Background release: Benecol meta-analysis **28.02.2011**

This background material provides you with more information on the following issues:

- plant stanols; what they are, what their mechanism of action is, and how they differ from plant sterols
- current understanding of the cholesterol-lowering properties of plant stanols and plant sterols and how the results of the new meta-analysis update this
- information on the prevalence of cardiovascular diseases, such as coronary heart disease (CHD)
- meta-analyses; what they are
- how the new meta-analysis by Musa-Veloso et al. [1] was carried out
- the ground-breaking results of the double efficacy of plant stanol esters compared with plant sterol ester

Properties of plant stanols

Plant stanol ester is the patented ingredient in Benecol® products which lowers LDL-cholesterol in blood. Elevated LDL-cholesterol is a major risk factor for heart disease. Reducing LDL-cholesterol reduces the risk of heart disease.

Plant stanols and plant sterols are a group of compounds found naturally in plant cells. When consumed in sufficient amounts, they reduce total- and LDL-cholesterol by blocking the absorption of cholesterol from the digestive tract. Plant stanols and plant sterols are not the same, however, as they have slightly different molecular structures which causes them to behave differently in the human body. For example, plant stanols are far less likely to be absorbed than plant sterols.

Western diets contain, on average, only 30-50 mg of plant stanols per day [2] so the level of plant stanols seen in an ordinary diet is not sufficient to lower cholesterol by a significant amount. Therefore, plant stanol ester is added to foods in quantities that enable effective cholesterol lowering. Regular daily consumption of 2 g of plant stanols lowers LDL-cholesterol by approximately 10%.

More than 90% of the plant stanols and sterols used in commercially available cholesterol-lowering foods are added to foods as esters. Plant stanol ester is produced by adding vegetable oil-based fatty acids to plant stanols. Esterification makes it easier to incorporate plant stanols into foods in amounts sufficient for cholesterol lowering.

Plant stanol ester can be incorporated into several different types of foods; margarines and spreads, cereal products, mini-drinks, yoghurts, soy-based-products, etc. These types of products are currently available on the market.

Cholesterol-lowering efficacy of plant stanol ester

Several scientific and authoritative bodies around the world recommend the daily consumption of 2 g plant stanols or plant sterols for reducing elevated cholesterol levels [3-8]. Plant stanol ester is among the few selected food ingredients permitted to use an EU Commission approved health claim

for the reduction of a disease risk factor. To date, more than 60 clinical trials have confirmed the efficacy and safety of plant stanol ester as a cholesterol-lowering ingredient in many different settings and populations, for example in:

- women, men and children
- individuals with normal or elevated cholesterol levels
- patients with coronary heart disease, type 1 or 2 diabetes, or the metabolic syndrome
- organ transplant patients
- patients using statin therapy
- people on an ordinary Western diet
- people on a strict cholesterol-lowering diet
- populations from Europe, North America, Asia, and Australia

Are plant stanol ester and plant sterol ester equally effective?

Up until now, it was generally understood that the maximal LDL- cholesterol-lowering effect of both plant stanol and sterol ester is about 10%. This is achieved with 2 g/day of plant stanols or plant sterols [9]. Higher intakes were thought to have no additional benefit. However, two recently published studies on the use of high daily intakes (up to 9 g) of plant stanols indicate that the cholesterol-lowering effect is significantly enhanced when daily intakes exceeds the currently recommended 2 g [10-11]. No such effect has been reported with plant sterols. As plant stanols and sterols have different molecular structures, it is scientifically plausible that there are differences in their LDL-cholesterol-lowering efficacy as well.

Further indication of differences in the efficacy of plant sterols and stanols came from the meta-analysis by Demonty et al., published in 2009. They reported that, when studies with plant sterols and stanols were pooled, the maximal LDL-cholesterol reduction was 12.3%. However, when plant stanols and plant sterols were analysed separately, a non-significant 6.7% difference was detected in their maximal relative LDL-cholesterol lowering capacity. Inspired by these data, Musa-Veloso et al. decided to investigate further and an updated meta-analysis comparing the effects of plant stanols and sterols was conducted.

The meta-analysis by Musa-Veloso et al. shows the double maximal efficacy of plant stanol ester compared with plant sterol ester

A meta-analysis is a study where data from several individual studies are collected and grouped for further analysis, thus making it possible to "see the big picture". Like puzzle pieces, these individual studies tell the same story but this is much clearer when the studies are put together. Meta-analyses examining the cholesterol-lowering abilities of plant stanols and plant sterols have been done before, but, in these meta-analyses, plant stanol and plant sterol data were grouped together or the intakes analysed have been low (0.6-2.5 g/d).

The meta-analysis by Musa-Veloso et al. is the first to analyse plant stanol and sterol data separately and over a wider range of intakes. The meta-analysis was conducted according to a high level of scientific rigor. Like all high-quality meta-analyses, it was done following the PRISMA-statement. A comprehensive and transparent literature search for the meta-analysis was conducted for the first time in May 2009 and updated for the last time in November 2010 to ensure that the data were current. Major scientific literature databases were searched for high-quality, randomized, controlled, clinical human studies. Study inclusion and exclusion criteria were pre-defined and

applied to all of the studies identified. Out of 3456 publications initially identified, 113 publications with 182 data sets met the inclusion criteria. In 137 of these data sets, plant stanols or plant sterols were administered in ester form. The data from the studies were collected individually by two investigators as double data entry ensures accuracy in the transcription of study data. Numerous statistical analyses were conducted to characterise the plant stanol (ester) and plant sterol (ester) data sets and to confirm the analytical results obtained.

The new meta-analysis showed that plant stanols and plant sterols do have differences in their cholesterol-lowering efficacy. The meta-analysis does not contradict previous findings that the effects of plant sterols and stanols are practically similar at the currently recommended level of 2 g/d. However, the analysis showed that the estimated maximal LDL-cholesterol reduction was 18.2% for plant stanol ester but only 9.1% for plant sterol ester. This difference in favour of plant stanol ester was statistically significant. The results demonstrated that, as the intake of plant stanol ester increased, LDL-cholesterol is reduced in a dose-dependent way. With an increased intake, the cholesterol-lowering effect of plant stanol ester can be doubled. In contrast, this dose-response was not seen for plant sterols. Exclusion of high-dose studies (> 4 g plant stanols/sterols per day) from the analysis did not change the results. Additional analyses also showed that the efficacy of plant stanol ester was not affected by the fat content of the diet, or by the type of food in which it was served.

Cardiovascular diseases worldwide

More people die every year from cardiovascular diseases (CVDs) than from any other cause. According to World Health Organisation (WHO) over 18 million people die from CVDs every year and the figure is increasing. Most of these deaths are caused by coronary heart disease (CHD) or stroke. Deaths due to CVDs represent approximately 29% of all global deaths. Elevated cholesterol is a major risk factor for CVD and it causes one third of CVDs worldwide. Reducing LDL-cholesterol reduces the risk of CVD. Most people in the world with high cholesterol levels do not get the treatment they need in order to reduce their cholesterol levels. [12,13,14]

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