Background: Increased serum lipoprotein(a) [Lp(a)] and high-sensitivity C-reactive protein (hsCRP) concentrations are independent risk factors for coronary heart disease (CHD). Xuezhikang, an extract of cholestin, effectively lowers fasting cholesterol and triglyceride concentrations. We studied whether xuezhikang lowered Lp(a) and hsCRP concentrations.

Methods: We randomly divided 60 CHD patients into two groups to receive xuezhikang (1200 mg daily) or placebo for 6 weeks. The fasting hsCRP concentration and the postprandial changes of serum lipid concentrations at 2, 4, and 6 h after a high-fat meal (800 calories; 50 g of fat) were measured before and after the 6-week protocol.

Results: The two groups had similar baseline fasting lipid and hsCRP concentrations. The postprandial triglyceride and Lp(a) concentrations were significantly increased (P < 0.05). After 6 weeks, the fasting and postprandial lipid concentrations decreased significantly in the xuezhikang group, accompanied by a significant reduction in fasting hsCRP concentration (P < 0.001). The placebo group had no significant change in lipid concentrations, whereas the fasting serum hsCRP concentration was reduced significantly (P < 0.05). The reduction in hsCRP was closely related to the changes in fasting Lp(a) concentration (r = 0.402; P < 0.05) and triglyceride area under the curve (r = 0.441; P < 0.001).

Conclusions: Xuezhikang effectively decreased fasting Lp(a) and postprandial triglyceride concentrations, which were associated with reductions of fasting hsCRP concentrations in CHD patients.

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The postprandial state is critical in atherogenesis. Abnormal metabolism of postprandial triglyceride-rich lipoproteins (TRLs) has been reported in patients with coronary heart disease (CHD) or risk factors (1). An association between postprandial increases in serum lipoprotein(a) [Lp(a)] concentrations and hypertriglyceridemia after fat intake has been observed in some studies (2, 3), although data from other studies were conflicting (4, 5). Increased plasma Lp(a) has been shown to be a risk factor for atherosclerosis (6). Lp(a) resembles a LDL particle, but with the addition of apolipoprotein(a) [apo(a)], which is similar to plasminogen; therefore, Lp(a) is a link between atherosclerosis and thrombosis. Moreover, Lp(a) may be involved in atherogenesis through an inflammatory mechanism. Recent evidence has shown that Lp(a) is correlated with inflammatory factors (7–11), including C-reactive protein (CRP).

Increased CRP is an important predictor of cardiovascular events, independent of traditional risk factors (12). High-sensitivity CRP (hsCRP) assays are needed for the measurement of CRP concentrations to predict the risk of acute coronary events. Increased fasting hsCRP concentrations have been reported in patients with CHD and equivalent risk factors compared with controls (13–15). Results from an increasing number of studies suggest that CRP is not only a novel factor of cardiovascular risk (16, 17) but also a target or end-point for prevention and treatment of CHD in addition to lipid control (18).

The effect of hydroxymethylglutaryl-CoA reductase inhibitors (statins) on Lp(a) concentration is controversial. Most studies have shown that statins decrease plasma LDL-cholesterol (LDL-C) and CRP concentrations but not Lp(a) (19–21). Xuezhikang is an extract of cholestin that
has been approved by the Food and Drug Administration as a Chinese red-yeast rice dietary supplement. It contains a family of monacolin-related substances, one of which is a naturally occurringLovastatin, in addition to unsaturated fatty acids and other substances (22, 23). Xuezhikang has been reported to markedly lower fasting total cholesterol and triglyceride concentrations (22–24), but little attention has been directed to a possible effect on serum hsCRP and Lp(a) concentrations. This study was designed to explore the changes in serum Lp(a) concentrations after a high-fat meal and the effects of xuezhikang on hsCRP and Lp(a) concentrations in CHD patients before and after a 6-week treatment with xuezhikang.

**Participants and Methods**

**PARTICIPANTS**

The study included 60 CHD patients who were admitted to our hospital between October 2001 and June 2002. CHD was diagnosed as a history of myocardial infarction and/or angiographically confirmed coronary atherosclerosis in patients with angina pectoris. Their dietary habits, including food content and amounts, and daily activity were investigated by use of the Nutrition and Health Questionnaire. The research protocol was approved by the Ethics Committee of Central South University. All participants gave fully informed consent before study entry.

All patients were in New York Heart Association class I or II and had no chest pain within the previous month. No patient had a history of diabetes, thyroid diseases, liver or kidney disease, malignancy, chronic consuming diseases, dyspepsia, or malabsorption. No patient took oral agents for hyperglycemia or hyperlipidemia. All patients refrained use of β-blockers and diuretics for a week and from nitrates, intravenous infusion, smoking, alcohol, and a fat-rich diet for 24 h before the high-fat meal.

**EXPERIMENTAL PROTOCOL**

At the end of a 4-week dietary advisory period, all patients were randomly divided into two groups to receive 600 mg of xuezhikang (300 mg of cholestien per capsule; WBL Peking University Biotech Co., Ltd) twice daily (xuezhikang group; n = 30) or placebo (placebo group; n = 30) after the first high-fat meal. The total study period was 6 weeks, at which time the oral high-fat tolerance test was repeated. All patients maintained a stable diet in terms of types and amounts of food according to dietary advice and took routine medications, including aspirin (100 mg/day), metoprolol, fosinopril, and nitrates during follow-up. Patients were not allowed to take other lipid-lowering drugs, vitamin supplements, or unsaturated fatty acids during the entire study period.

**ORAL HIGH-FAT TOLERANCE TEST**

All patients attended the hospital at 0700–0800 after a 12-h overnight fast. The oral high-fat tolerance test was undertaken as performed previously in our hospital by special nutritionists. The high-fat meal consisted of 800 calories with 50 g of fat (5 g of saturated fat, 345 mg of cholesterol), 28 g of protein, and 60 g of carbohydrates (25). The meals given for the fat tolerance studies were not adjusted for the weight of the participants because they had similar body mass indices. All participants finished the high-fat meal within 15 min. During the next 6 h, participants were allowed to drink only water and not to smoke, drink wine, or eat any foods. Only slow walking was allowed. Administration of oral drugs and intravenous infusions was prohibited until the last blood sample was collected. Patients who could not tolerate this test were excluded.

**LIPID MEASUREMENTS**

Fasting hsCRP was measured at 550 nm by a particle-enhanced immunoturbidimetric assay (Orion Diagnostica) on a HITACHI 7170A analyzer. The lower limit of detection for the method is 0.125 mg/L. The measurement range for hsCRP was 0.20–2.94 mg/L. The interassay CVs were 0.14% and 2.1% at mean values of 8.20 and 0.31 mg/L, respectively, and the intraassay coefficients of variation were 0.13% and 2.3% at mean values of 8.21 and 0.30 mg/L, respectively.

**hsCRP MEASUREMENTS**

Venous blood samples were collected before and 2, 4, and 6 h after the high-fat meal. Serum was separated at 4 °C and then stored at −30 °C. Serum total cholesterol, triglyceride, HDL-cholesterol (HDL-C), LDL-C, and Lp(a) concentrations were measured on a HITACHI 7170A analyzer by a specialist who was unaware of the study. Serum total cholesterol and triglyceride concentrations were measured by enzymatic methods, and HDL-C and LDL-C concentrations were measured by direct methods. The Lp(a) concentration was measured by an immunoturbidimetric method. The reagents were provided by Daiichi Pure Chemicals Co., Ltd. The inter- and intraassay CVs were controlled within 5.5% and 3.5%, respectively.

**STATISTICAL ANALYSIS**

Data were analyzed with SPSS (Ver. 10.0) and are presented as the mean (SD) unless other indicated. Lp(a) results are presented as the mean (SE). Because the hsCRP distribution was skewed, it is shown on the original scale [median (lower–upper quartile)] and log-transformed for distribution-dependent analyses. Differences between the intra- and intergroup means were analyzed by t-test or one-way ANOVA. Coefficients of correlation (r) were calculated by Pearson correlation analysis. General linear regression analysis with adjustment for differences in baseline variates was performed to assess the effect of xuezhikang treatment. The triglyceride and Lp(a) areas under the curve over the fasting concentration [TG-AUC and Lp(a)-AUC] were calculated by the trapezoidal method. Statistical significance was defined as $P < 0.05$. 


Results

There were no significant differences in clinical characteristics or fasting serum lipid and hsCRP concentrations between the patients in the xuezhikang group and placebo group (Table 1).

The serum total cholesterol, LDL-C, and HDL-C concentrations did not change significantly in postprandial period (data not shown), whereas the postprandial serum triglyceride and Lp(a) concentrations increased significantly and peaked at 4 h after a high-fat meal ($P < 0.05$). The xuezhikang and placebo groups had similar postprandial changes in serum Lp(a) and triglyceride concentrations (Table 1 and Figs. 1 and 2).

After a 6-week treatment with xuezhikang, the fasting triglyceride, total cholesterol, LDL-C, and Lp(a) concentrations decreased by 25%, 21%, 30%, and 23%, respectively ($P < 0.05$), and the HDL-C concentration increased by 16% ($P < 0.05$). The postprandial serum triglyceride and Lp(a) concentrations at all time points (2, 4, and 6 h) and the Lp(a)-AUC [to 64.3 (37.9) mmol/L · 6 h] and TG-AUC [to 3.14 (2.08) mmol/L · 6 h] decreased significantly ($P < 0.001$; Figs. 1 and 2) in the xuezhikang group, accompanied by a significant reduction in fasting hsCRP concentration [to 0.70 (0.25–1.35) mg/L; $P < 0.001$].

There was no significant change in fasting and postprandial serum lipid concentrations at the end of 6 weeks in the placebo group (data not shown), whereas the fasting serum hsCRP concentration was reduced significantly [to 1.90 (1.50–2.45) mg/L; $P < 0.05$]. Linear regression analysis showed that xuezhikang treatment significantly and independently predicted the changes in fasting triglyceride, total cholesterol, LDL-C, HDL-C, and hsCRP concentrations and in TG-AUC and Lp(a)-AUC ($P < 0.05$).

We found a correlation between the fasting serum Lp(a) and hsCRP concentrations ($r = 0.318; P < 0.05$). The change in TG-AUC was correlated with that of Lp(a)-AUC ($r = 0.398; P < 0.01$). The decrease in the fasting serum hsCRP concentration was closely related to the changes in the fasting Lp(a) concentration ($r = 0.402; P < 0.05$) and TG-AUC ($r = 0.441; P < 0.001$), but not to the changes in the fasting serum total cholesterol, triglyceride, HDL-C, and LDL-C concentrations and in Lp(a)-AUC.

Discussion

The postprandial state is important in atherogenesis because of the increased risk of postprandial hyperlipidemia and accompanying abnormalities. Postprandial hyperlipid-
idemia not only includes postprandial hypertriglyceridemia but also may involve increased serum Lp(a) concentrations. Plasma Lp(a) concentrations vary greatly among individuals, whereas the Lp(a) concentration for each individual seems to be constant and invariable in response to diet, even in CHD patients (4). However, some studies have demonstrated an acute increase in plasma Lp(a) after an oral fat load (2, 3). In hypertriglyceridemic patients, the postprandial plasma Lp(a) concentrations increased transiently at 4.5 h, decreased between 4.5 and 12 h, and recovered almost to initial concentrations by the next morning (2). We also observed a postprandial increase in serum Lp(a) concentrations, which reached a peak value at 4 h, the same time point as the postprandial triglyceride peak in CHD patients, and had no sharp decrease even at 6 h. These data indicate that there is a close relationship between the postprandial metabolism of TRLs and Lp(a).

The majority of apo(a) in plasma is characteristically associated with Lp(a). In the postprandial state, a small proportion of plasma apo(a) is found in the d <1.006 kg/L fraction of plasma by density gradient ultracentrifugation, associated with larger and less dense TRLs (26). Moreover, apo(a) in the TRLs fraction increased, whereas apo(a) in the d >1.006 fraction decreased after fat intake, suggesting a transfer of apo(a) from the d >1.006 fraction to the TRLs (2). Evidence supports that apo(a) in the TRL fraction of individuals with postprandial hypertriglyceridemia is not an integral component of plasma VLDL or chylomicrons, but represents the presence of noncovalently bound Lp(a) (26). Recently, Nassir et al. (27) observed that apo(a) secretion from hepatoma cells may be linked to elements of cellular triglyceride assembly and secretion, which raises the idea that the Lp(a) concentration in humans may be affected by alterations in the hepatic synthesis of TRLs. Because postprandially increasing TRLs are partly secreted by the liver, it would be anticipated that the change in the postprandial Lp(a) concentration was correlated with that of the postprandial triglyceride concentration in this study.

Investigations of the influence of statin therapy on Lp(a) concentrations are controversial. The Lp(a) concentration responds well to estrogen (28) and nicotinic acid (29, 30) but not to statins, which effectively lower plasma cholesterol concentrations, with some studies showing an increase (31, 32) and others showing no effect on Lp(a) concentration (19–21). Xuezhikang contains a family of monoclonal-related substances, one of which is a naturally occurring lovastatin (22, 23). However, the effect of lovastatin on Lp(a) is uncertain (30, 33). It has been reported that xuezhikang has a prominent lipid-modulating effect on the fasting total cholesterol, triglyceride, LDL-C, and HDL-C concentrations (22–24), which is consistent with our results. In the present study, xuezhikang reduced the fasting Lp(a) concentration as well as the postprandial Lp(a) and triglyceride concentrations, although the lipid-modulating mechanism may be complex.

A recent study in patients with atherosclerotic disease demonstrated that small doses of aspirin (81 mg/day) effectively decreased serum Lp(a) concentrations in patients with high Lp(a) concentrations (>300 mg/L) but not in those with low Lp(a) concentrations (<300 mg/L) (34). Similarly, in the present study we observed no significant change in Lp(a) concentrations as a result of routine treatment with aspirin (100 mg/day) for most of CHD patients with low Lp(a) concentrations (<300 mg/L).

It has been recognized that dyslipidemia and inflammation interact and play crucial roles in atherogenesis. Postprandial hypertriglyceridemia can induce a high inflammatory state in the circulation. The expression and concentrations of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1β, and interleukin-6, are increased after a fat meal, and the increase in cytokines concentrations was related to increases in postprandial triglyceride concentrations (35, 36). This suggests that eliminating postprandial hypertriglyceridemia may be helpful in inhibiting chronic inflammation. Chronic inflammation characterized by increased CRP concentrations strongly predicts cardiovascular disease and acute coronary events in patients with CHD and risk factors (12, 18). We found that hsCRP concentrations were closely correlated with Lp(a) concentrations in CHD patients. Lp(a) may act as an acute-phase reactant (24) and thus possibly contribute to acute cardiac events. Moreover, many studies have demonstrated a significant relationship between Lp(a) and CRP (13, 14) and other inflammatory factors, such as fibrinogen, interleukin-6 (7), complement 3 and 4 (8), and soluble cellular adhesion molecules (9), which suggests that Lp(a) may be involved in atherogenesis through an inflammatory mechanism.

The serum CRP concentration not only serves as an independent predictive factor for atherosclerotic cardiovascular diseases (12) but also as an indicator for estimating the effectiveness of treatment (18). It has been reported that statins have direct antiinflammatory effects on CRP concentration, which seem to be independent of their lipid-modulating effects in the fasting state (37, 38). In the present investigation, hsCRP concentrations in the xuezhikang group decreased significantly, although the placebo group also showed a mild reduction that could be attributed to aspirin, beta-blockers, and fosinopril, which have antiinflammatory effects. We found no relationship between the change in hsCRP concentration and the changes in fasting lipids, including total cholesterol, triglycerides, LDL-C, and HDL-C, but the decreases in fasting Lp(a) and postprandial triglyceride concentrations were significantly correlated with decreases in hsCRP in CHD patients, which had not been reported in previous studies (37, 38). This result suggests that xuezhikang may control chronic inflammation partly through an indirect antiinflammatory effect that results from lipid-lowering and other processes that reduce triggers and stimulators,
rather than the direct antiinflammatory effect from the naturally occurring statin-like elements.

This study was a clinical investigation, and further research is needed to explore the lipid-modulating mechanisms of xuezhikang. However, xuezhikang contains a family of naturally occurring statins (monacolins), one of which is lovastatin. It has been demonstrated that lovastatin, as well as other statins, lowers serum total cholesterol concentrations and inhibits cholesterol synthesis (39, 40). Thus, xuezhikang could have a similar effect on cholesterol synthesis, although its triglyceride-lowering mechanism is unclear.

Serum Lp(a) and hsCRP concentrations measured by immunoturbidimetric method may be interfered with by triglycerides. However, the highest fasting and postprandial triglyceride concentrations were 3.20 and 6.98 mmol/L, respectively, which are far lower than the extreme concentrations that affect Lp(a) and hsCRP assays. Thus, the association of CRP and Lp(a) with increased triglycerides could reflect a true physiologic phenomenon.

In conclusion, xuezhikang not only effectively decreased the fasting hsCRP and Lp(a) concentrations but also reduced the postprandial Lp(a) and triglyceride concentrations in CHD patients. Moreover, xuezhikang may modulate CRP secretion partly through a lipid-lowering mechanism.

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References


