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

Li-Yuan Zhu
The Second Xiangya Hospital, Central South University

Xing-Yu Wen
Xiangya School of Medicine, Central South University

Qun-Yan Xiang
The Second Xiangya Hospital, Central South University

Li-Ling Guo
The Second Xiangya Hospital, Central South University

Jin Xu
The Second Xiangya Hospital, Central South University

Shui-Ping Zhao
The Second Xiangya Hospital, Central South University

Ling Liu (✉ feliuling@csu.edu.cn)
The Second Xiangya Hospital, Central South University

Research

Keywords: nonfasting, coronary heart disease, LDL-C, non-HDL-C, Xuezhikang

DOI: https://doi.org/10.21203/rs.3.rs-97453/v1

License: Creative Commons Attribution 4.0 International License. Read Full License
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 cholesterol (LDL-C).
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

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 supplicative 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 χ² 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/m²)         | 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.

Funding

The study was supported by the National Natural Science Foundation of China [grant numbers 81270956 and 81470577] and the Fundamental Research Funds for the Central Universities of Central South University.

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.

Acknowledgments

We thank the patients for their participation in this study.

References

1. Group CCDRW: Summary of Chinese Cardiovascular Disease Report 2019. *Chinese Circulation Journal* 2020, *35*:833-854.

2. Masuda D, Yamashita S: Postprandial Hyperlipidemia and Remnant Lipoproteins. *J Atheroscler Thromb* 2017, *24*:95-109.

3. European Association for Cardiovascular P, Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, et al: ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the
European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011, **32**:1769-1818.

4. Zilversmit DB: *Atherogenesis: a postprandial phenomenon*. *Circulation* 1979, **60**:473-485.

5. Nakamura A, Monma Y, Kajitani S, Kozu K, Ikeda S, Noda K, Nakajima S, Endo H, Takahashi T, Nozaki E: *Different postprandial lipid metabolism and insulin resistance between non-diabetic patients with and without coronary artery disease*. *J Cardiol* 2015, **66**:435-444.

6. Gill JM, Caslake MJ, McAllister C, Tsofiou F, Ferrell WR, Packard CJ, Malkova D: *Effects of short-term detraining on postprandial metabolism, endothelial function, and inflammation in endurance-trained men: dissociation between changes in triglyceride metabolism and endothelial function*. j.gill@bio.gla.ac.uk. *J Clin Endocrinol Metab* 2003, **88**:4328-4335.

7. Langsted A, Freiberg JJ, Tybjaerg-Hansen A, Schnohr P, Jensen GB, Nordestgaard BG: *Nonfasting cholesterol and triglycerides and association with risk of myocardial infarction and total mortality: the Copenhagen City Heart Study with 31 years of follow-up*. *J Intern Med* 2011, **270**:65-75.

8. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, Watts GF, Sypniewska G, Wiklund O, Boren J, et al: *Fasting is Not Routinely Required for Determination of a Lipid Profile: Clinical and Laboratory Implications Including Flagging at Desirable Concentration Cutpoints-A Joint Consensus Statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine*. *Clin Chem* 2016, **62**:930-946.

9. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, Watts GF, Sypniewska G, Wiklund O, Boren J, et al: *Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine*. *Eur Heart J* 2016, **37**:1944-1958.

10. Tian F, Xiang QY, Zhang MY, Chen YQ, Lin QZ, Wen T, Liu L: *Changes in non-fasting concentrations of blood lipids after a daily Chinese breakfast in overweight subjects without fasting hypertriglyceridemia*. *Clin Chim Acta* 2019, **490**:147-153.

11. Langsted A, Nordestgaard BG: *Nonfasting lipids, lipoproteins, and apolipoproteins in individuals with and without diabetes: 58 434 individuals from the Copenhagen General Population Study*. *Clin Chem* 2011, **57**:482-489.

12. Lin QZ, Chen YQ, Guo LL, Xiang QY, Tian F, Wen T, Liu L: *Comparison of non-fasting LDL-C levels calculated by Friedewald formula with those directly measured in Chinese patients with coronary heart disease after a daily breakfast*. *Clin Chim Acta* 2019, **495**:399-405.

13. Namazi N, Khodamoradi K, Khamechi SP, Heshmati J, Ayati MH, Larijani B: *The impact of cinnamon on anthropometric indices and glycemic status in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials*. *Complement Ther Med* 2019, **43**:92-101.

14. Agah S, Akbari A, Heshmati J, Sepidarkish M, Morvaridzadeh M, Adibi P, Mazidi M, Farsi F, Ofori-Asenso R, Talley NJ, Feinle-Bisset C: *Systematic review with meta-analysis: Effects of probiotic supplementation on symptoms in functional dyspepsia*. *Journal of Functional Foods* 2020, **68**.
15. Akbari-Fakhrabadi M, Heshmati J, Sepidarkish M, Shidfar F: Effect of sumac (Rhus Coriaria) on blood lipids: A systematic review and meta-analysis. Complement Ther Med 2018, 40:8-12.

16. Chu JR, Gao RL, Zhao SP, Lu GP, Zhao D, Li JJ: Guidelines for the prevention and treatment of dyslipidemia in Chinese adults (revised in 2016). Chinese Circulation Journal 2016, 31:937-953.

17. Authors/Task Force M, Guidelines ESCcF, Societies ESCNC: 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019, 290:140-205.

18. Zhao SP, Liu L, Cheng YC, Li YL: Effect of xuezihkang, a cholestin extract, on reflecting postprandial triglyceridemia after a high-fat meal in patients with coronary heart disease. Atherosclerosis 2003, 168:375-380.

19. L L, SP Z, YC C, YL L: Xuezihkang decreases serum lipoprotein(a) and C-reactive protein concentrations in patients with coronary heart disease. Clinical chemistry 2003, 49:1347-1352.

20. Zhao SP, Liu L, Cheng YC, Shishehbor MH, Liu MH, Peng DQ, Li YL: Xuezihkang, an extract of cholestin, protects endothelial function through antiinflammatory and lipid-lowering mechanisms in patients with coronary heart disease. Circulation 2004, 110:915-920.

21. Zhao SP, Liu L, Gao M, Zhou QC, Li YL, Xia B: Impairment of endothelial function after a high-fat meal in patients with coronary artery disease. Coron Artery Dis 2001, 12:561-565.

22. Ling L, Zhao SP, Gao M, Zhou QC, Li YL, Xia B: Vitamin C preserves endothelial function in patients with coronary heart disease after a high-fat meal. Clin Cardiol 2002, 25:219-224.

23. Xu J, Chen YQ, Zhao SP, Liu L: Determination of optimal cut-off points after a high-fat meal corresponding to fasting elevations of triglyceride and remnant cholesterol in Chinese subjects. Lipids Health Dis 2019, 18:206.

24. Vogel RA, Corretti MC, Plotnick GD: Effect of a single high-fat meal on endothelial function in healthy subjects. Am J Cardiol 1997, 79:350-354.

25. Patsch JR, Karlin JB, Scott LW, Smith LC, Gotto AM, Jr.: Inverse relationship between blood levels of high density lipoprotein subfraction 2 and magnitude of postprandial lipemia. Proc Natl Acad Sci U S A 1983, 80:1449-1453.

26. Parmenter K, Wardle J: Development of a general nutrition knowledge questionnaire for adults. Eur J Clin Nutr 1999, 53:298-308.

27. Turconi G, Celsa M, Rezzani C, Biino G, Sartirana MA, Roggi C: Reliability of a dietary questionnaire on food habits, eating behaviour and nutritional knowledge of adolescents. Eur J Clin Nutr 2003, 57:753-763.

28. Langsted A, Freiberg JJ, Nordestgaard BG: Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation 2008, 118:2047-2056.

29. Miida T, Nakamura Y, Mezaki T, Hanyu O, Maruyama S, Horikawa Y, Izawa S, Yamada Y, Matsui H, Okada M: LDL-cholesterol and HDL-cholesterol concentrations decrease during the day. Ann Clin Biochem 2002, 39:241-249.
30. Grundy SM, Stone NJ, Bailey AL, Beam C, Birchter KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019, 73:e285-e350.

31. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020, 41:111-188.

32. Li JJ, Lu ZL, Kou WR, Bolli R, Chen Z, Wu YF, Yu XH, Zhao YC: Impact of long-term Xuezhi Kang therapy on cardiovascular events in high-risk patients with nonspecific, preexisting abnormal liver tests: a post-hoc analysis from Chinese Coronary Secondary Prevention Study (CCSPS). Int J Cardiol 2012, 154:362-365.

33. Group HPSC: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. The Lancet 2002, 360:7-22.

34. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al: Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation 2020, 141:e139-e596.

35. Zhao S, Peng D: Efficacy and safety of rosvuastatin versus atorvastatin in high-risk Chinese patients with hypercholesterolemia: a randomized, double-blind, active-controlled study. Curr Med Res Opin 2018, 34:227-235.

36. De Backer G: European guidelines on cardiovascular disease prevention in clinical practice Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). European Heart Journal 2003, 24:1601-1610.

37. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J, Jr., Grover S, Gupta M, et al: 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2016, 32:1263-1282.

38. Su X, Kong Y, Peng D: Evidence for changing lipid management strategy to focus on non-high density lipoprotein cholesterol. Lipids Health Dis 2019, 18:134.

39. Cicero AFG, Fogacci F, Banach M: Red Yeast Rice for Hypercholesterolemia. Methodist DeBakey Cardiovasc J 2019, 15:192-199.

40. Chen CH, Uang YS, Wang ST, Yang JC, Lin CJ: Interaction between Red Yeast Rice and CYP450 Enzymes/P-Glycoprotein and Its Implication for the Clinical Pharmacokinetics of Lovastatin. Evid Based Complement Alternat Med 2012, 2012:127043.

41. Sepidarkish M, Akbari-Fakhribadi M, Daneshzad E, Yavari M, Rezaeinejad M, Morvaridzadeh M, Heshmati J: Effect of omega-3 fatty acid plus vitamin E Co-Supplementation on oxidative stress parameters: A systematic review and meta-analysis. Clin Nutr 2020, 39:1019-1025.
42. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Jr., Juliano RA, Jiao L, Granowitz C, et al: Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019, 380:11-22.

43. Darvish Damavandi R, Mousavi SN, Shidfar F, Mohammadi V, Rajab A, Hosseini S, Heshmati J: Effects of Daily Consumption of Cashews on Oxidative Stress and Atherogenic Indices in Patients with Type 2 Diabetes: A Randomized, Controlled-Feeding Trial. *Int J Endocrinol Metab* 2019, 17:e70744.

44. Elmas E, Kalsch T, Suvajac N, Leweling H, Neumaier M, Dempfle CE, Borggrefe M: Activation of coagulation during alimentary lipemia under real-life conditions. *Int J Cardiol* 2007, 114:172-175.

45. Fogacci F, Banach M, Mikhailidis DP, Bruckert E, Toth PP, Watts GF, Reiner Z, Mancini J, Rizzo M, Mitchenko O, et al: Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2019, 143:1-16.

46. Committee of Cardio-Cerebro-Vascular Diseases of Gerontological Society of C, Working Group of Chinese Expert Consensus on the Use of X: [Chinese expert consensus on the use of Xuezhikang (2017 revised edition)]. *Zhonghua Nei Ke Za Zhi* 2018, 57:97-100.

47. Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM, Chinese Coronary Secondary Prevention Study G, Li S: Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol* 2008, 101:1689-1693.