Phosphatidylinositol increases HDL-C levels in humans

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Abstract Studies have shown that phosphatidylinositol (PI) can stimulate reverse cholesterol transport by enhancing the flux of cholesterol into HDL and by promoting the transport of high density lipoprotein-cholesterol (HDL-C) to the liver and bile. The goal of this study was to determine the safety and therapeutic value of PI after oral administration to normolipidemic human subjects. We performed a randomized 2 week study in 16 normolipidemic subjects. Subjects received either 2.8 or 5.6 g of PI, with or without food. PI was well tolerated by all subjects. PI significantly affected the levels of HDL-C and triglyceride in the plasma of subjects receiving PI with food. The lower dose showed a 13% increase in HDL-C, whereas the high dose showed an increase of 18% over the 2 week period. Both low- and high-dose groups showed significant increases in plasma apolipoprotein A-I. The high dose of PI also decreased plasma triglycerides by 36% in the fed subjects. These data suggest that after only 2 weeks, PI may have a comparable therapeutic value to niacin, with negligible side effects.—Burgess, J. W., T. A-M. Neville, P. Rouillard, Z. Harder, D. S. Beanlands, and D. L. Sparks. **Phosphatidylinositol increases HDL-C levels in humans. *J. Lipid Res.* 2005.** 46: **350–355.**

Supplementary key words high density lipoprotein-cholesterol • cholesterol • triglycerides • HDL elevating agents

Epidemiological studies have established an inverse association between high density lipoprotein-cholesterol (HDL-C) and coronary artery disease (CAD) (1). Controlled intervention trials suggest that a 1% increase in HDL-C will correspond to a 3% reduction in CAD event rate (2). Conservative treatment measures (e.g., dietary modification, smoking cessation, aerobic exercise) only increase HDL-C modestly (3), and available agents for increasing HDL-C are currently limited to niacin and the fibrates (4, 5). Unfortunately, although these drugs have been available for decades, their popularity has been limited by the side effects associated with therapeutic dosage regimes. Novel HDL therapeutic strategies are under development, and recent reports suggest that the cholesteryl ester transfer protein (CETP) inhibitors, Torcetrapib and JTT-705, may be promising new therapies for increasing HDL-C levels and treating CAD (6, 7). Increasing HDL levels by infusion of HDL or apolipoprotein A-I (apoA-I) Milano also appears to have direct effects on atherosclerosis in humans (8). Although results with these compounds hold promise, large prospective studies are needed to clarify how different strategies to increase HDL levels may impact the development and progression of CAD.

Studies over the last few decades have suggested that soy lecithin may also affect plasma HDL levels. Prolonged oral administration of soy lecithin at doses ranging from 12 to 48 g per day have resulted in significant reductions in serum cholesterol and triglyceride levels (9, 10) and increased HDL-C levels (9). Soy lecithin is a mixture of uncharged (phosphatidylcholine) and anionic [phosphatidylinositol (PI)] polar lipids. Oral administration of purified soy phosphatidylcholine has been shown to significantly decrease low density lipoprotein-cholesterol (LDL-C) and triglycerides (11, 12) but to have minimal effect on HDL-C (12–14). The contribution of the anionic constituents of soy lecithin has remained unclear.

We have previously reported that soy PI stimulates the reverse cholesterol transport pathway. PI promotes increased efflux of cholesterol from peripheral tissues to HDL and an increased transport and clearance of cholesterol through the liver, bile, and feces (15, 16). Therefore, a prospective study was designed to evaluate the effects of orally administered PI on HDL-C and other cardiovascular risk factors in normolipidemic volunteers. PI is well tolerated and acts rapidly to modify plasma HDL and triglyceride levels when administered with food.

Manuscript received 3 November 2004.

Published, JLR Papers in Press, December 1, 2004.
DOI 10.1194/jlr.M400438-JLR200

Abbreviations: CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; PI, phosphatidylinositol.

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METHODS

Study population

The study was approved by the Human Research Ethics Board of the University of Ottawa Heart Institute and by Health Canada Therapeutic Products Directorate. The characteristics of the study population are shown in **Table 1**. The trial cohort consisted of healthy men (n = 10) and women (n = 6) between 25 and 48 years of age. The exclusion criteria were as follows: HDL-C < 1.0 mmol/l and LDL-C > 5.0 mmol/l, known allergies to soy products, body mass index > 30 kg/m^2, pregnancy, and use of lipid-lowering drugs. There were no diabetics or smokers in the trial. Alcohol consumption during the trial was light to moderate (zero to six drinks per week). The subjects were asked to maintain their normal dietary and exercise habits throughout the study.

Study design

Baseline (t = 0) values were determined from blood draws after an overnight 12 h fast. Subjects were then randomized to one of four groups. Groups 1 (n = 3) and 2 (n = 5) were administered 2.8 and 5.6 g of PI, respectively, at 7:00 AM with water and remained without food until 10:00 AM, when the subjects were asked to have a low-fat breakfast, specifically a low-fat muffin or bagel with juice and/or coffee. Groups 3 (n = 3) and 4 (n = 5) were administered 2.8 and 5.6 g of PI, respectively, at 7:00 AM with a low-fat breakfast (as above). Dietary questionnaires returned from all subjects indicated compliance and that the breakfasts contained fewer than 500 calories. PI administration without food (groups 1 and 2) or with food (groups 3 and 4) was continued every day for 2 weeks. All blood draws during the drug administration phase were performed after an overnight fast and just before the daily administration of PI.

PI for this study was purified from soy lecithin by multiple hot ethanol extractions and acetone precipitation. The material was then dried to a fine powder by rotary evaporation. Thin-layer chromatography analysis on HPTLC plates, chromatographed with chloroform-ethanol-water-triethylamine (30:35:7:35), demonstrated essentially complete removal of phosphatidylcholine, phosphatidylethanolamine, lysophosphatidylcholine, and neutral lipids. TLC analysis against plant stanol and sterol reference standards (Matreya Biochemicals) indicated that these contaminants were also completely absent from PI, even after overloading of the TLC plates. PI was packaged into hard gelatin capsules for oral administration.

Laboratory assessment

After a 12 h overnight fast, venous blood was collected and submitted to the Department of Pathology and Laboratory Medicine at the Ottawa Hospital, Civic Campus, for hematology and chemistry analysis. The chemistry parameters included a complete blood count, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine kinase, and creatinine. Blood samples were also analyzed for serum lipid and lipoprotein evaluations, which included total cholesterol, HDL-C, LDL-C, and triglyceride. Total cholesterol, HDL-C, and plasma triglycerides were assayed enzymatically using a Synchron LX analyzer. Plasma apoA-I levels at days 0 and 14 were determined by the J. Alick Little Lipid Laboratory of St. Michael's Hospital (Toronto, Canada).

Statistical analysis

The differences observed between t = 0 and day 14 values were used to derive percentile changes for all of the lipid parameters. These values were used for paired two-tailed *t*-tests, and the significance of these differences is shown in **Table 2**. In addition, one-way ANOVA was used to test whether the differences observed between t = 0 and day 14 for each of the lipid parameters were significant between randomized groups. If an overall difference was found for a parameter, then pairwise comparisons using a Tukey adjustment for multiple comparisons were performed. $P < 0.05$ was regarded as statistically significant.

RESULTS

Sixteen subjects were randomized to the four groups, with both low and high dosages administered with and without food. No moderate or serious adverse events were documented during the treatment phase of the clinical trial. Blood chemistry measurements remained within normal ranges for all parameters and for all subjects throughout the investigation.

TABLE 1. Subject characteristics at study entry

				Plasma Lipids			
Study Group	Age	Sex	Body Mass Index	Total cholesterol	HDL-C	LDL-C	Triglyceride
	years		*kg/m^2*		*mmol/l*		
Group 1 (2.8 g without food)	26	Female	22.4	4.8	1.78	2.5	1.14
	29	Male	20.6	4.4	1.10	2.8	1.10
	28	Male	27.1	5.1	1.09	3.2	1.68
Group 2 (2.8 g with food)	33	Male	24.1	6.1	1.45	4.2	0.97
	45	Male	25.1	5.5	1.43	3.7	0.84
	36	Female	22.9	4.2	1.92	1.8	1.08
Group 3 (5.6 g without food)	33	Male	23.5	5.0	1.59	3.0	0.93
	44	Female	25.7	5.5	1.42	3.3	1.66
	30	Male	22.1	5.4	1.33	3.7	0.90
	25	Male	27.2	4.8	1.71	2.8	0.58
	38	Female	21.1	5.1	2.13	2.6	0.71
Group 4 (5.6 g with food)	27	Male	25.3	4.6	1.27	2.8	1.24
	48	Female	22.9	5.9	1.82	3.8	0.68
	33	Male	22.2	4.8	1.71	2.8	0.58
	36	Female	26.9	5.3	1.39	3.6	0.65
	26	Male	27.9	5.5	1.00	3.7	1.98

HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.

TABLE 2. Plasma lipids at baseline and after 14 days of treatment with phosphatidylinositol

Dose	Study Group	Time	Total Cholesterol	Triglyceride	HDL-C	LDL-C	Apolipoprotein A-I
				mmol/l			*mg/ml*
2.8 g	Without food (n = 3; 2 males, 1 female)	Baseline	4.47 ± 0.40	1.28 ± 0.94	1.35 ± 0.30	2.53 ± 0.45	nd
		14 days	4.80 ± 0.10	1.26 ± 0.36	1.34 ± 0.20	2.87 ± 0.40	nd
		Percent change	8.2 ± 11.8	20.5 ± 45.7	0.4 ± 8.8	13.9 ± 10.3	
	With food (n = 3; 2 males, 1 female)	Baseline	5.27 ± 0.78	1.20 ± 0.11	1.50 ± 0.40	3.20 ± 1.22	1.89 ± 0.43
		14 days	5.53 ± 0.55	1.15 ± 0.21	1.72 ± 0.54[a]	3.33 ± 1.08	2.01 ± 0.52
		Percent change	5.7 ± 7.1	−5.0 ± 9.1	13.3 ± 5.5	6.4 ± 9.0	6.25 ± 2.95*
5.6 g	Without food (n = 5; 2 males, 3 females)	Baseline	4.68 ± 0.30	0.94 ± 0.32	1.51 ± 0.42	2.78 ± 0.27	nd
		14 days	4.93 ± 0.27	0.87 ± 0.28	1.57 ± 0.41	2.96 ± 0.47	nd
		Percent change	5.7 ± 4.1	−3.3 ± 27.7	4.0 ± 3.3*	6.1 ± 8.9	
	With food (n = 5; 3 males, 2 females)	Baseline	4.96 ± 0.71	1.20 ± 0.38	1.26 ± 0.28	3.18 ± 0.78	1.63 ± 0.23
		14 days	4.90 ± 0.52	0.71 ± 0.15	1.47 ± 0.28[b,c]	3.08 ± 0.49	1.74 ± 0.34
		Percent change	−0.5 ± 9.1	−35.7 ± 21.8*	17.8 ± 5.3**	−0.5 ± 17.8	6.42 ± 7.23*

Values are expressed as means ± SD and as the means of individual percentage changes ± SD relative to baseline. nd, not determined. Significant difference between baseline and day 14 values was determined by Student's *t*-test: * $P < 0.05$; ** $P < 0.001$.

Differences between baseline and day 14 values differed significantly between randomized groups ($P < 0.05$) as determined by ANOVA:
[a] 2.8 g with food vs. 2.8 g without food; [b] 5.6 g with food vs. 2.8 g without food; [c] 5.6 g with food vs. 5.6 g without food.

Table 2 provides pretreatment and posttreatment lipid and lipoprotein levels for subjects in the various treatment groups. Administration of PI without food had a negligible effect on HDL-C levels with the lower dose but increased HDL-C by 4% ($P < 0.05$) with the high dose (Table 2). In contrast, when administered with food, PI showed an increase in plasma HDL-C levels, ranging from 5% to 23% (Table 2, **Fig. 1**). Pairwise comparisons showed the fed groups' responses to differ significantly from those of the groups that received the drug without food (Table 2). Subjects receiving the 2.8 g dose with food exhibited a mean increase in plasma HDL-C of 13%, and administration of 5.6 g of PI with food was associated with an 18% increase in plasma HDL-C ($P < 0.001$). HDL-C remained increased for several days after the treatment was ended. Two and 4 days after the last drug administration, the HDL-C levels were still increased by 10.1% and 5.8% relative to baseline values (data not shown). With the exception of one high-dose individual, all subjects receiving PI with food showed increased plasma apoA-I levels ranging from 2% to 15% (Table 2, **Fig. 2**). The mean increase of

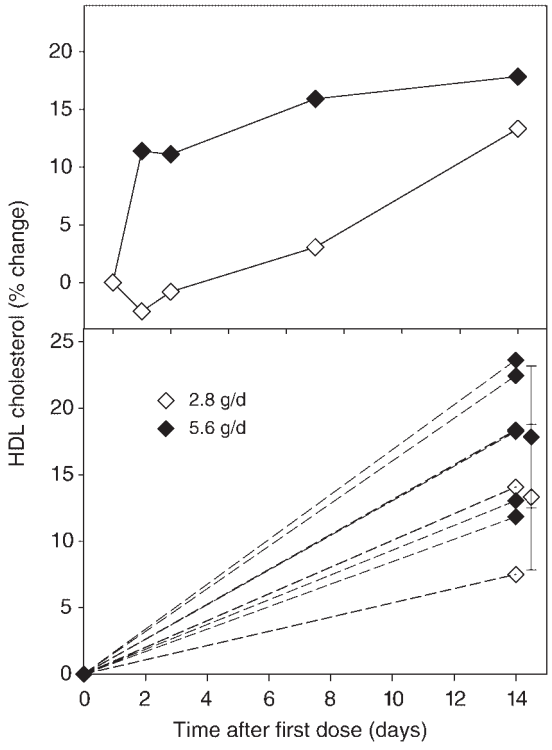

Fig. 1. Change in high density lipoprotein-cholesterol (HDL-C) in healthy volunteers receiving oral phosphatidylinositol (PI) with a meal. Mean percentile change in HDL-C levels (upper panel) and individual values on day 14 (lower panel) are shown for subjects who received 2.8 g (n = 3; open symbols) or 5.6 g (n = 5; closed symbols) of PI with a meal.

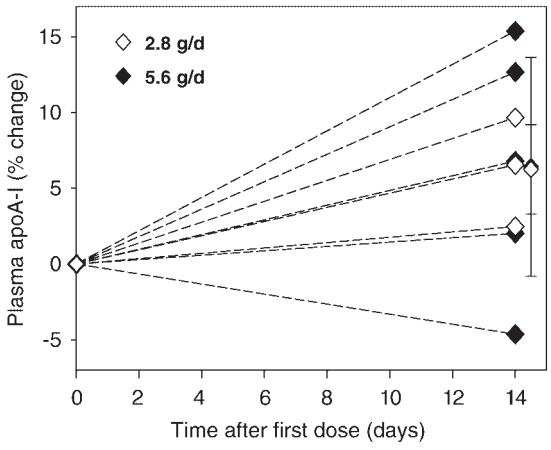

Fig. 2. Percent change in plasma apolipoprotein A-I (apoA-I) concentration in healthy volunteers receiving oral PI under fed conditions. Subjects received either 2.8 g (n = 3; open symbols) or 5.6 g (n = 5; closed symbols) of PI with a meal for 14 days.

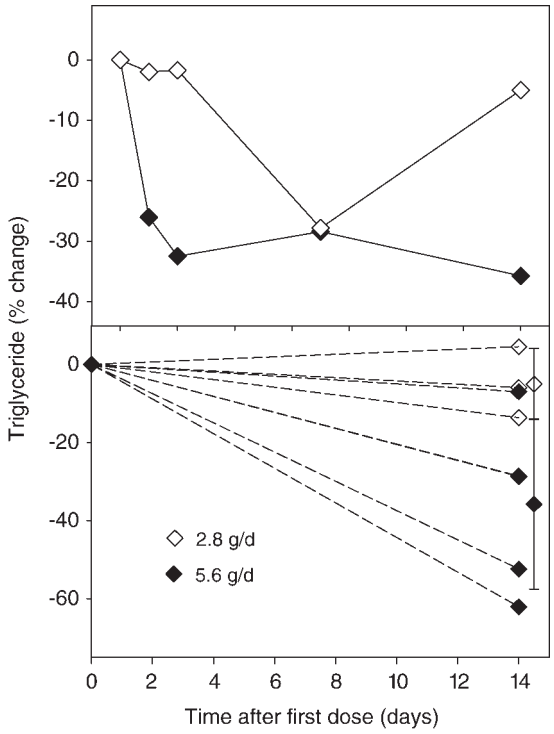

Fig. 3. Change in plasma triglycerides in healthy volunteers receiving oral PI with a meal. Mean percentile change in triglyceride levels (upper panel) and individual values on day 14 (lower panel) are shown for subjects who received 2.8 g (n = 3; open symbols) or 5.6 g (n = 5; closed symbols) of PI with a meal.

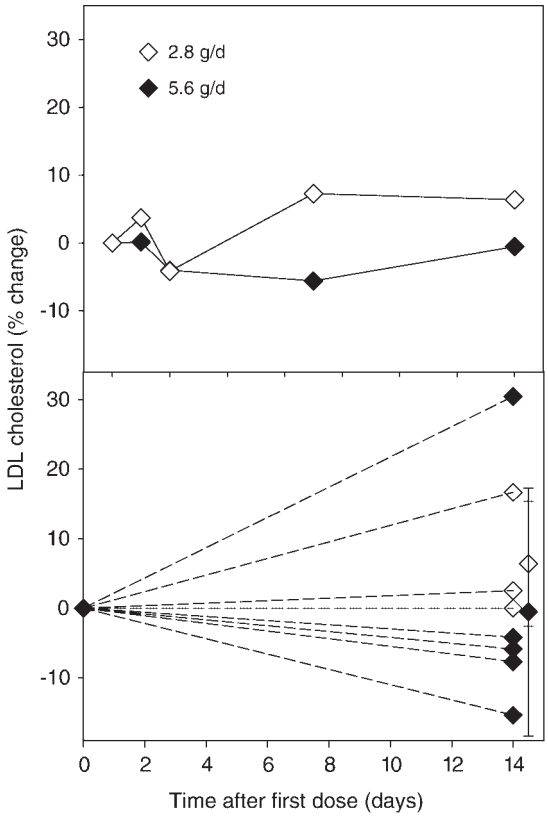

Fig. 4. Change in plasma low density lipoprotein-cholesterol (LDL-C) in healthy volunteers receiving oral PI with a meal. Mean percentile change in LDL-C levels (upper panel) and individual values on day 14 (lower panel) are shown for subjects who received 2.8 g (n = 3; open symbols) or 5.6 g (n = 5; closed symbols) of PI with a meal.

6.4% for both low- and high-dose groups represents a significant increase in apoA-I ($P < 0.03$).

Similar to observations with HDL, minimal changes in plasma triglycerides were observed when PI was administered without food, whereas significant reductions were evident when PI was taken with a meal (Table 2, **Fig. 3**). Subjects who received PI with food all exhibited decreased triglycerides, ranging from 5% to 60% (Fig. 3, lower panel). Individuals receiving the 5.6 g dose showed a significant decrease in plasma triglycerides of 36% ($P < 0.05$). There was also a mean 5% decrease in plasma triglycerides in the low-dose fed individuals, although this change was not statistically significant.

Plasma LDL-C levels remained unchanged in subjects receiving PI with or without food (**Fig. 4**, upper panel). It should be noted, though, that four of five subjects in the high-dose fed group showed substantive decreases in LDL-C, ranging from 4% to 14% (Fig. 4, lower panel).

DISCUSSION

It is becoming increasingly evident that low HDL-C can be an independent risk predictor of CAD even when LDL-C is low (17). Subjects with increased HDL (e.g., marathon runners and women) (18, 19) are at reduced risk of CAD, whereas primary isolated low HDL-C is a disorder characterized by an increased risk of CAD (20). It is also well documented that increased apoA-I production is antiatherogenic in animals (21, 22). Although therapeutic strategies to increase HDL-C levels have existed for several decades, problems with low efficacy and intolerable side effects have limited the popularity of the currently available drugs. HDL-C levels are effectively treated with fibrates and niacin. Niacin is currently the most effective HDL-increasing compound, providing increases in HDL of 25–30% after several months of treatment. The CETP inhibitors, Torcetrapib (Pfizer) and JTT-705 (Japan Tobacco), are also promising new therapies for increasing HDL-C levels and may have value as combination therapies with the statins (6, 7). Increasing HDL levels is thought to have even greater potential benefits than simply decreasing the risk for CAD. A novel therapy using infusions of apoA-I Milano has recently been shown to induce the regression of atherosclerosis in humans (8).

This study has shown that daily PI is well tolerated and will result in significant increases in HDL-C and apoA-I and reductions in plasma triglycerides when administered at 5.6 g/day. Changes in plasma lipid levels were evident after only a few days of treatment and did not reach a plateau by 2 weeks. The most significant effects were observed when PI was administered with food. The increase

in HDL-C in fed high-dose individuals reached 18% after only 2 weeks of administration. Because niacin can produce little change in HDL-C within 2 weeks, this result suggests that PI could equal or surpass the efficacy of niacin in longer term studies. All fed subjects demonstrated an increase in HDL-C levels. Plasma HDL-C in subjects who received PI without food also increased significantly with the high dose but changed little with the low dose of PI. Similarly, fed subjects showed major reductions in triglyceride, whereas subjects receiving PI without food exhibited highly variable triglyceride levels. These results suggest that intestinal absorption of PI may be sensitive to diet or increased biliary output associated with the ingestion of food.

PI appears to increase HDL-C levels by mobilizing a flux of cholesterol to HDL and blocking its transport and storage in LDL. Intravenous PI inhibits LCAT and CETP, increases efflux of cellular cholesterol to HDL, and increases transport of HDL-C to the liver, bile, and feces (15, 16). PI may therefore act to block the transfer and storage of cholesterol in the apoB pool and to stimulate reverse cholesterol transport. Our unpublished observations indicate that as much as 2–3% of orally administered PI traverses the intestinal tract in rats and rabbits. Therefore, the high dose used in this study should promote a plasma PI concentration that is close to that administered in our intravenous studies (15, 16). These effects would be expected to be transient, though, because PI has a very short half-life in the circulation (16). In this study, we observed no significant changes in lipoprotein charge during the trial, which suggests that PI did not accumulate in subject plasma. The intravascular effects of this compound may also parallel cellular metabolic effects, linked to a stimulation of inositol-signaling cascades. PI has significant lipid metabolic effects in a variety of different cell lines (15) and may therefore uniquely affect the enterohepatic metabolism of cholesterol and triglyceride. PI is a minor constituent (~2–4%) of lipoprotein phospholipids (23, 24), but studies suggest that PI may be a critical component of chyle and an important regulator of lipoprotein secretion (25, 26).

Because the mechanism of action of PI is distinct and different from that of the statins, both compounds may have additive effects, and as such, PI may have value as an adjunctive therapy in patients on statins. PI may also have direct value in CAD patients with reduced HDL-C but normal total cholesterol levels, in whom the risk of recurrent cardiovascular events is doubled (27, 28). Therefore, future studies are required to examine the effects of PI in patients with low HDL-C levels.

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