change in the lipid parameter and it remain contentious. This study states that vitamin k didn't have any effect on the lipid profile of the patients [50]. A cross sectional study conducted with 298 participants to estimate the correlations of vitamin K intake, body fat and lipid profile and glucose homeostasis in adults and in the elderly by using spearmen correlation and they found that there is no correlation between vitamin K and lipid profile [51].

Conclusion

A state of prolonged hyperlipidemia in an individual may increase their risk in the development of cardiovascular diseases. Dyslipidemia accompanied by other comorbid conditions such as hypertension, diabetes, obesity, osteoarthritis, or others may worsen the existing complications in the individual more aggressively.

Recent studies have shown that vitamins have an important role to play in the lipid metabolism. However, beyond any doubts, it is clear that a healthy lifestyle is very important for the overall physiological wellbeing of an individual.

In addition to this vitamin supplementation along with the anti-hyperlipidemic agents may be an effective treatment regimen and eventually may help reduce the cardiovascular risk and its associated complications.

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