Effect of xuezhikang, a cholestin extract, on reflecting postprandial triglyceridemia after a high-fat meal in patients with coronary heart disease

Shui-Ping Zhao a, Ling Liu a,*, Yan-Chun Cheng a, Yu-Ling Li b

a Department of Cardiology, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, China
b Department of Nutrition, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, China

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Abstract

The effect of xuezhikang on postprandial triglyceride (TG) level was investigated in patients with coronary heart disease (CHD) after a high-fat meal (800 cal; 50 g fat). Fifty CHD patients were randomly divided into two groups to accept xuezhikang (xuezhikang group) 1200 mg/day (600 mg twice daily) or not (control group) on the base of routine therapy which included aspirin, metoprolol and fosinopril and nitrates during the whole 6 weeks following-up. Xuezhikang significantly reduced fasting serum total cholesterol (TC) (∆20%), low-density lipoprotein cholesterol (LDL-C, ∆34%), TG (∆32%) and apoB (∆27%) levels, and raised fasting high-density lipoprotein cholesterol (HDL-C, 18%) and apoA-I (13%) levels (∆P < 0.001). The postprandial serum TG levels at 2, 4 and 6 h decreased 32, 38 and 43%, respectively, in xuezhikang group (∆P < 0.001). The TG area under the curve over the fasting TG level (TG-AUC) significantly decreased in CHD patients accepted xuezhikang with normal (less than 1.7 mmol/l) and elevated (1.74 to 2.92 mmol/l) fasting TG levels by 45 and 50%, respectively (∆P < 0.001). Routine therapy had no significant effect on the fasting and postprandial lipid and apolipoprotein levels. The change of TG-AUC was significantly related to the changes of fasting TG, TC, LDL-C, and HDL-C levels after the treatment, which were related to the changes of fasting apoA-I and apoB levels significantly (∆P < 0.001). Xuezhikang was shown to be beneficial in the treatment of reflecting postprandial triglyceridemia in CHD patients with normal and mildly elevated fasting TG levels.

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Keywords: Reflecting postprandial triglyceridemia; Xuezhikang; Coronary heart disease

1. Introduction

The relationship between hypertriglyceridemia and coronary heart disease (CHD) was controversial. However, there is accumulating evidence to support that hypertriglyceridemia and related abnormalities are strongly associated with an increased risk of CHD [1,2]. Recently, the large-scale Prospective Cardiovascular Münster (PROCAM) study and a large meta-analysis of 17 prospective trials found that hypertriglyceridemia was an independent risk factor for CHD, even after adjustment for low-density lipoprotein and high-density lipoprotein cholesterol [3,4]. It is proposed that the postprandial state is critical in atherogenesis [5]. An abnormal postprandial triglyceride (TG) metabolism has been shown in the patients with CHD or risk factors whose fasting TG levels are normal [6,7]. It was demonstrated that postprandial TG-rich lipoproteins (TRLs) and remnants could be more atherogenic [8–10]. The role of TG in CHD pathogenesis is thought to involve several mechanisms, such as effects on the metabolism of other lipoproteins [11], coagulation [12] and endothelial dysfunction [13]. So an elevated TG level needs specific treatment, especially in patients with CHD [14].

Patients with hypertriglyceridemia responded well to the use of lipid lowering drugs or supplement such as fibrates, nicotinic acids and n-3 fatty acids. Recently, 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA)
reductase inhibitors (known as statins) have shown comparable efficacy in reducing both fasting and post-prandial TG concentrations [15–17]. In addition, it was demonstrated that cholestin, a Chinese red-yeast rice dietary supplement, significantly reduced the fasting total cholesterol (TC), LDL-cholesterol and TG concentrations in the general population in United States [18]. Chinese researchers also found that xuezhikang, the extract of cholestin, markedly lowered the fasting TC and TG levels in patients with primary hyperlipidemia [19,20]. However, little attention has been directed to the possible effect of cholestin or xuezhikang on postprandial hypertriglyceridemia in patients with CHD. This study was designed to explore the effect of xuezhikang on postprandial TG level after a high-fat meal in Chinese patients with CHD.

2. Subjects and methods

2.1. Subjects and protocol

A total of 50 patients with CHD (33 men and 17 women, aged 51–68 years, mean age 58.1±5.4 years) who admitted to our hospital between February 2001 and January 2002 for diagnostic evaluation or treatment were recruited. CHD was diagnosed as having the history of myocardial infarction and/or angiographically proven CHD. Their dietary habits, constituents, quantity and daily activity were investigated by question interviewing using the nutrition and health questionnaire. The research protocol was approved by the Ethics Committee of Central South University. All subjects gave fully informed consent before study entry.

All patients were in New York Heart Association (NYHA) class I–II. No patient had a history of diabetes, thyroid diseases, liver and kidney diseases, malignancy, chronic consuming diseases, dyspepsia and malabsorption. No patient took oral hypoglycaemic or hypolipidemic agents. All patients refrained from β-blocker and diuretics for a week, from nitrates, intravenous infusion (5% glucose solution contains dansheng or shengmai which is a kind of Chinese medicine with mild vasodilator effect), smoking, drinking and fat-rich diet for 24 h before the high-fat meal.

At the end of a 4-week dietary advisory period, all patients were randomly divided into two groups to accept xuezhikang (300 mg cholesterol per capsule, WBL Peking University Biotech Co., Ltd., China) 600 mg twice daily (xuezhikang group) or not (control group) after the first high-fat meal. 1200 mg xuezhikang contains 10 mg natural occurring lovastatin [19]. The total following-up period was 6 weeks then the oral high-fat tolerance test was repeated. All patients kept the stable diet constituents and quantity according to lipid-lowering dietary advisory and accepted routine therapy including aspirin, metoprolol and fosinopril and nitrates during the whole following-up.

2.2. Methods

2.2.1. Oral high-fat tolerance test

All patients attended at 07:00–08:00 h after 12 h overnight fast. The oral high-fat tolerance test was undertaken as before in our hospital by special nutritionists [13]. The high-fat meal consisted of 800 cal with 50 g of fat (5 g of saturated fat, 345 mg of cholesterol), 28 g of protein and 60 g of carbohydrates. All subjects finished the high-fat meal in 15 min. Blood samples were taken before and at 2, 4 and 6 h after this meal. During the 6 h test subjects were allowed to drink only water and not to smoke, drink wine and eat any foods. Only slow walking was allowed. Administration of routine oral drugs and intravenous infusion were prohibitive until the last sample was collected.

2.2.2. Lipid measurements

All blood samples were centrifuged at 4 °C. Serum TC and TG levels were measured using enzymatic methods by a specialist who was unaware of the study. HDL-C level was enzymatically determined after precipitation of apolipoprotein B-containing lipoproteins using dextran sulfate/magnesium chloride. Low-density lipoprotein cholesterol (LDL-C) level was computed using the Friedewald formula: LDL-C = TC−HDL-C−(TG/2.2), given TG < 4.5 mmol/l. The apoA-I and apoB concentrations were assessed using an immunoturbidimetric method. Plasma glucose was measured using the glucose oxidase method. The inter- and intra-assay coefficients of variation were controlled within 5.5 and 3.5%, respectively.

2.2.3. Statistical analysis

Data were presented as the mean±S.D. Log-transformation was made for distribution-dependent analyses. Differences between the means intra- and inter-group were analyzed by t-test or one-way analysis of variance. Coefficients of correlation (r) were calculated by the Pearson correlation analysis. Data were analyzed with spss (version 10.0). Postprandial TG response was presented as the TG area under the curve over the fasting TG level (TG-AUC), calculated by the Trapezoidal method. Body mass index (BMI) was calculated as body weight in kilograms divided by squared height in meters. Statistical significance was assumed at a two-tailed value of P < 0.05.

3. Results

Table 1 showed the clinical characteristics of two groups. There were no significant difference in age,
Table 1
Clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Xuzhikang group (n = 25)</th>
<th>Control group (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.9 ± 5.7</td>
<td>58.6 ± 5.7</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>169</td>
<td>178</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 2.2</td>
<td>24.9 ± 1.6</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125 ± 16</td>
<td>129 ± 22</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81 ± 10</td>
<td>79 ± 7</td>
</tr>
<tr>
<td>FBS (mmol/l)</td>
<td>5.46 ± 0.53</td>
<td>5.35 ± 0.44</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose.

Table 2 showed the effect of xuezhikang on fasting lipid and apolipoprotein levels. The xuezhikang treatment led to significant reduction in fasting TC, LDL-C, TG, apoA-I and apoB levels, and significant increase in fasting HDL-C and apoA-I levels (P < 0.001). Routine therapy had no significant effect on the fasting lipid and apolipoprotein levels.

The serum TG levels at 2, 4 and 6 h increased significantly after a high-fat meal in patients with CHD at the baseline (P < 0.05). The baseline TG-AUC was similar in these two groups (6.15 ± 2.78 vs. 6.13 ± 2.27 mmol/l 6 h). After 6-week xuezhikang treatment, the postprandial serum TG levels decreased significantly at all time points (P < 0.001). The postprandial TG levels at 2, 4 and 6 h decreased 32, 38 and 43%, respectively, which was significantly different in control group. TG-AUC decreased 48% in xuezhikang group (to 3.15 ± 1.12 mmol/l 6 h, P < 0.001) while only 4% in control group (to 5.91 ± 2.22 mmol/l 6 h) (Fig. 1). In xuezhikang group TG-AUC decreased 45% (from 5.34 ± 2.11 to 2.90 ± 1.58 mmol/l 6 h, P < 0.001) in patients with normal fasting TG levels (less than 1.70 mmol/l, n = 9) and 50% (from 6.60 ± 3.06 to 3.30 ± 0.79 mmol/l 6 h, P < 0.001) in patients with mildly elevated TG levels (1.74 to 2.92 mmol/l, n = 16).

Taking all patients (n = 50) as a total population, the baseline fasting TG level correlated with the change of fasting TG level (r = 0.318) and the baseline TG-AUC (r = 0.327) significantly (P < 0.05). The change of TG-AUC was significantly related to the changes of fasting TG, TC, LDL-C, and HDL-C levels after the treatment (P < 0.001), which was related to the changes of fasting apoA-I and apoB levels significantly (P < 0.001) (Table 3).

Table 2
Changes of fasting lipid and apolipoprotein levels

<table>
<thead>
<tr>
<th></th>
<th>Xuzhikang group (n = 25)</th>
<th>Control group (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>After 6 weeks</td>
<td>% Change</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.99 ± 0.52</td>
<td>1.37 ± 0.40*</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>5.47 ± 0.55</td>
<td>4.37 ± 0.67*</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.14 ± 0.19</td>
<td>1.35 ± 0.21*</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.34 ± 0.41</td>
<td>2.20 ± 0.33*</td>
</tr>
<tr>
<td>apoA-I (g/l)</td>
<td>1.11 ± 0.14</td>
<td>1.26 ± 0.16*</td>
</tr>
<tr>
<td>apoB (g/l)</td>
<td>1.23 ± 0.26</td>
<td>0.89 ± 0.25*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>After 6 weeks</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>After 6 weeks</td>
<td>% Change</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.95 ± 0.34</td>
<td>1.89 ± 0.34</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>5.53 ± 0.40</td>
<td>5.39 ± 0.46</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.16 ± 0.13</td>
<td>1.15 ± 0.14</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.33 ± 0.33</td>
<td>3.09 ± 0.31</td>
</tr>
<tr>
<td>apoA-I (g/l)</td>
<td>1.08 ± 0.13</td>
<td>1.08 ± 0.12</td>
</tr>
<tr>
<td>apoB (g/l)</td>
<td>1.21 ± 0.15</td>
<td>1.15 ± 0.15</td>
</tr>
</tbody>
</table>

*, P < 0.001 when compared with the baseline values.

4. Discussion

This study demonstrated that CHD patients had an abnormal reflecting postprandial triglyceridemia after a high-fat meal even the fasting serum TG level was not very high. Xuezhikang treatment not only decreased TC and LDL-C levels and increased HDL-C levels effectively, it also decreased fasting, as well as postprandial TG concentrations. These results indicate that xuezhikang has an effective modulation not only on the fasting serum lipid levels but also on the postprandial metabolism of TRL particles.

There were several studies in humans about the effects of cholestin on the serum lipid levels. Cholestin is a proprietary Chinese red yeast rice, which has been regarded as a dietary supplement with lipid-lowering effect and is widely used in United States. Two studies reported that cholestin safely reduced fasting TC and LDL-C levels, while HDL-C concentration did not change significantly in healthy subjects [18] and patients with dyslipidemia related to human immunodeficiency virus [21]. Fasting TG level reduced with cholestin in the study by Heber [18] but did not change in the study by Keithley [21]. It was considered that cholestin had an exact effect on cholesterol level.

The results from studies of xuezhikang were identical compared with cholestin. Xuezhikang, the extract of cholestin, is a traditional Chinese medicine with HMG-CoA reductase inhibiting activity in China. Two com-
studies on the effects of xuezhikang (1.2 g/day) and simvastatin (Zocor, 10 mg/day) or gemfibrozil (1.2 g/day) were carried out [19,20]. It was demonstrated that xuezhikang significantly lowered TC, LDL-C, TG and raised HDL-C levels in Chinese patients with primary hyperlipidemia after 8-week treatment. Xuezhikang had the same lipid-lowering effect as Zocor [19] but inferior TG lowering effect to gemfibrozil [20]. We also observed that fasting TG and LDL-C levels achieved the National Cholesterol Education Program (NCEP)-defined target levels and HDL-C level increased on the base of diet control at the end of sixth week in CHD patients with elevated TC level who accepted xuezhikang. These studies support that xuezhikang made in China is a safe, effective lipid-lowering drug not on cholesterol but also on TG levels.

The novel finding of the present study was that xuezhikang treatment reduced the prominent reflecting postprandial triglyceridemia in CHD patients with normal or mildly elevated fasting TG levels. Reflecting postprandial triglyceridemia has been shown to predict CHD and therapy become necessary, especially for patients with CHD or CHD risk equivalent. There are a few reports on the effect of drugs on reflecting postprandial triglyceridemia. Patients with reflecting postprandial triglyceridemia have been shown to respond well to dietary control and to the use of lipid lowering drugs such as fibrates [22,23], nicotinic acids [24] and statins [15,16]. Moreover, the supplements, as well as omega-3 fatty acids, also have antihypertriglyceridemic effects [25]. In this study the reflecting postprandial triglyceridemia was related to the fasting TG level and similar relation existed between the reduction of them, which suggested that CHD patients should achieve lower fasting TG level than 1.70 mmol/l (NCEP-defined target level) to avoid reflecting postprandial triglyceridemia.

The mechanisms of xuezhikang modulating postprandial lipidemia may be complex. Xuezhikang contains lovastatin (monacolin K) but has a different lipid-modulating effect in contrast to lovastatin. Lovastatin had weaker effect on TG than atorvastatin [26]. The effect of lovastatin (40 mg once daily) on postprandial lipoprotein clearance was observed only in the patients with fasting hypertriglyceridemia (more than 1.75 or 1.80 mmol/l) other than patients with normal fasting TG levels [27,28]. It seems that statins are effective in decreasing TG level only in hypertriglyceridemic patients [29]. However, in this study xuezhikang reduced postprandial TG concentration in CHD patients with normal (less than 1.70 mmol/l) and mildly elevated TG levels (1.74–2.92 mmol/l) although the change of fasting TG level was associated with the baseline level. And

Fig. 1. The postprandial serum TG levels increased significantly at 2, 4, 6 h after a high-fat meal in two groups of CHD patients at baseline (# P < 0.05, A and B). After 6 weeks, the fasting and postprandial TG levels significantly reduced at all time points in xuezhikang group (0, 2, 4 and 6 h) (*, P < 0.001, A), while had no significant change in control group (B).

Table 3

<table>
<thead>
<tr>
<th>ATG-AUC</th>
<th>ΔTG</th>
<th>ΔTC</th>
<th>ΔLDL-C</th>
<th>ΔHDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.481*</td>
<td>0.638*</td>
<td>0.725*</td>
<td>−0.556*</td>
<td></td>
</tr>
<tr>
<td>ΔapoA-I</td>
<td>−0.566*</td>
<td>−0.545*</td>
<td>−0.686*</td>
<td>0.689*</td>
</tr>
<tr>
<td>ΔapoB</td>
<td>0.739*</td>
<td>0.598*</td>
<td>0.795*</td>
<td>−0.724*</td>
</tr>
</tbody>
</table>

ΔATG, ΔTC, ΔLDL-C, ΔHDL-C, ΔapoA-I and ΔapoB mean the change of fasting TG, TC, HDL-cholesterol, LDL-cholesterol, apoA-I and apoB levels after 6-week treatment; ΔTG-AUC, the change of TG area under the curve over the fasting TG level after 6-week treatment.*, P < 0.001.
1200 mg xuezhikang only contains 10 mg lovastatin [19] which could not entirely explain the reduction of postprandial TG concentration by xuezhikang.

The other components in xuezhikang may account for the prominent reduction of postprandial TG concentration. Cholesten contains other eight monacolins, which differ from lovastatin and may have significant cholesterol-lowering activity, in addition to unsaturated fatty acids, sterols, isoflavones, glycerides, trace elements, and other substances [18,20]. It had been suggested that the more effective the statin is in decreasing LDL-C, the more effective it will also be in decreasing TG levels in hypertriglyceridemia patients [29]. We also observed that change of TG-AUC was significantly related to the changes of fasting TC and LDL-C levels after the treatment. Moreover, unsaturated fatty acids is also an effective agent for lowering elevated serum TG levels [25]. So we agree with Heber [18] that the modulating effect of xuezhikang or cholesten on lipoproteins metabolism may result from a combination of actions of monacolins and other substances. On the other hand, the changes of the fasting serum lipid levels were associated with the reduction of apoB and the increment of apoA-I levels in this study. It suggested that xuezhikang may have an influence on the production and catabolism of apolipoproteins.

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References


