ORIGINAL RESEARCH

Investigation of the effects of *Chlorella vulgaris* as an adjunctive therapy for dyslipidemia: Results of a randomised open-label clinical trial

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Abstract

Aim: *Chlorella vulgaris* is a unicellular green microalga with several pharmacological activities including anti-hyperlipidemic effects. In spite of interesting preclinical findings, the clinical efficacy of *C. vulgaris* in dyslipidemia—whether alone or in combination with statins—has not been clarified. The present study aimed to investigate the impact of supplementation with *C. vulgaris* as an adjunctive therapy to atorvastatin in dyslipidemic subjects.

Methods: In a randomised, open-label clinical trial, 100 dyslipidemic subjects were randomly assigned to: (i) *Chlorella* group (n = 50, dropouts = 24), receiving *C. vulgaris* (600 mg/day) + atorvastatin (20 mg/day) for 8 weeks; or (ii) atorvastatin group (n = 50, dropouts = 13), receiving only atorvastatin (20 mg/day) for 8 weeks. Lipid profile and biomarkers of muscular, hepatic and renal injury were determined at baseline and at the end of the trial.

Results: There were significant reductions in serum total cholesterol ($P < 0.001$), low-density lipoprotein cholesterol ($P < 0.001$) and triglycerides ($P = 0.006$ in *Chlorella* and $P = 0.004$ in atorvastatin group) in both groups. No significant change in serum high-density lipoprotein cholesterol levels was observed in any of the groups. Serum aspartate aminotransferase levels were raised in both *Chlorella* ($P = 0.034$) and atorvastatin ($P = 0.002$) groups, whereas alkaline phosphatase was only elevated in the *Chlorella* group ($P = 0.028$). In comparison with baseline values, no significant change was observed in serum levels of alanine aminotransferase, creatine phosphokinase, creatinine, blood urea nitrogen and fasting blood sugar.

Conclusion: Based on the results, addition of *C. vulgaris* to atorvastatin therapy for 8 weeks does not appear to be associated with an improved control of serum lipid profile.

Key words: atorvastatin, *Chlorella vulgaris*, clinical trial, dyslipidemia, lipid profile.

Introduction

Dyslipidemia is a condition related to the abnormal metabolism of lipoproteins. It may be manifested by elevated circulating concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C) or triglycerides; or decreased concentrations of high-density lipoprotein cholesterol (HDL-C). This disorder is among the major and modifiable risk factors for atherosclerosis and coronary artery disease (CAD) as several studies have reported the relationship between serum total cholesterol levels and coronary risk.[1] Besides, serum cholesterol reduction is considered to be associated with decreased cardiovascular mortality.[2]

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-COA) reductase inhibitors—known as statins—are among the top selling drug classes worldwide, and the first-line pharmacologic therapy for dyslipidemia. Heretofore, several large-scale clinical trials have shown the effectiveness of these drugs in both primary and secondary prevention of CAD.[3–7]

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However, while statins possess effective and well-documented LDL-lowering properties, their effects on other aspects of dyslipidemia, that is hypertriglyceridemia and low HDL-C, are relatively limited.[8] This is especially important when taking into account the fact that a considerable fraction of patients with CAD—and even subjects without CAD—have hypertriglyceridemia and low HDL-C levels.[9] Besides, these features are classified among metabolic syndrome criteria. Therefore, combination therapy is recommended to address multiple lipid profile parameters and optimise dyslipidemia management.[8,10] Nevertheless, co-administration of certain statins with some other lipid-lowering agents has been associated with increased frequency of hepatotoxicity and myotoxicity.[11–13] Therefore, introduction of effective and safe agents, in particular from natural sources, would be highly welcome to reduce the statin dose—and thereby side effects—and improve the efficacy of statins on triglycerides and HDL levels.

Chlorella vulgaris is a unicellular green microalga which has been widely used as a food source and currently present in many commercially marketed dietary supplements.[14,15] This microalga is rich in various types of macro- and micro-nutrients and possesses a variety of pharmacological activities including anti-hyperlipidemic effects.[16–19] However, despite some interesting findings in animal studies, the clinical efficacy of *C. vulgaris*—whether alone or in combination with statins—in the treatment of dyslipidemia is still unexplored. The present study sought to investigate the impact of supplementation with *C. vulgaris* (commercially marketed under trade name Algomed®, Bioprodukte Prof. Steinberg Produktions- und Vertriebs GmbH & Co KG, Klötze, Germany), as an adjunctive therapy to atorvastatin, in a randomised clinical trial. The outcomes included changes in lipid profile parameters (in order to assess the impact of *C. vulgaris* in improving the hypolipidemic effects of atorvastatin) as well as changes in biomarkers of muscular, hepatic and renal injury (in order to assess the impact of *C. vulgaris* in reducing atorvastatin-associated side effects).

Methods

This was a randomised, open-label, clinical trial which was performed between 2009 and 2010 in the Baqiyatallah Hospital (Tehran, Iran) and Ministry of Health-related clinics. Men and women aged between 35 and 80 years who had not taken any lipid-lowering drug during the past 2 months and had elevated cholesterol (total cholesterol > 200 mg/dL or LDL-C > 130 mg/dL) or reduced HDL-C (<35 mg/dL) were included in the study.

Exclusion criteria were the presence of acute coronary syndrome, history of angioplasty or bypass surgery, thyroid, hepatic or renal (including nephrotic syndrome) abnormalities, pregnancy, lactation, intolerance to the prescribed medication for any reason, history of hypersensitivity to HMG-COA reductase inhibitors and concurrent use of medications that might affect on plasma lipids.

One hundred subjects met the eligibility criteria and were randomly assigned to: (i) *Chlorella* group (n = 50), receiving *C. vulgaris* (600 mg/day) + atorvastatin (20 mg/day) for 8 weeks; or (ii) atorvastatin group (n = 50), receiving only atorvastatin (20 mg/day) for 8 weeks.

C. vulgaris powder used in the study was in the form of 300 mg tablets which are commercially available under trade name ALGOMED® (Bioprodukte Prof. Steinberg Produktions- und Vertriebs GmbH & Co KG). The tablets contained 98% *C. vulgaris* powder, 1% separating agent (silicic acid) and 1% plant-based magnesium stearate. The tablets were ~9 mm in diameter and ~300 mg in weight.

Anthropometric parameters (including weight, height and body mass index (BMI)) together with fasted serum lipid profile (including total cholesterol, triglycerides, LDL-C AND HDL-C) and levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase (CPK), fasting blood sugar (FBS), creatinine and blood urea nitrogen (BUN) were measured for participants at baseline and at the end of study using routine laboratory tests. LDL-C was directly measured using commercial kit. Besides, information regarding self or family history of diabetes mellitus, hypertension, angina pectoris, stroke and cardiovascular disease hospitalisation; previous consumption of lipid-lowering drugs; and smoking habit and drug side effects were gathered using questionnaire at baseline and at the end of study.

The study protocol was approved by the Ethics Committee of the Baqiyatallah University of Medical Sciences (Tehran, Iran) and written informed consent was obtained from participants.

Sample size calculation (n = 50 in each group) was performed with an estimated power of 90% and $\alpha = 0.05$ to detect a 25% decrease in serum total cholesterol as there was no previous clinical report on the exact magnitude of effect of *C. vulgaris* on total cholesterol level.

Statistical analyses were performed using SPSS 17 for Windows software (SPSS Inc, Chicago, IL, USA). Values were presented as frequency (%) or mean ± SD. Between-group and within-group comparisons were performed using Mann–Whitney *U*-test and Wilcoxon signed rank test, respectively. Categorical variables were compared using chi-square or Fisher's exact test.

Results

From the 100 patients who were evaluated for the trial, 63 completed the study (n = 27 and 36 for the *Chlorella* and atorvastatin groups, respectively) (Figure 1).

The two groups were not significantly different at baseline regarding age ($P = 0.56$), gender ($P = 0.687$), anthropometric (including weight ($P = 0.842$), height ($P = 0.550$) and BMI ($P = 0.514$)) and the following biochemical parameters: serum triglycerides ($P = 0.207$), HDL-C ($P = 0.887$), ALT ($P = 0.889$), AST ($P = 0.051$), ALP ($P = 0.375$), CPK ($P = 0.913$), creatinine ($P = 0.155$) and BUN ($P = 0.156$). However, baseline values for serum LDL-C ($P < 0.001$), total cholesterol ($P = 0.001$) and FBS ($P = 0.035$) were significantly higher in the *Chlorella* compared with the atorvastatin group. The prevalence of present or past diabetes mellitus

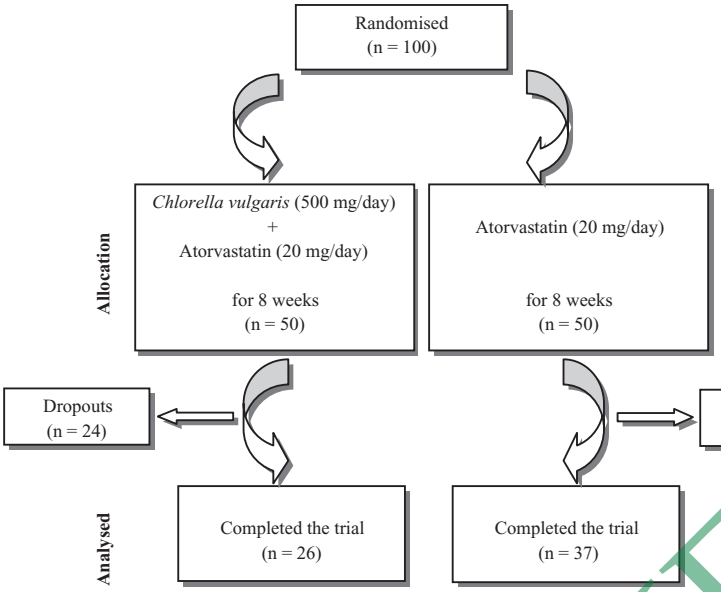

Figure 1 Flowchart of the trial.

(P = 0.059), hypertension (P = 0.941), angina pectoris (P = 0.634), stroke (P = 1.000) and hospitalisation due to cardiovascular diseases (P = 0.469) was not significantly different between the groups (Table 1). In the drug history, consumption of statins and fibrates was reported to be 53.8 and 26.9% in the *Chlorella* group, and 38.9 and 13.9% in the atorvastatin group. Consumption of herbal medications for hyperlipidemia was reported in 2% of the atorvastatin group while there was no report in the *Chlorella* group. Finally, 19.2% of individuals in the *Chlorella* and 41.7% in the atorvastatin group did not remember or had no history of anti-hyperlipidemic drug consumption.

In comparison to the baseline values, there was no significant change regarding weight (P = 0.141) and BMI (P = 0.144) in the *Chlorella* group. In contrast, these parameters were significantly reduced by the end of the trial in the atorvastatin group (P = 0.041 and P = 0.038 for weight and BMI, respectively; Table 1). The magnitude of changes in weight and BMI was significantly larger in the atorvastatin compared with the *Chlorella* group (P = 0.015, Table 2). With respect to FBS, no significant change was observed in any of the groups (P = 0.841 in the *Chlorella* and P = 0.707 in the atorvastatin group, Tables 1 and 2).

There were significant reductions in serum total cholesterol (P < 0.001), LDL-C (P < 0.001) and triglyceride (P = 0.006 in *Chlorella* and P = 0.004 in atorvastatin group) levels in both groups. However, no significant change was observed in serum HDL-C levels, neither in the *Chlorella* (P = 0.155) nor in the atorvastatin group (P = 0.446, Table 1). With respect to the magnitude of changes, there was no significant difference in any of the lipid profile parameters between the groups (Table 2).

Serum CPK levels remained statistically unchanged in both groups by the end of the trial (P = 0.515 in *Chlorella* and P = 0.080 in atorvastatin groups). In contrast, serum AST was raised in both *Chlorella* (P = 0.034) and atorvastatin (P = 0.002) groups. With respect to the serum ALP levels, significant elevations were only observed in the *Chlorella* (P = 0.028) but not in atorvastatin group (P = 0.286). Post-trial values for serum ALT, creatinine and BUN were not significantly different from those at baseline, neither in the *Chlorella* (P = 0.442, 0.300 and 0.295 for ALT, Cr and BUN, respectively) nor in the atorvastatin (P = 0.065, 0.361 and 0.420) group (Table 1). Finally, the magnitude of changes in serum CPK (P = 0.380), AST (P = 0.906), ALT (P = 0.470), creatinine (P = 0.689) and BUN (P = 0.840) was not different between the groups (Table 2).

Discussion

Dyslipidemia is regarded as one of the leading risk factors for CAD. However, it is fortunately among the modifiable coronary risk factors that could be managed to lower the risk of CAD. Although statin drugs are widely used as the first-line pharmacotherapy for dyslipidemia,[20] their effects on triglyceride and HDL-C levels are not as potent as their LDL-lowering activity.[8] This becomes important when considering that hypertriglyceridemia and low HDL-C are among the frequent lipid abnormalities and are associated with coronary risk. In addition, these abnormalities might be responsible for the incidence of CAD in patients with normal LDL-C levels.[9,21,22] On the other hand, as muscular and hepatic side effects of statins appear to be dose related, there are some concerns about the use of high-dose statin therapy. The aforementioned issues open avenues of research for finding novel hypolipidemic agents. These agents could be used as adjuncts in combination with statins to address non-LDL-C lipid profile parameters and reduce the required statin dose. In the present study, we investigated the effects of *C. vulgaris* in combination with atorvastatin on lipid

Table 1 Clinical and biochemical characteristics of *Chlorella* and atorvastatin groups

	Chlorella + atorvastatin group			*Atorvastatin group*		
Parameter	*Pre-trial*	*Post-trial*	*P-value*	*Pre-trial*	*Post-trial*	*P-value*
Age (years)	58.44 ± 6.93	—	—	62.06 ± 10.49	—	—
Female (%)	76.9			69.4		
Cardiovascular disease hospitalisation (%)	33.3	—	—	25.0	—	—
Hypertension (%)	59.3	—	—	58.3	—	—
Diabetes mellitus (%)	85.2	—	—	63.9	—	—
Angina pectoris (%)	33.3	—	—	27.8	—	—
Stroke (%)	0			2.8		
Smoking (%)	7.4	—	—	5.6	—	—
Family history of						
Diabetes mellitus (%)	88.5	—	—	80.6	—	—
Hypertension (%)	66.7	—	—	63.9	—	—
Cardiovascular disease hospitalisation (%)	14.8	—	—	12.1	—	—
Height (cm)	154.52 ± 8.74	—	—	156.6 ± 9.14	—	—
Weight (kg)	69.67 ± 12.21	69.98 ± 12.38	0.14	68.94 ± 11.20	68.50 ± 11.49	0.04
BMI (kg/m^2)	29.19 ± 4.41	29.33 ± 4.50	0.14	28.40 ± 4.54	28.30 ± 4.57	0.04
CPK (U/L)	87.00 ± 31.85	93.67 ± 42.44	0.52	90.59 ± 24.47	110.43 ± 24.51	0.08
ALT (U/L)	20.89 ± 7.91	22.56 ± 6.37	0.44	20.78 ± 8.75	23.08 ± 8.61	0.07
AST (U/L)	14.88 ± 5.64	17.95 ± 5.91	0.03	18.07 ± 5.37	21.25 ± 6.10	0.00
ALP (U/L)	185.00 ± 72.87	211.30 ± 85.23	0.03	206.48 ± 66.83	197.70 ± 53.46	0.29
Total cholesterol (mmol/L)	6.65 ± 0.63*	5.48 ± 0.73	<0.001	5.91 ± 1.00	4.79 ± 0.79	<0.001
Triglycerides (mmol/L)	2.57 ± 0.76	2.16 ± 0.64	0.01	2.27 ± 0.81	1.94 ± 0.64	0.00
LDL-C (mmol/L)	4.06 ± 0.65**	2.97 ± 0.51	<0.001	3.30 ± 0.83	2.54 ± 0.60	<0.001
HDL-C (mmol/L)	1.32 ± 0.26	1.38 ± 0.31	0.16	1.33 ± 0.36	1.30 ± 0.33	0.45
FBS (mmol/L)	10.13 ± 3.21***	10.11 ± 3.20	0.84	8.43 ± 2.52	8.18 ± 2.35	0.71
BUN (mmol/L)	11.61 ± 2.14	12.19 ± 2.09	0.30	10.48 ± 2.69	10.91 ± 2.79	0.42
Cr (μmol/L)	68.95 ± 12.38	71.60 ± 8.84	0.30	75.14 ± 15.91	77.79 ± 8.84	0.36

Values are expressed as mean ± standard deviation.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CPK, creatine phosphokinase; Cr, creatinine; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Significant difference in baseline values between the groups: *$P = 0.001$; **$P < 0.001$; ***$P = 0.035$.

Table 2 Magnitude of change in clinical and biochemical parameters of *Chlorella* and atorvastatin groups

Parameter	*Chlorella + atorvastatin group*	*Atorvastatin group*	*P-value*
Weight (kg)	0.17 ± 0.65	−0.29 ± 0.79	0.02
BMI (kg/m^2)	0.08 ± 0.30	−0.12 ± 0.31	0.02
CPK (U/L)	3.00 ± 37.59	12.71 ± 22.93	0.38
ALT (U/L)	1.19 ± 5.50	2.20 ± 6.03	0.47
AST (U/L)	2.82 ± 4.08	3.14 ± 4.74	0.91
ALP (U/L)	14.10 ± 15.89	5.70 ± 26.76	0.55
Total cholesterol (mmol/L)	−1.17 ± 0.88	−1.12 ± 1.18	0.57
Triglycerides (mmol/L)	−0.40 ± 0.61	−0.33 ± 0.56	0.84
LDL-C (mmol/L)	−1.06 ± 0.33	−0.30 ± 0.37	0.07
HDL-C (mmol/L)	0.03 ± 0.09	−0.01 ± 0.09	0.13
FBS (mmol/L)	−0.02 ± 2.50	−0.25 ± 1.54	0.74
BUN (mmol/L)	0.57 ± 2.58	0.43 ± 2.44	0.84
Cr (μmol/L)	3.54 ± 15.91	2.65 ± 13.26	0.69

Values are expressed as mean ± standard deviation.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CPK, creatine phosphokinase; Cr, creatinine; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

profile parameters as well as biomarkers of hepatic (ALT, AST and ALP), muscular (CPK) and renal (Cr and BUN) damage.

The findings indicated that supplementation with *C. vulgaris* for 8 weeks is not associated with an enhanced control of serum lipid profile parameters nor any significant effect on biomarkers of muscular, hepatic and renal injury. As far as we are aware, this study is among few studies that have evaluated the clinical impact of *C. vulgaris* supplementation on lipid profile. In an earlier animal study, addition of powdered *C. vulgaris* (1%) to a high-cholesterol diet was reported to suppress the increase in total and beta lipoprotein levels, and significantly inhibit the development of aortic atheromatous lesions whereas no inhibitory effect on these parameters was observed for clofibrate as a positive control.[16] In a later study, glycolipid and phospholipid fractions of *C. vulgaris* as well as powdered *Chlorella* were reported to inhibit the elevation of serum lipids in cholesterol-fed rats. Besides, glycolipid and phospholipid fractions increased faecal excretion of steroids.[17] In another study on mice, it was found that addition of *C. vulgaris* to a high-fat diet in mice significantly inhibits the increase of serum triglycerides as well as hepatic content of both triglycerides and total cholesterol. However, no significant effect was observed on serum levels of total cholesterol, HDL-C and ALT.[16] Lee *et al*. also investigated the effects of this microalga on lipid metabolism in high-fat fed Wistar rats and reported that supplementation with *C. vulgaris* is associated with decreased serum and liver concentrations and increased faecal excretions of total lipids, total cholesterol and triglycerides. However, serum ALT, AST and HDL-C levels were not affected by *C. vulgaris* supplementation.[18] Finally, in a recent study by Jeong *et al*. it was reported that hepatic concentrations of triglycerides, but not total lipids and total cholesterol, are reduced in normal and diabetic rats supplemented with *C. vulgaris*. However, serum fasting blood glucose, ALT and AST as well as insulin sensitivity index were not found to be significantly affected by *Chlorella* supplementation.[23] In contrast, 10% *Chlorella* intake was found in another investigation to reduce both fasting glucose concentration and insulin sensitivity in high-fat fed rats.[24]

These hypolipidemic properties of *C. vulgaris* have been hypothesized to be, at least in part, due to the decreased intestinal fat absorption as *C. vulgaris* contains diverse nutritional factors, in particular dietary fibre (~15.6 g/100 g *Chlorella*) which has well-known hypolipidemic effects due to binding to dietary fat and bile acids in the intestine. Besides, *Chlorella* contains even a higher content of niacin (~23.8 mg/100 g *Chlorella*), which is a reputed medication for hyperlipidemia with promising triglyceride-lowering and HDL-C-increasing properties. Omega-3 fatty acids which are found in *Chlorella* may also be responsible for the hypotriglyceridemic effects of this microalga aside from their several other health benefits.[25] In addition to the aforementioned micronutrients, *Chlorella* contains other important constituents, such as dietary antioxidants, which could exert favourable effect in the prevention of cardiovascular disorders. Some ingredients of *C. vulgaris* tablets and their respective amounts have been shown in Table 3.

Table 3 Some ingredients of *Chlorella vulgaris* tablets and their respective amounts

Ingredient	*Quantity*
Fat (g/100 g)	8.65
Protein (g/100 g)	52.0
Carbohydrates (g/100 g)	13.6
Ash (g/100 g)	6.56
Water (g/100 g)	3.63
Dietary fibre (g/100 g)	15.6
Energy (kcal/100 g)	340
Fatty acids	
Saturated fatty acid (g/100 g)	2.16
Monounsaturated fatty acid (g/100 g)	1.69
Polyunsaturated fatty acid (g/100 g)	3.34
Trans-fatty acid (g/100 g)	0.06
ω-*3 Fatty acids*	
Linoleic acid (g/100 g)	1.282
α-Linolenic acid (g/100 g)	1.964
ω-*6 Fatty acids*	
Octodecatetaenoic acid (g/100 g)	0.003
Eicosadienoic acid (g/100 g)	0.011
Arachidonic acid (g/100 g)	0.009
Docosatetraenoic acid (g/100 g)	0.020
Vitamins	
β-Carotene (mg/100 g)	180.8
Vitamin B1 (mg/100 g)	1.5
Vitamin B2 (mg/100 g)	4.8
Vitamin B3 (mg/100 g)	23.8
Vitamin B5 (mg/100 g)	1.3
Vitamin B6 (mg/100 g)	1.7
Vitamin B12 (μg/100 g)	125.9
Vitamin C (mg/100 g)	15.6
Folic acid (μg/100 g)	26.9
Biotin (μg/100 g)	191.6
Para-amino-benzoic acid (mg/100 g)	0.6
Minerals	
Phosphorus (mg/100 g)	959
Potassium (mg/kg)	2 1450
Magnesium (mg/kg)	4425
Calcium (mg/kg)	2710
Iron (mg/kg)	680
Copper (mg/kg)	19.0
Zinc (mg/kg)	54.5
Manganese (mg/kg)	39.5
Iodine (mg/kg)	12.9
Chromium (mg/kg)	0.575
Miscellaneous	
Lutein (mg/100 g)	84.3
Lycopin (mg/100 g)	0.307
Zeaxanthin (mg/100 g)	0.679
Chlorophyll (g/kg)	15.21

Co-administration of atorvastatin and *C. vulgaris* was also assessed for its impact on the serum levels of

biomarkers for muscular, hepatic and renal injury. Supplementation with *Chlorella* did not appear to prevent against elevation of serum AST and ALP. There was no significant difference in the levels of serum CPK as a biomarker of muscular injury, and serum creatinine and BUN as biomarkers of renal function between the groups. Taken together, the present findings do not support a protective effect of *Chlorella* on statin-induced muscle and liver injury.

The difference in the rate of weight and BMI change that was observed between the groups is likely due to the differences in diets and/or physical activity rather than any direct effect from atorvastatin or *C. vulgaris*. According to our dietary records, the frequency of weekly fat consumption in the atorvastatin group during the course of trial was lower compared with baseline, which might have contributed to the observed weight loss in this group. In contrast, the frequency of weekly fat meals was increased in the *Chlorella* group compared with baseline records. However, there has not been any definitive scientific evidence regarding weight gain or weight loss as a side effect of statin therapy, nor has been any strong evidence to show any adverse effect of *C. vulgaris* supplementation on weight. Changes in weight that are seen by statin use mainly pertain to idiosyncratic reactions and are thus very unpredictable.

The results of the current trial should be interpreted with respect to its limitations and pilot nature. First, the dropout rate in the current trial was relatively high and might have caused insufficient power to detect significant differences between the groups. In addition, this study investigated the impact of adjunctive therapy with *C. vulgaris* but the net anti-hyperlipidemic effect of *C. vulgaris* is unclear. Therefore, clarification of the effects of *C. vulgaris* monotherapy on lipid profile and other biochemical parameters would be helpful and recommended to be performed in future trials.

In summary, the results of the current investigation indicated that addition of *C. vulgaris* (600 mg/day) to atorvastatin therapy (20 mg/day) for 8 weeks is not associated with an improved control of serum lipid profile parameters. As in the present study equal doses of atorvastatin were administered to the groups, it remains to be identified whether similar effects on lipid profile would be achieved by combination therapy with *C. vulgaris* and low-dose statin. Hence, future large-scale and placebo-controlled trials using different doses of statins could be helpful for a better assessment of hypolipidemic activity of *C. vulgaris* and its application as an adjunctive therapy to reduce the dose of statins.

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