Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement[1–4]

David Heber, Ian Yip, Judith M Ashley, David A Elashoff, Robert M Elashoff, and Vay Liang W Go

See corresponding editorial on page 175.

ABSTRACT

Background: We examined the cholesterol-lowering effects of a proprietary Chinese red-yeast-rice supplement in an American population consuming a diet similar to the American Heart Association Step I diet using a double-blind, placebo-controlled, prospectively randomized 12-wk controlled trial at a university research center.

Objective: We evaluated the lipid-lowering effects of this red-yeast-rice dietary supplement in US adults separate from effects of diet alone.

Design: Eighty-three healthy subjects (46 men and 37 women aged 34–78 y) with hyperlipidemia [total cholesterol, 5.28–8.74 mmol/L (204–338 mg/dL); LDL cholesterol, 3.31–7.16 mmol/L (128–277 mg/dL); triacylglycerol, 0.62–2.78 mmol/L (55–246 mg/dL); and HDL cholesterol 0.78–2.46 mmol/L (30–95 mg/dL)] who were not being treated with lipid-lowering drugs participated. Subjects were treated with red yeast rice (2.4 g/d) or placebo and instructed to consume a diet providing 30% of energy from fat, <10% from saturated fat, and <300 mg cholesterol daily. Main outcome measures were total cholesterol, total triacylglycerol, and HDL and LDL cholesterol measured at weeks 8, 9, 11, and 12.

Results: Total cholesterol concentrations decreased significantly between baseline and 8 wk in the red-yeast-rice–treated group compared with the placebo-treated group [($\bar{x}$ ± SD) 6.57 ± 0.93 mmol/L (254 ± 36 mg/dL) to 5.38 ± 0.80 mmol/L (208 ± 31 mg/dL); $P <$ 0.001]. LDL cholesterol and total triacylglycerol were also reduced with the supplement. HDL cholesterol did not change significantly.

Conclusions: Red yeast rice significantly reduces total cholesterol, LDL cholesterol, and total triacylglycerol concentrations compared with placebo and provides a new, novel, food-based approach to lowering cholesterol in the general population. *Am J Clin Nutr* 1999;69:231–6.

KEY WORDS Chinese red yeast rice, *Monascus purpureus*, lipid-lowering rice food, HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, dietary supplement, placebo treatment, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, triacylglycerol

INTRODUCTION

Red yeast rice is the fermented product of rice on which red yeast (*Monascus purpureus*) has been grown. The use of red yeast rice in China was first documented in the Tang Dynasty in 800 AD. It has been used to make rice wine, as a food preservative for maintaining the color and taste of fish and meat (1), and for its medicinal properties. A complete and detailed description of its manufacture is found in the ancient Chinese pharmacopoeia, *Ben Cao Gang Mu-Dan Shi Bu Yi*, published during the Ming Dynasty (1368–1644) (2). In this text, red yeast rice is characterized as mild and useful for improving blood circulation. In China, consumption of red yeast rice has been studied in animals and humans and has been found to reduce cholesterol concentrations by 11–32% and triacylglycerol concentrations by 12–19% (3–7). Red yeast rice continues to be a dietary staple in many Asian countries, including China and Japan, with typical consumption ranging from 14 to 55 g · person^{-1} · d^{-1} (0.5 to 2 oz) (8). Red yeast rice has also been used in the Asian American community in the United States since World War II. Reducing cholesterol concentrations was shown, in several large prospective clinical trials, to be useful in the primary and secondary prevention of heart disease and the other complications of atherosclerosis (9–12). The current study was conducted to examine the efficacy and safety of red yeast rice in lowering cholesterol concentrations in an American population consuming a diet similar to the American Heart Association Step I diet. A double-blind, prospective, randomized design was used to attempt to separate the effects of the diet from those of the supplement.

SUBJECTS AND METHODS

This research study was approved by the Institutional Review Board (Human Subject Protection Review Committee) of the

[1] From the Center for Human Nutrition and Division of Clinical Nutrition, the Departments of Medicine and Biomathematics, UCLA School of Medicine, Los Angeles.

[2] Supported by an unrestricted educational grant from Pharmanex, Inc, Simi Valley, CA; the University Medical Research Foundation; and the UCLA Clinical Nutrition Research Unit NIH grant no. CA 42710.

[3] Address reprint requests to D Heber, UCLA Center for Human Nutrition, 900 Veteran Avenue, Room 1-2-217, Los Angeles, CA 90095-1742. E-mail: dheber@med1.medsch.ucla.edu.

[4] D Heber is cochair of the Pharmanex Medical Advisory Board. Pharmanex, Inc, Simi Valley, CA.

Received February 11, 1998.

Accepted for publication September 11, 1998.

University of California, Los Angeles. Procedures followed were in accord with the ethical standards set forth in the Helsinki Declaration of 1975 as revised in 1983. As required by the Human Subject Protection Review Committee, all subjects were told about possible rare side effects of liver and muscle toxicity observed with cholesterol-lowering drugs. All subjects provided written, informed consent to participate. Patients were randomly assigned to the Chinese red-yeast-rice dietary supplement–(Cholestin, Pharmanex, Inc, Simi Valley, CA) and placebo-treated groups.

Subjects

Subjects were recruited with newspaper advertisements and posted announcements. Seven hundred twenty-eight potential participants were interviewed by telephone in a preliminary screening. Of these, a total of 238 were invited to a screening visit, at which a fasting blood sample was taken for a lipid panel. Subjects with LDL cholesterol >4.14 mmol/L and triacylglycerol concentrations <2.94 mmol/L in a screening sample sent to an outside reference laboratory were entered into the run-in phase. Subjects had not been treated previously for hypercholesterolemia and were required to have normal results for liver and renal function tests at baseline. Subjects taking any lipid-regulating drugs, hormone replacement therapy, immunosuppressive agents, drugs known to affect lipid concentrations, or drugs known to be associated with rhabdomyolysis, including erythromycin and cyclosporine, were excluded from the study. Subjects taking insulin or oral hypoglycemic agents or having an endocrine disease known to lead to lipid abnormalities were also excluded. A total of 83 subjects (46 men and 37 women) completed the trial.

Methods

Eligible subjects were asked to return for a screening physical examination and repeat fasting blood drawings on 2 occasions. Blood samples were analyzed in the Biomarker Laboratory of the UCLA Center for Human Nutrition. During a 1-wk run-in phase, placebo capsules were provided to assess compliance with pill-taking. Food-frequency questionnaires (FFQs) were completed before randomization, and subjects were provided with an American Heart Association pamphlet entitled *An Eating Plan for Healthy Americans* to instruct them in the Step I diet (<30% of energy from fat, <10% of energy from saturated fat, and <300 mg cholesterol/d). Subjects were then randomly assigned in a double-blind fashion to receive capsules containing either rice powder placebo or 2.4 g red yeast rice daily. Placebo capsules were designed to resemble the dietary supplement as closely as possible. For the treatment group, fermented red yeast rice was pulverized and 600 mg of this milled preparation was encapsulated in each gelatin capsule under Good Manufacturing Practices conditions (Pharmanex, Inc, Simi Valley, CA). The composition of red yeast rice is shown in **Table 1**.

Dietary counseling was provided at the initiation of the study and was standardized so the placebo and treated groups would receive comparable intervention. Body weight was determined by using a calibrated doctor's scale accurate to 0.1 kg. At 8, 9, 11, and 12 wk, fasting blood samples were drawn for lipid assessment. At 12 wk subjects had a second metabolic panel done for assessment of liver and renal function tests. At baseline and at 8 and 12 wk FFQs, developed and validated by Kristal et al (13), were given to assess dietary intake. The FFQ was self-administered and contained questions about the patients' usual food intake patterns during the 3 mo before the initial and after the last FFQ at 8 and 12 wk.

TABLE 1
Composition of Chinese red-yeast-rice dietary supplement

Component	Percentage by wt
	%
Rice starch	73.4
Fiber	0.8
Protein	5.8
Moisture	3–6
Total natural pigment	<0.33
Ash	<3
Phosphorus (organic phosphorus 0.02%)	0.44
Trace elements[2]	Trace
Total HMG-CoA reductase inhibitors	0.4
Monacolin K	0.2
Monacolin K (hydroxy-acid form)	0.1
Dihydromonacolin	<0.01
Monacolin I	0.03
Monacolin II (hydroxy-acid form)	<0.01
Monacolin III	0.02
Monacolin IV	0.02
Monacolin V	0.02
Monacolin VI	0.01
Fatty acids	
Saturated (palmitic and stearic)	<0.5
Mono- and polyunsaturated such as oleic, linoleic, linolenic, and other fatty acids	<1.5

[1] Data are based on unpublished analyses on file with Pharmanex, Inc, Simi Valley, CA. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.
[2] Calcium, aluminum, iron, manganese, magnesium, copper, and silver.

Plasma cholesterol concentrations were determined by using standard enzymatic methods established in the UCLA Clinical Nutrition Research Unit Biomarker Laboratory (14). Interassay CVs were <4%; intraassay variation was <2%. HDL (α)-cholesterol concentrations were also determined enzymatically after precipitation of apoprotein B–rich lipoproteins with heparin and manganese chloride (15). LDL-cholesterol concentrations were calculated by using the Friedewald equation (16), which assumes that circulating VLDLs consist of 80% triacylglycerols and 20% cholesterol. The laboratory has participated successfully for 7 y in the Centers for Disease Control and Prevention CDC-NHLBI Lipid Standardization Program (laboratory ID no. LSP 266) meeting all standards of accuracy and precision required by the program.

Statistical analysis

The statistical design was double-blind and randomized, with 2 treatments and repeated measures. Eighty-eight white subjects were randomly assigned to 2 treatment groups. Lipid and nutrient variables were measured as follows: lipid data were gathered twice at baseline and at 8, 9, 11, and 12 wk. The 2 baseline measurements were averaged, as were the 8- and 9-wk and the 11- and 12-wk data. The FFQs were analyzed based on the data collected at baseline, 8 wk, and 12 wk. The sample size was obtained as follows: the primary variable was total cholesterol and the sample size was based on a two-tailed *t* test with a significance level of 0.05, a power level of 0.90, and with an anticipated effect size d = difference of means/standard deviation = −0.7. The required

sample size was 44 in each group for a total of 88. The biostatistical coinvestigators prepared the randomization schedule for the first 80 subjects using the random permuted block design. The remaining 8 subjects were randomly assigned by staff using the schedule of the first 8 of the 80 patients described above. The primary endpoint for total cholesterol was the 12-wk mean of each treatment group.

The baseline means of the study characteristics, both primary and secondary, were compared by 2 independent sample *t* tests (17). Treatment means for each secondary variable were compared separately at 8 and 12 wk by using 2 independent sample Student's *t* tests, except that the variables obtained from the FFQs were compared by using Wilcoxon's rank-sum test (18) because their distributions were nonnormal. Pairwise comparisons for each variable between 8 and 12 wk and baseline were carried out by the paired *t* test or Wilcoxon's signed-rank test (19) for each treatment group. Additionally, differences for each primary variable between 8 wk and baseline were compared between treatment groups. Also, these differences between 12 wk and baseline were compared between treatment groups by using the two-sample *t* test.

Analysis of covariance models (17) were obtained for the lipid variables. The covariance models were carried out separately for the lipid measures at 8 and 12 wk. Terms in the covariance included baseline lipid value, treatment group, sex, age, and initial body weight. In addition, to study the relation between weight and change in lipids, we obtained the correlations between change in weight and change in lipid value using the nonparametric correlation method, Kendall's τ (17). A repeated-measures analysis of variance (17) was conducted to compare the time trend curves for each lipid between treatment groups. A P value <0.05 was considered significant.

RESULTS

Subject accrual and retention

Eighty-eight patients were enrolled and randomly assigned to the treatment groups. Of the patients assigned, 83 completed the study, 4 subjects discontinued early, and 1 was dropped for protocol violation. One subject withdrew from the red-yeast-rice–treated group and 3 withdrew from the placebo-treated group. Follow-up visits were conducted within 3 d of the target date.

Baseline characteristics

The important baseline characteristics by treatment are shown in **Tables 2** (lipid variables) and **3** (nutritional and demographic variables). There were no significant differences in the baseline lipid variables and demographic and dietary variables between the treatment and control groups.

Primary outcome measures

The total cholesterol concentration decreased significantly between baseline and 8 wk in the red-yeast-rice–treated group compared with the placebo-treated group ($P < 0.05$). Total cholesterol concentrations at 8 and 12 wk differed significantly ($P < 0.05$) between the 2 groups. At 8 wk, the mean total cholesterol concentration was 5.38 ± 0.80 mmol/L (208 ± 31 mg/dL) in the red-yeast-rice–treated group compared with 6.57 ± 0.93 mmol/L (254 ± 36 mg/dL) in the placebo-treated group. Furthermore, total cholesterol concentrations at both 8 and 12 wk differed significantly from baseline ($P < 0.05$) in the red-yeast-rice–treated group. At 8 wk, every subject in the red-yeast-rice–treated group experienced a reduction in total cholesterol, whereas there was no significant difference in total cholesterol concentration at 8 and 12 wk compared with baseline in the placebo–treated group. The difference between baseline and 12 wk was 1.03 ± 0.54 mmol/L (40 ± 21 mg/dL) in the red-yeast-rice–treated group and 0.13 ± 0.52 mmol/L (5 ± 20 mg/dL) in the placebo-treated group (Table 2).

LDL cholesterol concentrations at 8 and 12 wk differed significantly ($P < 0.001$) between the 2 groups. At 12 wk, the mean LDL-cholesterol concentration in the red-yeast-rice–treated group was 3.49 ± 0.70 mmol/L (135 ± 27 mg/dL) compared with 4.53 ± 0.85 mmol/L (175 ± 33 mg/dL) in the placebo-treated group. Furthermore, LDL-cholesterol concentrations at 8 and 12 wk within the red-yeast-rice–treated group differed significantly ($P < 0.001$) from baseline. At 8 wk, all but one of the red-yeast-rice–treated subjects experienced a drop in LDL cholesterol. On the other hand, in the placebo-treated group there was no significant difference between baseline and 8 wk or between baseline and 12 wk. The difference in LDL-cholesterol concentrations in the red-yeast-rice–treated group between baseline and 12 wk was 1.01 ± 0.49 mmol/L (39 ± 19 mg/dL) compared with 0.13 ± 0.57 mmol/L (5 ± 22 mg/dL) in the placebo-treated group.

Triacylglycerol concentrations at 8 and 12 wk differed significantly ($P = 0.05$ and $P = 0.05$, respectively) between the 2 groups. At 12 wk, mean triacylglycerol concentrations in the red-yeast-rice–treated group were 1.4 ± 0.5 mmol/L (124 ± 44 mg/dL) compared with 1.65 ± 0.53 mmol/L (146 ± 47 mg/dL) in the placebo-treated group. Mean triacylglycerol concentrations within the red-yeast-rice–treated group differed from baseline at 8 wk ($P = 0.05$) but not at 12 wk ($P = 0.054$). On the other hand, in the placebo-treated group there was no significant difference

TABLE 2
Lipid concentrations of hyperlipidemic subjects receiving 2.4 g red yeast rice in capsules (treatment) or rice powder placebo (control) supplements daily[1]

	Treatment group (n = 42)			Control group (n = 41)		
	Baseline	Week 8	Week 12	Baseline	Week 8	Week 12
	mmol/L			*mmol/L*		
Triacylglycerols	1.50 ± 0.54	1.33 ± 0.46[2,3]	1.40 ± 0.50[2]	1.61 ± 0.52	1.60 ± 0.59	1.65 ± 0.53
Total cholesterol	6.47 ± 0.78	5.38 ± 0.80[2,3]	5.43 ± 0.80[2,3]	6.59 ± 0.75	6.57 ± 0.93	6.47 ± 0.93
HDL cholesterol	1.29 ± 0.34	1.29 ± 0.34	1.29 ± 0.36	1.19 ± 0.26	1.19 ± 0.26	1.19 ± 0.28
LDL cholesterol	4.47 ± 0.70	3.47 ± 0.70[2,3]	3.49 ± 0.70[2,3]	4.65 ± 0.78	4.63 ± 0.83	4.53 ± 0.85

[1] $\bar{x}$ ± SD. Conversion factor to mg/dL for triacylglycerols, 0.01129; for cholesterol, 0.02586.
[2] Significantly different from baseline, $P < 0.05$.
[3] Significantly different from control group at the same week, $P < 0.05$.

TABLE 3
Demographic and dietary characteristics of subjects[1]

	Treatment group (n = 42; 24 M, 18 F)			Control group (n = 41; 22 M, 19 F)		
	Baseline	Week 8	Week 12	Baseline	Week 8	Week 12
Intake						
Total energy (kJ)[2]	6611 ± 2134 (1580 ± 510)	6443 ± 2218 (1540 ± 530)	5607 ± 2050[3] (1340 ± 490)	7448 ± 3849 (1780 ± 920)	6987 ± 2887 (1670 ± 690)	6694 ± 3012 (1600 ± 720)
Total fat (g/d)	55 ± 26	54 ± 26	44 ± 21[3,4]	66 ± 46	60 ± 40	59 ± 37
Saturated fat (g/d)	19 ± 10	19 ± 11	15 ± 8[3]	23 ± 18	20 ± 15	20 ± 14
Monounsaturated fat (g/d)	20 ± 10	20 ± 10	16 ± 8[3]	24 ± 17	22 ± 15	21 ± 14
Polyunsaturated fat (g/d)	11 ± 5	11 ± 6	9 ± 5[4]	14 ± 9	13 ± 9	13 ± 8
Cholesterol (mg/d)	202 ± 161	190 ± 116	154 ± 70	241 ± 194	214 ± 146	224 ± 173
Fiber (g/d)	16 ± 6	16 ± 6	15 ± 6[3]	17 ± 7	17 ± 10	15 ± 8
Weight (kg)[5]	363 ± 73 (165 ± 33)		361 ± 68 (164 ± 31)	370 ± 75 (168 ± 34)		370 ± 75 (168 ± 34)
Body mass index (kg/m^2)	27 ± 6		27 ± 6	27 ± 5		27 ± 5

[1] $\bar{x}$ ± SD. Age of treatment group, 62 ± 8 y; age of control group, 61 ± 10 y.
[2] Kilocalories in parentheses.
[3] Significantly different from baseline, $P < 0.05$.
[4] Significantly different from control group at same week, $P < 0.05$.
[5] Pounds in parentheses.

between baseline and 8 wk or baseline and 12 wk. The difference between baseline and 12 wk in the red-yeast-rice–treated group was 0.10 ± 0.34 mmol/L (9 ± 30 mg/dL) and in the placebo-treated group was −0.03 ± 0.41 mmol/L (−3 ± 36 mg/dL).

HDL-cholesterol concentrations did not differ significantly within or between groups at baseline, 8 wk, or 12 wk.

Multiple regression analyses were carried out for each of the 4 lipids measured. In each case, the lipid measurement at 12 wk was the outcome variable. Each regression model examined the effects of baseline lipid, sex, age, treatment group, and initial weight. We obtained the following results. For total cholesterol, baseline total cholesterol and treatment group were significantly correlated with total cholesterol values at 12 wk ($P < 0.001$ for both). The coefficient for baseline total cholesterol is near 1.0, indicating that the change scores are a valid way of comparing the groups. For triacylglycerol, baseline triacylglycerol and treatment group were significantly correlated with triacylglycerol concentration at 12 wk ($P < 0.001$ and $P = 0.05$, respectively). For LDL cholesterol, baseline LDL and treatment group were significantly correlated with LDL-cholesterol concentration at 12 wk ($P < 0.001$ for both). A repeated measures analysis of variance showed a significant treatment effect for red yeast rice compared with placebo.

Nutrition variables

Comparisons within and between study groups at baseline, 8 wk, and 12 wk for total energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and fiber are shown in Table 3. There were no significant differences in dietary intake within or between groups at 8 wk. Blood lipid differences between the red-yeast-rice–treated and placebo-treated groups were already evident at a time (8 wk) when there were no differences in dietary intake. Differences in dietary intake cannot, therefore, account for the observed decrease in cholesterol concentrations. Furthermore, there were no differences in body weight between or within groups at any time. In addition, when using Kendall's τ test, there was no significant correlation between changes in weight lipid changes, eliminating weight change as an explanation for the observed changes in lipid concentrations. At 12 wk, the treatment group reported reduced intake of total energy, saturated fat, monounsaturated fat, and fiber compared with baseline, but not when compared with the placebo-treated group. Reported total fat intake and polyunsaturated fat intake were lower than reported at baseline, as well as when compared with the placebo-treated group.

Safety data

There were no serious adverse effects in any of the 88 subjects randomly assigned. In the placebo-treated group, 3 subjects reported minor adverse effects, including *1*) development of a rash that responded to prednisone and antihistamine, *2*) headaches, and *3*) concurrent development of pneumonia during the study. There were no reported adverse events in the red-yeast-rice–treated group, except for 1 subject who reported an intercurrent hospitalization for musculoskeletal chest pain at his 12-wk visit. He continued taking the dietary supplement while hospitalized and had a normal results for an electrocardiogram stress treadmill test performed by his outside physician. His chest pain resolved and was not related to the dietary supplement.

Liver function indicators at baseline and 12 wk are shown in **Table 4**. There were no significant differences between treatment groups at baseline or 12 wk. Within groups, urea nitrogen and γ-glutamyltranspeptidase values differed significantly between baseline and 12 wk. Both were lower at 12 wk than at baseline. There were no abnormal liver or renal function test results at any time for any subject under study.

TABLE 4
Liver function indicators of subjects[1]

	Treatment group (n = 42)		Control group (n = 41)	
	Baseline	Week 12	Baseline	Week 12
Alanine aminotransferase (U/L)	22 ± 9	20 ± 8	21 ± 9	21 ± 11
Aspartate aminotransferase (U/L)	24 ± 5	23 ± 6	22 ± 6	22 ± 6
Urea nitrogen (mmol/L)	6 ± 1	5 ± 1[2]	6 ± 1	6 ± 1
γ-Glutamyltranspeptidase (U/L)	27 ± 18	23 ± 19[2]	23 ± 13	21 ± 11
Lactate dehydrogenase (U/L)	155 ± 25	152 ± 23	158 ± 28	152 ± 19

[1] $\bar{x}$ ± SD.
[2] Significantly different from baseline, $P < 0.05$.

DISCUSSION

In this double-blind, randomized, placebo-controlled prospective study, red yeast rice significantly reduced cholesterol concentrations, beyond effects that could be accounted for by diet alone, and without significant adverse effects. The subjects in this study were instructed in a diet recommended as part of the National Cholesterol Education Program. There are no perfect ways to monitor diet, but the FFQ selected is a validated and accepted tool for this purpose and has been used in other dietary intervention studies (13) and monitors any systematic changes that may have occurred. The usual instructions given to patients are designed to test whether there is a change in cholesterol concentrations with diet alone. Failing this, medications are prescribed to lower cholesterol.

In 1979, Endo (20) discovered that a strain of *Monascus* yeast naturally produced a substance that inhibits cholesterol synthesis, which he named monacolin K (also known as mevinolin and lovastatin), as well as a family of 8 monacolin-related substances with the ability to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. In addition to the inhibitors of HMG-CoA reductase, red yeast rice has been found to contain sterols (β-sitosterol, campesterol, stigmasterol, and sapogenin), isoflavones and isoflavone glycosides, and monounsaturated fatty acids (*see* Table 1). The quantities of the family of inhibitors of HMG-CoA reductase contained in red yeast rice are inadequate to explain the magnitude of the lowering of cholesterol observed in this study by comparison with evaluations of lovastatin (21). The monacolin K content is only 0.2%, or ≈5 mg. Therefore, 5 mg is the relevant comparison to 20–40 mg lovastatin. At this concentration, the mixture of monacolins and other substances present in the red yeast rice may have some effect on cholesterol biosynthesis not explained by the monacolin K content. The effect is unlikely to be due solely to a single species of monacolin, but rather to result from a combination of actions of monacolins and other substances in the red yeast rice.

Extensive animal studies of red-yeast-rice extracts have been conducted. In rabbits, one extract (Xuezhikang) lowered cholesterol concentrations by 44% and 59% at doses of 0.4 and 0.8 mg/kg, respectively (3). In an acute toxicity study in mice, there were no toxic effects noted when a single dose of the extract was administered at 533 times the typical human dose (4). Rats were also treated with doses of 5.0 $g \cdot kg^{-1} \cdot d^{-1}$ for 90 d with no evidence of toxicity on histopathologic examination or in biochemical liver function tests (alanine aminotransferase and aspartate aminotransferase) (5). This corresponds to a dose roughly 50 times that used in humans.

Studies in humans have been conducted in China with both more and less concentrated extracts of the red yeast rice than in our red-yeast-rice–treated group. In 324 hypercholesterolemic subjects treated with Xuezhikang (1.2 g/d containing 13.5 mg total monacolins) for 8 wk, serum cholesterol concentrations decreased by 23%, triacylglycerols decreased by 36.5%, and HDL-cholesterol concentrations increased by 19.6%. Two to 4 wk before the initiation of this study, subjects were instructed to cease taking all medications and were provided with dietary counseling (6). In a second study, an earlier version of the red-yeast-rice supplement containing 10–13 mg total monacolins was given to 101 hypercholesterolemic subjects. Total cholesterol decreased by 19.5% and triacylglycerol decreased by 36.1% in the treated group. HDL-cholesterol concentrations increased by 16.7% in this study (7). These and other Chinese studies were similar to this study in showing a marked effect of the constituents of this dietary supplement on cholesterol concentrations. However, there were differences in the ethnicity and serum lipid concentrations of the populations studied. Furthermore, a rice placebo was used in the present study in a double-blind fashion, whereas the Chinese studies used different natural preparations in the comparison group rather than a matched placebo capsule.

The benefits of statin drugs on the primary prevention of heart disease (10) and in the secondary prevention of recurrent heart disease (9, 11) have been shown in several large, prospective clinical trials. These studies have increased interest in the use of statins for heart disease prevention, such as for individuals with hypercholesterolemia and modest cholesterol elevations. Although it is acknowledged that side effects with statins are rare and dose related, there are data indicating that some statins may cause liver function abnormalites and, under certain circumstances, rhabdomyolysis (19).

A clinical trial in 5608 men and 997 women with average cholesterol concentrations showed that lovastatin reduced the risk of a first acute major coronary event (22). The authors suggested a "need for reassessment of the national Cholesterol Education Program guidelines regarding pharmacological intervention." However, an accompanying editorial raised concerns about the economic impact of the use of cholesterol-lowering drugs by the general population with average cholesterol concentrations (23). The currently available Chinese red yeast rice preparation used in the present study costs $20–30/mo, whereas cholesterol-lowering drugs cost $120–300/mo, with an average cost of $187/mo (24). When considering a population-based public health approach to lowering cholesterol and preventing coronary artery disease, the lower cost of the red-yeast-rice dietary supplement compared with prescription drugs could provide a new and novel approach for the maintenance of healthier cholesterol concentrations.

This study was an important first step in establishing that the observed effects of red yeast rice in China were not due to diet alone but could be clearly related to this Chinese red-yeast-rice dietary supplement in a placebo-controlled, randomized trial. This study also established the need for a study on the long-term safety and efficacy of this supplement in a larger population. The effects observed on triacylglycerol concentrations and HDL-cholesterol concentrations in the Chinese studies also need to be examined in future studies by using carefully controlled diets in appropriately selected populations.

REFERENCES

1. Stuart MD. Chinese materia medica—vegetable kingdom. Taipai, Republic of China: Southern Materials Center, Inc, 1979.
2. Ying Sing S. T'ien Jung K'ai Wu—Chinese technology in the seventeenth century. Sun E-T and Sun S-C, transl. London: Pennsylvania State University Press, 1966;291–4.
3. Zhu Y, Li CL, Wang YY. Effects of Xuezhikang on blood lipids and lipoprotein concentrations of rabbits and quails with hyperlipidemia. Chin J Pharmacol 1995;30:4–8.
4. Li CL, Li YF, Hou ZL. Xuezhikang toxicity study. Bull Chinese Pharmacol Soc 1995;12:3.
5. Zhu Y, Li CL, Wang YY, Zhu JS, Chang J, Kritchevsky D. *Monascus purpureus* (red yeast): a natural product that lowers blood cholesterol in animal models of hypercholesterolemia. Nutr Res 1998;18:71–81.
6. Wang J, Su M, Lu Z, et al. Clinical trial of extract of *Monascus pur-*

pureus (red yeast) in the treatment of hyperlipidemia. Chin J Exp Ther Prep Chin Med 1995;12:1–5.
7. Shen Z, Yu P, Su M, et al. A prospective study on Zhitai capsule in the treatment of primary hyperlipidemia. Nat Med J China 1996;76: 156–7.
8. Mei F. Red yeast flavored duck. In: Fang Mei's illustrated cookbook of regional Chinese cuisine. Guangxi, China: Guangxi National Press, 1990;177–88.
9. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
10. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.
11. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
12. Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results. JAMA 1984;251:351–74.
13. Kristal AR, Shattuck AL, Henry HJ. Patterns of dietary behavior associated with selecting diets low in fat: Reliability and validity of a behavioral approach to dietary assessment. J Am Diet Assoc 1990; 90:214–20.
14. Lipid Research Clinics Program. Manual of laboratory operations. Volume I. Lipid and lipoprotein analysis. Bethesda, MD: National Heart Lung Institute, National Institutes of Health, 1974;1:499–502.
15. Warnick GR, Albers JJ. A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high-density lipoprotein cholesterol. J Lipid Res 1978;19:65–73.
16. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
17. Fisher LD, Van Belle G. Biostatistics: a methodology for the health sciences. New York: John Wiley & Sons, Inc, 1993.
18. Wilcoxon F. Individual comparisons by ranking methods. Biometrics Bull 1945;1:80–3.
19. Lehmann EL. Nonparametrics: statistical methods based on ranks. San Francisco: Holden-Day, 1975.
20. Endo A. Monacolin K, a new hypocholesterolemic agent produced by a *Monascus* species. J Antibiot (Tokyo) 1979;32:852–4.
21. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-efficacy and safety follow-up. Am J Cardiol 1994;74:667–73.
22. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with Lovastatin in men and women with average cholesterol levels. JAMA 1998;279:1615–22.
23. Pearson TA. Commentary: lipid-lowering therapy in low-risk patients. JAMA 1998;279:1659–61.
24. Perreault S, Hamilton VH, Lavoie F, Grover S. Treating hyperlipidemia for the primary prevention of coronary disease: are higher doses of lovostatin cost-effective? Arch Intern Med 1998;158: 375–81.

Low-fat, high-sugar diet and lipoprotein profiles

Dear Sir:

The recent paper by Dreon et al (1) reported that a very-low-fat diet is not associated with improved lipoprotein profiles in men. The dietary nutrient data presented in their Table 1 show that at the same time that the percentage of energy from fat decreased from 31.8% to 10.4%, that from carbohydrates increased from 52.1% to 75.7%, with half of the carbohydrate energy derived from simple sugars. Only near the end of the paper did Dreon et al mention that potential differences in metabolic effects of complex compared with simple sugars need to be considered.

It has long been known that simple sugars generate much more triacylglycerol than do complex carbohydrates (2), as well as less HDL cholesterol (3–5). More recently, it has been recognized that triacylglycerols are a risk factor for ischemic heart disease (IHD; 6).

Another way of assessing the effect of fat and carbohydrates on IHD is to consider the dietary profiles of several countries along with their IHD mortality rates. Presented in **Table 1** are consumer food supply data that were obtained from the Food and Agriculture Organization (7) and 1986 IHD mortality rates that were obtained from the World Health Organization (8). The simple sugars category is approximated by sweeteners, lactose, and 50% of the fruit energy.

What is readily apparent from Table 1 is that there is no relation between the fraction of the diet derived from total carbohydrates and IHD mortality rates, and little relation between grams of fat and IHD mortality rates. However, there is a hint that there is a relation between the fraction of the diet derived from simple carbohydrates and IHD mortality rates. In the data presented in Table 1, lactose has the highest correlation with IHD mortality. The linear regression results for lactose are $r = 0.97$ ($P = 0.006$) for males and $r = 0.95$ ($P = 0.014$) for females. Lactose has long been associated with IHD mortality rates for men and older women according to the ecologic approach (9, 10), although no case-control or cohort studies have been conducted to confirm this finding. In addition, sweeteners have recently been associated with IHD mortality for women between the ages of 35 and 64 y (10).

William B Grant

12 Sir Francis Wyatt Place
Newport News, VA 23606-3660
E-mail: Wbgrant@norfolk.infi.net

TABLE 1
Dietary components of national diets for 1983 and ischemic heart disease (IHD) mortality rates for 1986[1]

	Cuba	Finland	Hong Kong	Japan	United States
Energy					
(kJ)	13 110	12 660	11 660	11 730	13 720
(kcal)	3133	3026	2786	2803	3279
Fat (g)	81.9	129.6	106.4	73	135.7
Carbohydrates					
Total					
(kJ)	8786	6217	5460	7494	6891
(kcal)	2100	1486	1305	1791	1647
(% of energy)	67	49	47	64	50
Complex (% of energy)	41	32	35	51	29
Simple[2]					
(kJ)	2770 + 427 + 276	1480 + 494 + 322	1030 + 150 + 255	1280 + 134 + 188	2350 + 347 + 381
(kcal)	663 + 102 + 40	354 + 118 + 48	247 + 36 + 38	305 + 32 + 28	561 + 83 + 58
(% of energy)	27	18	12	14	22
IHD mortality rate (cases/100 000)					
Men > 75 y of age	2857	3398	1117	679	2958
Women > 75 y of age	2752	2402	767	515	2269

[1] Food supply data from the Food and Agriculture Organization (7); IHD mortality rates from the World Health Organization (8).
[2] Includes sweeteners, lactose, and estimated sugar in fruit.

REFERENCES

1. Dreon DM, Fernstrom HA, Williams PT, Krauss RM. A very-low-fat diet is not associated with improved lipoprotein profiles in men with a predominance of large, low-density lipoproteins. Am J Clin Nutr 1999;69:411–8.
2. Reiser S. Health implications of food carbohydrates: heart disease and diabetes. In: Lineback DR, Inglett GE, eds. Food carbohydrates. Westport, CT: AVI Publishing Co, Inc, 1982;11:170–205.
3. Albrink MJ, Ullrich MD. Interaction of dietary sucrose and fiber on serum lipids in healthy young men fed high carbohydrate diets. Am J Clin Nutr 1986;43:419–28.
4. Yudkin J, Eisa O, Kang SS, Meraji S, Bruckdorfer KR. Dietary sucrose affects plasma high density lipoprotein cholesterol concentration in young men. Ann Nutr Metab 1986;30:261–6.
5. Archer SL, Liu K, Dyer AR, et al. Relationship between changes in dietary sucrose and high density lipoprotein cholesterol: The CARDIA Study. Ann Epidemiol 1998;8:433–8.
6. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease. Circulation 1998;97:1029–36.
7. Food and Agriculture Organization of the United Nations. Food balance sheets. Rome: FAO, 1996.
8. World Health Organization. World health statistics annual. Geneva: WHO, 1992.
9. Segall JJ. Epidemiological evidence for the link between dietary lactose and atherosclerosis. In: Colaco CA, ed. The glycation hypothesis of atherosclerosis. Austin, TX: Landes Bioscience, 1997:185–209.
10. Grant WB. Milk and other dietary influences on coronary heart disease. Altern Med Rev 1998;3:281–94.

Coronary artery disease risk factors in south Asian and American premenopausal women

Dear Sir:

We enjoyed very much the most interesting work of Kamath et al (1) on the cardiovascular disease risk factors of south Asian and American premenopausal women. Their study raises several important questions. It is not clear how many subjects were consuming *trans* fatty acids and Indian ghee nor how much of these substances were being consumed. These substances are known to have adverse effects on coronary artery disease (2). *trans* Fatty acids also cause increases in lipoprotein(a) [Lp(a)] (3) and n−3 fatty acids from fish oil can decrease Lp(a) concentrations. It would be interesting to know the intake of n−3 fatty acids in the 3 groups. It is not clear why Indians and Pakistanis had lower plasma insulin concentrations than the Americans, despite having greater abdominal fat and lower physical activity levels than the Americans, factors which are known to predispose hyperinsulinemia (4).

People of south Asian origin are accustomed to consuming low-fat diets (<20% of energy/d) and having physically demanding occupations (5). In one population survey (6, 7), of 3257 Indian women aged 25–64 y we found that coronary artery disease risk factors, including dietary fat intake, were significantly greater in the higher social classes 1 and 2 than in the lower social classes 3–5. There were no significant differences in fruit and vegetable intakes between social classes, indicating that dietary fat intake and physical inactivity may be important determinants of coronary artery disease risk in people of south Asian origin. One cross-sectional survey of 515 rural and 595 urban subjects showed that plasma concentrations of HDL were comparable in both men (1.18 ± 0.13 and 1.21 ± 0.22 mmol/L, respectively) and women (1.21 ± 0.16 and 1.28 ± 0.24 mmol/L, respectively) (8). However, 2-h plasma insulin was significantly higher in urban men and women than in rural subjects, indicating that it may be influenced by environmental factors (**Table 1**). Plasma concentrations of total cholesterol and triacylglycerols were significantly greater in urban than in rural subjects (Table 1). In a more recent study, plasma zinc concentrations and zinc intakes were inversely associated with high Lp(a) concentrations, indicating that poor zinc intake may cause increased Lp(a) concentrations more in urban than in rural subjects (9). In a randomized, single-blind controlled trial in 463 patients, we showed that a fat-reduced diet plus moderate physical activity decreased plasma insulin and associated disturbances, resulting in significant reductions in cardiac events (10).

Ram B Singh

Heart Research Laboratory
Medical Hospital and Research Centre
Civil Lines
Moradabad 10 (UP) 244001
India
E-mail: rbsingh@nde.vsnl.net.in or icn@nde.vsnl.net.in

REFERENCES

1. Kamath SK, Hussain EA, Amin D, et al. Cardiovascular disease risk factors in 2 distinct ethnic groups: Indian and Pakistani compared with American premenopausal women. Am J Clin Nutr 1999;69:621–31.
2. Singh RB, Niaz MA, Ghosh S, et al. Association of *trans* fatty acids (vegetable ghee) and clarified butter (Indian ghee) intake with higher risk of coronary artery disease in rural and urban populations with low fat consumption. Int J Cardiol 1996;56:289–98.

TABLE 1
Coronary artery disease risk factors in rural and urban subjects[1]

	Men		Women	
	Rural (n = 280)	Urban (n = 314)	Rural (n = 235)	Urban (n = 281)
Total cholesterol (mmol/L)	4.38 ± 1.2	5.82 ± 1.4[2]	4.32 ± 1.1	5.71 ± 1.2[2]
HDL cholesterol (mmol/L)	1.18 ± 0.13	1.21 ± 0.22	1.21 ± 0.16	1.28 ± 0.24
Triacylglycerol (mmol/L)	1.46 ± 0.55	1.72 ± 0.62[2]	1.44 ± 0.53	1.71 ± 0.61[2]
2-h Plasma insulin (pmol/L)	154.6 ± 36.6	315.7 ± 52.4[3]	152.0 ± 31.4	296.0 ± 47.8[3]

[1] $\bar{x}$ ± SD. Data from reference 8.
[2,3] Significantly different from rural group: [2] $P < 0.01$, [3] $P < 0.05$.

3. Mensink R, Zock PL, Katan MB, Hornstra G. Effect of dietary *cis* and *trans* fatty acids on serum lipoprotein(a) levels in humans. J Lipid Res 1992;33:1493–501.
4. Singh RB, Rastogi SS, Niaz MA, Postiglione A. Association of central obesity and insulin resistance with high prevalence of diabetes and cardiovascular disease in an elderly population with low fat intake and lower than normal prevalence of obesity: the Indian paradox. Coron Artery Dis 1998;9:559–64.
5. Singh RB, Niaz MA, Ghosh S, et al. Low fat intake and coronary artery disease in a population with higher prevalence of coronary artery disease: the Indian paradox. J Am Coll Nutr 1998;17:342–50.
6. Singh RB, Beegom R, Mehta AS, et al. Social class, coronary risk factors and undernutrition, a double burden of diseases in women during transtition in five Indian cities. Int J Cardiol 1999;69:139–47.
7. Singh RB, Verma SP, Niaz MA. Social class and coronary artery disease in India. Lancet 1999;353:154–5.
8. Singh RB, Niaz MA, Rastogi V, et al. Prevalence of coronary artery disease and coronary risk factors in the elderly rural and urban populations of north India. Cardiol Elderly 1996;4: 111–7.
9. Singh RB, Niaz MA, Rastogi SS, et al. Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of north India. J Am Coll Nutr 1998;17:561–70.
10. Singh RB, Rastogi V, Rastogi SS, et al. Effect of diet and moderate exercise on central obesity and associated disturbances, myocardial infarction and mortality in patients with and without coronary artery disease. J Am Coll Nutr 1996;15:592–601.

Erratum

Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VLW. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. Am J Clin Nutr 1999;69:231–6.

In Table 3, weight values for subjects were calculated incorrectly. Under the treatment group heading, the weight ($\bar{x}$ ± SD, in kg) at baseline and week 12 should read 75 ± 15 and 74.5 ± 14, respectively; under the control group heading, the weight should read 76 ± 15 at both baseline and week 12.