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Treatment with Abacor®, a soy-based dietary supplement, further reduces plasma concentrations of total and low-density lipoprotein cholesterol in statin-treated hypercholesterolaemic patients

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Abstract

Background: Many patients prescribed cholesterol-reducing drugs do not achieve target cholesterol levels. Soy protein reduces plasma cholesterols in patients with untreated hypercholesterolaemia. *Objective:* To test whether Abacor®, a newly developed soy-based dietary supplement, further reduces plasma cholesterol concentrations when given to hypercholesterolaemic patients in statin treatment. *Design:* In total, 49 patients (m/f = 34/15, age 43–79 years) completed the study. All had a plasma LDL cholesterol concentration >3.0 mmol/l at baseline despite statin treatment. Within the study, participants received statin monotherapy for 6 weeks, statin + Abacor® for 6 weeks and finally statin monotherapy for further 6 weeks. *Results:* The plasma concentrations of total cholesterol and of LDL cholesterol were significantly lower at visit 5 (6 weeks of combination treatment) than the mean value of the concentrations at visit 3 and visit 6 (both after 6 weeks of statin monotherapy), 5.5 ± 0.1 vs. 5.9 ± 0.1 mmol/l, $p < 0.0004$ and 3.3 ± 0.1 vs. 3.6 ± 0.1 mmol/l, $p < 0.0006$. *Conclusion:* The soy-based dietary supplement Abacor® has a total and LDL cholesterol reducing effect when given as supplement to statins in hypercholesterolaemic patients.

Keywords: Cardiovascular risk; Hypercholesterolaemia; Isoflavones; Soy; Statins

Industrial relevance: Soy is a potential candidate for having a cholesterol lowering effect. A newly developed soy-based dietary supplement was studied regarding it's reducting effect on plasma cholesterol concentration. Interestingly the results of the study indicate the effectiveness of the supplement and suggest that is more effective in male than in female patients.

1. Introduction

Atherosclerotic cardiovascular disease is the most frequent cause of death in the Western societies (Castell, 1984). Hypercholesterolaemia is a main cardiovascular risk factor and reduction of plasma cholesterol concentrations reduces the risk of cardiovascular disease (The International Task Force for Prevention of Coronary Heart Disease, 1998; Wood et al., 1998).

However, despite the availability of cholesterol-lowering drugs such as 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors (statins), which reduce the endogenous cholesterol synthesis in the liver, as many as 40% of patients with established coronary heart disease and hypercholesterolaemia do not achieve target plasma concentrations of cholesterols (Euroaspire I and II Group, 2001). The inadequate treatment is likely to be caused by a combination of insufficient pharmacological effect and a reluctance to perform the necessary multiple statin dose escalations, in part of concern for potentially serious adverse effects such as muscle and liver toxicity (Stein, 2002). The serious adverse effects as well as milder adverse effects such as gastrointestinal discomfort and insomnia are all dose related.

Hence, it would be an attractive alternative to increase the statin dose instead to supplement the statin with an add-on treatment capable of improving cholesterol control. Such a supplementary treatment should be without serious adverse effects by itself and without interactions with the statins which could increase the risk of muscle and liver toxicity. Such a supplementary treatment would be espe-

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cially valuable to patients in whom maximum doses of statins fail to control the hypercholesterolaemia.

Soy is a candidate for such a supplementary treatment since several studies have indicated a cholesterol-lowering effect of soy both in animals (Terpstra, West, Fennis, Schouten, & van der Veen, 1984) and in humans, the latter firmly evidenced by a recent meta-analysis (Anderson, Johnstone, & Cook-Newell, 1995). Based on these results, health claims for cardiovascular risk reduction by soy have been approved by both the U.S. Food and Drug Administration (FDA) and by the Joint Health Claims Initiative (JCHI) in the United Kingdom.

By which mechanism soy reduces plasma cholesterol concentrations is not clear, but the soy content of both isoflavones, cotyledon fibre and phospholipids are hypothesised to contribute to this effect (Hori et al., 2001; Lo, 1990; Tham, Gardner, & Haskell, 1998).

It was the aim of the present study to test whether Abacor®, a newly developed soy-based dietary supplement, further reduces plasma cholesterol concentrations in patients with hypercholesterolaemia already treated with statins, despite this treatment having plasma cholesterol concentrations above target levels.

2. Material and methods

2.1. Study population

Eligible for the study were statin-treated hypercholesterolaemic patients (>18 years of age) with established atherosclerotic coronary heart disease or elevated cardiovascular risk. Inclusion criterion was plasma LDL cholesterol concentration at screening (on unchanged statin treatment for at least 6 weeks) of 3.0 mmol/l or higher but not exceeding 4.5 mmol/l. The upper limit was introduced to avoid the scenario that patients with unacceptable high plasma concentration of LDL cholesterol for the study period of 20 weeks be maintained on unchanged treatment should the Abacor® be ineffective.

Exclusion criteria were (1) treatment with cholesterol-lowering drugs or dietary supplements of any kind other than the prescribed statin and Abacor® at any time during the study, (2) treatment with other drugs having a potential effect on the lipid metabolism including oral or injection corticosteroids, raloxifene, tamoxifen, tibolon, thyroxin, insulin, orlistat, estrogens and progesterones at any time during the study except stable (unchanged >1 year) postmenopausal hormonal substitution or hormonal contraception, (3) treatment with inhibitors of CYP3A4 (cyclosporin, oral antimycotics, macrolid antibiotics) at any time during the study, (4) known diabetes or fasting blood glucose $=6.7$ mmol/l at baseline, (5) known hypo-/hyperthyreosis or a plasma concentration of thyroidea-stimulating hormone (TSH) <0.4 mU/l or >4 mU/l combined with plasma concentrations of free thyroid hormones (T3 and T4) outside reference intervals (2.2–5.4 and 9.1–23.8 pmol/l, respectively) at baseline, (6) plasma concentration of creatinine kinase (CK) >230 U/l at baseline, (7) plasma concentration of aspartate aminotransferase (ASAT) >50 U/l at baseline, (8) plasma concentration of alkaline phosphatase >275 U/l at baseline, (9) plasma concentration of albumin <500 μmol/l at baseline, (10) plasma concentration of creatinine >150 μmol/l at any time during the study, (11) plasma concentration of triglycerides >4.5 mmol/l at baseline, (12) diseases or conditions which may interfere with either the conduction of the study (including cancer within the previous 5 years, unstable angina pectoris, cardiac insufficiency in level NYHA III and IV), or which may influence the absorption of Abacor® or the statin (intestinal resections, etc.), (13) known allergy to statins or soy, (14) pregnancy and breast-feeding and (15) fertility for women unless safe prevention is used (contraceptive pills, contraceptive coil, depot injection gestagen).

2.2. Product tested

Abacor is a newly developed soy-based dietary supplement containing isolated soy protein and having standardised high contents of isoflavones, cotyledon fibres and phospholipids. It contains 33% isolated soy protein with an isoflavon content of minimum 3.4 mg/g soy protein (Solae, St. Louis, USA). The content of dietary fibre in the product is 10.7% of which a minimum of 76% is cotelydon fibre. The fat content is 10% (approximately 70% unsaturated fatty acids) and the phosphatidylcholin content is minimum 2.5%. Two sachets of each 45 g were consumed daily corresponding to an intake of 30 g soy protein.

2.3. Study design

The study was a prospective open label single centre cohort study with six study visits. To minimise a possible effect unrelated to the product tested both an initial and a final period with the same statin medication as the participants' prestudy prescription were included. At the screening visit (-2 weeks) blood samples were drawn for lipid and safety analyses, vital signs taken and medical history obtained. Patients who qualified for participation in the study met for a baseline inclusion visit 2 weeks later (0 weeks). At this visit study medication identical to the patients prestudy statin prescription was distributed and patients were given heart protective dietary advice in accordance with the National Cholesterol Education Program step 1 diet (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, 2002)). The advices included encouragement to eat more vegetables and fruit, more fish and lean meat and to eat less high-fat dairy products, less meat and to avoid snacks, etc. Furthermore, to reduce the use of cooking fat and if necessary then to use fluid vegetable cooking fat. These advices were reinforced at each study visit. At the

third visit (6 weeks), both unchanged statin and Abacor® 2 × 45 g were distributed. A fourth visit after 1 week of the combination therapy was included (week 7) to ensure sufficient compliance with the Abacor® soy powder consumption and to detect a possible early effect on plasma lipids of this treatment. At the fifth visit (week 12), only statin was distributed and after a final 6 weeks on statin monotherapy patients met for the final sixth visit (week 18). At all visits, blood samples were drawn, vital signs measured, medication compliance recorded and adverse events monitored. The study was performed in accordance with the principles of "good clinical practice" (GCP).

2.4. Methods

Height and weight were measured without shoes and heavy clothes. Blood pressure was measured by a standard mercury manometer after at least 10 min of rest in the sitting position. The blood sample analyses were all performed at an accredited hospital laboratory (ISO 15189). The methods used were for: (1) Total cholesterol: CHOD/PAP, Roche, Cobas Integra 400, coefficient of variation 2% (Sugiuchi et al., 1995). (2) HDL cholesterol: formation of LDL, VLDL and Chylomicron complexes resistant for PEG modified enzymes, HDL cholesterol + 2nd generation, Roche, Cobas Integra 400, coefficient of variation 1% (Sugiuchi et al., 1995). (3) LDL cholesterol: calculated by Friedwalds formula. (4) Triglycerides: enzymatic colorimetric method (GPO/GAP), Roche, Cobas Integra 400, coefficient of variation 2% (McGowan, Artiss, Strandbergh, & Zak, 1983). (5) TSH: micro-particle enzyme immuno-analysis (MEIA), AxSYM Ultra sensitive, hTSH II-analyses, Abbott, coefficient of variation 10%. (6) CRP: agglutination with latex particles, Roche, Cobas Integra 400, coefficient of variation 3%. (7) Albumin: Vitros 950, Ortho Clinical Diagnostics, coefficient of variation 1.4%. (8) Creatinine: Vitros 950, Ortho Clinical Diagnostics, coefficient of variation 1%. Glucose: Vitros 950, Ortho Clinical Diagnostics, coefficient of variation 1%. (9) CK: Vitros 950, Ortho Clinical Diagnostics, coefficient of variation 5%. (10) ASATVitros 950, Ortho Clinical Diagnostics, coefficient of variation 3%. (11) Alkaline phosphatases: Vitros 950, Ortho Clinical Diagnostics, coefficient of variation 2%. All analyses were performed on blood samples taken from fasting subjects.

2.5. Statistics

The study was designed to detect a reduction in plasma LDL cholesterol concentration of 0.4 mmol/l with a power of 80% at a p value level of 0.01 (a standard deviation of the change in LDL cholesterol concentration of 0.8 mmol/l was hypothesised). Normally distributed continuous variables are given as mean ± S.E.M. and non-normally distributed continuous variables as median (range). Plasma lipids and other measurements at visits 4 and 5 (1 and 6 weeks of combined Abacor® and statin treatment, respectively) were compared to the mean value of those parameters at visit 3 and visit 6 (both after 6 weeks of statin monotherapy) by Wilcoxon's matched pairs tests. Associations between baseline characteristics including type and dose of statin treatment and the reduction of plasma total and LDL cholesterol concentrations by supplementary treatment with Abacor® were sought by Pearson's correlation tests. Difference in the occurrence of adverse events during statin monotherapy and during statin + Abacor® combination therapy was tested by Fischer's exact test. A probability value of <0.05 was considered significant in all analyses.

2.6. Ethics

All subjects included gave their written informed consent to participation before any study-related procedure. The study was performed in accordance with the Second Helsinki Declaration and was approved by the regional ethical committee.

3. Results

3.1. Demographics and baseline characteristics

A total of 67 subjects were screened for the study and 53 (79%) were eligible for participation and subsequently included. Four discontinued the study, two because of non-serious adverse events (nausea and vomiting, respectively, during the combination treatment) and two because they did not want to attend the required visits. Data from the remaining 49 subjects (15 women and 34 men, 43–79 years

Table 1
Patient demographics and clinical characteristics

Characteristic	
Age, years (mean ± S.E.M.)	59 ± 1
Range	43–79
Sex, male/female	34/15
Male %	69
Family history of premature cardiovascular disease (myocardial infarction <55 years of age in a 1. degree relative), no. (%)	22 (45)
Patient history documented IHD, no. (%)	
Myocardial infarction	8 (16)
Coronary artery bypass graft	11 (22)
PTCA	9 (18)
Any of the above	20 (41)
History of hypertension, no. (%)	29 (59)
Smokers, no. (%)	8 (16)
Prior smokers, no. (%)	21 (43)
Current cigarette consumption, smokers	
Median (range)	10 (4–20)
Number of pack-years, all [median (range)]	9 (0–116)
Baseline lipid values, visit 2 (mmol/l; mean ± S.E.M.)	
Total cholesterol	5.9 ± 0.1
LDL cholesterol	3.6 ± 0.1
HDL cholesterol	1.7 ± 0.1
Triglycerides (median (range))	1.3 (0.4–3.0)

Table 2
Statin treatment and concomitant medication

Medication	Number of patients using the medication within the study (%)
Baseline statin treatment	
Atorvastatin 10 mg/day, no. (%)	5 (10)
Atorvastatin 20 mg/day	1 (2)
Atorvastatin 40 mg/day	7 (14)
Fluvastatin 20 mg/day	1 (2)
Lovastatin 20 mg/day	1 (2)
Pravastatin 20 mg/day	7 (14)
Pravastatin 40 mg/day	6 (12)
Simvastatin 10 mg/day	5 (10)
Simvastatin 20 mg/day	8 (16)
Simvastatin 40 mg/day	7 (14)
Simvastatin 80 mg/day	1 (2)
Concomitant medication	
Slow release nitro-glycerine, no. (%)	3 (6)
Acetylsalicylic acid	25 (51)
ACE inhibitors	10 (20)
Angiotensin II receptor antagonists	6 (12)
Beta blockers	13 (27)
Calcium antagonists	9 (18)
Digoxin	1 (2)
Diuretics	10 (20)
Amiodarone	1 (2)
Dipyridamole or clopidogrel	2 (4)
Estrogen replacement	4 (27 of female patients)
H_2 blockers or proton pump inhibitors	3 (6)
Antihistamines	2 (4)
Finasteride	1 (2)
Antibiotics	3 (6)
NSAIDs	1 (2)
Anxiolytics	2 (4)
Terbutaline	1 (2)
Inhalation glucocorticoids	1 (2)

of age (59 ± 1)) are included in the analyses. All participants are Caucasians. Patient demographics and baseline characteristics are summarised in Table 1 and statin treatment and concomitantly medication in Table 2.

3.2. Lipids

The plasma concentrations of total cholesterol and of LDL cholesterol were significantly lower at visit 5 (6 weeks of combination treatment) than the mean value of the concentrations at visit 3 and visit 6 (both after 6 weeks of statin monotherapy), 5.5 ± 0.1 vs. 5.9 ± 0.1 mmol/l, $p < 0.0004$ and 3.3 ± 0.1 vs. 3.6 ± 0.1 mmol/l, $p < 0.0006$.

No significant differences in plasma HDL cholesterol and triglyceride concentrations were found between statin monotherapy and statin + Abacor® combination therapy periods (Table 3).

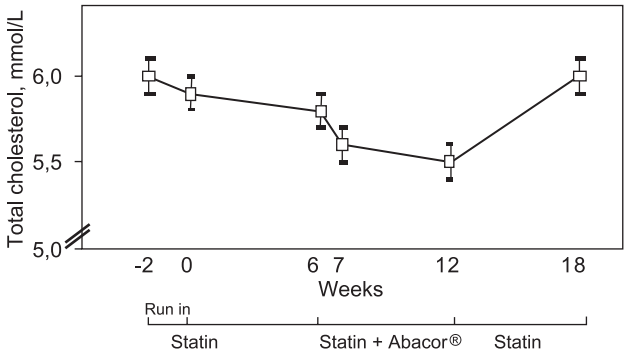

Fig. 1. Plasma total cholesterol concentration (mean ± S.E.M.) in all participants ($n = 49$) at week 2 (screening), at week 0 (baseline), at week 6 (after 6 weeks of statin monotherapy), at week 7 (after 1 week of statin and Abacor® combination therapy), at week 12 (after 6 weeks of statin and Abacor® combination therapy) and at week 18 (after a second 6-week period of statin monotherapy).

The plasma concentrations of total and LDL cholesterols were already lower at visit 4 (1 week of combination treatment) than the mean value of concentrations at visit 3 and visit 6, 5.6 ± 0.1 vs. 5.9 ± 0.1, $p < 0.0001$ and 3.3 ± 0.1 vs. 3.6 ± 0.1, $p < 0.0006$.

Plasma concentrations of total cholesterol and LDL cholesterol at all study visits are shown in Figs. 1 and 2.

The differences in total and LDL cholesterol concentrations between visit 5 and the mean of visit 3 and visit 6 were unrelated to baseline cholesterol concentrations and age, but significantly positively associated with male sex ($p < 0.01$ and $p < 0.005$ for total and LDL cholesterol, respectively). Post hoc analyses of the differences in plasma concentrations of total and LDL cholesterol suggest that the effect of Abacor® was greater in males than in the total study population whereas no significant effect was detectable in women (Tables 4 and 5).

No associations between either dose or type of statin and the reduction in total and LDL cholesterol concentrations as result of the combination treatment were found (data not shown).

3.3. Other variables

No effect of the Abacor® + statin combination was found on weight, blood pressure, heart rate, plasma concentrations of TSH, C-reactive protein (CRP), creatinine, glucose, CK,

Table 3
Differences in plasma lipid concentrations between statin monotherapy and statin + Abacor® combination therapy, all participants ($n = 49$)

Lipid	Statin mean of visits 3 and 6	Statin/Abacor visit 5	Absolute difference	% Difference	p Value
Total cholesterol, mmol/l	5.9 ± 0.1	5.5 ± 0.1	-0.4 ± 0.1	-6.0 ± 1.6	<0.0004
LDL cholesterol	3.6 ± 0.1	3.3 ± 0.1	-0.3 ± 0.1	-7.8 ± 2.4	<0.0006
HDL cholesterol	1.7 ± 0.1	1.6 ± 0.1	-0.0 ± 0.0	-0.0 ± 0.0	NS
Triglycerides	1.4 (0.5–3.4)	1.5 (0.5–4.0)	−0.0 (−1.6 to +2.2)	−0.0 (−0.6 to +1.6)	NS

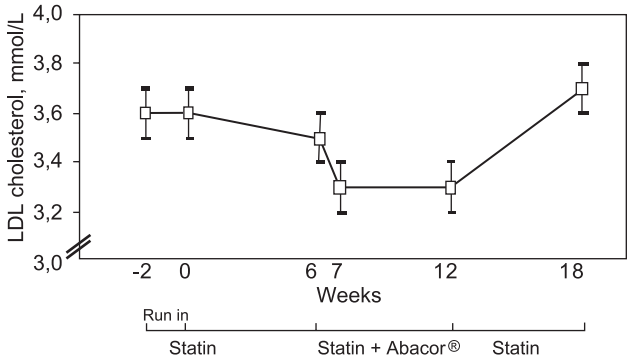

Fig. 2. Plasma LDL cholesterol concentration (mean ± S.E.M.) in all participants ($n = 49$) at week 2 (screening), at week 0 (baseline), at week 6 (after 6 weeks of statin monotherapy), at week 7 (after 1 week of statin and Abacor® combination therapy), at week 12 (after 6 weeks of statin and Abacor® combination therapy) and at week 18 (after a second 6-week period of statin monotherapy).

ASAT or alkaline phosphatases compared to statin monotherapy (data not shown).

3.4. Compliance

Compliance for consumption of Abacor® was 95 ± 2% and for consumption of statin 98 ± 3%.

3.5. Adverse events

Two serious adverse events were seen (the definition included events that were life threatening, significantly or permanently disabling, resulted in death or new or prolonged hospitalisation, or being medically significant). Both events were hospitalisation due to unstable angina pectoris in subjects with known coronary heart disease in the combination treatment period and both events were considered unrelated to the study treatment. In both patients, antiangina medication was adjusted, the conditions resolved and the subjects continued and completed the study.

The number of non-serious adverse events in the Abacor® + statin combination period was higher than the mean number of adverse events in the two statin monotherapy periods, 13 vs. 5, although this difference did not reach statistical significance.

The difference was entirely due to more gastrointestinal complaints (meteorism, borborygmi, diarrhea, obstipation and nausea). In the majority of the patients, these complaints were mild and temporary. However, two patients discontinued the study due to such complaints.

4. Discussion

This study demonstrates that Abacor®, the soy-based dietary supplement tested, further reduces plasma concentrations of total and LDL cholesterols in hypercholesterolaemic patients who despite treatment with statins have elevated plasma concentration of LDL cholesterol.

Interestingly, the additional cholesterol-lowering effect of Abacor® was detectable already after 1 week of combination treatment. However, the effect was further increased after 6 weeks.

The cholesterol-lowering effect was consistent across the different types of statins, which constituted the basic lipid lowering treatment of the study.

Abacor® was well tolerated with high compliance for the consumption and only slight gastrointestinal discomfort as mainly temporary side effect. Importantly, no increase in the plasma concentrations of muscle and liver enzymes were found as result of the supplementary treatment with Abacor®.

The reductions of plasma concentrations of total and LDL cholesterols were comparable with the expected reductions by doubling the dose of statins and in a post hoc analysis of the men included with a quadrupling of the dose. Such effects will be especially important for patients who receive a maximum dose of statins.

Hence, the cholesterol-lowering effect of soy previous reported in humans (Anderson et al., 1995) is confirmed when the soy is given in combination with statins. This is in accordance with a recent study showing a favourable effect in rabbits of a combined treatment with soy and simvastatin (Giroux, Lavigne, Moorjani, & Jacgues, 1997).

The cholesterol-lowering effect of taking soy as a supplement to statin treatment in this study was found in patients with only moderately elevated plasma total and LDL cholesterol concentrations (5.9 ± 0.1 and 3.6 ± 0.1 mmol/l, respectively) and was not associated with baseline cholesterol concentrations. This is important since the cholesterol-lowering effect of soy in previous studies has been found positively correlated with the baseline cholesterol concentration (Anderson et al., 1995). These studies included patients with more pronounced hypercholesterolaemia and the present study demonstrates that also patients in statin treatment with only moderate hypercholesterolaemia benefit from soy consumption.

A result of potential importance in the present study is that the cholesterol-lowering effect of Abacor in post hoc analyses was associated with the sex of the participants. In

Table 4
Differences in plasma lipid concentrations between statin monotherapy and statin + Abacor® combination therapy, male participants ($n = 34$)

Lipid	Statin mean of visits 3 and 6	Statin/Abacor visit 5	Absolute difference	% Difference	p Value
Total cholesterol, mmol/l	5.9 ± 0.1	5.3 ± 0.1	− 0.6 ± 0.1	− 9.0 ± 1.9	< 0.0002
LDL cholesterol	3.6 ± 0.1	3.1 ± 0.1	− 0.5 ± 0.1	− 12.0 ± 2.4	< 0.000005
HDL cholesterol	1.6 ± 0.1	1.5 ± 0.1	− 0.1 ± 0.0	− 0.0 ± 0.0	NS
Triglycerides	1.5 (0.8–3.4)	1.5 (0.7–4.0)	− 0.1 (− 1.6 to + 2.2)	− 0.1 (− 0.6 to + 1.6)	NS

Table 5
Differences in plasma lipid concentrations between statin monotherapy and statin + Abacor® combination therapy, female participants ($n = 15$)

Lipid	Statin mean of visits 3 and 6	Statin/Abacor visit 5	Absolute difference	% Difference	p Value
Total cholesterol, mmol/l	6.0 ± 0.2	6.1 ± 0.2	0.0 ± 0.2	0.0 ± 0.0	NS
LDL cholesterol	3.6 ± 0.1	3.6 ± 0.2	+0.1 ± 0.2	0.0 ± 0.1	NS
HDL cholesterol	1.9 ± 0.1	1.8 ± 0.1	− 0.0 ± 0.0	− 0.0 ± 0.0	NS
Triglycerides	1.3 (0.5–2.2)	1.5 (0.5–2.3)	+0.1 (− 0.6 to +0.4)	+0.1 (− 0.3 to +0.3)	NS

men, the effect was more pronounced than in the total material whereas no significant effect was seen in women. Hence, a supplementary treatment with soy to hypercholesterolaemic patients treated with statins may be beneficial in men but not in women. However, only 15 women participated in the study and a sex difference in the plasma cholesterol-lowering effect of soy needs further testing in prospective studies adequately powered to answer the question. A sex difference in the cholesterol-lowering effect of soy has to our knowledge not been described before. However, several small studies where a positive effect has been described has studied exclusively men (Bakhit et al., 1994; Potter, Bakhit, & Essex-Sorlie, 1993) and such studies have been included in the meta-analysis demonstrating a significant cholesterol-lowering effect of soy in humans (Anderson et al., 1995). Our results are in accordance with a recent study of perimenopausal women where no cholesterol-lowering effect of soy was seen (Dent et al., 2001). However, also studies with female participants have indicated a cholesterol-lowering effect of soy (Carroll et al., 1978). Whether these discrepancies might reflect differences in menopausal status of female study participants remains to be established.

The mechanism(s) by which soy reduces plasma cholesterol is not known. Enhancement of bile excretion, thyroid hormonal changes and changes in glucose hormonal homeostasis have all been hypothesised (Beynen, 1990; Forsythe, 1990; Potter, 1996; Sanchez & Hubbard, 1991) and special emphasis been attributed to the soy content of isoflavones, cotyledon fibre and phospholipids (Hori et al., 2001; Lo, 1990; Tham et al., 1998).

In the present study, plasma concentrations of TSH and fasting blood glucose was measured at each visit and the concentrations were identical in the Abacor® + statin treatment period and the statin monotherapy periods.

It is not possible from the results of the present study to establish whether it is the soy protein or any of the other components of the soy that reduces plasma cholesterol.

The indication of a possible sex difference in the response to Abacor® supplementary treatment could, however, reflect a special importance of the isoflavone content. Isoflavones are known to be weak estrogens binding to the estrogen receptors and may thereby initiate a cholesterol-lowering effect similar to that of estradiol (Knight & Eden, 1996; Verdeal & Ryan, 1979). If this is an important part of the cholesterol-lowering effect of soy, it may explain the observed greater effect in men than in women. Results from studies on the role of isoflavones in the cholesterol-lowering effect of soy are conflicting. Isoflavones alone have failed to show cholesterol-lowering effects (Hodgson, Puddey, Beilin, Mori, & Croft, 1998) and other studies have indicated that the cholesterol-lowering effect of soy requires the presence of isoflavones (Crouse et al., 1999; Gardner, Newell, Cherin, & Haskell, 2001). However, results opposing the requirement of isoflavones for a cholesterol-lowering effect of soy are also reported (Fukui et al., 2002).

Limitations of the present study include the open label design and the lack of a placebo group. However, the design of the study with an initial 6-week period with unchanged statin medication after dietary instructions should reduce a potential ‘‘cholesterol-lowering effect’’ by the participants’ awareness of and possible lifestyle changes due to the study participation itself. The risk of a ‘‘regression towards the mean’’ effect was also limited by this design, and furthermore by the few screen failures resulting of invitation of patients in our lipid ambulatory known to have unsatisfactory effect of their present statin medication.

Furthermore, plasma cholesterol concentrations after the combination therapy period were also compared with concentrations after a second period of statin monotherapy at the end of the study. Plasma cholesterol concentrations had then returned to the concentrations found before the combination therapy was initiated.

In conclusion, this study shows that the soy-based dietary supplement Abacor® is well tolerated, safe and has a total and LDL cholesterol-lowering effect when given in addition to statins to hypercholesterolaemic patients whose plasma lipid concentrations are not adequately controlled by their present statin treatment. Abacor® could be an attractive alternative to increasing the statin dose. The results of the present study may also indicate that the cholesterol-lowering effect of Abacor® is more pronounced in male than in female patients.

Acknowledgements

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