Effect of Lysine, Vitamin B_6, and Carnitine Supplementation on the Lipid Profile of Male Patients With Hypertriglyceridemia: A 12-Week, Open-Label, Randomized, Placebo-Controlled Trial

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ABSTRACT

Background: Fat metabolism is known to be altered in hypertriglyceridemia. Fat oxidation requires carnitine, which can be obtained either from the diet (animal or dairy products) or through synthesis in the body using both lysine and vitamin B_6.

Objective: The goal of this study was to investigate the effect of lysine, vitamin B_6, and carnitine supplementation on both glycemia and the lipid profiles, specifically triglyceride (TG) levels, in men with hypertriglyceridemia.

Methods: This 12-week, randomized, placebo-controlled clinical trial was conducted at a Lebanese medical center. A total of 85 hypertriglyceridemic (TG> 150 mg/dL) male patients were randomized to 1 of 5 groups and given supplements of lysine (1 g/d), vitamin B_6 (50 mg/d), lysine (1 g/d) + vitamin B_6 (50 mg/d), carnitine (1 g/d), or placebo for 12 weeks. The lipid profile (TG, total cholesterol, LDL-C, and HDL-C) and fasting plasma glucose levels were assessed at baseline and at 6 and 12 weeks.

Results: Adults (~50 years) Lebanese males from a low socioeconomic status in Beirut were given the appropriate supplements. Vitamin B_6 supplementation was associated with a significant reduction in total cholesterol and HDL-C of ~10%. In addition, plasma TG was reduced by 36.6 mg/dL at 6 weeks, whereas levels in the placebo group increased by 18 mg/dL; this difference failed to reach statistical significance. No major changes in the lipid profile were observed in the lysine and carnitine groups or when lysine was added to vitamin B_6.

Conclusion: Vitamin B_6 supplementation in these male patients with hypertriglyceridemia reduced plasma total cholesterol and HDL-C concentrations. (*Clin Ther.* 2012;34:1674–1682)

Key words: carnitine, hypertriglyceridemia, lipid profile, lysine, vitamin B_6.

INTRODUCTION

Hypertriglyceridemia (fasting plasma triglyceride [TG] >150 mg/dL) is classified into 2 types, primary and secondary. Primary hypertriglyceridemia is believed to be caused by various genetic defects whereas the secondary type seems to be the result of acquired causes, including obesity, diabetes, excessive alcohol use, high carbohydrate intake, and use of certain medications. However, most cases of hypertriglyceridemia are caused by a combination of >1 factor. The secondary type of hypertriglyceridemia is associated with alterations in lipid metabolism related to abnormalities in the transport, synthesis, or oxidative capacity of fatty acids.[1,2]

Carnitine palmitoyltransferase, an enzyme that controls the availability of long-chain fatty acids for mitochondrial oxidation,[3–6] requires carnitine for its synthesis. Carnitine itself can be synthesized in the body or obtained from an individual's diet, predominantly from meat and dairy products.[7] Endogenous synthesis of carnitine occurs primarily in the liver and kidneys and requires 2 essential amino acids (lysine and methionine) and vitamin B_6.[4,5] Lysine deficiency reportedly reduces carnitine levels in the body and increases lipid

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accumulation.[8,9] Lysine supplementation of a lysine-deficient diet (eg, a wheat diet) was found to diminish the TG level of tissues and improve muscle carnitine levels.[9] Feeding rats a 72% rice diet, which contains no detectable carnitine and is limited in lysine, increased hepatic lipid (TG and total cholesterol) accumulation; these lipid levels were decreased by 40% with lysine (0.2%) supplementation.[8] These studies suggest that cereal-based diets, which are limited in lysine, have the potential to negatively affect carnitine synthesis[10,11] and, in turn lipid status, but this has yet to be shown in humans. Moreover, a diet deficient in vitamin B_6 was reported to reduce carnitine biosynthesis,[12] and the addition of a vitamin B_6 antagonist, L-amino-D-proline, to a perfused rat liver was found to lower carnitine concentrations, a reduction that was reversed by the administration of vitamin B_6.[13] Thus, vitamin B_6 is needed for carnitine synthesis,[4,12] which implies that low vitamin B_6 levels can impair carnitine synthesis and hence alter the lipid profile.[14]

In Lebanon, a high prevalence of hypertriglyceridemia (52.4% in men) is associated with a high percentage of energy intake from carbohydrates, in which cereal and cereal products are the main component. These products are mainly consumed by individuals of low to moderate socioeconomic status.[15] In addition, premenopausal Lebanese women of low to moderate socioeconomic status reportedly have low vitamin B_6 levels and high plasma TG levels.[16] Based on these findings, it is reasonable to postulate that subjects of low socioeconomic status are at risk of having inadequate supplies of lysine, carnitine, and vitamin B_6, which can be attributed to the consumption of a diet high in cereals and low in animal proteins. This hypothesis is also plausible given that the country imports ~75% of its wheat consumption[17] and has no flour fortification policy.

We hypothesized that an inadequate intake of lysine and vitamin B_6, in combination with a low intake of carnitine (associated with reduced consumption of animal protein), would lower the body's capacity to synthesize carnitine. Under such conditions, the capacity to oxidize fatty acids would be reduced, thus leading to fatty acid accumulation. The current study was therefore designed to investigate the effect of lysine, vitamin B_6, and carnitine supplementation on the lipidemic and glycemic profiles of hypertriglyceridemic male subjects of low socioeconomic status. The study was conducted on a small number of subjects and thus was restricted to males to minimize the effect of other variables and possible confounders, especially because lipid metabolism is known to be affected by sex hormones and the use of oral contraceptives.[18]

PATIENTS AND METHODS

The study was approved by the institutional review board of the American University of Beirut. Subjects were identified from the medical records of the Rafic Hariri Medical Center (Tarik Al Jadida, Beirut, Lebanon) that caters to a catchment area of individuals with low socioeconomic status. Patients with hypertriglyceridemia were contacted and asked to come to the center if they were willing to participate in the study and sign an informed consent form. A total of 100 male patients with a history of high TG levels (>150 mg/dL) and no history of renal, hepatic, or gastrointestinal disease, cancer, or alcohol or drug abuse were randomly divided into 5 groups (n = 20 each group) and maintained on their respective supplement for 12 weeks: lysine tablets (1 g/d), vitamin B_6 tablets (50 mg/d), lysine (1 g/d) + vitamin B_6 (50 mg/d) tablets, carnitine tablets (1 g/d), and placebo tablets (**Figure**).

During the first visit, fasting (10–12 hours) blood samples were collected, anthropometric measurements were taken, and patients were given 50 tablets, which was sufficient for the first part of the study (a period of 6 weeks). Patients were asked to maintain their normal eating habits and use of medications. They were contacted by telephone every 2 weeks to ensure their compliance and well-being. During the second meeting (week 6), patients were weighed, fasting blood samples were collected, and the patients were given the rest of the supplements (40 tablets), sufficient for the remainder of the study period (another 6 weeks). At 12 weeks (final visit), patients were weighed, and fasting blood samples were collected. The dropout rate was 15%, and a total of 85 subjects completed the study. During the experimental period, none of the patients reported any discomfort regarding ingestion of the different supplements. Plasma was extracted and stored at −80°C until analysis. Plasma lipid profile (TG, total cholesterol, LDL-C, and HDL-C) and fasting plasma glucose (FPG) concentrations were determined by using the SYNCHRON CX System (Coulter 2000 [Johnson&Johnson company, Rochester New York]).

Statistical Analysis

Data were analyzed by using Stata version 10 (StataCorp LP, College Station, Texas) and SPSS version 16 (SPSS Inc, Chicago, Illinois). Statistical treatment of

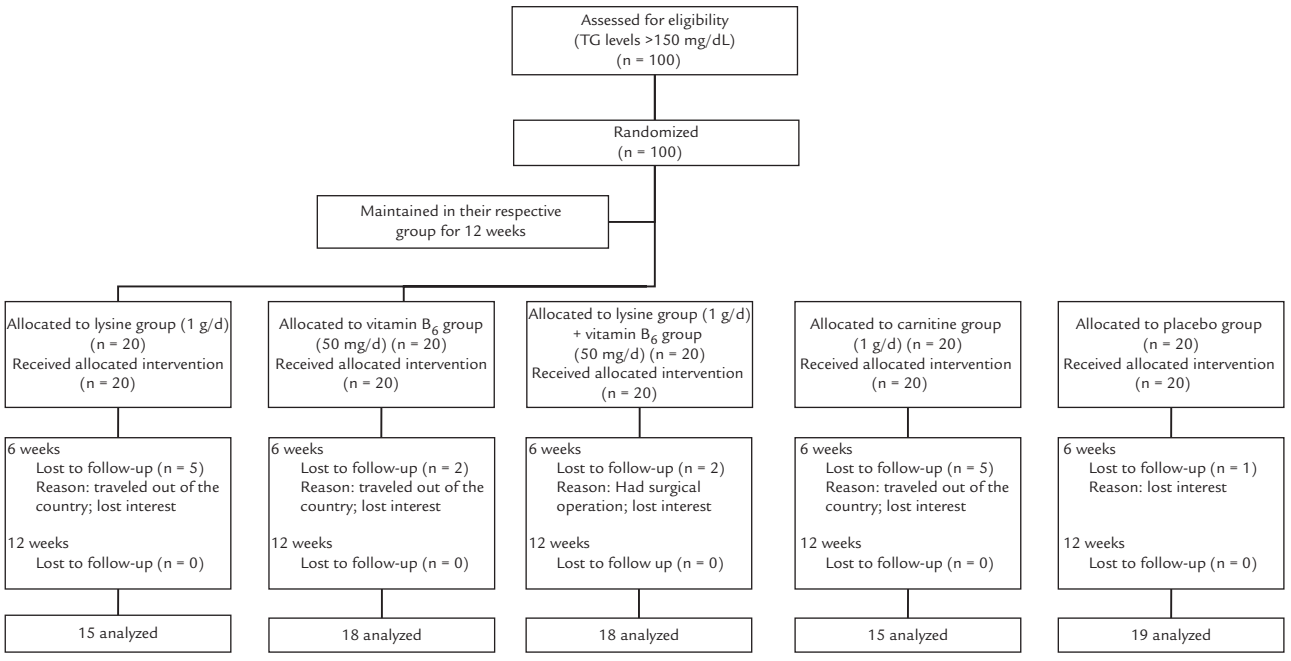

Figure. Protocol flow diagram.

the data included 1-way ANOVA for comparison of the baseline patient characteristics. At each time point, an unpaired *t* test was used for the comparison of mean changes in each parameter in each treatment group compared with placebo. The level of significance was set at 0.05.

RESULTS

Baseline Characteristics

Baseline anthropometric characteristics (age and body mass index) did not differ significantly between groups (Table I). Moreover, other characteristics such as educational level, family or personal history of heart disease, smoking, and diabetes were not significantly different between groups. The number of patients with hypertension or taking antihypertension medication was significantly different between groups.

Weight at baseline was similar between groups, and the changes in weight at 6 and 12 weeks (Table II) in the treatment groups were similar to that of the placebo group.

Plasma TG Levels

Baseline plasma TG concentrations in the placebo group were similar to those in the treatment groups (Table III). At week 6, the change in TG levels of the placebo group was similar to that of the treatment groups, and a comparable pattern was observed at week 12. However, at the end of the study, plasma TG of the lysine and the vitamin B_6 groups decreased slightly, whereas that of the other groups increased by a similar magnitude; these changes were not statistically significant.

Total Cholesterol

At baseline, plasma total cholesterol concentrations of the placebo group were similar to those of the treatment groups. At week 6, changes in total cholesterol levels in the vitamin B_6 and lysine + vitamin B_6 groups were significantly lower than that of the placebo group (Table IV). This reduction sustained its significance in the vitamin B_6 group at week 12.

Plasma HDL-C

At baseline, HDL-C concentrations of the treatment groups were not different from that of the placebo group. At week 6, changes in HDL-C levels of the different groups were similar to that of the placebo group (Table V). However, the change in HDL-C levels in the lysine and vitamin B_6 groups were significantly lower than that of the placebo group at week 12.

Table I. Baseline patient characteristics. Values are given as no. (%), unless otherwise indicated.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)	*P**
Age, mean (SD), y	51.79 (12.31)	56.8 (11.17)	49.3 (11.29)	51.39 (11.97)	55.6 (10.70)	NS
Body mass index, mean (SD), kg/m^2	29.93 (3.80)	32.12 (3.56)	31.47 (4.85)	29.69 (3.01)	31.34 (5.42)	NS
Educational level						NS
<Secondary	12 (63.16)	11 (73.33)	9 (50.00)	9 (50.00)	8 (53.33)	
≥Secondary	7 (36.84)	4 (26.67)	9 (50.00)	9 (50.00)	7 (46.67)	
Family history of heart disease	3 (15.79)	3 (20.00)	3 (16.67)	4 (22.22)	5 (33.33)	NS
Personal heart disease	4 (21.05)	2 (13.33)	4 (22.22)	1 (5.56)	6 (40.00)	NS
Duration of high TG levels, mean (SD)	3.11 (3.93)	5 (7.10)	4.56 (6.35)	2 (2.79)	7.53 (5.15)	NS
Smoker	9 (47.37)	6 (40.00)	7 (38.89)	10 (55.56)	5 (33.33)	NS
Hypertension	5 (26.32)	9 (60.00)	4 (22.22)	2 (11.11)	7 (46.67)	0.022*
Antihypertensive drug use	5 (26.32)	10 (66.67)	8 (44.44)	3 (16.67)	6 (40.00)	0.04*
Diabetes†	5 (26.32)	6 (40.00)	4 (22.22)	3 (16.67)	8 (53.33)	NS
Antidiabetic drug use	3 (15.79)	5 (33.33)	3 (16.67)	2 (11.11)	5 (33.33)	NS
Fibrate use	0 (0.00)	3 (20.00)	2 (11.11)	2 (11.11)	2 (13.33)	NS
Statin use	1 (5.26)	2 (13.33)	4 (22.22)	2 (11.11)	5 (33.33)	NS

TG = triglyceride.
*ANOVA *P* value, $P < 0.05$.
†Patients were considered to have diabetes if they had baseline fasting plasma glucose >126 mg/dL on the basis of at least 2 measurements or if they declared taking antidiabetic drugs.

Plasma LDL-C

No significant differences were observed in LDL-C concentrations between the placebo group and the treatment groups at baseline. At week 6, the changes in LDL-C levels in the vitamin B_6 groups were significantly lower than that of the placebo group, but the magnitude of changes failed to sustain significance at week 12 (**Table VI**). Thus, no statistically significant changes were observed between placebo and the treatment groups at week 12.

Fasting Plasma Glucose

Baseline FPG was similar between the placebo and treatment groups. At weeks 6 and 12, the change in FPG in the placebo group was similar to that of the treatment groups; although the magnitude of changes was higher in the lysine group, this did not reach the level of statistical significance (**Table VII**).

DISCUSSION

The current study was designed to investigate the effect of lysine, vitamin B_6, and carnitine supplementation on the lipid profile of hypertriglyceridemic male patients living in an area associated with low socioeconomic status, which makes them at risk of having low levels of these nutrients. The fact that hypertriglyceridemia is usually associated with other components of the metabolic syndrome made it difficult to obtain homogenous groups, and this limitation is likely to have had an impact on our results and their interpretation. However, the minimal changes in lipids and glucose status that were observed in the placebo group, as well as the similarity in weight changes of the different groups throughout the study, implies that the changes in the treatment groups were mainly attributable to the supplement rather than other confounding factors such as a change in eating habits.

In the current study, vitamin B_6 supplementation was found to reduce the different components of the lipid profile by ~10%, significantly lowering levels of total cholesterol and HDL-C. This finding is in line with animal and human studies,[19,20] in which pyridoxine supplementation of atherosclerotic patients with

Table II. Mean patient weight at baseline and changes in weight at study weeks 6 and 12.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)
Baseline weight, kg					
Mean (SD)	89.6 (16.1)	94.5 (12.4)	91.6 (16.9)	87.8 (10.8)	95.0 (19.5)
*P**		NS	NS	NS	NS
△ Weight at week 6, kg					
Mean (SD)†	−1.66 (3.1)	−1.70 (3.1)	−0.6 (4.7)	−0.36 (1.3)	−0.93 (1.8)
*P**		NS	NS	NS	NS
△ Weight at week 12, kg					
Mean (SD)‡	−2.71 (3.77)	−2.1 (3.9)	−2.1 (5.0)	−1.0 (1.9)	−2.0 (2.5)
*P**		NS	NS	NS	NS

*Unpaired *t* test, comparison with placebo.
†Change at week 6 = mean (weight week 6 − body weight week 0).
‡Change at week 12 = mean (weight week 12 − body weight week 0).

low plasma pyridoxal phosphate (PLP) levels was reported to significantly decrease total cholesterol and LDL-C levels, while having minimal effects on TG and HDL-C.[20] The magnitude of the decrease was similar to that of the current study.

The exact mechanism by which vitamin B_6 alters lipid profiles is unclear. Vitamin B_6 is known to play a role in the desaturation and elongation of fatty acids, methylation of phospholipids, and mobilization of unsaturated fatty acids from triglycerides to phospholipids.[21] Increased delta-desaturase activity reportedly stimulates prostaglandin E_1 synthesis, which in turn inhibits cholesterol biosynthesis and subsequently modifies cholesterol levels.[19] This is supported by the finding that prostaglandin E_1 treatment of rats was found to decrease the concentrations of total lipids, cholesterol, TG, phospholipids, and all HDL-C lipid fractions.[22] Conversely, PLP

Table III. Plasma triglyceride (TG) concentration at baseline and changes after intake of the supplements.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)
Baseline TG, mg/dL					
Mean (SD)	252.2 (82.6)	245.4 (100.6)	247.7 (106.1)	252.0 (92.0)	233.2 (72.6)
*P**		NS	NS	NS	NS
△ TG at week 6, mg/dL					
Mean (SD)†	50.11 (136.34)	−8.87 (146.61)	−19.39 (120.68)	−12.39 (79.73)	16.47 (77.26)
*P**		NS	NS	NS	NS
△ TG at week 12, mg/dL					
Mean (SD)‡	18.42 (101.23)	−11.40 (126.0)	−36.61 (146.75)	29.94 (123.37)	20.13 (67.46)
*P**		NS	NS	NS	NS

*Unpaired *t* test, comparison with placebo.
†Change at week 6 = mean (TG week 6 − TG week 0).
‡Change at week 12 = mean (TG week 12 − TG week 0).

Table IV. Plasma total cholesterol (TC) concentration at baseline and changes after intake of the supplements.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)
Baseline TC, mg/dL					
Mean (SD)	203.4 (36.6)	211.1 (39.0)	236.1 (43.1)	225.4 (60.3)	213.7 (41.2)
*P**		NS	NS	NS	NS
△ TC at week 6, mg/dL					
Mean (SD)†	11.63 (28.75)	−3.93 (36.26)	−17.17 (36.32)	−6.39 (22.95)	3.67 (35.00)
*P**		NS	0.011	0.043	NS
△ TC at week 12, mg/dL					
Mean (SD)‡	2.63 (37.16)	−11.67 (45.53)	−21.50 (36.46)	−8.72 (38.82)	−7.87 (40.54)
*P**		NS	0.05	NS	NS

*Unpaired *t* test, comparison with placebo.
†Change at week 6 = mean (TC week 6 − TC week 0).
‡Change at week 12 = mean (TC week 12 − TC week 0).

was reported to prevent nonenzymatic glycosylation of proteins by competitive inhibition,[23] which consequently leads to an increase in antithrombin III activity.[20] Nonenzymatic glycosylation of antithrombin III decreases its activity, which may lead to abnormal accumulation of fibrin that can result in long-term vascular complications, particularly in patients with diabetes.[24] Moreover, glycosylated LDL-C has diminished ability to be bound and degraded,[25] and thus the inhibition of LDL-C glycosylation by PLP would enhance the catabolism of LDL-C. Vitamin B_6 was also proposed to affect the lipid profile through its capacity to inhibit steroid hormone receptors,[26] especially because steroid hormones (eg, glucocorticoid, testosterone) reported affect the lipid profile.[27,28]

Table V. Plasma HDL-C concentration at baseline and changes after intake of the supplements.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)
Baseline HDL-C, mg/dL					
Mean (SD)	34.8 (6.4)	36.7 (8.7)	40.7 (6.8)	38.5 (6.9)	36.1 (4.5)
*P**		NS	NS	NS	NS
△ HDL-C at week 6, mg/dL					
Mean (SD)†	−0.84 (4.51)	−1.54 (4.32)	−3.94 (5.31)	−1.94 (3.98)	−1.93 (3.49)
*P**		NS	NS	NS	NS
△ HDL-C at week 12, mg/dL					
Mean (SD)‡	−0.47 (4.18)	−2.40 (4.03)	−3.72 (3.83)	−2.94 (4.62)	−1.73 (3.26)
*P**		0.037	0.02	NS	NS

*Unpaired *t* test, comparison with placebo.
†Change at week 6 = mean (HDL-C week 6 − HDL-C week 0).
‡Change at week 12 = mean (HDL-C week 12 − HDL-C week 0).

Table VI. Plasma LDL-C concentration at baseline and changes after intake of the supplements.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)
Baseline LDL-C, mg/dL					
Mean (SD)	112.0 (30.9)	117.5 (30.7)	137.7 (41.2)	123.3 (41.8)	117.7 (27.9)
*P**		NS	NS	NS	NS
△ LDL-C at week 6, mg/dL					
Mean (SD)†	1.11 (16.32)	−3.20 (21.83)	−14.83 (25.72)	−6.17 (16.76)	2.40 (22.81)
*P**		NS	0.029	NS	NS
△ LDL-C at week 12, mg/dL					
Mean (SD)‡	−3.79 (18.86)	−5.67 (24.01)	−12.56 (26.15)	−10.72 (24.33)	−4.07 (29.40)
*P**		NS	NS	NS	NS

*Unpaired *t* test, comparison with placebo.
†Change at week 6 = mean (LDL-C week 6 − LDL-C week 0).
‡Change at week 12 = mean (LDL-C week 12 − LDL-C week 0).

The failure of carnitine supplementation in our study to affect FPG and the lipid profile is consistent with other reports[29,30] in which L-carnitine (1 g/d) supplementation for 6 months failed to affect the glycemic and lipidemic profiles of patients newly diagnosed with diabetes.[29] In addition, diet supplementation of patients with type 2 diabetes using carnitine (3 g/d) for 12 weeks failed to affect LDL-C, HDL-C, glycosylated hemoglobin, or total cholesterol, whereas FPG levels decreased significantly by ~13% when L-carnitine was added to preexisting treatment with hypoglycemic drugs.[30] The low impact of carnitine supplementation on lipid profiles indicates that the effect of vitamin B_6 may not have been related to its capacity to stimulate endogenous carnitine synthesis.[4] This is also supported by the finding that the alteration in lipid profile was not affected by the addition of lysine to vitamin B_6, fur-

Table VII. Fasting plasma glucose (FPG) concentration at baseline and changes after intake of the supplements.

Characteristic	Placebo (n = 19)	Lysine (n = 15)	Vitamin B_6 (n = 18)	Lysine + Vitamin B_6 (n = 18)	Carnitine (n = 15)
Baseline FPG, mg/dL					
Mean (SD)*	116.8 (34.0)	137.1 (56.9)	117.6 (50.7)	108.2 (31.3)	137.9 (54.8)
P†		NS	NS	NS	NS
△ FPG at week 6, mg/dL					
Mean (SD)‡	−1.26 (13.67)	−18.90 (37.50)	−7.56 (29.74)	−3.0 (13.20)	−1.29 (35.22)
P†		NS	NS	NS	NS
△ FPG at week 12, mg/dL					
Mean (SD)§	−4.37 (12.56)	−8.80 (30.60)	−6.56 (28.89)	−3.78 (16.43)	−10.29 (22.90)
P†		NS	NS	NS	NS

*One abnormally high glucose level was excluded.
†Unpaired *t* test, comparison with placebo.
‡Change at week 6 = mean (FPG week 6 – FPG week 0).
§Change at week 12 = mean (FPG week 12 – FPG week 0).

ther indicating that the effect of vitamin B_6 on lipid profiles was not related to its capacity to synthesize carnitine.

Lysine supplementation alone, however, was found to decrease FPG by ~10% in our study, although this did not reach the level of statistical significance. Using a similar dose of lysine for 45 days reportedly decreased postprandial plasma glucose levels in patients with type 2 diabetes by 50 mg/dL.[16] In addition, acute lysine ingestion with glucose was also found to decrease postprandial plasma glucose concentrations.[31] Such a decrease in glucose was attained without any increase in postprandial insulin, indicating an improvement in insulin sensitivity.[19,31] Lysine was reported to improve insulin receptor tyrosine kinase activity in Wistar rats[32] and in monocytes of patients with type 2 diabetes.[22]

CONCLUSIONS

In this preliminary study, vitamin B_6 supplementation in male patients with hypertriglyceridemia reduced the plasma cholesterol fractions (especially total cholesterol and HDL-C). Carnitine supplementation failed to produce any significant changes in the lipid profile.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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