Abstract

Cardiovascular disease (CVD) is the main cause of death in the adult population of industrialized societies, and it is well known that as oxidized low-density lipoprotein (LDL) is an inflammatory component of the atherosclerotic process, hypercholesterolemia is one of the main risk factors contributing to the appearance and progression of CVD. On the other hand, plant sterols and plants stanols, commonly known as phytosterols, are substances found in the cells of plants and are long been known to be effective in reducing serum cholesterol concentration by competing with dietary and biliary cholesterol for intestine absorption. With this reason, it has been suggested that these cholesterol-lowering effect of phytosterols may ultimately help for preventing CVD. However, some research has shown that not all phytosterols supplementation may be beneficial, and those individual with sitosterolemia may be susceptible to overload. Also, limited evidence supports a decrease in fat soluble vitamins and carotenoid concentrations through the decrease in the number of available lipoprotein carriers by phytosterols consumption. However, it has been demonstrated that supplementation with food rich in carotenoids can attenuate these adverse effects. Thus, normal populations consuming a healthy diet and not exceeding their daily intake of sterols should be of no concern. With regard to phytosterols intake associated with therapeutic effects, intake of phytosterol-enriched products of about 1.5~2.5g/day has been recommended to reduce plasma low-density lipoprotein cholesterol (LDL-C) without any reported side effects based on pertinent research on phytosterols. In several meta-analyses, a dose-response relationship was found between the amount of phytosterol intake and the LDL-C lowering effect of phytosterols. In addition, there was no difference in cholesterol-lowering effect between phytosterol enriched foods and phytosterol supplements provided by capsule or tablet. Thus, the proposed method is to decrease total cholesterol (TC) through exercise and controlled dietary mechanisms to free up carrier molecules for these fat-soluble vitamins. In conclusion, it is wise to consider the supplementation of phytosterols/stanols in the human diet, and appropriate intake of phytosterols/stanols could be used in place of statin drugs with reduced side effects as an alternative treatment.

[Keywords] Protection, Cholesterol, Plant Sterol, Plant Stanol, Cardiovascular Disease

1. Introduction

Health is determined by social, economic, environmental and physical factors, as well as individual characteristics and behaviors[54][55][56]. However, if we are not physically healthy, we cannot achieve the meaning of health on other components of health. Therefore, it can be said that physical health is relatively more important than other health components. In addition, physical health can be achieved by an individual’s healthy eating habits and regular physical activity[57][58]. However, in a modern society represented by industrialization, economic growth, and automation, it is difficult to maintain regular exercise and a healthy diet in daily...
life. On the contrary, hypokinetic diseases such as CVD, diabetes, and obesity by insufficient movement or exercise including excessive calorie intake are becoming a social problem[1].

Among them, CVD is the leading cause of death worldwide, especially in industrialized societies[1]. According to the Causes of Death Statistics in 2018 of the Statistics Korea, it was reported that approximately 62.4% of all death was accounted for CVD in 2018[2]. Dyslipidemia represented by high levels of total cholesterol, low-density lipoprotein, and triglycerides(TG), and low levels of high-density lipoprotein(HDL-C) is known to one of the major risk factors leading to CVD[3][4]. Although there are various medications such as Lovastatin and Vytorin that help improve hypercholesterolemia by inhibiting cholesterol formation in the body[5], the relevant experts generally emphasize therapeutic lifestyle changes such as exercise, diet, smoking cessation, and weight control to improve blood lipid profiles[6]. Of course, smoking cessation, exercise, and diet are all represented as the cost-effective therapeutic lifestyle change strategies for reducing the risk of CVD[7][8][9], but dietary control, in particular, could be the most important strategy in that it is easiest to maintain in our daily life. According to some reports, incorporating foods enriched with plant sterols or stanols into the daily diet can substantially enhance the cholesterol-lowering effect of diet and ultimately reduce CVD[10][11]. It is well established that dietary plant sterols reduce plasma cholesterol concentrations by inhibiting intestinal cholesterol absorption. It was also suggested that daily intake of 2g of plant sterols or stanols can reduce LDL-C by about 10%[12][13], and a recent study reported that plant sterol containing food consumption(plant sterol 2g/day for 6 weeks) had lowering effect on LDL-C and TG[53].

Considering the action of phytosterols/stanols associated with the cholesterol-lowering effect in the body, it may be worthwhile to comprehensively summarize the basic information of phytosterols/stanols and the effects of phytosterols/stanols based on the most recent studies in terms of health care and nutrition. Therefore, the purpose of the present study was to examine the nutritional function of plant sterols or stanols as cholesterol lowering agents and to provide an insight about their possible protective effect on CVD.

2. Phytosterols Biochemistry

Plant sterols, also known as phytosterols, are found in the cell membranes of plants and function in permeability and fluid exchange within the cell. Sitosterol, campesterol, and sigmasterol are the primary forms of phytosterols found in nature, and these phytosterols are abundant in fat-rich vegetable food including fruits, nuts, legumes, cereals, and vegetable oils[14][15]. Phytosterols cannot be synthesized in the human body, so they are derived solely from vegetables and vegetable products[16]. The structure of the phytosterol is similar to that of cholesterol with exception of a change in the side chain at carbon 24. The difference in the side chain of sitosterol is an ethyl group whereas the side chain of the campesterol is a methyl group. The stigmasterol has an ethyl group attached, similar to sitosterol with a double bond formed at carbon 22. As the plant stanols or phytostanols are a saturated version of the phytosterols with no double bond in the sterol ring[17], phytostanols are not abundant in nature.

3. Metabolism of Phytosterols/Stanols

Phytosterols and cholesterols from diet and liver must be encircled by the bile salts that form micelles for absorption. The micelles transport lipids such as sterols and fatty acids to the cells lining of the intestinal walls, at which time lipids are released from the micelles and passively diffused into the interior of the intestinal cells. Within the intestinal cell, water-soluble glycerol and short and medium-chain fatty acid directly diffuse into the bloodstream, but cholesterol is
esterified by acyl cholesterol acyl transferase (ACAT), combined with chylomicrons, and then entered into the lymphatic system. On the other hand, unesterified cholesterol and phytosterols are transported back into the intestinal lumen by the adenosine triphosphate-binding cassette (ABC) transporter A1[18]. Those phytosterols and cholesterol that are incorporated into chylomicrons enter the circulation and are taken by the liver. In the liver, cholesterol and phytosterols from chylomicrons are repackaged into other lipoproteins or excreted from the liver in the bile. Approximately 95% of bile acids are reabsorbed in the small intestines, and remainder are excreted in the feces[19].

4. Plausible Mechanisms of Phytosterols/Stanols on the Prevention of Cardiovascular Disease

4.1. Effects of phytosterols/stanols on cholesterol absorption

The benefits of phytosterols/stanols over cholesterol-lowering effect have been evidenced in a number of studies, and the possible mechanisms for this can be discussed by the effects of these two substances on cholesterol absorption and metabolism.

Phytosterols/stanols can cause cholesterol-lowering effect by interfering with the absorption of dietary and biliary cholesterol from the intestinal lumen. As mentioned earlier, cholesterol must be solubilized in the form of micellar for absorption. However, phytosterols/stanols are more hydrophobic than cholesterol, and they have a higher affinity with micelles than cholesterol. That is, phytosterols/stanols compete with cholesterol for absorption in the intestines. Therefore, this mechanism could decrease overall amount of cholesterol absorption because it inhibits the binding of cholesterol with micelles in the gastrointestinal track[20].

In addition, it was reported that campesterol absorption is approximately three times slower than cholesterol absorption[21][22]. Different absorption rates were also found between phytosterols; sitosterol is three times slower than campesterol absorption in the intestines[21][22]. Due to this slow absorption rate of phytosterols, approximately 95% of dietary phytosterols are absorbed through the colon. These means that a different intestinal absorption rate of phytosterols/stanols from cholesterol absorption can also affect their hypocholesterolemic effects by interfering with the absorption of cholesterol from the small intestines to the large intestine.

In contrast to the rate of phytosterol intestinal absorption, the biliary excretion rate of phytosterols is much faster than cholesterol when it is transferred from the liver in the bile. While both sitosterol and campesterol are excreted faster than cholesterol, sitosterol is excreted faster than campesterol[23]. This fast excretion of phytosterols are also effective in reducing cholesterol absorption by displacing cholesterol from micelles and result in low net cholesterol absorption from dietary and biliary cholesterol in the intestinal tract[20].

Phytosterol/stanol-induced liver X receptor (LXR) gene activation also decreases the level of cholesterol[24]. ABC transporter A1 is considered to be the cholesterol gatekeeper in the intestine membrane because it actively pumps phytosterol and unesterified cholesterol out of the enterocytes and send back into the intestinal lumen[18]. When the LXR is activated, it has positive relationship with ABC transporter A1 mRNA expression which regulate cellular cholesterol levels by transporting cholesterol back into the intestinal lumen[18]. The higher ABC transporter A1 expression by LXR agonists may induce reducing intestinal cholesterol absorption[25]. Therefore, the ABC transporter A1 elevating effects of phytosterols/stanols were then considered to be a plausible explanation of how cholesterol is absorbed into the intestinal lumen.
4.2. Effects of phytosterols/stanols on cholesterol metabolism

As described above, phytosterols/stanols appear to lower cholesterol concentrations by not only interfering with micellar absorption of cholesterol in the intestines, but also by disrupting cholesterol homeostasis by affecting cholesterol efflux through the ABC transporters. For this reason, a decrease in intestinal-derived cholesterol supplied in the form of chylomicrons into the body causes several mechanisms to restore cellular cholesterol homeostasis.

Cells may increase endogenous cholesterol synthesis to restore cellular cholesterol homeostasis, and Miettinen, Tilvis and Kesäniemi(1990) reported that phytosterol consumption increased endogenous cholesterol synthesis[26]. Also, cellular cholesterol homeostasis can be maintained by receptor-mediated cholesterol uptake. In response to the decreased intestinal cholesterol absorption, LDL-receptor expression of cell surface is up-regulated to enhance circulating LDL-C absorption, and this process rather reduces the concentration of serum cholesterol[27]. In addition, the increased cholesterol concentration by these mechanisms inhibits the activation of sterol regulatory element-binding protein and suppresses the transcription of the genes coding for 3-hydroxy-3-methylglutaryl coenzyme A reductase involved in cholesterol and LDL-receptor synthesis[28][29]. As a final result, the mechanisms for maintaining cellular cholesterol homeostasis reduce serum LDL-cholesterol concentration, and ultimately can be positive for cardiovascular disease prevention.

5. Therapeutic Effects of Phytosterols/Stanols on Circulating Cholesterol

Cholesterol-lowering effect of phytosterols/stanols has been confirmed by multiple studies since the original literature on this relationship was reported by Pollak and Kritchevsky in 1951’s[30]. Recently, it was suggested that phytosterols as a part of a heart-healthy diet have a non-pharmacological therapeutic effect on lowering serum concentrations of total cholesterol and LDL-C[31].

Recommended dietary intake for phytosterols/stanols ranges from 200mg to 2-3g a day. Phytosterols/stanols can be found in foods that are rich in dietary fibers and foods high in unsaturated fatty acids. For example, sources high in phytosterol concentration include corn oil(912mg), canola oil(668mg), wheat bran(200mg), and frozen broccoli(44mg)[17]. It has been reported a decrease in cholesterol concentrations in humans, associated with a diet supplemented with phytosterols/stanols incorporated into different fat matrices of common foods[32][33]. Maki et al.(2001) reported that a 50% fat spread incorporated with 1.1 and 2.2g of phytosterols per day reduced LDL-C 7.6% and 8.1%, respectively, whereas Davison et al.(2001) and Jones et al.(2003) reported no differences in LDL-C levels using reduced-fat spreads[32][34][35]. Mattson, Volpenhein and Erickson[1977][36] found that esterification of sitostanol or sitosterol with fatty acids enhanced solubility in margarines, and Katan et al.(2003) reported that when phytosterols/stanols are added to foods such a margarine, up to a 15% reduction in serum TC and LDL has been reported[12].

Most recently, Salo and Kuusisto(2016) reported that yoghurt drinks containing 1.6 or 2.0g of plant stanols significantly decreased LDL-C by 9.4% and 8.1%, respectively[37]. Sarkkinen et al.(2018) investigated the effect of phytostanol enriched cereal-based snack bar consumption on serum TC and LDL-C, and they showed that 1.6g plant stanol containing cereal-based snack bar consumption (consumed twice a day for 4 weeks) significantly decreased LDL-C and non-HDL-C by 8.6% and 9.2%, respectively, as compared to the placebo group[33]. Also, Penchalaraju et al.(2018) examined cholesterol-lowering efficacy of phytosterol-enriched low fat foods(flavored milk, yogurt, fruit bar, and soya milk)[38]. They found that serum TC and LDL-C were significantly decreased after 30days consumption of phytosterol-enriched foods: flavored
milk(2.5 and 2.6%), yogurt(4.3 and 5.3%), fruit bar(5.0 and 9.1%), soya milk(8.7 and 12.6%), respectively[38].

The cholesterol-lowering effect of phytosterols/stanols also appears not only by phytosterol-enriched foods but also by consumption of phytosterol-containing supplement forms such as capsule or tablet[39]. In a recent study that was examined a cholesterol-lowering effect of a new phytosterol emulsion-containing supplements, they found significant decrease in LDL-C concentration(by 10.2%) through 4-week consumption of the supplement(1.5g/day phytosterol equivalents)[40]. Shaghaghi, Abumweis and Jones(2013) suggested that plant sterols/stanols-containing supplements were associated with clinically significant decrease in LDL-C levels, and plant sterol/stanol dose ranged from 1.0 to 3.0g/day during 4~6 weeks was effective for significant reduction in LDL-C in their study[41]. In addition, according to a meta-analysis examined cholesterol-lowering efficacy of phytosterol compositions of enriched product, it was confirmed that phytosterol and stanol were effective to reduce LDL-C levels, and there was a dose-response effect with LDL-C reductions[42].

The recommendations for intake with a single dose or periodically throughout the day remains to be questioned, although there was evidence that the time period of supplementation did not affect the capability of phytosterols to act as cholesterol-lowering agents[43]. Plat et al.(2000) investigated the effect of margarine and shortening enriched with plant stanol esters on serum lipids and lipoproteins when consumed three times per day or an equal dose of plant stanol esters once a day[43]. As a result, plant stanol ester consumption once a day or three times a day significantly reduced serum total and LDL cholesterol concentrations, and there was no significant difference on total and LDL cholesterol concentrations between the two different intake methods. This no relation between the consumption frequency of phytosterols/stanols and the reduction in LDL-C was confirmed by another well designed study[44]. Therefore, the distribution of phytosterol/stanol intake during a day on the cholesterol-lowering effect may not be an important determinant of efficacy.

6. Safety and Risks of Phytosterols/Stanols Consumption

According to extensive safety evaluation studies including animal and cell model, it is considered that phytosterols/stanols consumption is relatively safe. However, one of the concerns is the interaction of phytosterols/stanols with plasma level of fat-soluble vitamins, most notably tocopherols and carotenoids, because phytosterols/stanols inhibit the solubility of cholesterol in mixed micelles. However, limited evidence supported the disruption of fat-soluble vitamins and carotenoids concentration as a result of plant sterol supplementation[45]. But even in that study, the length of this acute study and the fact that they did not control the diet prior to the start of the study leaves question to the accuracy of its prediction. Indeed, most studies support that phytosterols/stanols intake does not cause a significant reduction in fat-soluble vitamins and carotenoids[46], and Noakes et al.(2002) reported that an increase in foods containing high levels of carotenoids could prevent the decline in carotenoid concentrations[47].

Another concern related to phytosterols/stanols consumption is the possibility that phytosterols/stanols intake may accelerate the atherosclerotic inflammatory process. This possibility is supported by certain individuals with sitosterolemia who have developed premature congestive heart failure[48]. Sitosterolemia is a condition which results in very high levels of plant sterols accumulation in the body. This condition is diagnosed as an increase in sterol levels and mutation in the gene that codes for its transporters, ABCG5 and ABCG8, which are responsible for carrying phytosterols and unesterified cholesterol from the enterocyte or the
liver to the intestinal lumen. With regard to the association between high blood phytoster-ols/stanols levels and premature coronary heart disease (CHD) incidence, it was suggested that phytosterols are more readily oxidized than cholesterol, and these oxidative properties of phyto-sterols could affect the risk of atherosclerosis [49].

Despite the negative concerns about high phytosterol effect on sudden CHD, Kratz et al. (2007) demonstrated that the normal recommended supplementation of sterols (2g/d) in patient with diagnosed sitosterolemia increased blood phytosterol concentration moderately which indicated that the capacity to excrete the phytosterols is not completely diminished at higher intakes [50]. It was also reported that CHD risk was not significantly increased in genetically muta-ted mice without ABCG5 and ABCG8 transporters and plasma levels of sterols higher than 20-fold, and phytosterol concentration was not significantly higher in middle-aged men and women with coronary calcium [51]. In addition, Baumgartner et al. (2019) confirmed that the oxidation status of phytosterols are not associated with cardiovascular disease risk [52]. Although there are some negative concerns associated with phytosterols/stanols intake, it is assumed that the LDL-C lowering benefit of phytosterols outweighs any cardiovascular risk. Nevertheless, more research is needed to examine the effects of excessive plant sterol supplementation on this population with sitosterolemia, and excessive overload should probably not be recommended for the public in general.

7. Conclusion

Overall, most studies report total and LDL-cholesterol lowering effects of phytoster-ols/stanols supplementation with HDL-C benefit to only a lesser degree. Based on pertinent research on phytosterols/stanols and their advocacy for lowering cholesterol concentrations, and improving cardiovascular health, it is wise to consider the supplementation of phytoster-ols/stanols in the human diet. It can be adequately hypothesized based on past literature that the administration of these bioactive food components combined with reduced-caloric diets and structured exercise regimens can be substituted for expensive cholesterol lowering medications as the first line of defense in cardiovascular disease risk management. However, only a few studies on the interaction between phytosterols/stanols intake and exercise have been re-port ed to date, and further research is needed on this topic.

8. References

8.1. Journal articles


### 8.2. Books


### 8.3. Additional references

9. Contribution

9.1. Authors contribution

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