# Comparison of the Reduction of LDL-C or nonHDL-C induced by Red Yeast Rice Extract, Xuezhikang, between Fasting and Postprandial States in Patients with Coronary Artery Disease

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**Research**

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# Abstract

**Background:** Xuezhikang, an extract of red yeast rice, effectively lowers fasting and postprandial triglyceride (TG) levels. It was unknown that whether Xuezhikang could contribute the lipid management goals, low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (nonHDL-C) at fasting and postprandial states in patients with coronary artery disease (CAD).

**Methods:** Fifty CAD patients were divided into Xuezhikang (XZK, n=25) group and control (CON, n=25) group randomly to receive red yeast rice exact, 1200mg/d Xuezhikang capsules or not for 6 weeks (6w). Blood lipids were detected repeatedly before and after 6w at 0, 2, 4 and 6 hours (h) after a standard breakfast with 800kcal.

**Result:** When taking all patients as a whole (n=50), serum LDL-C level decreased while TG and RC levels increased significantly at 2, 4 and 6 h after breakfast ($P$ 0.05). Serum nonHDL-C level mildly but significantly increased at 4h and 6h after breakfast ($P$ 0.05). Short-term Xuezhikang treatment decreased tAUCs of TC, TG, LDL-C, nonHDL-C and RC whereas increased that of HDL-C significantly ($P$ 0.05). Serum LDL-C level showed a drop of 27.8%, 28.1%, 26.2%, 25.3% at 0, 2, 4 and 6 h, respectively, after breakfast. Serum nonHDL-C level showed a drop of 27.6%, 28.7%, 29.0% and 28.0% at 0, 2, 4 and 6 h, respectively. There was no significant difference in the percentages of reduction in LDL-C or nonHDL-C level among four time-points.

**Conclusions:** Xuezhikang significantly decreased LDL-C or nonHDL-C level with similar percentages of reduction between fasting and postprandial states in patients with CAD, indicating that postprandial blood lipids detected at the same time point after a daily meal could replace fasting blood lipids to evaluate the efficacy of cholesterol-lowering therapy in CAD patients, unwilling or unable to keep a fasting state.


# Introduction

Atherogenesis is a postprandial or non-fasting phenomenon. This opinion was firstly put forward in 1979 by Zilversmit[1] who considered that abnormal lipid metabolism in postprandial state could contribute to atherosclerosis. Postprandial lipids testing in the early stage was usually performed after a high-fat meal, and main attention was paid to postprandial hypertriglyceridemia and its mechanism inducing atherosclerosis via clinical observations with small samples, while various cholesterol parameters, such as total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), were rarely mentioned in the postprandial state[2]. Recently, the detection of postprandial blood lipids after a daily meal according to individual dietary habits started to be applied in prospective studies with large populations. It was showed that stepwise increasing levels of postprandial cholesterol as well as postprandial triglyceride (TG) were similarly associated with stepwise increasing risk of myocardial infarction[3]. Moreover, postprandial LDL-C had prognostic value similar to that of fasting LDL-C on the prediction of all-cause mortality and cardiovascular mortality[4]. Thus, it has been

recommended that postprandial blood samples can be routinely used for the assessment of plasma lipid profiles in patients with coronary artery disease(CAD)on stable drug therapy or those preferred to postprandial lipids detection[5, 6]. However, it was unclear whether the postprandial detection of blood lipids was suitable for the follow-up of CAD patients receiving the first treatment of statins, especially in evaluating the efficacy of lipid-lowering drugs.

It is known that there is a postprandial drop in some cholesterol parameters after one time of habitual food intake. According to the European joint consensus statement about postprandial lipids detection, the maximal mean reductions in TC, LDL-C and nonHDL-C at 1–6 h after habitual food intake were considered insignificant and only 0.2 mmol/L in the Copenhagen population [7]. However, Chinese subjects showed a larger drop in postprandial LDL-C level after a daily breakfast, more than 0.3 mmol/L in calculated LDL-C according to Friedewald formula[8]. Postprandial reduction in LDL-C 0.2 or 0.3 mmol/L may lead to the different evaluation on cholesterol controlling if depending on a certain target level. It might be more suitable to judge the efficacy of cholesterol controlling according to the percentage reduction of LDL-C rather than to the absolute LDL-C level if the subject prefers to postprandial lipid detection during the follow-up visits. Interestingly, serum nonHDL-C level did not change at 2 or 4 h after a high-fat breakfast containing 800 kcal and 50 g fat in Chinese patients with CAD[9, 10], indicating that postprandial nonHDL-C level after a certain high-fat meal could be suitable for postprandial evaluation of cholesterol-controlling for its stability[11].

As a natural statin, Xuezhikang, extracts from red yeast rice, has been recommended in the secondary prevention of CAD by the guidelines for prevention and treatment of dyslipidemia in Chinese adults (2016 revised edition)[12]. It was demonstrated that Xuezhikang significantly improved the prognosis of Chinese patients with CAD through comprehensive regulating lipids. Although there was evidence that Xuezhikang effectively inhibited the postprandial increases in TG and lipoprotein(a) levels [13, 14], its effect on postprandial LDL-C and nonHDL-C levels was never mentioned. It is worth noting that a high-fat breakfast with 800 kcal in our previous studies[9, 13, 15, 16] has obviously lower calories than those in other studies[2, 17], and it could be similar to the habitual or daily breakfasts in some individuals in the real world. Thus, the present study aimed to explore the effects of short-term Xuezhikang treatment (1200 mg/d) on the postprandial levels of LDL-C and nonHDL-C levels in CAD patients who were accustomed to a breakfast with 800 kcal and 50 g fat, and compare the difference in the percentage reduction in LDL-C or nonHDL-C level among fasting state and 2, 4, 6 h postprandially.

## Materials And Methods

# Study design and population:

The study protocol was approved by the Ethics Committee of Central South University (Hunan, China), and was conformed to the ethical guidelines of the 1975 Declaration of Helsinki. A written informed consent was signed by all the participants. The study population consisted of 50 patients who were newly diagnosed as CAD for a history of myocardial infarction or/and angiographically with CAD. They

were hospitalized and never took any lipid-lowering drug before admission. All subjects were investigated about their dietary habits before initiation of the study. The inclusion criteria: New York Heart Association (NYHA) class I or II; no history of diabetes, thyroid diseases, liver and kidney diseases, malignancy, chronic consuming diseases, dyspepsia and malabsorption; no oral hypoglycemic or hypolipidemic agents; their habitual breakfasts containing at least 800 kcal and 50 g fat.

All patients had a 4-week of the dietary advisory period and then were randomly divided into two groups (each n = 25). After at least 12 h of overnight fasting, all patients were given a standard breakfast with 800 kcal and 50 g fat. Then they received Xuezhikang(1200 mg/d, 600 mg cholestin per capsule, WBL Peking University Biotech Co., Ltd., China)or not. After six weeks, the same standard breakfast was repeated. All patients kept a steady diet according to lipid-lowering dietary advisory and accepted routine therapy, including aspirin, metoprolol, and fosinopril and nitrates during a 6-week follow-up.

# Standard breakfast and collection of blood samples

The standard breakfast in this study consisted of 800 kcal with 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 allowed to drink only a small amount of water and not to smoke, drink wine or eat any foods. Vigorous exercise was forbidden and only slow walking was allowed. Intravenous infusion was prohibitive until the last blood sample was collected.

# Lipid profiles measurement

Blood samples were separated at 4℃ and stored at -20℃. Serum levels of TC, TG, and HDL-C were measured on an automatic biochemistry analyzer (Hitachi 7170, Tokyo, Japan) by a specialist who had no idea of this study. LDL-C level was calculated according to the Friedewald formula, i.e. LDL-C = TC-HDL-C－TG/2.2 (mmol/L), only when TG level was < 4.5 mmol/L, otherwise it was measured by a commercially direct method. Levels of nonHDL-C and remnant lipoprotein cholesterol (RC) were estimated according to two formulas, nonHDL-C = TC－HDL-C and RC = nonHDL-C－LDL-C, respectively.

# Statistical analysis

The data was analyzed with SPSS (version 23.0) and Graph Pad prism 8.0 software. Unless otherwise noted, quantitative variables were expressed as mean ± standard deviations and categorical variables were expressed as number or percentage. Differences between intra- and inter- group means were analyzed by unpaired *t* test or one-way ANOVA. Categorical variables were compared with a $\chi^2$ analysis. Total area under the curve (tAUC) of each lipid parameter and increment of AUC (iAUC) of RC and TG were estimated by trapezoid methods after breakfast. Statistical significance was assumed at a two-tailed value of $P < 0.05$.

## Results

# Clinical characteristics of recruited patients

Baseline characteristics, including sex, age, body mass index (BMI), heart rates, smoking habits, hypertension, blood pressure, fasting blood glucose and creatine, were roughly matched in Xuezhikang (XZK) group and control (CON) group. Moreover, there was no significant difference in fasting level of TG, TC, LDL-C, HDL-C, nonHDL-C or RC between 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 (mm Hg) | 125 ± 16 | 129 ± 22 | 0.526 |
| DBP (mm Hg) | 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 |
| NonHDL-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 |

# Effects of an 800 kcal meal on blood lipids

When taking all patients as a whole (n = 50), there was no significant difference in TC levels between fasting and postprandial states. Other two cholesterol parameters decreased significantly after breakfast (*P*0.05), although the postprandial reduction in HDL-C was very mild while that in LDL-C was relatively obvious, especially at 4 h postprandially. On the other hand, postprandial nonHDL-C, TG and RC levels increased significantly after a high-fat meal (*P*0.05). However, the postprandial elevation of nonHDL-C was very mild while those of TG and RC were obvious, especially at 4 h postprandially (Fig. 1A, 1B).

# Changes in postprandial levels of blood lipids between two groups before and after 6w.

XZK group and CON group showed similar postprandial changes in blood lipids after a high-fat meal at baseline. Six-week treatment of Xuezhikang significantly increased HDL-C levels and decreased TG, TC, LDL-C, nonHDL-C and RC levels in both fasting and postprandial states ($P$ 0.01). However, there was no significant difference in fasting levels of and postprandial changes in blood lipids before and after 6w in CON group (Fig. 2A-2E).

Then, tAUC was calculated to reflect total postprandial changes in blood lipids within 6 h after a high-fat meal. There was no significant difference in baseline tAUC of TG (18.0 vs. 17.9h·mmol/L), TC (32.5 vs. 32.9h·mmol/L), LDL-C (19.1 vs. 19.2h·mmol/L), HDL-C (6.7 vs. 6.8h·mmol/L), nonHDL-C (25.7 vs. 26.1h·mmol/L) or RC(6.7 vs. 6.9h·mmol/L) between two groups. After 6w, tAUC of TG, TC, LDL-C, nonHDL-C, or RC was significantly lower and that of HDL-C was significantly higher than its baseline value in XZK group ($P$ 0.01) but not in CON group (Fig. 2F).

# Comparisons of fasting and postprandial percentage of reduction in LDL-C and non- HDL-C level before and after 6w in XZK group

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, after breakfast. Serum nonHDL-C level 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, after breakfast. There was no significant difference in the percentages of reduction in LDL-C or nonHDL-C level between fasting and postprandial states (Fig. 3).

## Discussion

In this study, effects of short-term (6w) treatment of Xuezhikang on different cholesterol parameters, including TC, LDL-C, HDL-C, nonHDL-C and RC, in postprandial state were firstly explored. As LDL-C and nonHDL-C levels are regarded as the primary and secondary targets of cholesterol-controlling of CAD patients, their changes are particularly important. Xuezhikang obviously decreased fasting and postprandial levels of LDL-C and nonHDL-C after a standard breakfast. More importantly, there was no significant difference in the percentages of reduction in LDL-C or nonHDL-C level among four different time points. It indicated that postprandial LDL-C and nonHDL-C levels could take the place of their fasting values in evaluating the efficacy of statins, such as Xuezhikang, in CAD patients through calculating the percentages of reduction in those two parameters, especially in those preferred to postprandial lipid detection or were unable to keep the fasting state because of the risk or discomfort deriving from hungry.

At present, the applicable subjects for postprandial detection of blood lipids after a habitual meal include those for blood lipid screening, for cardiovascular risk assessment, with acute coronary syndrome, receiving stable treatment of lipid-lowering drugs, with diabetes and hypoglycemia risk, the elderly and children, and those prefer to postprandial detection[18]. For the subjects in this study, they were used to a daily breakfast with calories ≥ 800 kcal and fat ≥ 50 g. A standard breakfast in this study can be regarded as a habitual meal for them. Thus, the findings from this study could be applicable to those CAD patients with similar dietary habits.

Among all cholesterol parameters, TC level was the most stable one after breakfast, then followed by HDL-C and nonHDL-C levels whose changes did not exceed 0.1 mmol/L in this study. RC level obviously increased with the increase in TG level. However, LDL-C level obviously reduced after breakfast. Some scholars speculated that postprandial reduction in LDL-C level was likely induced by hemodilution due to fluid intake[7, 19]. Although the potential cause of postprandial reduction in LDL-C level in this study was not very clear, it reminded that clinicians should cautiously evaluate the cholesterol-lowering effect if according to the postprandial LDL-C level, especially when the clinical situation and treatment of a certain CAD patient were still unstable. If fasting LDL-C level was detected in the first visit for one patient, and postprandial LDL-C level was detected in the second visit one month later, then the difference between two times of LDL-C levels could not only derive from the lipid-lowering drug that he was taking, but also due to the postprandial reduction of LDL-C level after a habitual meal. For a certain patient with expected fasting target of LDL-C level 1.8 mmol/L, it could be difficult to decide if his postprandial LDL-C level 1.65 mmol/L reached the target or not. It indicated that it could be inappropriate to evaluate a postprandial LDL-C value according to a fixed fasting target of LDL-C level in some cases.

With the update of the Chinese and Western guidelines for the management of dyslipidemia, the evaluation on the percentage reduction in LDL-C level gets more and more important[12, 20, 21]. Considering significant reduction in LDL-C level after breakfast in this study, the percentage of reduction was calculated to compare effects of Xuezhikang on LDL-C level among fasting and postprandial time-points. After 6 w, fasting and postprandial LDL-C levels presented parallel declines at four time-points. Fasting and postprandial drops in LDL-C level were about from 25.3–28.2%, which were consistent with the classifying Xuezhikang as one of moderate-intensity (25%-49%) statins in the revised Chinese guidelines for dyslipidemia in adults in 2016[20]. More importantly, there was no significant difference in the percentages of reduction in LDL-C level among four different time-points. It suggested that if LDL-C level was detected after a meal in the first visit for one patient, it was able to repeatedly detected at the same time-point after a similar meal in the second visit 6 w later. The percentage reduction in postprandial LDL-C levels between two visits would be very close to that in fasting ones. That is to say, postprandial LDL-C levels could be used to evaluating cholesterol controlling even for unstable patients, if the patient ate a completely same meal at two visits and his blood sample was taken at the same time-point after the meal.

Compared to LDL-C level, nonHDL-C level changed mildly after breakfast in this study, which could be related to the obvious increase in RC level. After all, nonHDL-C level is the sum of LDL-C level and RC level

at each time-point. The percentage of reduction in nonHDL-C level was slightly higher than that in LDL-C level at each postprandial time-point, which could be associated with the effect of Xuezhikang inhibiting the postprandial increment of RC level. Similar to LDL-C level, nonHDL-C level also showed very close percentages of reduction among four different time-points. It supports that nonHDL-C as well as LDL-C can be detected and evaluated in the postprandial state in the visit of follow-up for those patients who are unwilling or unable to keep fasting state[11, 20], as long as they can eat the same meal and then take a test at the same time after a meal.

The mechanism of Xuezhikang on reducing blood lipids is complex. Xuezhikang contains lovastatin, but it is not the same as lovastatin. In addition to natural lovastatin (i.e. monacolin K), Xuezhikang contains other 12 kinds of natural monacolins that are homologues of statins[22]. There is 24 mg of natural statins in each Xuezhikang capsule. Additionally, it comprises unsaturated fatty acids and sterols that could help to lower blood lipids[23]. Compared with 10 mg lovastatin, 1200 mg Xuezhikang has stronger effects on lowering cholesterol and TG levels[23, 24]. Just because of the ability to improve blood lipids at both fasting and postprandial states, Xuezhikang was found to effectively reduced the risk of myocardial infarction and death in Chinese patients with CAD[25]. In the real world, some patients take Xuezhikang because of their intolerance to synthetic statins. In this study, the percentage of reduction in LDL-C level was less than 30%, the combination with other cholesterol-lowering drugs with different mechanisms can be recommended to get a better therapeutic effect if the patient needed[26].

Several limitations existed in this study. Firstly, it was a clinical observation with small sample. Secondly, the time window for postprandial observation was only 6 hours to avoid the discomfort from hunger.

In conclusion, Xuezhikang, a natural statin, significantly decreased LDL-C or nonHDL-C level with similar percentages of reduction between fasting and postprandial states. Postprandial detection of lipids at a same time-point after a same meal could replace fasting detection to evaluate the efficacy of cholesterol-controlling in CAD patients, but not be limited to fasting state..

## Abbreviations

CAD
Coronary artery disease; TC:total cholesterol; LDL-C:low-density lipoprotein cholesterol; HDL-C:high-density lipoprotein cholesterol; TG:triglyceride

## 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 analysed during the current study are available from the corresponding author on reasonable request.

# Competing Interests

The authors have declared that no conflict of interest exists.

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# Authors' 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.

# Acknowledgments

Not applicable

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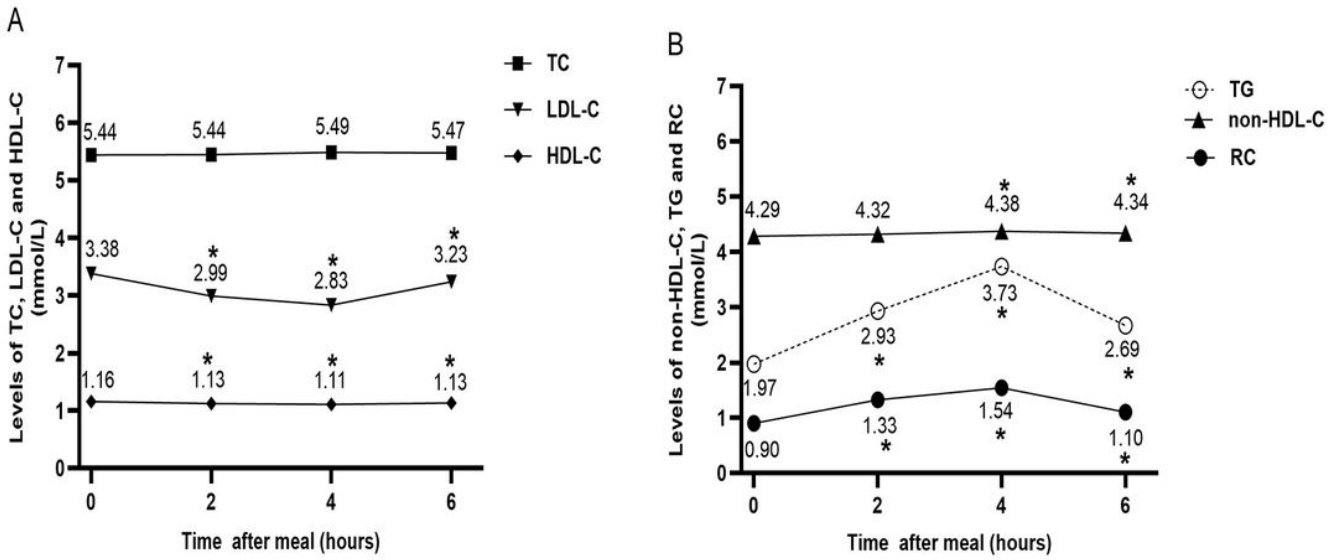
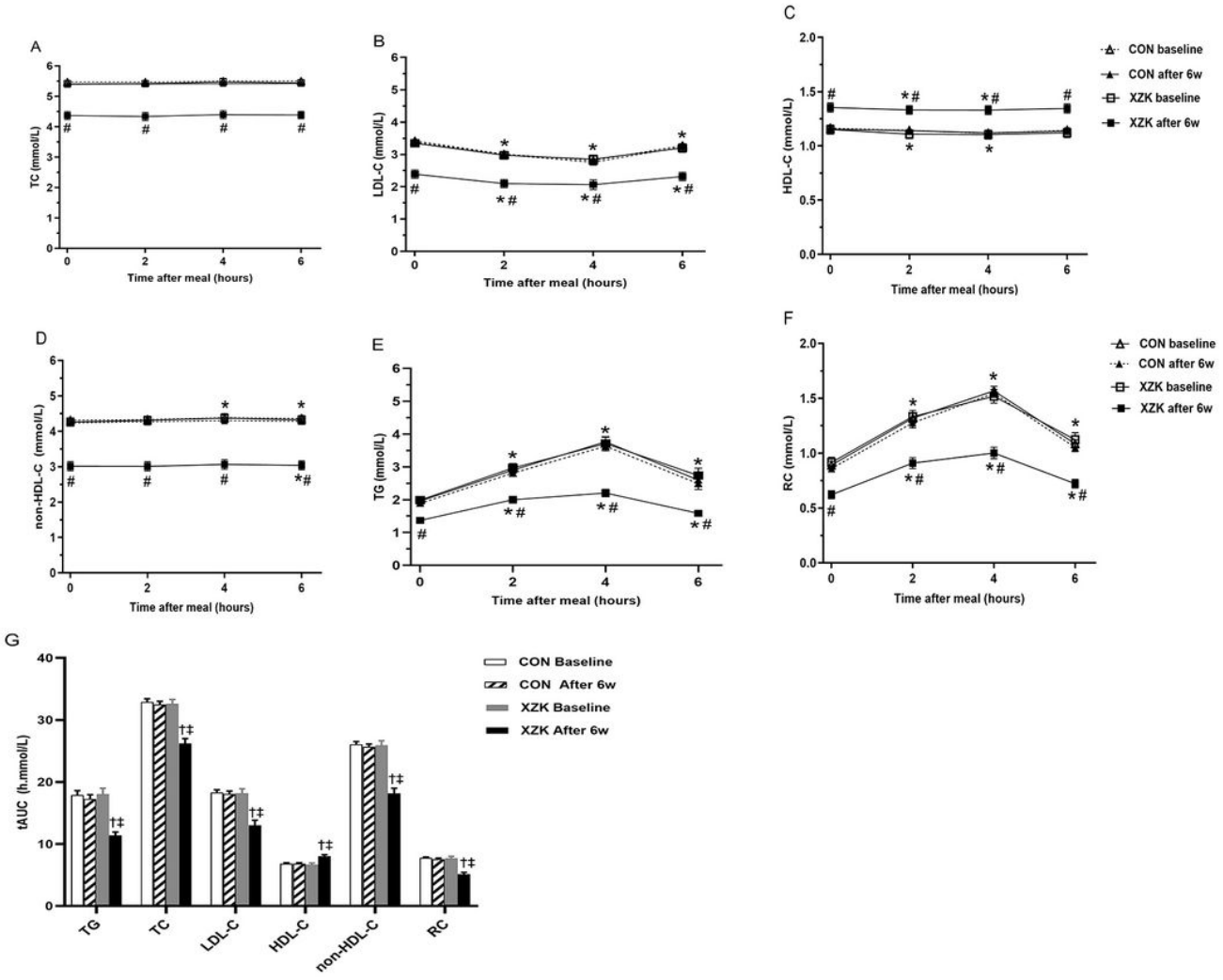
# Figures



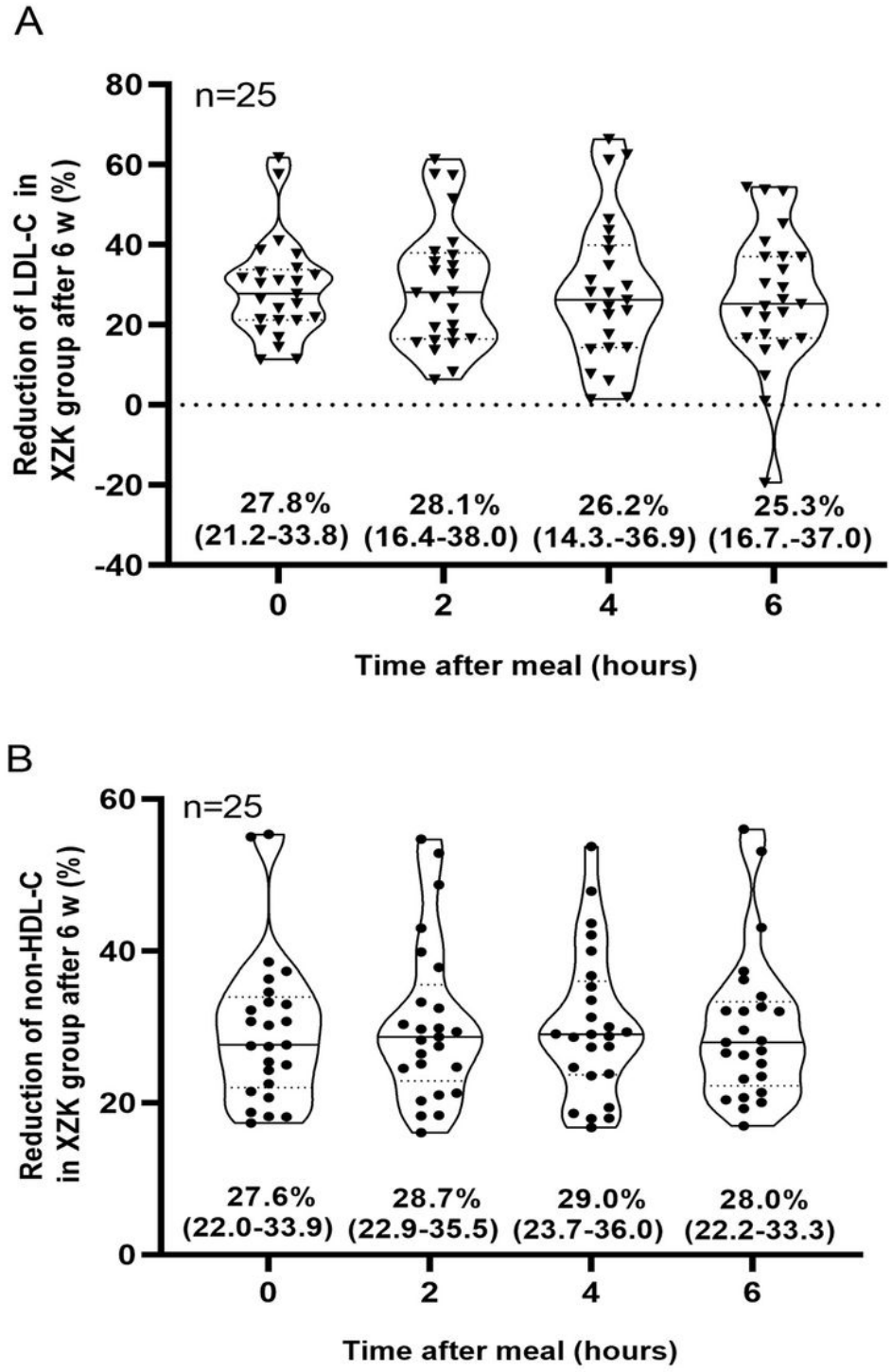

## Figure 1

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




## Figure 2

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




## Figure 3

Comparisons of the percentages of reduction in LDL-C and nonHDL-C levels among different time-points after 6-week treatment of Xuezhikang (n=25). The percentage of reduction in LDL-C (A) or nonHDL-C (B) level before and at 2, 4 and 6h after breakfast after 6-week treatment of Xuezhikang. Data were expressed with median and interquartile range.