

# The role of B-glucan, plant stanols, and oxy(phyto)sterols in managing cardiovascular risk

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## SUMMARY

Cardiovascular disease (CVD) is the leading cause of death in many parts of the world. The conventional risk factors for CVD include smoking, unhealthy dietary habits, physical inactivity, being overweight, hypertension, and abnormal blood lipid levels. As these factors are strongly influenced by behavioral factors, there is now broad consensus that encouraging people to adopt a healthy lifestyle (i.e. not smoking, being physically active, and eating a healthy diet) is fundamental to reduce CVD risk. The inability of the established risk factors to account for all the variations in CVD between and within populations has further led to the emergence of a number of novel CVD risk markers. These factors include oxidative stress, infectious agents, and increased levels of small-dense low-density lipoproteins (sdLDL), C-reactive protein (CRP), and oxysterols.

Dietary therapy is effective to reduce CVD risk and mortality, associated with high serum LDL cholesterol levels. Functional foods made to lower the atherogenic LDL particles, and thereby the risk for CVD, are therefore gaining a prominent position in dietary guidelines. Such foods contain (or lack) one or more functional components and therefore provide positive health effects beyond their traditional nutritional value. Examples of such food components with FDA-approved health claims are the water-soluble fiber  $\beta$ -glucan from oats and barley, and plant sterols and stanols. These functional foods are in particular helpful for those individuals with elevated serum LDL cholesterol levels, if the product is substituted for a standard product and eaten as part of a cholesterol-lowering diet and in conjunction with a healthy lifestyle.

The aim of the studies described in this thesis was to investigate the role of (combining) different dietary components, such as oat  $\beta$ -glucan, plant stanols, and oxy(phyto)sterols in managing CVD risk. Within this objective, we have formulated several specific research questions, as described below.

The combined intake of oat  $\beta$ -glucan and plant stanols may be more effective than either component alone. In our first study (**Chapter 3**), we therefore investigated the effects of a simultaneous intake of oat  $\beta$ -glucan and plant stanols on lipid metabolism in mildly hypercholesterolemic volunteers. In a randomized, controlled, 3-period crossover study, 40 mildly hypercholesterolemic men and women received for 4 weeks either control muesli (5 g of wheat fiber),  $\beta$ -glucan enriched muesli (5 g of oat  $\beta$ -glucan), or combination muesli [5 g of oat  $\beta$ -glucan plus 1.5 g of plant stanols (as their fatty acids)]. The  $\beta$ -glucan enriched muesli effectively lowered serum LDL cholesterol concentrations by 5%. Addition of plant stanols to this muesli further lowered serum LDL cholesterol levels by 4%. The muesli rich in  $\beta$ -glucan increased bile acid synthesis and decreased cholesterol absorption, in line with the proposed cholesterol-lowering mechanism of viscous soluble fibers. The addition of plant stanols did not influence bile acid synthesis, but decreased cholesterol absorption and raised cholesterol synthesis, also in correspondence to their suggested working mechanism. We concluded that muesli rich in oat  $\beta$ -glucan effectively lowered serum LDL cholesterol concentrations. Addition of plant stanols to the  $\beta$ -glucan-enriched muesli further lowered LDL cholesterol levels, although less than predicted. We therefore speculated that the presence of the viscous soluble fiber oat  $\beta$ -glucan or the food matrix may modulate the cholesterol-lowering efficacy of the plant stanols.

Besides their hypocholesterolemic effects, *in vitro* and animal studies have suggested that oat  $\beta$ -glucan and phytosterols may also affect inflammatory processes. To explore whether the effects of oat  $\beta$ -glucan and plant stanols on CVD risk may be mediated in part by affecting inflammation, we examined in **Chapter 4** the effects of these functional food ingredients on inflammatory markers. Pro-inflammatory cytokine (IL-6, IL-8, and TNF $\alpha$ ) production by PBMC and whole blood after LPS stimulation did not differ between the treatments. Also plasma levels of hs-CRP, a marker for low-grade systemic inflammation, were the same. No effects of oat  $\beta$ -glucan consumption on gene expression (human atherosclerosis PCR array) of PBMC were observed, while only 3 out of 84 genes from the atherosclerotic risk panel were differentially expressed after addition of the plant stanols. We concluded that consumption of oat  $\beta$ -glucan with or without plant stanols effectively lowered LDL cholesterol levels, but did not influence inflammatory parameters in slightly hypercholesterolemic subjects.

The link between high serum LDL cholesterol levels and CVD has been clearly established. However, evidence is accumulating that high levels of triacylglycerols (TAG), also known as hypertriglyceridemia, and low levels of HDL

cholesterol are also causally related to CVD. In a second study (**Chapter 5**), we therefore investigated the effects of plant stanols on the serum lipoprotein profile in 26 men and women, especially selected for elevated fasting serum TAG concentrations. After a 1-week run-in period, during which control margarine (containing 60% absorbable fats) was used, subjects were randomized to receive daily either control margarine or plant stanol-enriched margarine [2.5 g/d of plant stanols (as esters)] for 3 weeks. Consumption of plant stanols significantly decreased serum total and LDL cholesterol levels. A significant interaction between baseline TAG values and response-to-treatment was found. Supplementation of plant stanols lowered serum TAG concentrations, particularly in subjects with high baseline TAG concentrations (>2.3 mmol/L). Additionally, a significant interaction between baseline number of total LDL particles and plant stanol intake was found. Consumption of plant stanols lowered the total number of LDL particles, primarily in subjects with elevated baseline values, and this was mainly due to a decrease in the sdLDL particles. We therefore concluded that consumption of plant stanols not only lowered serum LDL cholesterol, but also serum TAG concentrations, especially in subjects with elevated serum TAG concentrations.

Oxysterols are suggested to be atherogenic and accordingly may also play an active role in the pathogenesis of CVD. Plant sterols structurally resemble cholesterol and the presence of one or more unsaturated bonds makes plant sterols susceptible to oxidation as well. However, it is unknown whether oxysterols are atherogenic, as has been suggested for oxysterols. In a third study (**Chapter 6**), we therefore examined the effects of oxysterols and oxysterols on serum lipoproteins and atherosclerotic lesion development in female transgenic mice. After a 2-week run-in period, 33 female heterozygous LDL receptor-deficient (LDLR<sup>+/-</sup>) mice were randomized to receive either control diet (atherogenic diet), oxysterol diet (control diet with 0.025% oxysterols), or oxysterol diet (control diet with 0.025% oxysterols) for 35 weeks. At the end of the experiment, serum cholesterol concentrations did not differ between the treatments. Also cholesterol exposure and lipoprotein profiles were similar. Nevertheless, a shift toward more severe lesions was found after the oxysterol and oxysterol diets compared to the control diet (no difference between oxysterols and oxysterols). Lesion size and collagen content did however not differ between the different treatments. We concluded that not only dietary oxysterols, but also dietary oxysterols may promote the development of atherosclerosis in LDLR<sup>+/-</sup> mice, primarily by a shift toward more severe atherosclerotic lesions.

Taken together, functional foods enriched with the viscous soluble fiber oat  $\beta$ -glucan and plant stanols effectively lower the atherogenic LDL particles, and thereby the risk profile for CVD. However, the combined intake of oat  $\beta$ -glucan and plant stanols lowered LDL cholesterol less than expected, possibly because of interference of the viscous soluble fiber with the plant stanol efficacy. Modulation of inflammatory markers may also be a valuable step in managing CVD risk, but consumption of oat  $\beta$ -glucan and plant stanols did not influence markers related to inflammation within a period of 4 weeks. Possibly, a more rigorous or longer-lasting change in dietary patterns is needed to achieve significant effects on markers of inflammation. Recent findings have highlighted not only elevated LDL cholesterol, but also elevated TAG levels as an important risk factor for CVD. We now found that plant stanols not only lowered LDL cholesterol, but also serum TAG levels, particularly in subjects with high baseline TAG levels. Oxysterols have also emerged as a risk factor for CVD. Phytosterols may undergo similar oxidative processes, and therefore oxysterols may have the same atherogenic potential. In our animal study, consumption of oxysterols and oxysterols promoted atherosclerotic lesion development by a shift toward more severe lesions. How these results compare to the human situation, warrants further study.