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VISCOUS SOLUBLE FIBER COMBINED WITH PHYTOSTEROLS AND POLICOSANOL REDUCES LDL-CHOLESTEROL AND INCREASES HDL-CHOLESTEROL IN HYPERCHOLESTEROLEMIA

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ABSTRACT: ***This pilot study investigates the efficacy of a combination of nutraceuticals in improving lipid levels. The tested product combines viscous soluble fiber with phytosterols, policosanol, and an extract of Chrysanthemum morifolium. All four ingredients have been shown to have cholesterol-lowering potential, but all through different biological mechanisms. The test product is the first to combine these four cholesterol-lowering mechanisms in one product. Twenty-five subjects completed an 8-week open label study design. The product was taken twice daily before the main meals. Fasting lipid panels were measured at baseline, 4, and 8 weeks. The total cholesterol levels were reduced 8.2% (p<0.05) after 8 weeks, and 10.7% (p<0.01) in a subgroup of subjects with total cholesterol levels >200 mg/dL at baseline. LDL-cholesterol was reduced 4.8% (p<0.01) and 24.5% (p<0.001), and 30.6% (p<0.00001) in subgroups of subjects having baseline LDL-cholesterol levels >130 and >160 mg/dL, respectively. HDL-cholesterol levels were increased 8.3% (p<0.05). This nutraceutical combination therapy is promising as a first line intervention, and may serve as an adjunct therapy to pharmaceutical lipid lowering prescription therapy.***

KEY WORDS: Atherosclerosis, Cholesterol, Fiber, Nutraceuticals, Phytosterols, and Policosanol

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INTRODUCTION

Elevated total cholesterol (TC), LDL-cholesterol (LDL-c), and reduced HDL-cholesterol (HDL-c) levels have been determined a major risk factor for the development of cardio vascular disease, and the formation of atherosclerotic plaques. (Yusuf *et al.,* 2004) Improving these lipid levels has been effective in lowering the risk for the development of heart disease and stroke. (Corvol *et al.,* 2003; Huxley *et al.,* 2002) Conventional first line treatment for hypercholesterolemia is focused on dietary changes and life style, and if not adequately successful, followed by pharmaceutical interventions, such as statins, fibrates, and bile-acid sequestrants. In the last decades, an increasing number of non-pharmaceutical intervention therapies has been developed, and tested in randomized clinical trials. Examples are viscous soluble fiber, (Anderson *et al.* , 1999; Anderson *et al.* , 2000; Chandalia, 2000; Jenkins *et al.* , 2002; Knopp *et al.* , 1999; Sprecher and Pearce, 2002) phytosterols, and phytostanols, (Jenkins *et al.* , 2005; McPherson *et al.* , 2005; Plat and Mensink, 2005; Thompson, 2005; von Bergmann *et al.* , 2005) and policosanol. (Castano *et al.* , 2002; Crespo *et al.* , 1999) These nutritional intervention therapies have generally shown moderate lipid lowering success, and are therefore not always an intervention option for immediate hypercholesterolemia. Nevertheless, there is a growing awareness among the public about potential side effects of pharmaceutical compounds in general and of statin lipid lowering prescription therapy in particular. This has resulted in an increasing demand for dietary or phototherapeutic approaches to lowering cholesterol.

Traditionally, interventional therapies, both pharmaceutical and dietary, influence only one mechanism to lower cholesterol. While effective for pharmaceuticals, the one-mechanism approach for dietary intervention has shown limited success. At least theoretically, a product combining different mechanisms to lower cholesterol, should have an enhanced efficacy, when compared to a mono-mechanism approach. An increasing number of pharmaceutical intervention therapies has also adopted this concept, (Vasudevan and Jones, 2005) such as using the combination of statins and ezetimibe. (Davidson, 2003; Kosoglou *et al.* , 2005)

In this study, we investigated the lipid lowering efficacy of a nutraceuticals combination product, based on a viscous soluble fiber drink, combined with three other phytonutrients: phytosterols, policosanol, and *Chrysanthemum morifolium*. All four individual ingredients have independent data about their lipid-lowering potential. This product therefore approaches lipid lowering through a potentially synergistic combination of 4 different mechanisms.

MATERIALS AND METHODS

Subjects

The study used a protocol which was approved by an outside institutional review board, and deemed in compliance with the Declaration of Helsinki V. (World Medical Association, 2000) Subjects were invited from a pool of 125 office staff of the research institute. Subjects were informed about the study through a mass communication, to exclude pressure to participate. The identity of the subjects was kept confidential at all times. Subjects were eligible to participate in the trial if they were between 18 and 75 years old, and if the baseline (BL) value for LDL-c was 110 mg/dL or higher. Subjects were not eligible to participate if they suffered from type-1 diabetes, severe hypertension, defined as at least 180/100 mmHg, or had any other health condition that may interfere with the study results, as judged by the principle investigator. The subjects were also excluded if they suffered from an allergy against any of the ingredients in the tested product, or if they had any medical condition in which fiber consumption is contra-indicated, *e.g.* Crohn's disease. Subjects were allowed to use vitamin or mineral supplements, provided they did not contain any of the tested ingredients. Pregnant women or breast-feeding women were excluded. If subjects had only one regular meal per day, they were also excluded. Finally, a history of alcohol or drug abuse, psychological or other mental issues that are likely to invalidate the informed consent, or limit the ability of the patient to comply with the protocol requirements resulted in exclusion from this trial. Subjects were not compensated for their participation in the trial. The recruitment was spread out over a period of 2 weeks.

Study procedures

All potential subjects for this study were screened to evaluate their eligibility to participate by an interview with the principle investigator. After signing informed-consent forms, the participants in this study used the test product prior to lunch and dinner for a period of 8 weeks. The product was supplied as a powder in a canister that included 60 dosages, and subjects were instructed to mix one dosage (6.5 grams, measured with a scoop) at a time with about 230 ml of water, and drink the product about 10 – 15 minutes before the meal. A lipid panel, including TC, LDL-c, HDL-c, TG, and cardio vascular risk ratio was measured at baseline (BL), 4 weeks, and 8 weeks. The cholesterol measurements were performed on-site using a Cholestech LDX system (Cholestech Corp. Hayward, CA). The subjects were instructed to come in fasted before each measuring day. Fasted was defined as having no food or drinks other than water since going to bed the previous night. Visit windows were set at plus or minus 2 days. The subjects were instructed to continue with normal daily activities during their participation in the trial, and not make any changes to normal diet, and physical activities. Compliance with the protocol was promoted by a weekly phone call with all participants. Side effects of the product were evaluated during these weekly phone calls, and at the end of the trial using a questionnaire. Compliance was assessed using a questionnaire and an interview with the subjects at the end of the trial.

Composition of the test product

The tested product is marketed under the brand name BiosLife (Unicity International, Orem, UT). A unitary dose of the product comprises of 3.3 grams of dietary fiber consisting of guar gum (1.2 grams), gum Arabic (0.65 grams), locust bean gum (0.61 grams), pectin (0.42 grams), and oat fiber (0.35 grams). This fiber mix comprises of more than 90 % soluble fiber. The product further contains a vitamin and mineral mix, including vitamins A, B1, B2, B6, B11, B12, C, E, and minerals selenium, chromium, zinc, and calcium. All vitamins and minerals are added at or close to their respective RDAs. The test product further comprises 1.0 gram of esterified phytosterols (including sitosterol, stigmasterol, and campesterol), 6 mg of policosanol (standardized to 60 % octocosanol), and 12.5 mg aqueous extract of *Chrysanthemum morifolium.* All subjects used two packets per day of this formula. All individual ingredients of the tested product have demonstrated safety records for long-term use, and therefore we decided not to collect safety data for the test product. (Carabin and Flamm, 1999; Chen *et al.* , 2005; Plat and Mensink, 2005)

Data analysis and statistical methods

The results were analyzed as means in the group. Within-group differences over time were analyzed using 2-tailed paired *t* tests for dependent groups, after the normality of the data was determined. These procedures were used for all measured parameters. Statistical significance was defined as a p-value of 0.05 or lower. Variations in measurements are indicated as standard errors of the mean (± SEM).

RESULTS

Thirty-seven subjects expressed interest in participating in the trial. Twenty-five subjects completed the 8-week protocol. Reasons for discontinuation were all related to lack of time or further interest in participation. Of this group 13 subjects were male, and 12 female. The age of the group varied between 61, and 25, with a mean age of 40.2 ± 1.8 years. Four subjects were post-menopausal. The BL lipid levels of this group were: TC 213.6 ± 7.8 mg/dL; LDL-c 130.6 ± 8.1 mg/dL; HDL-c 47.8 ± 3.0 mg/dL; TG 175.8 ± 15.5 mg/dL, and cardio vascular risk ratio (defined as TC/HDL-c) 4.9 ± 0.3.

Compliance was estimated to be at least 60 %. In this small-scale pilot trial, however, no one was excluded based on low compliance. Side effects reported were generally mild, and included gastro-intestinal discomfort, flatulence, and diarrhea, but the side effects reported were not a reason to discontinue with participation in the trial, and typically disappeared after several days. The side effects reported were in line with previous studies that tested fiber supplementation. (Sprecher and Pearce, 2002)

Total Cholesterol

The TC levels in the whole group were significantly reduced by 8.2 %. The subgroup of subjects having TC levels of 200 mg/dL or more at BL showed a statistically significant reduction of 10.7 % after 8 weeks.

LDL cholesterol

The mean change in LDL cholesterol for the total group amounted to 1.6 % after 4 weeks and 4.8 % after eight weeks. The reduction after 8 weeks was significant. LDL-c reductions for subgroups of subjects having LDL values at BL of more than 130 mg/dL and 160 mg/dL amounted to 24.5 % and 30.6 %, after 8 weeks, respectively. Both reductions were statistically significant.

HDL cholesterol

HDL-c was increased significantly in the total group by 8.3 %. For the subgroup of subjects with HDL-c levels of 40 mg/dL or lower at BL, the mean change in HDL-c was 12.0 %, but not significant.

Triglycerides

After 8 weeks, triglyceride levels were changed by 5.7 % for the whole group, and 14.9 % for the sub group of subjects having TG levels of 150 mg/dL or more at BL. Both changes did not reach statistical significance. The differences after 4 weeks of intervention did reach significance, and were reductions of 16.4% for the total group and 21.4% for the subgroup having TG levels of 150 mg/dL or more at BL.

Cardio vascular risk ratio

The risk ratio for the whole group was significantly reduced by 5.3 %, and by 24.2 % for the subgroup of subjects having risk ratio levels higher than 5.0 at BL. The detailed results for all parameters are listed in Table 1.

TABLE 1. Lipid level and cardiovascular risk ratio changes after t=4 and t=8 weeks using the nutraceutical combination product. All lipid concentrations are in mg/dL. The changes refer to changes from baseline (BL).

	Group	N	# Men	Age	BL	t=4	Δ(%)	p	t=8	Δ (%)	p
TC	Total	25	13	40.2	214	208	-2.7	n.s.	196	-8.2	*
	> 200	16	8	40.6	237	224	-5.2	n.s.	211	-10.7	**
LDL	Total	25	13	40.2	131	129	-1.6	n.s.	111	-4.8	**
	> 130	11	6	36.0	168	159	-5.6	n.s.	127	-24.5	***
	> 160	7	2	38.7	182	166	-8.9	n.s.	127	-30.6	***
HDL	Total	25	13	40.2	48	50	+4.7	n.s.	52	+8.3	*
	< 40	9	7	38.1	32	35	+9.1	n.s.	37	+12.0	n.s.
TG	Total	25	13	40.2	176	147	-16.4	*	166	-5.7	n.s.
	> 150	14	8	44.6	228	179	-21.4	**	194	-14.9	n.s.
Ratio[a]	Total	25	13	40.2	4.89	4.71	-3.7	n.s.	4.14	-5.3	*
	> 5.0	11	7	37.0	6.51	6.27	-3.6	n.s.	5.04	-24.2	*

* p<0.05; ** p<0.01; *** p<0.001, [a]defined as TC/HDL.

DISCUSSION

The tested product in this study is a fiber drink, based on 3.3 grams mostly soluble fiber combined with vitamins, minerals, esterified phytosterols, policosanol, and an aqueous extract of *Chrysanthemum morifolium*. The product has been designed to lower cholesterol using four different biological mechanisms. These four mechanisms are:

1. Bile-acid sequestration. Bile acids are needed to digest fat, and they are being synthesized using the cholesterol pool in the body. After aiding in fat digestion, the bile acids, along with the cholesterol are re-absorbed in the system and re-utilized by the liver. The total size of the cholesterol pool is largely unchanged by this mechanism, since the gross amount of cholesterol used from the pool to synthesize bile acids is returning back into our body. When the soluble fiber present in the test product enters the digestive tract before the meal, the fiber forms a gel matrix due to the acidic condition in the stomach. This matrix sequesters the bile acids and prevents them from being re-absorbed, but rather excreted. Fibers are also fermented in the colon by bacteria to yield short-chain fatty acids, such as acetates, propionates, and butyrates that may inhibit cholesterol synthesis. This mechanism alone is known to lower LDL cholesterol by 5 – 15 % after 8 weeks. (Anderson *et al.* , 1999; Jenkins *et al.* , 2002; Knopp *et al.* , 1999; Sprecher and Pearce, 2002) A randomized placebo-controlled study with the fiber mixture present in the tested product was published by Sprecher and Pearce in 2002. (Sprecher and Pearce, 2002)

2. Dietary absorption inhibition. Cholesterol is actively absorbed from the small intestine into the blood by transporter proteins. (Thurnhofer and Hauser, 1990) Phytosterols are plant components that have a similar chemical structure to cholesterol. When phytosterols are present in the digestive tract before the meal, they displace real cholesterol in the absorption processes. (Ikeda *et al.* , 1989; Ikeda *et al.* , 1988a; Ikeda *et al.* , 1988b) In this way serum cholesterol is lowered. This mechanism alone has been shown to lower LDL-cholesterol by 5 – 15 % after about 8 weeks. (Ostlund, 2004)

3. Cholesterol synthesis inhibition. A critical step in the cholesterol biosynthetic route is the conversion of HMG-CoA into mevalonate, performed by HMG-CoA reductase. Policosanol is a sugar cane extract that has been shown to inhibit this enzyme.(McCarty, 2002) This mechanism alone has been shown to lower LDL-cholesterol 15 – 30 % after 8 weeks. (Castano *et al.* , 2002; Castano *et al.* , 2001; Castano *et al.* , 2003; Castano *et al.* , 1999; Varady *et al.* , 2003) Two recently published studies, however, failed to show an effect of policosanol. (Berthold *et al.* , 2006; Greyling *et al.* , 2006)

4. Enhancement of cholesterol metabolism. Cholesterol is converted into several other biomolecules in our body. One process that uses cholesterol is the synthesis of cholic acid, the most predominant member of the bile acids. The enzyme responsible for the conversion of cholesterol to 7α-cholesterol, which is the first metabolite on the pathway to cholic acid, is 7α-hydroxylase.(Lathe, 2002) Chen *et al.* published that an aqueous extract of *Chrysanthemum morifolium* enhances the function this enzyme,

thereby promoting the metabolism and removal of serum cholesterol. (Chen *et al.* , 2000)

This nutraceuticals combination product has been designed to optimize lipoprotein levels, and as a result, to reduce the risk for developing cardio vascular health concerns. Total cholesterol levels in this study did not change with impressive numbers. Since TC is derived from the sum of LDL-c and HDL-c (and others), and most study participants showed considerable HDL-c increases, the overall reduction in TC is smaller than would be observed in statin intervention studies. (Edwards and Moore, 2003)

The test product reduces LDL cholesterol in the total study group significantly with 4.8 % after 8 weeks. This small overall reduction may be explained by the relative healthy dietary habits of the study population, limiting the effect of dietary intervention to optimize cholesterol levels in the total group. The reductions are greater in subgroups of subjects that have higher LDL cholesterol levels at BL, which is in line with expectations. For a subgroup with "borderline high" LDL-c levels, as defined by the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP), (National Institute of Health, 2001) the reduction after 8 weeks amounts to 24.5 %. For "high" BL levels, (National Institute of Health, 2001) LDL cholesterol was reduced with 30.6 %. These reductions are clinically relevant, and may be compared with reductions reached by average dosages of statin lipid lowering medication, for hyperlipidemic subjects.(Edwards and Moore, 2003) It is evident that the tested product is more effective in subjects with higher BL LDL-c levels. Higher LDL-c levels are generally associated with less healthy dietary habits, (Hata and Nakajima, 2000) and this may explain why dietary intervention may be more effective for this group. The test product is likely to have a direct mechanistic effect on indigenous cholesterol production (policosanol) and clearance (*Chrysanthemum morifolium*), and a change on dietary factors influencing cholesterol absorption (fiber, phytosterols). Because this study did not evaluate baseline diet characteristics of the subjects, we are unable to discriminate the serum lipid effects between the different mechanisms. Follow-up studies performed by our laboratory focus on this research question.

The relative low increase in HDL in the total group is likely a result of the high mean BL value for HDL. This hypothesis is supported by the observation that for people having HDL baseline levels of 40 mg/dL or lower, the mean change is higher (although not significant in our small sample size). Analyzing only the responders in this group (7 out of 9), gives a statistically significant increase of 28.6 %. The two individuals in this group that did not respond to the treatment may be subjects with low compliance, or subjects that have a biochemical reason for not responding, since these subjects were also non-responders in LDL reduction.

It is known that statin prescription therapy has limited efficacy in increasing high-density lipoprotein levels in clinically relevant amounts.(Edwards and Moore, 2003) Clinicians are increasingly aware of the need of reducing LDL-c, while at the same time increasing HDL-c. (Kuvin *et al.* , 2006) The Framingham heart study revealed that increasing HDL-c may equally important as decreasing LDL-c. (Nam *et al.* , 2006) Our HDL-c results for the responder group may open up an alternative, or adjunct therapy to lipid-lowering prescription therapy. The data suggest that responding patients with with mild to moderate hypercholesterolemia can reduce their LDL-c adequately using nutraceutical combination therapy, and at the same time increase HDL-c.

There is increasing concern among patients about the safety of prescription medication, in particular statins, because of existing side effects, such as muscle weakness, and liver damage. (Silva *et al.* , 2006) Although the prevalence of these side-effects is rather low, (Law and Rudnicka, 2006) patients are exploring the availability of natural therapies as a first line intervention to lower their cholesterol levels. Our preliminary data warrant the further exploration of this nutraceutical combination as a first line treatment for hyperlipidemia. According the NCEP guidelines, the first intervention for high cholesterol should be the so-called Therapeutic Lifestyle Change Diet. (National Institute of Health, 2001) Part of this dietary guideline is the intake of fiber at minimum daily levels of 25 – 30 grams. The average dietary consumption of adults in the USA is well below this level. (Liu *et al.* , 2002) Two servings of the test product provide 6.6 grams of dietary fiber, and can therefore serve to partly fill the gap between actual and advised dietary consumption of fiber.

The cardio vascular risk ratio is defined as TC divided by HDL. Although ATP III does not define this ratio as a therapy target, many studies show that the TC/HDL cholesterol ratio is a powerful predictor of CHD risk. (National Institute of Health, 2001) The American Heart Association defines a risk ratio of lower than 5.0 as preferential, if there are no other risk factors present. The combined results on the lipid fractions have significantly benefited the ratio values for our study participants.

We limited the study period to 8 weeks for practical reasons. It is unknown if the observed improvements in lipid profiles persist for longer times. Some reports indicate that results of intervention trials with phytosterols over longer periods (up to 1 year) may be less pronounced than for shorter periods. (Ostlund, 2004) To our knowledge, similar findings have not been reported for the other ingredients in this tested product. Future studies should therefore study the test product during longer follow-up periods.

CONCLUSION

Viscous soluble fiber combined with phytosterols, policosanol, and an aqueous extract of *Chrysanthemum morifolium* is a promising natural dietary intervention to lower LDL cholesterol, and to increase HDL cholesterol, simultaneously. These changes result in an improved risk profile for heart disease among otherwise healthy young individuals. The changes observed in LDL-c for subjects with "borderline high" and "high" cholesterol levels may be compared to the treatment effects reached for average dosages of statin medication. This combination product is promising in providing a natural dietary approach to successfully improving lipid profiles. This pilot study warrants further study with this

ingredient combination in larger groups, for longer follow-up periods, and with better compliance.

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