Comparison of the Reductions in LDL-C and Non-HDL-C Induced by the Red Yeast Rice Extract Xuezhikang Between Fasting and Nonfasting States in Patients With Coronary Heart Disease

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Research

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Abstract

Background: Xuezhikang, an extract of red yeast rice, effectively lowers fasting blood lipid levels. However, the influence of Xuezhikang on nonfasting levels of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) has not been explored in Chinese patients with coronary heart disease (CHD).

Methods: Fifty CHD patients were enrolled and randomly divided into two groups (each n = 25) to receive 1200 mg/d Xuezhikang or not for six weeks as routine therapy. Blood lipids were measured repeatedly before and after six weeks of treatment at 0, 2, 4 and 6 hours (h) after a standard breakfast containing 800 kcal and 50 g fat.

Result: Serum LDL-C levels significantly decreased, from a fasting level of 3.88 mmol/L to nonfasting levels of 2.99, 2.83 and 3.23 mmol/L at 2, 4 and 6 h, respectively, after breakfast (P<0.05), while there was no significant difference in total cholesterol (TC) levels between the fasting value and the values at any nonfasting time-points. The serum non-HDL-C level mildly increased from a fasting level of 4.29 mmol/L to nonfasting levels of 4.32, 4.38 and 4.34 mmol/L at 2, 4 and 6 h postprandially, respectively, and the difference reached statistical significance only at 4 and 6 h after breakfast (P < 0.05). There was no difference in fasting and nonfasting blood lipids between the two groups at baseline. After six weeks of Xuezhikang treatment, patients had significantly lower fasting and nonfasting serum levels of LDL-C and HDL-C (P < 0.05) than they did pretreatment. LDL-C levels were reduced by 27.8%, 28.1%, 26.2% and 25.3% at 0, 2, 4 and 6 h, respectively, and non-HDL-C levels were reduced by 27.6%, 28.7%, 29.0% and 28.0% at 0, 2, 4 and 6 h, respectively, after breakfast. There was no significant difference in the percent reductions in LDL-C and non-HDL-C levels among the four different time-points.

Conclusions: A six-week Xuezhikang (1200 mg/d) treatment significantly decreased LDL-C and non-HDL-C levels, with similar percent reductions in fasting and nonfasting states in CHD patients. This may indicate that nonfasting blood lipids detected at the same time point after a standard meal could replace fasting blood lipids when evaluating the efficacy of cholesterol control in CHD patients who are unwilling or unable to fast.

1 Introduction

According to the Chinese Cardiovascular Report 2019, eleven million Chinese individuals suffer from coronary heart disease (CHD). The mortality rate of CHD was 115.32/100000 in urban residents and 122.04/100000 in rural residents[1]. Compared with fasting hypertriglyceridemia, elevated fasting low-density lipoprotein cholesterol (LDL-C) levels are more closely associated with CHD, although evidence also shows that nonfasting hypertriglyceridemia is an independent risk factor for CHD[2]. Hypertriglyceridemia represents an increase in triglyceride (TG)-rich lipoproteins and their remnant-like particles (RLPs) in peripheral circulation. RLPs are considered to be as atherosclerotic as low-density lipoprotein (LDL). Reducing LDL-C levels is the primary goal of cholesterol control. The secondary goal is to control the level of non-high-density lipoprotein cholesterol (non-HDL-C)[3].

It is known that atherogenesis is a nonfasting phenomenon[4]. Nonfasting lipids were initially detected after a high-fat meal, and primary attention was given to the change in the nonfasting level of TG but not other cholesterol parameters[5, 6]. Recently, detection of nonfasting blood lipids after a daily meal was performed in prospective studies with large populations[7]. It has been recommended that nonfasting blood samples be routinely used for the assessment of lipid profiles in CHD patients on stable drug therapy or those who prefer nonfasting lipid detection[8, 9]. However, it was unclear whether nonfasting detection of blood lipids was suitable for follow-up in CHD patients receiving their first treatment with statins, especially when evaluating the efficacy of lipid-lowering drugs.

There is a drop in some nonfasting cholesterol parameters after a daily meal[10]. The maximal mean reduction in LDL-C or non-HDL-C 1–6 h after habitual food intake was only 0.2 mmol/L, which was considered insignificant in a population from Copenhagen[11]. However, Chinese subjects had a larger drop in nonfasting LDL-C levels after a daily breakfast; the drop was more than 0.3 mmol/L, when LDL-C was calculated according to the Friedewald formula[12]. The nonfasting reduction in LDL-C may influence evaluations of cholesterol control. Thus, it could be more suitable to judge the efficacy of cholesterol control according to the percent reduction in LDL-C rather than the absolute LDL-C level in the nonfasting state.

Patients with type 2 diabetes and functional dyspepsia could benefit from dietary supplementation with cinnamon, probiotics and sumac[13–15]. As a natural statin, Xuezhikang, which is extracted from red yeast rice, has been recommended in the secondary prevention of CHD by the guidelines for the prevention and treatment of dyslipidemia in Chinese adults (2016 revised edition)[16, 17]. Xuezhikang significantly improved the prognosis of Chinese patients with CHD through comprehensive regulation of lipids, including lowering of nonfasting TG and lipoprotein(a) levels [18, 19], although its effect on nonfasting LDL-C and non-HDL-C levels was never mentioned. The high-fat breakfast with 800 kcal that was used in our previous studies[18, 20–23] has relatively fewer calories than those in other studies[24, 25], and this calorie level could be close to that of the habitual or daily breakfasts of some individuals. Thus, we aimed to explore the effects of short-term Xuezhikang treatment (1200 mg/d) on the nonfasting LDL-C and non-HDL-C levels of CHD patients who were accustomed to consuming a breakfast with 800 kcal and 50 g fat and to compare the difference in the percent reduction in LDL-C and non-HDL-C levels between the fasting value and the values at the nonfasting time-points.

2 Materials And Methods

2.1 Study design and population:

The study protocol was approved by the Ethics Committee of Central South University (Hunan, China) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was given by all the participants. This randomized, single-blind, placebo-controlled study was performed in consecutive patients (n = 50). Patients who visited the second Xiangya Hospital between February 2001 and January 2002 for diagnostic evaluation or treatment were recruited. Enrolled patients were divided into the Xuezhikang and placebo groups at a 1:1 ratio according to an odd or even number that they randomly selected by themselves. Their dietary habits, nutrient intake, quantity of food intake, and daily activity were investigated by open-question interviewing using the nutrition and health questionnaire[26, 27].

The inclusion criteria were as follows: male or female ≥ 18 y old; New York Heart Association (NYHA) class I or II; CHD that was defined as a history of myocardial infarction and/or angiographically proven coronary atherosclerosis with angina pectoris; subjects who tolerated a breakfast containing at least 800 kcal and 50 g fat well.

The exclusion criteria were as follows: diabetes; thyroid diseases; liver and kidney diseases; malignancy; chronic consuming diseases, including malignant tumors, tuberculosis, chronic atrophic gastritis, severe trauma, burns, systemic lupus erythematosus, chronic suppurative infection and chronic blood loss; and use of oral hypoglycemic or hypolipidemic agents.

All patients had a four-week dietary advisory period. After at least 12 h of overnight fasting, patients were given a standard breakfast with 800 kcal and 50 g fat. Then, they either received Xuezhikang (1200 mg/d, 600 mg cholestin per capsule, WBL Peking University Biotech Co., Ltd., China) or did not. After six weeks, the same standard breakfast was repeated. All patients maintained a steady diet according to lipid-lowering dietary advice and accepted routine therapy, including aspirin, metoprolol, fosinopril and nitrates, during a six-week follow-up. No patient dropped out of the study during the six-week follow-up.

2.2 Standard breakfast and collection of blood samples

The standard breakfast in this study contained 800 kcal, 50 g of fat, 28 g of protein, and 60 g of carbohydrates. Blood samples were taken before and at 2, 4 and 6 h after this meal. During the 6-h test, patients were now allowed to smoke, drink wine or eat any foods, with the option of consuming a little water. Vigorous exercise, including running and talking loudly, was forbidden, and only slow walking was allowed in a certain range of ward areas. Intravenous infusion was prohibited until the last blood sample was collected.

2.3 Lipid profile measurements

Blood samples were separated at 4 °C and stored at -20 °C. Serum levels of total cholesterol (TC), TG, and HDL-C were measured on an automatic biochemistry analyzer (Hitachi 7170, Tokyo, Japan) by a specialist who was blinded to this study. LDL-C levels were calculated according to the Friedewald formula, i.e., LDL-C = TC-HDL-C−TG/2.2 (mmol/L), when the TG level was < 4.5 mmol/L; otherwise, it was measured by a commercially direct method. The cholesterol content in RLPs is termed remnant lipoprotein cholesterol (RC). non-HDL-C and RC levels were estimated according to two formulas, non-HDL-C = TC−HDL-C and RC = non-HDL-C−LDL-C, respectively.

2.4 Statistical analysis

The data were analyzed with SPSS version 23.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 8.0.2 (GraphPad Corp, San Diego, CA, USA) software. Unless otherwise noted, quantitative variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers or percentages. Intragroup comparisons among multiple time points were performed by one-way ANOVA for quantitative variables, and comparisons between two different time points were performed by *t* test. The difference in intergroup means was analyzed by independent *t* test. Categorical variables were compared with χ^2 analysis. The total area under the curve (tAUC) of each lipid parameter and the increment of the AUC (iAUC) for RC and TG were estimated by trapezoidal methods after breakfast. Statistical significance was assumed at a two-tailed value of $P < 0.05$.

3 Results

3.1 Clinical characteristics of the recruited patients

Baseline characteristics, including sex, age, body mass index (BMI), heart rate, smoking habits, hypertension status, blood pressure, fasting blood glucose and creatinine, were roughly matched in the Xuezhikang (XZK) and control (CON) groups. Moreover, there was no significant difference in the fasting levels of TG, TC, LDL-C, HDL-C, non-HDL-C or RC between the two groups (Table 1).

Table 1
Clinical characteristics of patients.

	XZK group (n = 25)	CON group (n = 25)	*P* value
Age (years)	57.88 ± 5.69	58.64 ± 5.67	0.639
Male (n)	16	16	1.000
BMI (kg/m^2)	24.79 ± 2.16	24.91 ± 1.15	0.815
Smoker (n)	8	8	1.000
Hypertension (n)	12	12	1.000
SBP (mmHg)	125 ± 16	129 ± 22	0.526
DBP (mmHg)	81 ± 10	79 ± 7	0.432
Heart rate (1/min)	77 ± 7	77 ± 6	0.964
FBS (mmol/L)	5.46 ± 0.53	5.35 ± 0.44	0.437
Creatinine (umol/L)	108.17 ± 9.75	110.16 ± 7.37	0.421
TG (mmol/L)	2.00 ± 0.52	1.95 ± 0.34	0.686
TC (mmol/L)	5.47 ± 0.55	5.53 ± 0.40	0.628
LDL-C (mmol/L)	3.34 ± 0.41	3.33 ± 0.33	0.973
HDL-C (mmol/L)	1.15 ± 0.19	1.16 ± 0.13	0.767
Non-HDL-C(mmol/L)	4.32 ± 0.54	4.37 ± 0.35	0.685
RC (mmol/L)	0.98 ± 0.56	1.04 ± 0.36	0.672

3.2 Effects of an 800-kcal breakfast on blood lipids

To analyze the changes in nonfasting blood lipids in CHD patients at baseline, we pooled all patients together (n = 50). There was no significant difference in TC levels between the fasting and nonfasting states. The other two cholesterol parameters decreased significantly after breakfast ($P < 0.05$); although the reduction in nonfasting HDL-C was very mild, that in LDL-C was relatively obvious, especially 4 h postprandially. On the other hand, nonfasting non-HDL-C, TG and RC levels increased significantly after a high-fat breakfast ($P < 0.05$). However, the elevation of nonfasting non-HDL-C was very mild, while that of TG and RC was obvious, especially 4 h postprandially (Fig. 1A, 1B).

3.3 Changes in nonfasting levels of blood lipids between the two groups before and after six weeks

The XZK and CON groups showed similar changes in nonfasting blood lipids after a high-fat breakfast compared with baseline. Six weeks of treatment with Xuezhikang significantly increased HDL-C levels and decreased TG, TC, LDL-C, non-HDL-C and RC levels in both the fasting and nonfasting states (*P*<

0.01). However, there was no significant difference in fasting levels of blood lipids and their nonfasting changes before and after six weeks in the CON group (Fig. 2A-2E).

Then, tAUC was calculated to reflect overall changes in nonfasting blood lipids within 6 h after a high-fat breakfast. There was no significant difference in the baseline tAUC for TG (18.0 vs. 17.9 h·mmol/L), TC (32.5 vs. 32.9 h·mmol/L), LDL-C (19.1 vs. 19.2 h·mmol/L), HDL-C (6.7 vs. 6.8 h·mmol/L), non-HDL-C (25.7 vs. 26.1 h·mmol/L) or RC (6.7 vs. 6.9 h·mmol/L) between the two groups. After six weeks, the tAUC for TG, TC, LDL-C, non-HDL-C, and RC was significantly lower, while that for HDL-C was significantly higher, than the baseline values in the XZK group ($P < 0.01$) but not the CON group (Fig. 2F).

3.4 Comparisons of fasting and nonfasting percent reductions in LDL-C and non-HDL-C levels before and after six weeks in the XZK group

After six weeks of Xuezhikang treatment, the serum LDL-C level showed a drop of 27.8% in the fasting state and of 28.1%, 26.2% and 25.3% at 2, 4 and 6 h, respectively, postprandially. Serum non-HDL-C levels showed a drop of 27.6% in the fasting state and of 28.7%, 29.0% and 28.0% at 2, 4 and 6 h, respectively, postprandially. There was no significant difference in the percent reductions in LDL-C and non-HDL-C levels between the fasting and nonfasting time-points (Fig. 3).

4 Discussion

In this study, the patients consumed an identical breakfast before and after six weeks of Xuezhikang treatment, and nonfasting blood lipids were detected at the same time-points after breakfast. It was found that the percent reduction in LDL-C at any time point after breakfast was similar to that in the fasting state, suggesting that the percent reduction in nonfasting LDL-C level can be used to evaluate the efficacy of cholesterol control for CHD patients who are unwilling or unable to keeping the fast state, as can the nonfasting non-HDL-C level. This means that nonfasting LDL-C and non-HDL-C levels can be used in place of their fasting values when evaluating the efficacy of statin treatment in specific CHD patients if the following conditions can be met: the same breakfast has been eaten, and blood lipids are detected by the same commercial kits at the same time points after a meal.

It is noteworthy that the detection of nonfasting blood lipids in clinical practice was originally recommended to be carried out after a daily meal[8, 9]. The CHD patients recruited for this study regularly consumed a daily breakfast of > 800 kcal and > 50 g of fat. The standard breakfast in this study can be regarded as a customary breakfast. Thus, the findings from this study could apply to CHD patients with similar dietary habits.

Among all cholesterol parameters, LDL-C levels were obviously reduced after breakfast. TC levels were the most stable after breakfast, followed by HDL-C and non-HDL-C levels, whose changes did not exceed 0.1 mmol/L in this study. However, the RC level increased with increasing TG levels. Some scholars speculated that a reduction in nonfasting LDL-C levels was likely induced by hemodilution due to fluid intake[11, 28]. Others attributed the decrease to biological rhythm and found that LDL-C and HDL-C levels were significantly lower from after breakfast until midnight than they were before breakfast[29]. Although the potential cause of the reduction in nonfasting LDL-C levels in this study was not very clear, we should cautiously evaluate the cholesterol-lowering effect during follow-up if the LDL-C level is detected in a nonfasting state. For example, if the fasting LDL-C goal was < 1.8 mmol/L, it was difficult to decide whether a nonfasting LDL-C level of 1.65 mmol/L reached the target. This result indicates that it could be inappropriate to evaluate the nonfasting LDL-C level according to the fasting LDL-C goal.

With the update of the Chinese and Western guidelines for the management of dyslipidemia in adults, evaluation of the percent reduction in LDL-C level has become increasingly important[16, 30, 31]. For the nonnegligible reduction in LDL-C levels after breakfast in this study, the percent reduction was calculated to compare the effects of Xuezhikang on LDL-C levels between the fasting level and the levels at the nonfasting time points. After six weeks, LDL-C levels presented parallel changes at four different time points, with a percent reduction between 25.3% and 28.2%. More importantly, there was no significant difference in the percent reductions in LDL-C level among the four different time points. This suggested that if the LDL-C level was detected after a habitual breakfast in the first visit in one patient, it can be detected repeatedly at the same time point after an identical breakfast at the second visit six weeks later. That is, nonfasting LDL-C levels could even be used to evaluate cholesterol control in unstable patients.

In the present study, the percent reduction in LDL-C level was less than 27.8%, which was very close to that reported by other studies, including 28.5% by the China Coronary Secondary Prevention Study (CCSPS) and 27% by a Food and Drug Administration Phase II clinical study [32]. It is known that with every 1% decrease in LDL-C level, the relative risk of cardiovascular events is reduced by 1% [33]. Because Chinese patients with CHD had lower baseline LDL-C levels than Western patients[1, 34, 35], a nearly 30% reduction in LDL-C induced by a six-week Xuezhikang treatment made the mean fasting LDL-C level < 2.6 mmol/L in 76% of CHD patients, which was the LDL-C goal recommended by the guidelines of the National Cholesterol Education Program in 2002 [36]. Considering that this study was completed in 2002, a nearly 30% reduction in LDL-C level was clinically significant at that time.

Compared to LDL-C levels, non-HDL-C levels changed mildly after breakfast in this study, which could be related to the obvious increase in RC levels. The non-HDL-C level includes the LDL-C level and the RC level at each time-point. The percent reduction in non-HDL-C level was slightly greater than that in LDL-C level at each nonfasting time point, which could be due to Xuezhikang inhibiting the increment in the nonfasting TG and RC levels. Similar to the LDL-C level, the non-HDL-C level also showed very similar percent reductions among the four different time points. This finding supports that non-HDL-C levels can be detected and evaluated in the nonfasting state during follow-up for those who are unwilling or unable to keep fasting state[30, 37, 38].

The mechanism of Xuezhikang in reducing blood lipids is complex. Xuezhikang contains natural lovastatin (i.e., monacolin K) and 12 other kinds of natural monacolins (24 mg in each Xuezhikang capsule) that are homologs of statins. Additionally, it comprises other ingredients, such as sterols[39]. Compared with 10 mg lovastatin, 1200 mg Xuezhikang showed more potent effects for lowering cholesterol and TG levels[40]. CCSPS demonstrated that Xuezhikang significantly decreased the risk of cardiovascular events and total mortality by 30% and 33%, respectively, in Chinese patients with CHD, which was not completely explained by the decrease in LDL-C induced by natural statins in Xuezhikang[32]. Other components of Xuezhikang, such as unsaturated fatty acids, sterols and flavonoids, may also play essential roles in cardiovascular protection [39]. New evidence has shown that unsaturated fatty acids not only have antioxidative and TG-lowering effects but also further reduce cardiovascular events based on statin treatment[41–43].

At one point, there was concern about the safety of Xuezhikang[44]. According to a recent meta-analysis of 53 randomized controlled trials with a total of 8,535 patients (4,437 in the red yeast rice treatment arm and 4,303 in the control arm), the use of monacolin K is not associated with an increased risk of muscular adverse events (OR 0.94, 95% CI, 0.53–1.65)[45]. In the real world, some patients could take Xuezhikang because of their intolerance to synthetic statins[46]. Xuezhikang should be taken as two capsules orally after meals twice a day[47]. Combining other cholesterol-lowering drugs, such as proprotein convertase subtilisin/kexin type 9 inhibitor and ezetimibe, can achieve a better therapeutic effect if needed by the patient.

Several limitations existed in this study. First, this study was a single-blind clinical observational study with a small sample. According to the previous recommendations of international guidelines around 2000[36]. statin treatment was initiated after ineffective lifestyle interventions in CHD patients. That was why half of the participants in this study did not receive Xuezhikang treatment immediately after the diagnosis of CHD. It is worth carrying out a randomized, double-blind clinical trial with a larger sample in the future. Second, more relevant lipid profiles and inflammatory markers should be detected during throughout the day in the future, although a certain type of breakfast may trigger the fluctuation of inflammation and metabolism parameters that are linked to biological rhythms.

In conclusion, six weeks of Xuezhikang treatment (1200 mg/d) significantly decreased LDL-C and non-HDL-C levels, with similar percent reductions between the fasting and nonfasting states, in CHD patients. This result indicates that nonfasting blood lipids detected at the same time point after a standard meal could replace fasting blood lipids when evaluating the efficacy of cholesterol control in CHD patients who are unwilling or unable to fast.

Abbreviations

CHD
coronary heart disease; TC:total cholesterol; LDL-C:low-density lipoprotein cholesterol; HDL-C:high-density lipoprotein cholesterol; TG:triglyceride; RLP:remnant-like particle; RC:remnant lipoprotein cholesterol; BMI:body mass index; SBP:systolic blood pressure; DBP:diastolic blood pressure; FBS:fasting blood sugar; CCSPS:China Coronary Secondary Prevention Study.

Declarations

Ethics approval and consent to participate

All participants provided written consent before entering the study according to the regulations of the Ethics Committee of the Second Xiangya Hospital of Central South University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors have declared that no conflicts of interest exist.

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Author Contributions

Li-Yuan Zhu and Ling Liu wrote the manuscript and reviewed the literature. Ling Liu and Shui-Ping Zhao designed the study and collected the data. Li-Yuan Zhu, Xing-Yu Wen, Qun-Yan Xiang, Li-Ling Guo and Jin Xu analyzed the data and prepared the figures and tables. All authors approved the final manuscript.

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Figures

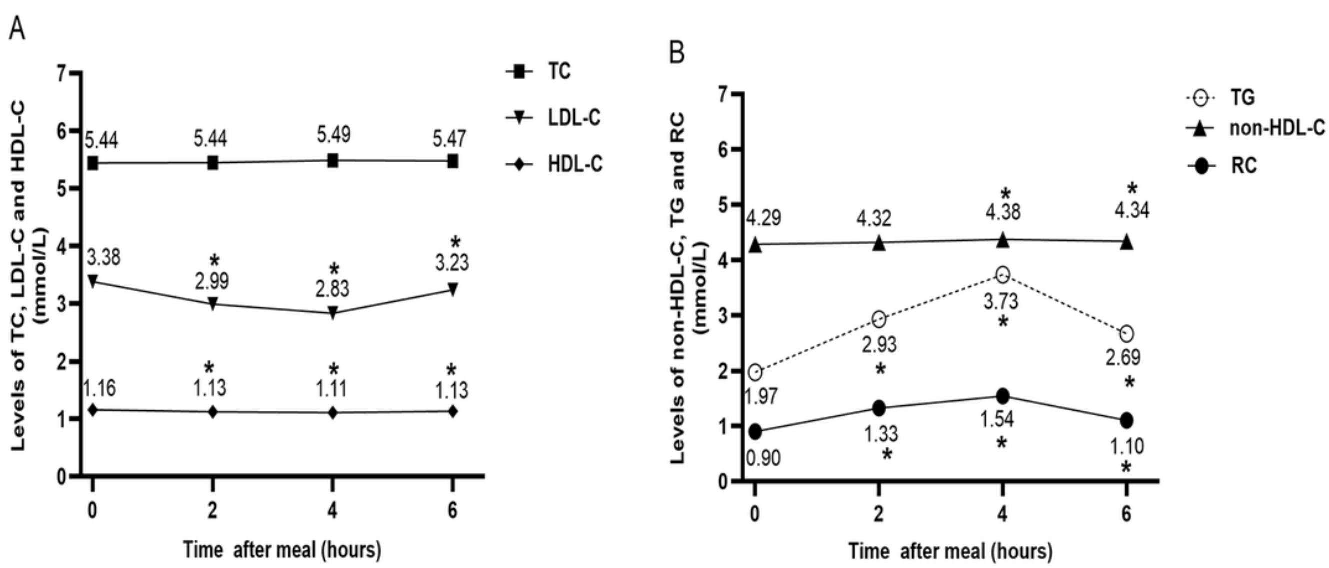

Figure 1

Comparisons of the percent reductions in LDL-C and non-HDL-C levels among different time points after six weeks of Xuezhikang treatment (n=25). The percent reduction in LDL-C (A) and non-HDL-C (B) levels before and at 2, 4 and 6 h after breakfast after six weeks of Xuezhikang treatment. Data are expressed as the median and interquartile range.

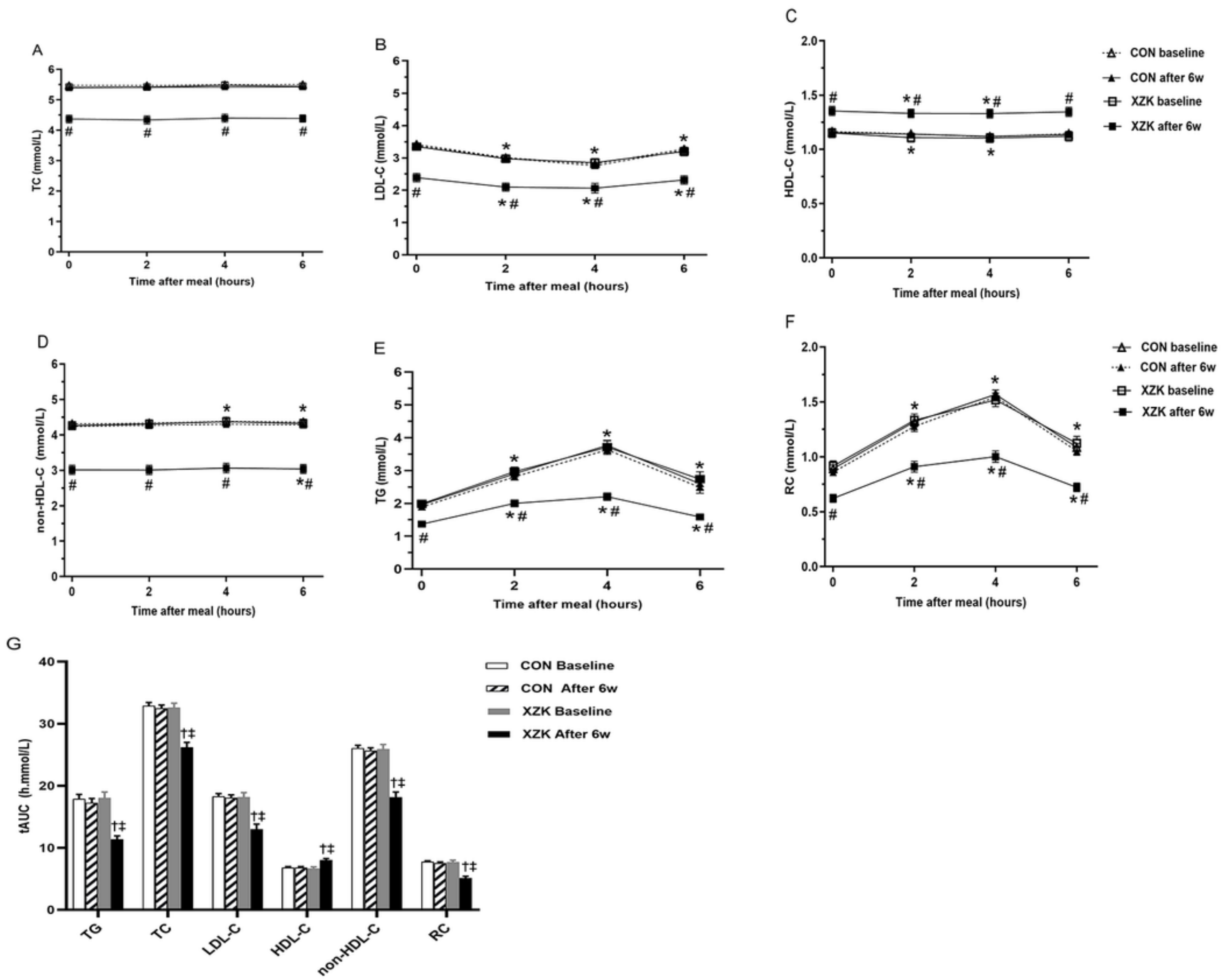

Figure 2

Effect of XZK treatment on nonfasting levels of blood lipids after a high-fat meal. (A-F) Changes in fasting and nonfasting levels of blood lipids between the two groups before and after 6 w. * $P < 0.05$ when compared with the fasting level in the XZK group. # $P < 0.05$ when compared with the CON group at the same time point after six weeks. Data are expressed as the mean±SEM. (G) Comparisons of the tAUC for blood lipids after a high-fat meal before and after six weeks in the two groups. † $P < 0.01$ when compared with the CON group after six weeks. ‡ $P < 0.01$ when compared with the XZK group at baseline. Data are expressed as the mean ± SEM.

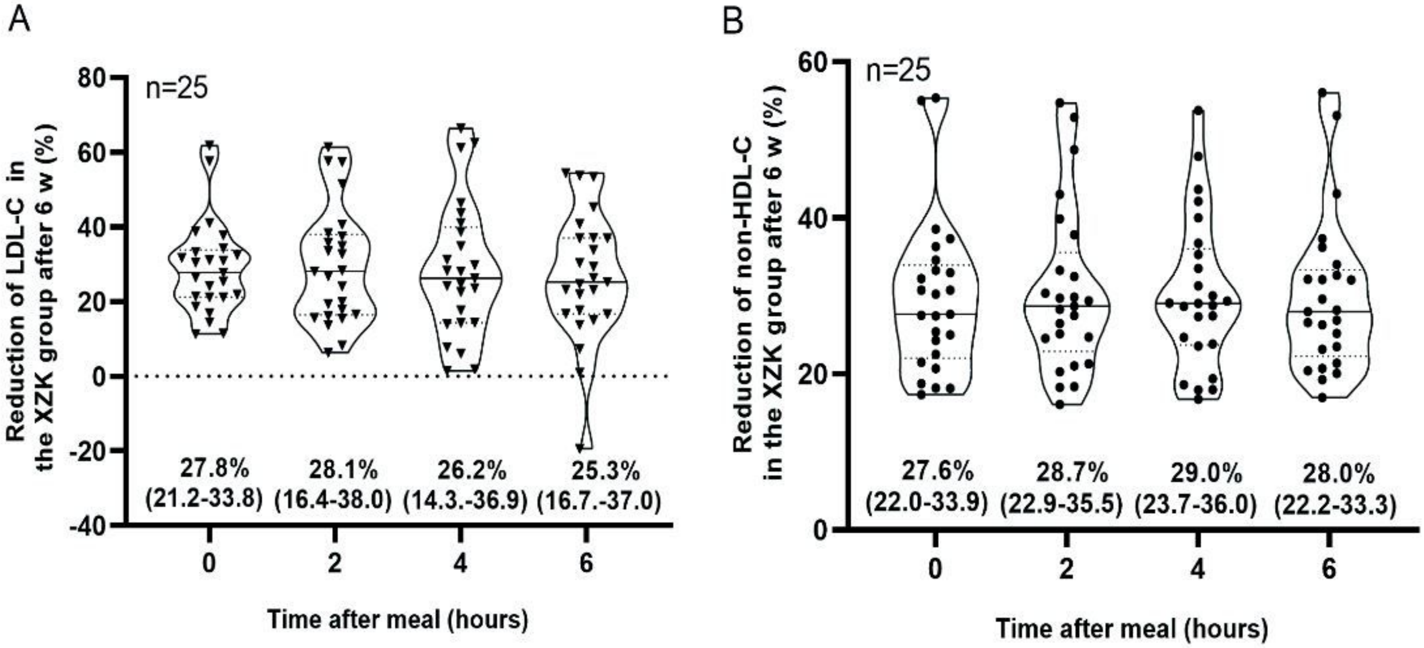

Figure 3

Effect of a high-fat meal on nonfasting levels of blood lipids in all patients at baseline (n=50). (A) Changes in nonfasting serum levels of TC, LDL-C, and HDL-C after a high-fat meal at baseline. (B) Changes in nonfasting serum levels of TG, non-HDL-C, and RC after a high-fat meal at baseline. * P < 0.05 when compared with the fasting level of the same parameter. Data are expressed as the mean ± SEM. TC: total cholesterol (A); LDL-C: low-density lipoprotein cholesterol (B); HDL-C: high-density lipoprotein cholesterol (C); non-HDL-C: non-high density lipoprotein cholesterol (D); TG: triglyceride (E); RC: remnant cholesterol (F).