ORIGINAL ARTICLE

Benefits of a Long-term Therapy with Policosanol on Older Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Coronary disease is the major complication and leading cause of death among patients with diabetes mellitus (DM). Hyperlipidemia is common in patients with diabetes, and the high frequency of coronary disease in diabetics is partly a consequence of the abnormalities of lipid metabolism. Policosanol is a mixture of higher primary aliphatic alcohols purified from sugar cane wax with cholesterol-lowering effects. The objective of the present study was to investigate the benefits of long-term therapy with policosanol on older patients with dyslipidemia due to type 2 DM. **Materials and Methods:** This was a prospective, randomized, double-blinded, and placebo-controlled study including 239 elderly patients with type 2 diabetes which was randomized to policosanol or placebo once a day with evening meal for 24 months. Changes in low-density lipoproteins-cholesterol (LDL-C) were considered as the primary efficacy variable. Changes in other lipid profile variables being secondary variables. **Results:** After 1 year, policosanol lowered significantly LDL-C, total cholesterol, and triglycerides while raised high-density lipoproteins-cholesterol (HDL-C) levels. Policosanol effects persisted during the whole study. At study completion, policosanol reduced LDL-C (29.5%), total cholesterol (21.9%), triglycerides (16.9%), and raised HDL-C (12.4%). The frequency of serious adverse events (SAE) was lower ($P < 0.01$) in policosanol patients (6/119, 5%) than in placebo (26/120, 43.3%), and four patients, all placebo, died during the study, four of them due to myocardial infarction. No impairment of safety indicators was observed. Policosanol no modify the control of glucose of these patients. **Conclusions:** The present results demonstrate long-term treatment with policosanol significantly lower amount of vascular SAE and produce relevant positive changes on serum lipid profile in older patients with dyslipidemia due to type 2 DM.

Key words: Policosanol, cholesterol-lowering, older diabetic patients, lipid profile

INTRODUCTION

Coronary disease is the major complication and leading cause of death among patients with diabetes mellitus (DM).[1] Hyperlipidemia is common in patients with diabetes, and the high frequency of coronary disease in diabetics is partly a consequence of the abnormalities of lipid metabolism.[2]

A combination of lifestyle measures, including glycemic control, is the first-choice therapy for dyslipidemia management in diabetes. Nevertheless, adherence to these measures alone is often not sufficient, and lipid-lowering drugs must be prescribed.[3]

Policosanol is a mixture of higher primary aliphatic alcohols purified from sugar cane (*Saccharum officinarum*), wax with cholesterol-lowering effects.[4] Policosanol inhibits cholesterol synthesis by regulating the activity of hydroxymethylglutaryl coenzyme through the increase of AMP kinase activity,[5] increasing low-density lipoproteins (LDL) receptor-dependent processing, and catabolic rate of LDL.[6]

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Previous studies conducted in diabetic patients with hypercholesterolemia treated with policosanol showed that policosanol was effective and well-tolerated in these patients.[7-11]

The objective of this present study was to investigate the benefits of long-term therapy with policosanol on older patients with dyslipidemia due to type 2 DM.

MATERIALS AND METHODS

The study was conducted according to the principles reflected in the Helsinki statements, as well as the recommendations of the World Health Organization and the Cuban regulations on Good Clinical Practices. The study protocol was approved by the Ministry of Public Health and by the Ethics Committee in Clinical Research of the Medical-Surgical Research Center (Havana, Cuba).

This was a prospective, randomized, double-blinded, placebo-controlled study including 239 elderly patients with type 2 diabetes that was randomized to policosanol (5 mg) or placebo once a day with evening meal for 24 months.

Older patients with Type 2 diabetes of both sexes, aged between 60 and 80 years, were randomized if after the baseline period, they showed total cholesterol ≥5.2 mmol/L, low-density lipoproteins-cholesterol (LDL-C) ≥3.4 mmol/L, and triglycerides <4.52 mmol/L, if exclusion criteria were not present.

Patients were excluded if they had active renal or diagnosed neoplastic diseases, severe hypertension, uncontrolled diabetes, or poor cognitive function. Patients who had experienced unstable angina, myocardial infarction, stroke, or any serious adverse events (SAE) within the 3 months before enrolment were also excluded from the study.

Changes in LDL-C were considered as the primary efficacy variable. Treatment was considered as effective if LDL-C was significantly reduced by ≥15%,[12] changes in other lipid profile variables being secondary variables.

Safety and tolerability analyses included physical and laboratory safety indicators and tolerability analysis included all data on adverse events (AE).

Blood samples were drawn after 12 h overnight fasting. Lipid profile and laboratory safety indicators were assessed by enzymatic methods using reagent kits (Roche). Laboratory tests were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan).

All data were analyzed according to intention-to-treat principle so that analyses were based on data of all randomized patients, as randomized. *t*-test was used to compare continuous variables during the study. Comparisons between groups of categorical data were made using the χ^2 test. All statistical tests were two-tailed, with significance at $\alpha = 0.05$. Statistical analyses were performed using Statistica for Windows (Release 4.2; Copyright StatSoft, Inc., US).

RESULTS AND DISCUSSION

Both groups were comparable at baseline, which supports their homogeneity (data no shown for simplicity). The mean age of study patients was around 65 years at baseline, being still young for preventive measures and related effects on life quality and expectancy. Most patients were women (82.8%) and hypertensive (72.8%). In turn, the frequency of concomitant medications was high, which is characteristic of the elderly.

The total number of withdrawals in the policosanol group was significantly lower ($P < 0.05$) than in the placebo [Table 1]. Of 239 elderly patients, 63 (26.4%) discontinued the study, 43/120 placebo (35.8%), and 20/119 policosanol (16.8%) patients. Of them, 35 patients (28 placebo and seven policosanol) ($P < 0.01$) discontinued prematurely the study due to some AE, the frequency of policosanol patients who discontinued the study due to AE being also lower than in the placebo, a fact consistent with the frequency of SAE in both groups.

After 1 year, policosanol lowered significantly ($P < 0.0001$ vs. placebo) LDL-C, total cholesterol, and triglycerides, while raised ($P < 0.001$ vs. placebo) high-density lipoproteins-cholesterol (HDL-C) levels. Policosanol effects persisted during the whole study. At study completion, policosanol reduced LDL-C (29.5%), total cholesterol (21.9%), triglycerides (16.9%), and raised HDL-C (12.4%) [Table 2].

The present results support that policosanol efficacy is also evident in older diabetic patients and is consistent with the previous report. The changes, here, reported for LDL-C; total cholesterol and HDL-C are consistent with the expected response to policosanol long-term therapy, but reductions on triglycerides, however, were superior that those reported in previous studies. No significant change of any lipid profile variable occurred in the placebo group.

Thus, the frequency of SAE was lower ($P < 0.01$) in policosanol patients (6/119, 5%) than in placebo (26/120, 43.3%), and four patients, all placebo, died during the study, four of them due to myocardial infarction [Table 3].

The frequency of all vascular SAE, cardiovascular, cerebrovascular, all deaths to vascular causes, and all deaths was lower than in the placebo, consistently with LDL-C lowering and pleiotropic effects of policosanol, all beneficial

Table 1: Withdrawal analysis of study

Withdrawals due to AE	Placebo (*n*=119)	Policosanol (*n*=120)	*P*-value*
Withdrawals due to vascular SAE	26	6	*P*<0.01
Withdrawals due to mild and moderate AE	2	1	
Subtotal due to all AE	28 (23.5)	7 (5.8)	*P*<0.01
Withdrawals due to other reasons			
Unsatisfactory efficacy	8	1	*P*<0.05
Travels abroad + changes to other towns	1	2	
Address changes	1	2	
Unwillingness to follow-up	4	6	
Protocol violations	1	2	
Subtotal due to other reasons	15 (12.6)	13 (10.8)	ns
Total of withdrawals	43 (36.1)	20 (16.7)	*P*<0.05

AE: Adverse events, SAE: Serious adverse events, *Comparison with placebo (χ^2 test)

Table 2: Changes (%) on lipid profile

Treatment	LDL-C	Total cholesterol months	HDL-C	Tryglicerides
Policosanol	−29.5^{+++}	−21.9^{+++}	+12.4^{++}	−16.9^{+++}
Placebo	+1.7	+0.4	−0.4	−2.7

LDL-C: Low-density lipoproteins-cholesterol, HDL-C: High-density lipoproteins-cholesterol, ++*P* < 0.001; +++*P* < 0.0001 comparison with placebo (*t*-test for independent samples)

Table 3: SAE occurred during the study

SAE	Policosanol (*n*=120)		Placebo (*n*=119)	
	n	%	*n*	%
Vascular SAE				
Fatal myocardial infarction	0	0.0	4	3.4
Non-fatal myocardial infarction	0	0.0	6	5.0
Unstable angina	1	0.8	3	2.5
Congestive heart failure	1	0.8	2	1.7
Subtotal	2	1.7	15	12.6^{+}
Cerebrovascular SAE				
Stroke	1	0.8	0	0.0
Transient ischemic attacks	1	0.8	4	3.4
Subtotal	2	1.7	4	3.4
Peripheral artery disease SAE				
Severe leg ischemic	0	0.0	2	1.7
Total of vascular SAE	4	3.3	21	17.6^{++}
Non vascular SAE				
Fatal cancer	0	0.0	1	0.8
Non-fatal cancer	1	0.8	1	0.8
Fractures	1	0.8	2	1.7
Pneumonia	0	0.0	1	0.8
Subtotal	2	1.7	5	4.2
Total of SAE	6	5.0	26	21.8^{++}

SAE: Serious adverse events, +*P*<0.05, ++*P*<0.01 comparison with placebo (χ^2 test)

for vascular function, thus preventing the occurrence of vascular events.

The overall of policosanol patients reporting mild and/or moderate AE was similar than in placebo.

No impairment of safety indicators was observed. Policosanol no modify the control of glucose of these patients. Nevertheless, a reduction of systolic and diastolic blood pressure was observed in policosanol patients compared with placebo (data no shown for simplicity).

CONCLUSIONS

The present results demonstrate long-term treatment with policosanol significantly lower amount of vascular SAE and produce relevant positive changes on serum lipid profile in older patients with dyslipidemia due to type 2 DM.

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How to cite this article: Fernández-Travieso JC, López-González LE, Illnait-Ferrer J, Fernández-Dorta L, Gamez-Menéndez R, Mendoza-Castaño S, Mesa-Angarica M, Alvarez-Valera E. Benefits of a Long-term Therapy with Policosanol on Older Patients with Type 2 Diabetes Mellitus. Clin Res Diabetes Endocrinol 2020;3(2):1-4.