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A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects

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Summary *Background* Soy protein is effective in lowering plasma cholesterol, LDL cholesterol and triglyceride concentrations. It has not been conclusively answered, whether and to what extent other soy constituents may also contribute to this effect. *Objective* To investigate the change in blood lipid levels after application of two soy-based supplements containing soy protein either without (SuproSoy®) or with (Abacor®) soy fiber and phospholipids in a randomized placebo-controlled triple-armed study. *Methods* 121 hypercholesterolemic adults (66 females, 55 males) were recruited and randomly assigned to one of three treatments. Over 8 weeks they received daily either 25 g soy protein (as a component of the supplements Abacor® or SuproSoy®) or 25 g milk protein (as a component of placebo). Serum lipids were measured at baseline and after 4, 6 and 8 weeks. *Results* After 8 weeks of supplementation total cholesterol levels were reduced by 8.0 ± 9.6 % (Abacor®) and 3.4 ± 8.3 % (SuproSoy®); LDL cholesterol levels by 9.7 ± 11.7 % (Abacor®) and 5.4 ± 11.6 % (SuproSoy®); and Apolipoprotein B levels by 6.9 ± 14.6 % (Abacor®) and 4.0 ± 12.4 % (SuproSoy®). Serum levels of HDL cholesterol and triglycerides remained unchanged. *Conclusions* A preparation combining isolated soy protein with soy fibers and phospholipids showed twice the lipid-lowering effect of a preparation containing isolated soy protein alone. Therefore, such soy-based supplements can be useful in reducing the cardiovascular risk.

Key words blood cholesterol – cardiovascular disease – soy protein – soy phospholipids – nutritional supplements

Introduction

Cardiovascular diseases cause almost 40 % of all deaths in industrialized countries. Control of this major public health problem includes early recognition of the related risk factors. It is widely accepted that dyslipidemia, in particular hypercholesterolemia, is one of the leading risk factors for atherosclerosis and coronary heart disease [1]. Along with hypertension and tobacco consumption, increased cholesterol levels account for approximately 50 % of all coronary heart diseases [2].

In view of the central role that elevated levels of blood lipids, especially LDL cholesterol, play in the genesis of atherosclerosis, therapeutic and dietary approaches to their treatment and prevention are highly relevant. Established lipid-lowering drugs, although effective, may be accompanied by serious adverse reactions [3, 4]. As alternative, early dietary interventions are recommended, such as the restriction of saturated fatty acids

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[3], increased intake of dietary fibers [5, 6] and of protein-rich legumes, preferably soy [7].

The mechanism by which soy products exert a lipid-lowering effect is yet unknown. The following possibilities are under discussion: activation of the LDL receptor by essential amino acids from soy protein [8]; stimulation of fecal bile acid excretion by soy fiber [9]; inhibition of endogenous cholesterol synthesis [10]. Numerous clinical studies have been performed to demonstrate that soy protein could cause significant decreases in the serum levels of total and LDL cholesterol and triglycerides [11–20]. The published results, however, remain controversial, which can be attributed either to different study designs or to cofactors in the soy preparations used. Different treatment durations were used, e. g. 5 [13], 6 [17], 16 [20] or 24 [12] weeks, as well as different daily soy protein intake levels, ranging from 17 to 124 g [11]. The dosage-response relationship has been investigated in recent studies [17, 20]. Otherwise, soy products differ considerably in their composition, containing proteins, isoflavones and other soy ingredients of various structures and in varying quantities. Isoflavone content of isolated soy protein is closely linked to their lipid-lowering action [21, 22]. Various clinical trials have shown that the decrease in plasma cholesterol levels achieved with soy protein supplementation is dosage dependent for the isoflavone concentration [14–16, 23]. Independent cholesterol-lowering and antiatherogenic effects have been observed for soy components such as cotyledon fibers [24, 25] or phospholipids [26–29]. There is, however, a lack of data about cooperative effects of soy constituents in respect to their efficacy as cholesterol-lowering agents.

This randomized, double blind triple-armed study was intended to compare the cholesterol-lowering effects of a soy protein commercial preparation (SuproSoy®) and a soy protein commercial preparation enriched with fiber and phospholipids (Abacor®).

Methods

This study enrolled 121 adults (66 women and 55 men), who met the following inclusion criteria: total serum cholesterol concentration of 5.8–7.9 mmol/l; serum LDL cholesterol $\geq$ 3.4 mmol/l; serum triglycerides $<$ 4.5 mmol/l; ages 30–70; and written informed consent. The exclusion criteria were severe cardiovascular, gastrointestinal, hepatic, renal or endocrine diseases; hypertension ($>$ 160/100 mmHg); myocardial infarction or apoplexy; familiar hypercholesterolemia; diabetes mellitus type-1 and type-2 under drug therapy; severe obesity (BMI $\geq$ 35 kg/m^2); use of lipid-lowering drugs in the 4 weeks previous to the trial; adverse reactions to milk proteins or other components of the verum and placebo preparation; drug or alcohol abuse; HIV infection or clinically manifest AIDS; plans to reduce weight during the study period; pregnancy or breast-feeding; participation in a clinical trial within 4 weeks previous to the trial; or potential compliance problems due to insufficient knowledge of the German language. Concomitant medications, which could not be expected to notably influence the study results, were permitted.

The study complied with the good clinical practice recommendations of the European Union as approved by the Ethics Committee of the Humboldt University, Medical School (Charité), Berlin, and was conducted between July and December 2001. The trial was performed as a randomized, placebo-controlled, double blind study. For an individual trial period of 8 weeks and by means of a block randomization procedure, participants were assigned to one of three groups, receiving daily either 77.5 g Abacor® (containing 25 g soy protein), 71.9 g SuproSoy® (containing 25 g soy protein), or 76.4 g placebo (containing 25 g protein derived from caseinate and skimmed milk powder). The respective protein supplements (for a list of ingredients see Table 1) were distributed at the regular examinations. Participants received their daily supply in 2 separate sachets, which they were advised to suspend in cold water and ingest with the morning and evening meals, respectively. At each assessment, compliance with the treatment schedule was checked by counting the returned sachets.

Assessments took place at baseline and after 4, 6, and 8 weeks and involved evaluation of the general clinical condition and blood sampling to determine serum levels of total, LDL and HDL cholesterol, triglycerides, and apolipoprotein B. All blood analyses were performed by the laboratory "Quadriga", Berlin, Germany, which is certified by the national Institute for Standardization and Documentation in Medical Laboratories and fulfills the guidelines of the German Federal Medical Association. Serum lipid profiles including measurement of total cholesterol and triglyceride concentrations were analyzed by Olympus AU 2700 (Olympus, Ireland). The coefficient of variation (CV) is 3.0 % and 2.6 %, respectively. LDL and HDL cholesterol concentrations were analyzed by Olympus AU 600 (Olympus, Ireland). The CV is 2.7 % and 3.4 %, respectively. Serum concentrations of apolipoprotein B were measured by Beckman Image (Beckman Coulter, Fullerton, California, USA). The CV is 2.6 %.

To ensure tolerance, basic clinical data and safety parameters were determined at the initial and final evaluation and the general physical condition and occurrence of undesirable effects were recorded during each assessment. Data were recorded on dBase IV® (Borland; Scottsvalley, Calif) by double data entry and evaluated with SPSS® for Windows™ (Chicago, Ill) according to the full-analysis procedure. In addition to variance analysis and the F-test, the t-test for coupled observations was applied.

Table 1 Composition of the study preparations (daily dosage = 2 sachets)

	Abacor®*		SuproSoy®**		Placebo	
Ingredient	Per 100 g	Per sachet	Per 100 g	Per sachet	Per 100 g	Per sachet
Total, g	100	38.8	100	35.9	100	38.2
Energy, kcal	352	136.5	387	138.7	345	132.0
Energy, kJ	1473	571.1	1618	580.3	1443	552.3
Total carbohydrate, g	30.7	11.9	43.7	15.7	46.8	17.9
Lactose, g	4.1	1.6	–	–	17.0	6.5
Fructose, g	21.4	8.3	20.9	7.5	17.0	6.5
Maltodextrin, g	2.6	1.0	18.9	6.8	9.7	3.7
Fat, g	10.3	4.0	7.0	2.5	2.6	1.0
Total protein, g	36.3	14.1	39.8	14.3	36.7	14.0
Caseinate, g	–	–	–	–	22.7	8.7
Soy protein, g	32.2	12.5	34.8	12.5	–	–
Protein, g, from:						
Skimmed milk powder	2.8	1.1	–	–	12.1	4.6
Cream powder	–	–	3.6	1.3	0.3	0.1
Cocoa powder	1.3	0.5	1.4	0.5	1.7	0.7
Total fiber, g	13.1	5.1	2.5	0.9	2.6	1.0
Soy fiber, g	8.3	3.2	–	–	–	–
Isoflavonoids, mg	124.3	48.3	134.3	48.2	–	–
Total phospholipids, g	5.2	2.0	–	–	–	–
Phosphatidylcholine, g	2.6	1.0	–	–	–	–
Sodium, g	0.13	0.05	0.08	0.03	0.24	0.09

* Registered trademark of NutriPharma A/S, Copenhagen, Denmark
** Registered trademark of Protein Technology International Inc., St Louis, MO, USA

Results

Of the 121 subjects initially enrolled, 3 subjects experienced a total of 7 non-serious adverse events that were unrelated to treatment with the study preparations. Two of these terminated the trial prematurely by their own choice but did undergo a final examination; 5 others were excluded without final examination due to insufficient compliance. Table 2 summarizes the baseline characteristics of the 116 participants included in the analysis. From these, as well as from further clinical data and life-style assessments, the three study groups appear to have sufficiently homogenous baseline values.

The development of total cholesterol levels within the three study groups during the trial is shown in Table 3 and Fig. 1. After 8 weeks of treatment, total cholesterol levels decreased by 0.56 ± 0.67 mmol/l in the Abacor® group and by 0.24 ± 0.58 mmol/l in the SuproSoy® group, while a slight rise of 0.07 ± 0.82 mmol/l was observed in the placebo group. This means that a decline by 8 % compared to baseline (9 % compared to placebo) was achieved upon treatment with Abacor® and a decline by 3.4 % compared to baseline (4.4 % compared to placebo) resulted from treatment with SuproSoy®. The total cholesterol-lowering effect was significantly different from placebo for treatment with Abacor® ($p < 10^{-3}$), but not with SuproSoy® ($p = 0.065$). In direct comparison, the differences observed between the two soy treatments were also statistically significant ($p = 0.025$).

Table 2 Baseline characteristics of participants (values are given as means ± SD)

Group	Sex (f/m)	Age	Height (cm)	Weight (kg)
Abacor®	22/17	53.0 ± 11.4	169.9 ± 8.6	76.1 ± 15.1
SuproSoy®	23/16	56.3 ± 10.3	170.0 ± 8.3	77.2 ± 11.5
Placebo	17/21	55.8 ± 8.0	171.4 ± 9.4	77.1 ± 13.1
P Value*	0.41	0.31	0.64	0.91

* Differences between all treatment groups by analysis of variance

In accordance with the total cholesterol values, serum concentrations of LDL cholesterol also decreased under soy protein treatment (Table 3; Fig. 2). At the end of the 8-week-trial, values were reduced by 0.42 ± 0.51 mmol/l in the Abacor® group and by 0.24 ± 0.51 mmol/l in the SuproSoy® group. In the placebo group, a minor increase of 0.04 ± 0.58 mmol/l was observed. In percentages, declines compared to baseline amounted to 9.7 % and 5.4 % for the Abacor® and SuproSoy® regimens, respectively. LDL cholesterol changes within both soy treatment groups differed significantly from the placebo values ($p < 0.001$ and $p = 0.033$, respectively). Differences between the two treatment groups, however, were not statistically significant ($p = 0.12$). Of the other efficacy parameters, serum levels of HDL cholesterol and triglycerides were not significantly different between treat-

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Table 3 Blood lipid levels (values are given as means ± SD)

	Abacor®	SuproSoy®	Placebo	P Value*
Total cholesterol [mmol/l]				
Baseline	6.97±0.60	7.03±0.55	6.85±0.47	0.33
Changes:				
4 Weeks	−0.53±0.79	−0.42±0.64	−0.27±0.63	0.29
6 Weeks	−0.53±0.66	−0.29±0.59	−0.08±0.75	0.016
8 Weeks **	−0.56±0.67	−0.24±0.58	+0.07±0.82	< 0.001
** P values from paired group comparisons:			Abacor®/SuproSoy® = 0.025 Abacor®/placebo < 0.001 SuproSoy®/placebo = 0.065	
LDL cholesterol [mmol/l]				
Baseline	4.36±0.55	4.41±0.47	4.26±0.43	0.41
Changes:				
4 Weeks	−0.17±0.68	−0.14±0.75	+0.06±0.63	0.29
6 Weeks	−0.17±0.64	−0.13±0.53	+0.11±0.75	0.12
8 Weeks **	−0.42±0.51	−0.24±0.51	+0.04±0.58	0.001
** P values from paired group comparisons:			Abacor®/SuproSoy® = 0.12 Abacor®/placebo < 0.001 SuproSoy®/placebo = 0.033	
HDL cholesterol [mmol/l]				
Baseline	1.51±0.35	1.51±0.28	1.47±0.28	0.83
Changes:				
4 Weeks	−0.09±0.17	−0.03±0.14	−0.10±0.14	0.10
6 Weeks	−0.11±0.19	0.0±0.14	−0.04±0.14	0.01
8 Weeks	−0.09±0.23	−0.02±0.12	−0.03±0.17	0.21
Triglycerides [mmol/l]				
Baseline	1.77±0.95	1.83±0.76	1.85±0.84	0.91
Changes:				
4 Weeks	−0.11±0.75	+0.07±0.60	+0.11±0.76	0.36
6 Weeks	+0.02±0.87	+0.09±0.58	+0.08±0.85	0.92
8 Weeks	−0.09±0.72	−0.01±0.47	+0.09±0.82	0.53
Apolipoprotein B [g/l]				
Baseline	1.35±0.20	1.36±0.22	1.32±0.14	0.61
Changes:				
4 Weeks	−0.11±0.19	−0.09±0.21	−0.03±0.18	0.18
6 Weeks	−0.14±0.19	−0.11±0.18	−0.04±0.17	0.037
8 Weeks**	−0.09±0.20	−0.05±0.17	+0.04±0.22	0.013
** P values from paired group comparisons:			Abacor®/SuproSoy® = 0.34 Abacor®/placebo = 0.007 SuproSoy®/placebo = 0.044	

* Differences between all treatments by analysis of variance

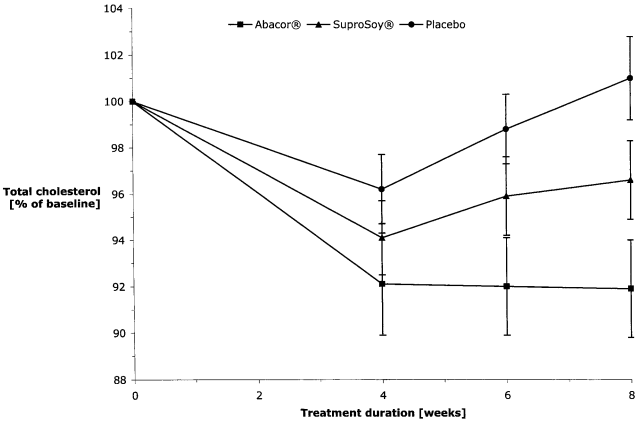

Fig. 1 Changes of serum total cholesterol levels over the eight-week trial period (values are given as means ± SEM)

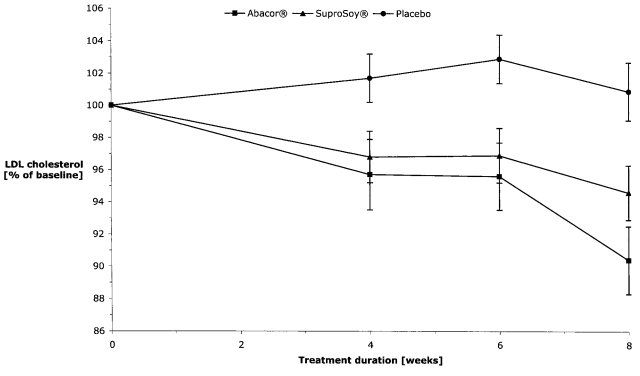

Fig. 2 Changes of serum LDL cholesterol levels over the eight-week trial period (values are given as means ± SEM)

Table 4

weeks	Abacor		SuproSoy		Placebo	
0	100	0	100	0	100	0
4	92.1	2.2	94.1	1.6	96.2	1.5
6	92	2.1	95.9	1.7	98.8	1.5
8	91.9	2.1	96.6	1.7	101	1.8
0	100	0	100	0	100	0
4	95.7	2.7	96.8	2.5	101.7	2.0
6	95.6	2.8	96.9	2.0	102.9	2.1
8	90.4	2.5	94.6	1.9	100.9	1.9

ment groups (Table 4). Concentrations of apolipoprotein B, on the other hand, fell by 0.09 ± 0.02 g/l and 0.05 ± 0.16 g/l in the Abacor® and SuproSoy® groups, respectively, while they rose by 0.04 ± 0.21 g/l in the placebo group (Table 4). Decreases obtained with both active treatment regimens were statistically significant as compared with placebo ($p = 0.007$ for Abacor® and $p = 0.044$ for SuproSoy®).

The clinical data such as body weight, heart rate, blood pressure, body temperature, or hematological profiles did not undergo any changes during the trial period, nor did they significantly differ between study groups.

Discussion

The serum cholesterol concentration is influenced by several variables. It changes with increasing cholesterol content in the diet, the efficiency of its absorption in the

small intestine, endogenous cholesterol synthesis, and the release of free cholesterol from peripheral tissues [33]. It seems reasonable to attempt lowering cholesterol levels by controlling dietary cholesterol intake. However, a meta-analysis of large international nutrition studies revealed a mean decrease of cholesterol values of only 2 % with this approach [34]. Supplementation with dietary fiber or other food ingredients proved to be more successful. Therefore, a meta-analysis of 38 trials on the efficacy of soy protein showed that total and LDL cholesterol levels declined on average by 9.3 and 12.9 %, respectively [11]. However, the trials included were of varying duration, involved daily soy protein dosages between 17 and 124 g and, moreover, soy products of different protein, isoflavone and fiber content. Although, in those studies a clear dosage-response relationship was missing, the cholesterol reduction achieved significantly diminishes the risk of cardiovascular diseases. A 10 % decrease of cholesterol in 35 to 44 year old men has been found to reduce the heart attack risk by half [35]. This is important in all affluent societies. In Germany, 60–70 % of the adult population exceeds a blood cholesterol level of 5.2 mmol/l [36], although values of < 5.0 mmol/l for total cholesterol and < 3.0 mmol/l for LDL-cholesterol are currently recommended [37].

Participants in this study had average baseline values of 7.08 mmol/l for total cholesterol and 4.38 mmol/l for LDL cholesterol, which are substantially above the threshold for hypercholesterolemia. Apolipoprotein B, the major apoprotein of LDL, was slightly elevated with a mean value of 1.34 g/l. Serum concentrations of HDL cholesterol and triglycerides were within the normal range. After randomization, the three study groups did not differ significantly with respect to anamnesis and life-style.

The trial results reveal a distinct beneficial effect from active treatment with soy protein preparation regarding three risk factors for coronary heart disease: total cholesterol, LDL cholesterol, and apolipoprotein B, which is supposed to have the same impact on cardiovascular health as LDL cholesterol [38]. The slight increase in cholesterol levels in the placebo group may be attributable to the composition of the placebo preparation, which contained a large proportion of casein. Casein, which is a frequently used control substance in clinical trials on protein supplements and their effect on blood cholesterol, has been shown to increase cholesterol and triglyceride concentrations in some cases [39]. However, this moderate "reverse placebo effect" can hardly account for the substantial cholesterol reductions in both verum groups compared to baseline, nor does it affect the observed differences between the two verum treatments. The combination of soy constituents present in Abacor® proved to be approximately twice as efficient as the alternative treatment with SuproSoy®, which had also achieved only moderate effects in a previous clinical study [14]. Both soy-derived fibers and phospholipids have been proved to exert lipid-lowering effects as individual substances. Phosphatidylcholine, in particular, is assumed to activate reversed cholesterol transport by increasing the cholesterol uptake of HDL molecules and the biliary cholesterol excretion [30–32]. Although some clinical trials failed to show a lipid-lowering effect [40], several others did result in cholesterol reduction during the treatment with phosphatidylcholine [26–29] employing dosages that correspond to the 2 g that are provided daily by Abacor®. The Commission E of the German Drug Authority recommends soy lecithin and lecithin-enriched soy phospholipids for the treatment of "moderate disturbances of fat metabolism, especially hypercholesterolemia" in dosages corresponding to 1.2–3.5 g phosphatidylcholine daily [41].

Both trial preparations are complex mixtures of ingredients and neither contains pure soy protein. It is therefore not possible to conclude if the additional effects of the mixture present in Abacor® are due to its content of phospholipids or fibers or both. An explanation involving protein quality or structure of the two products can be excluded since both products have been manufactured using SuproSoy® isolated soy protein as their basis. This, however, appeared to be highly fragmented in its protein constituents in a recent proteomic investigation [42], and we have in the meantime performed a clinical trial employing a new isolated soy protein preparation [43], the results of which will be fully published in due course.

None of the safety parameters showed significant differences compared to the baseline values. Tolerability of the study preparations was very good; no adverse effects were observed.

In summary, supplemental intake of 25 g soy protein daily resulted in significant decreases in serum concentrations of total and LDL cholesterol and apolipoprotein B. The use of soy protein as a nutritional supplement was shown to be likely to diminish the risk of coronary heart disease. The efficacy of Abacor® was approximately twice that of SuproSoy®.

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