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RESEARCH ARTICLE

EFFECTS OF POLICOSANOL ON SERUM LIPID LEVELS IN HEALTHY SUBJECTS: AN EXPLORATORY POST HOC ANALYSIS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL COMPARATIVE STUDY

EFECTOS DEL POLICOSANOL SOBRE LOS NIVELES SÉRICOS DE LÍPIDOS EN SUJETOS SANOS: UN ANÁLISIS EXPLORATORIO POST HOC DE UN ESTUDIO COMPARATIVO PARALELO, DOBLE CIEGO Y CONTROLADO CON PLACEBO

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ABSTRACT

Objective: Hypercholesterolemia is a major risk factor for coronary heart disease. There is evidence of the benefits of lowering cholesterol levels in subjects with borderline to mildly elevated serum total cholesterol (TC) levels (5.0-6.0mmol/L). Policosanol is a cholesterol-lowering drug made from purified sugar cane wax and now is also used as a cholesterol-lowering nutraceutical owing to its safety profile in some countries. The current exploratory post hoc analyses sought to investigate whether policosanol is efficacious to lower mildly elevated cholesterol levels at the normal ranges in healthy participants with borderline serum LDL-C levels, who previously participated in a randomized controlled trial. **Methods:** Data was obtained from a previous 14-week, single-center, prospective, double-blind, placebo-controlled, parallel-group, comparative study conducted in subjects with serum TC levels ≥ 4.8 to < 6.0mmol/L. After a six-week run-in period with instructions on lifestyle changes, participants were randomly assigned to two groups to receive either 5 mg of policosanol or placebo once daily with dinner for eight weeks. Lipid profile, safety indicators, adverse events (AEs), and treatment adherence were assessed. Data of thirty-nine participants were included in this analysis (policosanol = 16, placebo = 23). **Results:** After 8 weeks of supplementation, participants in the policosanol group exhibited statistically significant decreases in serum TC (-13.84%), LDL-C (-23.89%), LDL-C/HDL-C (high-density lipoprotein cholesterol) ratio (-30.45%) and increase in HDL-C (10.80%) versus baseline (week 0) while no significant changes were observed in the placebo group. The reductions on policosanol group were also significant compared to placebo. There were no significant changes observed on triglyceride. **Conclusion:** From the above results, it is concluded that policosanol supplementation has the potential to lower mildly elevated cholesterol levels at the normal ranges in healthy subjects and to be used as a cholesterol-lowering nutraceutical to improve the risk factor of hypercholesterolemia for coronary heart disease.

Keywords: policosanol, hypercholesterolemia, LDL cholesterol, borderline level, cholesterol-lowering nutraceutical.

RESUMEN

Objetivo: La hipercolesterolemia es un factor de riesgo importante para la enfermedad coronaria. Existe evidencia de los beneficios de reducir los niveles de colesterol en sujetos con niveles de colesterol total (CT) sérico entre limítrofes y ligeramente elevados (5,0-6,0 mmol/L). El policosanol es un fármaco hipocolesterolemiante elaborado a partir de cera purificada de caña de azúcar y, debido a su perfil de seguridad, también se utiliza actualmente como nutracéutico hipocolesterolemiante en algunos países. Los análisis exploratorios post hoc actuales buscaron investigar si el policosanol es eficaz para reducir los niveles de colesterol ligeramente elevados dentro de los rangos normales en participantes sanos con niveles séricos de c-LDL limítrofes, que participaron previamente en un ensayo controlado aleatorizado. **Métodos**: Los datos se obtuvieron de un estudio comparativo de 14 semanas, unicéntrico, prospectivo, doble ciego, controlado con placebo, de grupos paralelos, realizado en sujetos con niveles séricos de CT ≥ 4,8 a < 6,0 mmol/L. Tras un período de preinclusión de seis semanas con instrucciones sobre cambios en el estilo de vida, los participantes fueron asignados aleatoriamente a dos grupos para recibir 5 mg de policosanol o placebo una vez al día con la cena durante ocho semanas. Se evaluaron el perfil lipídico, los indicadores de seguridad, los eventos adversos (EA) y la adherencia al tratamiento. Se incluyeron los datos de treinta y nueve participantes en este análisis (policosanol = 16, placebo = 23). **Resultados**: Tras 8 semanas de suplementación, los participantes del grupo de policosanoles mostraron disminuciones estadísticamente significativas en el CT sérico (-13,84%), el C-LDL (-23,89%), la relación C-LDL/C-HDL (-30,45%) y un aumento del C-HDL (10,80%) en comparación con el valor inicial (semana 0), mientras que no se observaron cambios significativos en el grupo placebo. Las reducciones en el grupo de policosanoles también fueron significativas en comparación con el placebo. No se observaron cambios significativos en los triglicéridos. **Conclusión:** De los resultados anteriores, se concluye que el tratamiento con policosanol tiene el potencial de reducir los niveles de colesterol levemente elevados en rangos normales en sujetos sanos y de usarse como un nutracéutico reductor del colesterol para mejorar el factor de riesgo de hipercolesterolemia para la enfermedad cardíaca coronaria

Palabras clave: policosanol, hipercolesterolemia, colesterol LDL, nivel límitrofe, nutracéutico para reducir el colesterol.

INTRODUCTION

Elevated total cholesterol (TC) and particularly low-density lipoprotein cholesterol (LDL-C) levels are major risk factors for coronary heart disease (CHD) (Tsao *et al*. 2023) (Jones *et al*. 2023) (Zhang *et al*. 2021). Clinical studies (Jones *et al*. 2023) (Zhang *et al*. 2021) (Ference *et al*. 2017) (Scudeler *et al*. 2024) (Burger *et al*. 2024) (Mhaimeed *et al*. 2024) (Yang *et al*. 2024) have shown that lowering LDL-C reduces morbidity and mortality in the primary and secondary prevention of CHD.

Reducing serum LDL-C below a specific level (≤3.37mmol/L) is the primary goal in the management of hypercholesterolemia. The use of therapeutic lifestyle changes (TLCs), including adherence to the National Cholesterol Education Program (NCEP) Step I cholesterol-lowering diet, smoking cessation, and any type of systematic physical exercise, is the first-line therapy for hypercholesterolemia (Lis *et al*. 2023) (van Ootmerssen *et al*. 2025) (Krumholz *et al*. 2025). Adherence to TLCs allows many individuals, mainly those with borderline or mildly elevated LDL-C (3.4-4.0mmol/L) and TC (5.0-6.0mmol/L) levels, to achieve the desired serum levels of these lipids (Lis *et al*. 2023). Cholesterol-lowering drugs in addition to TLCs may be required to achieve these participants' lipid goals (Lis *et al*. 2023) (van Ootmerssen *et al*. 2025) (Krumholz *et al*. 2025). Additional benefits can be obtained by increasing the serum high-density lipoprotein cholesterol (HDL-C) level or reducing the triglyceride (TG) level.

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are considered first-line therapy for hypercholesterolemia (Fulcher *et al*. 2015) (Mach *et al*., 2019), with the starting dose dependent on the severity of hypercholesterolemia. In patients with mildly or even moderately increased levels of LDL-C (<3.4mmol/L) and TC (5.0–<7.8mmol/L), low or standard doses of statins usually are prescribed initially, and higher doses rarely are necessary. With statins, dose adjustment generally is recommended after 6 weeks of therapy. Although statins are generally well tolerated, they are associated with some adverse events (AEs), with gastrointestinal disturbances and increased liver aminotransferase activities being the most common, and muscle-related AEs occurring less frequently but having more serious consequences, such as rhabdomyolysis (Morris *et al*. 2025) (Oberhoffer *et al*. 2025). Because cholesterol-lowering drug therapy also may be suitable for subjects with mildly elevated serum TC levels, especially those at high risk for CHD, the search for lipid-lowering drugs that are as effective as low-dose statins but with a better tolerability profile is justified.

Policosanol is a cholesterol-lowering drug composed of a mixture of high- aliphatic primary alcohols purified from sugar cane (*Saccharum officinarum*, L.) wax (Mas, 2000) (Pons *et al*. 1994). This drug has proven cholesterol-lowering efficacy in type II hypercholesterolemia (Canetti *et al*. 1995) (Benitez *et al*. 1997) (Mas *et al*. 1999, 2001) (Castaño *et al*. 1999, 2000, 2001) and dyslipidemia secondary to type 2 diabetes mellitus (Torres *et al*. 1995) (Crespo *et al*. 1999). Policosanol inhibits cholesterol biosynthesis between acetate consumption and mevalonate production (Menéndez *et al*. 1994, 1996) through the indirect regulation of HMG-CoA reductase activity (Menéndez *et al*. 2001). Policosanol increases LDL receptor-dependent processing (Menéndez *et al*. 1994), enhancing the catabolic rate of LDL (Menéndez *et al*. 1996). Clinical trials (Canetti *et al*. 1995) (Benitez *et al*. 1997) (Mas *et al*. 1999, 2001a) (Castaño *et al*. 1999, 2000, 2001) (Fernández *et al*. 2001) (Mas *et al*. 2001b) (Torres *et al*. 1995) (Crespo *et al*. 1999) and postmarketing studies (Fernández *et al*. 1998) (Mas *et al*. 1999) (Fernández *et al*. 2004) have shown that policosanol is safe and well tolerated. The therapeutic range of policosanol is 5 to 20mg/day.

Previous studies of the short- and long-term effects of policosanol have been conducted in populations with hypercholesterolemia ranging from mild (TC 5.0 and <6.1 mmol/L) to severe (TC ≥7.8 mmol/L) (Canetti *et al*. 1995) (Benitez *et al*. 1997) (Mas *et al*. 1999, 2001a) (Castaño *et al*. 1999, 2000, 2001) (Fernández *et al*. 2001) (Mas *et al*. 2001b) (Torres *et al*. 1995) (Crespo *et al*. 1999). Most of the participants included in these studies had moderate hypercholesterolemia (TC≥6.1 and <7.8mmol/L), whereas participants with mild hypercholesterolemia have not been included in some studies due to the limits of inclusion criteria (TC≥6.1 mmol/L).

A previous study (Castaño *et al*. 2003) was undertaken to investigate the efficacy and tolerability of policosanol 5 mg/day in participants with borderline to mildly elevated serum TC levels. The primary efficacy variable was the decrease in LDL-C to the individual participant's goal level, with treatment efficacy defined as a decrease in LDL-C ≥15% from baseline, whenever this proportion was different with respect to placebo.

Policosanol is now used as a cholesterol-lowering nutraceutical owing to its well-established safety profile (Fernández *et al*. 1998) (Mas *et al*. 1999) (Fernández *et al*. 2004) in Australia, Korea and Japan. But little has discussed whether policosanol can lower cholesterol in healthy subjects with or below borderline serum LDL-C (3.10-<3.62mmol/L) as a nutraceutical ingredient.

The current exploratory post hoc analyses aimed to perform a stratified statistical analysis among healthy participants with borderline serum LDL-C levels from the previous study (Castaño *et al*. 2003) and sought to investigate whether policosanol is effective in reducing borderline cholesterol levels in healthy subjects.

MATERIALS AND METHODS

The previous 14-week, prospective, double-blind, randomized, placebo-controlled, parallel-group, comparative study was conducted at the Medical Surgical Research Center (Havana, Cuba). The participants were enrolled at the Veterans' House of Plaza Zone (Havana, Cuba) on a voluntary basis; they did not receive compensation for their participation in the study. The independent ethics committee of the Medical Surgical Research Center approved the study protocol.

Participants

Men and women aged 25 to 75 years with documented borderline to mildly elevated serum TC levels (5.0-6.0mmol/L) were eligible for the study. After a 6-week, diet-only run-in period, participants with TC ≥4.8 to <6.0mmol/L were enrolled. The lower limit (4.8mmol/L) was chosen to avoid eliminating an excessive number of participants because TC tended to decrease with diet during the run-in period. Participants also were required to have a serum TG level <4.52mmol/L after the run-in period.

Participants with active renal disease, neoplastic disease, severe hypertension (diastolic blood pressure [DBP] ≥120 mmHg), and uncontrolled diabetes mellitus (serum glucose level >7.5mmol/L) were excluded from the study. Participants with a history of myocardial infarction, stroke, or coronary surgery within the 3 months prior to the study also were excluded. Pregnant, possibly pregnant, or breastfeeding participants were not included. Female participants of childbearing age were required to use an effective method of birth control throughout the study. All participants provided written informed consent to participate.

METHODS

The previous study included 4 visits (recruitment, treatment assignment, interim, and final follow-up). At recruitment (visit 1), a complete medical history was taken, and participants entered a 6-week run-in period during which they were to discontinue all existing lipid-lowering therapy and incorporate TLCs (NCEP Step I diet and recommendations to stop smoking and be as physically active as possible [although no formal exercise program was recommended]) into their lifestyles. This diet consisted of a daily consumption of cholesterol <300 mg/d and a daily intake of total fat (saturated, polyunsaturated, and monounsaturated fatty acids), 8% to 10%; carbohydrates, ≥55%; and protein, ~15% of total calories (i.e., those needed to maintain a desirable body weight) (Lis *et al*. 2023) (van Oortmerssen *et al*., 2025). These TLCs were continued throughout the study.

After run-in, laboratory lipid profile (LDL-C, TC, HDL-C, TG) and tolerability indicators (physical: body weight, heart rate, systolic and diastolic BP [SBP and DBP, respectively]; biochemical: alanine and aspartate aminotransferase activities [ALT and AST, respectively], and serum glucose and creatinine levels) were determined. At visit 2 (treatment assignment), eligible participants were randomized, under double-blind conditions, to receive policosanol 5 mg or placebo tablets, once daily with the evening meal for 8 weeks. Study medications were given in identical packages identified by a code number and the treatment number assigned successively. Participants were randomized in balanced groups (1:1) of 2 using an independent computer-determined method.

After ingestion, participants returned for interim and final follow-up visits (visits 3 and 4, respectively), the interval between which was 1 week. Participants underwent physical examinations at all 4 visits; laboratory analysis was performed at visits 2 and 4. Compliance with treatment and diet, as well as AEs, were assessed at visits 3 and 4.

The placebo group was included as a parallel control to detect any systematic bias due to adherence to lifestyle in both groups, any change in concomitant medications, or any other factor that could induce a systematic change in any study variable. The placebo group also was included because few data regarding the efficacy of policosanol in mild hypercholesterolemia are available, and no study had previously been conducted in such a specific subset of participants (i.e., participants with borderline to mildly elevated TC levels), according to a MEDLINE search of studies published from 1991 to 2002 and including the key term policosanol. Because all participants were following the TLC regimen and treatment duration was short, participants receiving placebo were not at increased risk for complications, including myocardial infarction, angina pectoris, stroke or transient ischemic attacks, compared with run-in, when they were following the lipid-lowering dietary regimen.

Efficacy Analysis

Change in serum LDL-C level was the primary efficacy variable. Treatment was considered effective only if ≥70% of participants treated with policosanol achieved LDL-C reductions ≥15% from baseline, whenever this percentage was different with respect to placebo (Schectman & Hiatt, 1996).

The current exploratory post hoc analyses focused on serum lipids profile changes (LDL-C, TC, HDL-C, TG, LDL-C/HDL-C ratio) among healthy participants with borderline serum LDL-C levels (LDL-C<3.62mmol/L) after intake of policosanol for 8 weeks. A flowchart of study participants for the post hoc analysis is shown in Figure 1.

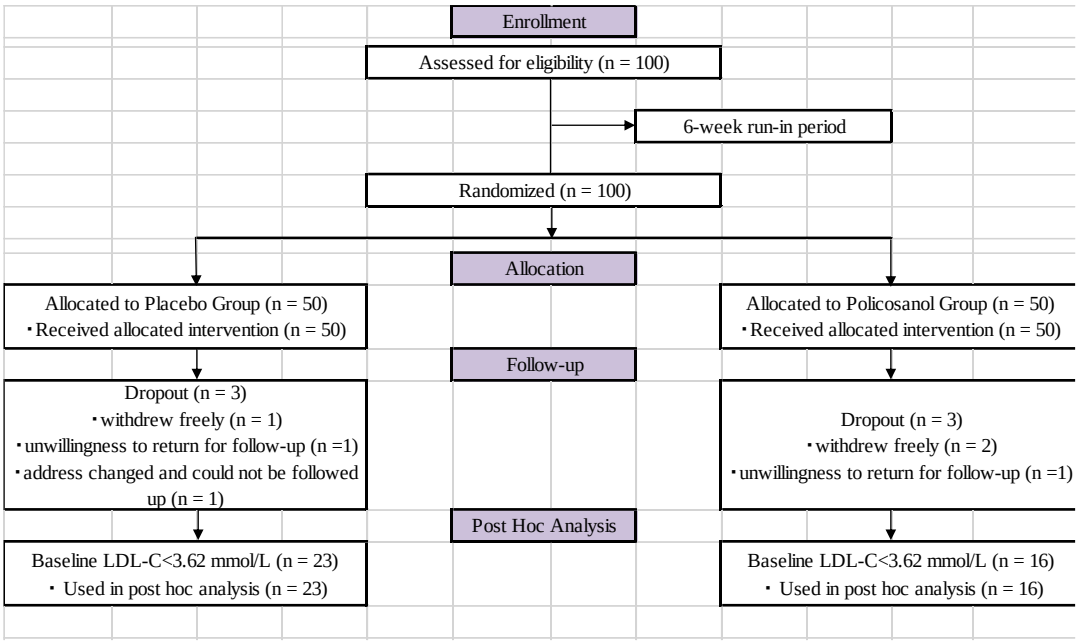

***Fig 1**. The flowchart of study participants for the post hoc analysis.*

Laboratory Analysis

Blood samples were drawn between 8:00am and 8:30am after a 12-hour fast, and aliquots were taken for laboratory assessment. Serum TC and TG levels were determined by enzymatic methods using reagent kits (F. Hoffmann-La Roche Ltd., Basel, Switzerland). Serum HDL-C levels were determined according to the cholesterol content present in the supernatant obtained after beta-lipoprotein precipitation (Seigler & Wu, 1981). LDL-C values were calculated using the Friedewald equation (Friedewald *et al.* 1972). Blood sampling and analysis were performed by laboratory technicians at the study center.

Laboratory tolerability indicators were determined using routine enzymatic laboratory tests and reagent kits. All laboratory tests were performed using the Hitachi 719 autoanalyzer (Hitachi, Tokyo, Japan) located at the laboratory of the Medical Surgical Research Center.

Statistical Analysis

In the previous study, all data were analyzed by the intent-to-treat approach (i.e., analyses included all participants as randomized). For the primary efficacy variable, it was assumed that policosanol 5 mg/day would show a difference in LDL-C reduction of ≥15% compared with placebo. Based on an 80% power and a 5% significance level, a sample size of 90 participants was considered sufficient. Allowing for an estimated withdrawal rate of 10%, at least 100 participants had to be recruited.

For current post hoc analyses, all the serum lipids profile data for healthy participants with borderline serum LDL-C levels (LDL-C<3.62mmol/L) collected from the previous study (Castaño *et al.* 2003) were statistically treated by using an ANOVA analysis followed by a paired t-test for within-group comparison (week 8 versus week 0 in each group) and an unpaired t-test for between-group comparison (policosanol 5 mg/day versus placebo at week 8). All tests were 2-tailed. The value of $p<0.05$ was considered significant. Statistical analyses were performed using SPSS statistics version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

RESULTS

An original dataset composed of 100 participants (Castaño *et al.* 2003) was screened to include only healthy participants with borderline serum LDL-C levels (LDL-C<3.62mmol/L). This screening procedure yielded 39 total participants, 16 in the policosanol group and 23 in the placebo group. The values of the lipid profile variables at baseline and after 8

weeks of treatment are shown in Table 1 and percentage changes in serum lipid parameters after 8 weeks of treatment with policosanol 5 mg/day or placebo are shown in Table 2. The 2 groups had similar profiles at baseline. In the policosanol group, the mean (SD) serum LDL-C level decreased significantly from 3.35 (0.23) mmol/L to 2.56 (0.34) mmol/L ($p<0.00001$ vs baseline and placebo) with a significant decrease in percentage change (-23.89%) versus placebo (2.81%) ($p<0.00001$). Also in the policosanol group, the mean (SD) serum TC level decreased significantly from 4.96 (0.09) mmol/L to 4.28 (0.29) mmol/L ($p<0.00001$ vs baseline and placebo) with a significant decrease in percentage change (-13.84%) versus placebo (1.86%) ($p<0.00001$), and the mean (SD) HDL level increased significantly from 1.06 (0.20) mmol/L to 1.18 (0.26) mmol/L ($P < 0.01$ vs baseline), while no significant change when compared with placebo. The percentage change of HDL-C (10.80%) in policosanol group significantly increased when compared with placebo (-0.73%) ($p<0.00001$). In addition, the LDL-C/HDL-C rations were calculated and compared. In the policosanol group, the mean (SD) serum LDL-C/HDL-C ratio decreased significantly from 3.27 (0.74) to 2.27 (0.53) ($p<0.00001$ vs baseline and placebo) with a significant decrease in percentage change (-30.45%) versus placebo (4.15%) ($P < 0.00001$). There were no significant changes for TG within and between groups before and after policosanol or placebo treatment.

Table 1. Lipid profile of healthy subjects with LDL-C<3.62mmol/L at baseline (week 0) and after 8 weeks of treatment with policosanol 5 mg/day (n = 16) or placebo (n = 23)

Serum Lipid Parameters/Treatment Duration	Placebo (n = 23)	Policosanol (n = 16)
Total cholesterol (mmol/L)		
0 week	4.93 ± 0.08	4.96 ± 0.09
8 weeks	5.02 ± 0.31	4.28 ± 0.29^{***+++}
LDL-C (mmol/L)		
0 week	3.28 ± 0.17	3.35 ± 0.23
8 weeks	3.37 ± 0.33	2.56 ± 0.34^{***+++}
HDL-C (mmol/L)		
0 week	1.10 ± 0.17	1.06 ± 0.20
8 weeks	1.09 ± 0.13	1.18 ± 0.26**
Triglyceride (mmol/L)		
0 week	1.48 ± 0.47	1.47 ± 0.62
8 weeks	1.52 ± 0.48	1.47 ± 0.72
LDL-C/HDL-C ratio		
0 week	3.03 ± 0.48	3.27 ± 0.74
8 weeks	3.13 ± 0.47	2.27 ± 0.53^{***+++}

Note: Data are expressed as mean ± SD. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol, **: $p < 0.01$ versus week 0 when compared within-group by using paired t-test. ***: $p < 0.00001$ versus week 0 when compared within-group by using paired t-test. $^{+++}$: $p < 0.00001$ versus placebo at week 8 when compared between-group by using unpaired t-test.

Table 2. Percentage changes in serum lipid parameters after 8 weeks of treatment with policosanol 5 mg/day (n = 16) or placebo (n = 23)

Percent of Changes in Serum Lipid Parameters from week 0 to week 8 (%)	Placebo (n = 23)	Policosanol (n = 16)
Total cholesterol	1.86 ± 5.83	-13.84 ± 4.93^{+++}
LDL-C	2.81 ± 8.76	-23.89 ± 7.09^{+++}
HDL-C	-0.73 ± 5.91	10.80 ± 12.93^{+++}
Triglycerides	5.03 ± 16.75	-3.00 ± 14.99
LDL-C/HDL-C ratio	4.15 ± 13.20	-30.45 ± 10.57^{+++}

Note: Data are expressed as mean ± SD. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; $^{+++}$: $p < 0.00001$ versus placebo at week 8 when compared between-group by using unpaired t-test.

DISCUSSION

The post hoc analysis results show that policosanol (5 mg/day) administered for 8 weeks was effective in decreasing LDL-C in healthy participants with borderline serum LDL-C values. Also, policosanol produced additional beneficial changes in the lipid profile of the participants, as the reductions in serum levels of TC and LDL-C were accompanied by an increase in HDL-C. The effects of policosanol on LDL-C and TC levels in the post hoc analysis are consistent with the previous study and those reported for this dose and treatment duration in populations with broad ranges of TC indicating mild to severe hypercholesterolemia (Castaño *et al*. 1999, 2001) (Mas *et al*. 2001) (Crespo *et al*. 1999).

The increase in serum HDL-C level in the policosanol group was also within the expected range, although the extent of the change varied from that found in a previous study (Castaño *et al*. 1999). This change is an additional benefit of policosanol treatment that may contribute to reducing the risk for CHD after long-term administration. Likewise, although the effects of policosanol on TG have not been consistent in all studies, modest but significant reductions have been obtained in some (Mas *et al*. 1999) (Castaño *et al*. 2000) (Crespo *et al*. 1999).

Studies in animals and humans have shown that policosanol has pleiotropic properties that offer additional benefits in preventing atherosclerosis and complications, such as the inhibition of platelet aggregation (Arruzazabala *et al*. 1993a, 1993b, 1996, 1997, 1998) (Valdes *et al*. 1996) (Carbajal *et al*. 1998) (Castaño *et al*. 2003) and lipid peroxidation (Menéndez *et al*. 2000a, 2000b).

LDL-C/HDL-C ration has been considered as a risk factor for coronary heart disease (Matsumoto *et al*. 2011) (Hu *et al*. 2024) (Kunutsor *et al*. 2017). In the current post hoc analysis, LDL-C/HDL-C ratios were calculated and assessed. In the policosanol group, serum LDL-C/HDL-C ratio decreased significantly from 3.27 to 2.27 with a significant decrease in percentage change (-30.45%). This dramatic change is considered due to the decrease in LDL-C and the increase in HDL-C.

CONCLUSIONS

Policosanol is an effective cholesterol-lowering drug and a nutraceutical ingredient to be used in improving serum lipids profile to decrease the major risk factor for coronary heart disease. Policosanol has pleiotropic properties that offer additional benefits in preventing atherosclerosis and complications, such as the inhibition of platelet aggregation and lipid peroxidation. In the current report, daily supplementation (5 mg) of policosanol for 8 weeks significantly improved serum lipids profile in healthy participants with mildly elevated cholesterol levels at the normal ranges. Also, policosanol produced additional beneficial changes in the lipid profile of the participants, as the reductions in serum levels of TC and LDL-C were accompanied by an increase in HDL-C. However, this is an exploratory post hoc analysis report, further studies in healthy subjects with borderline serum LDL-C level at normal ranges are needed for effective nutraceutical use.

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