Non-Fasting Changes of Hs-CRP Level in Chinese Patients With Coronary Heart Disease After A Daily Meal

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Research Article

Keywords: non-fasting, daily meal, high-sensitivity C-reactive protein, statins treatment, coronary heart disease

Posted Date: December 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1195738/v1

Abstract

High-sensitivity C-reactive protein (hs-CRP) is a key inflammatory factor in atherosclerotic cardiovascular diseases. In Chinese patients with coronary heart disease (CHD), the changes in hs-CRP levels after a daily meal and the effect of statins on those were never explored. A total of 300 inpatients with CHD were included. Hs-CRP levels were measured in fasting and non-fasting state at 2 hour (h) and 4h after a daily breakfast. Group with fasting hs-CRP ≤ 3mg/L had significantly higher percentage of patients with statins using ≥ 1 month (m) than that with fasting hs-CRP > 3mg/L (51.4% vs. 23.9%, $P < 0.05$). Hs-CRP levels were significantly higher in non-fasting state ($P < 0.05$). Interestingly, the hs-CRP didn't elevate significantly in inpatients with statins using ≥ 1m in hs-CRP > 3mg/L group, but it elevated significantly after meal in inpatients without and with statins using < 1m ($P < 0.05$). About 32% of patients with non-fasting hs-CRP > 3mg/L came from those with fasting hs-CRP ≤ 3mg/L. In conclusion, hs-CRP levels increased significantly in CHD patients after a daily meal. When fasting hs-CRP > 3mg/L but not ≤ 3mg/L, statins work partly in reducing hs-CRP elevation in non-fasting state.

Introduction

High-sensitivity C-reactive protein (hs-CRP) is a well-known inflammatory factor, which is strongly associated with atherosclerotic cardiovascular diseases[1–3]. A large-sample study in Chinese ischemic stroke population showed that the higher hs-CRP level, the higher the risk of all-cause death would be[4]. Moreover, elevated hs-CRP level is also associated with the increased risk of major adverse cardiac events in patients after percutaneous coronary intervention[5]. Hs-CRP level > 3mg/L is regarded as high hs-CRP level and predicts elevated risk for the first cardiovascular events[6]. Thus, hs-CRP level is an important predictor of cardiovascular events in primary or secondary prevention.

Serum hs-CRP level can be affected by a lot of factors, such as sex, age, waist circumference and systolic blood pressure[7, 8]. In addition, food intake also exerts an important role in hs-CRP level. We previously observed that the non-fasting hs-CRP levels significantly increased at 4 hours (h) after a high-fat meal (800 calories, 50 g fat) only in non-coronary heart disease (CHD) patients at high risk for cardiovascular events, but not in healthy controls[9]. It suggested that the different populations could have different inflammation responses after a high-fat meal. For most of the day, humans are in the postprandial (i.e., non-fasting) state due to the eating habbits, i.e., most people eat food three times a day. Until now, there was no study to explore the changes in hs-CRP levels after a daily meal in Chinese patients with CHD.

Statins using can reduce cardiovascular risk in both primary and secondary prevention through controlling cholesterol levels[10, 11]. It was found that statins can reduce the cardiovascular events in asymptomatic individuals with elevated hs-CRP levels, even without hyperlipidemia[12, 13]. Interestingly, The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) and the Cardiovascular Inflammation Reduction Trail (CIRT) concluded completely opposite which both used antiinflammation therapy. The potential explanation is the baseline CRP level is significantly different between CANTOS

and CIRT, and maybe only subjects with high level of hs-CRP can benefit from statins anti-inflammation[14, 15]. We reported that fluvastatin (40mg/d) effectively reduced non-fasting hs-CRP levels after a high-fat meal in non-CHD patients at high risk for cardiovascular events[9]. However, the effect of statins using on the non-fasting hs-CRP levels after a daily breakfast but not a high-fat meal in CHD patients is unclear.

In the present study, we aimed to learn about the fasting and non-fasting hs-CRP levels after a daily breakfast in hospitalized patients with CHD according to their eating habits, and to analysis the effect of long-term statin therapy on postprandial CRP levels in patients with different fasting CRP levels.

Results

Clinical Characteristics and Fasting Biochemical Examinations in Two Groups

There was no significant difference in age, sex, body mass index (BMI), heart rate, the percentages of smoking, hypertension or diabetes between two groups. CHD patients with fasting hs-CRP ≤ 3mg/L had a higher percentage of cases with long-term [i.e., ≥ 1 month (m)] statins using than those with hs-CRP > 3mg/L (51.4% vs. 23.9%, $P < 0.05$), while they had a lower percentage of cases with short-term (i.e., < 1m) and without statins using than those with hs-CRP > 3mg/L (48.6% vs. 76.1%, $P < 0.05$) (Table 1).

Table 1
Comparisons of baseline characteristics between two groups.

	Fasting hs-CRP ≤ 3mg/L (n = 212)	Fasting hs-CRP > 3mg/L (n = 88)	*P*-value
Age, y	60.1 ± 10.0	61.3 ± 9.9	0.183
Male, n (%)	154 (72.6)	65 (73.9)	0.828
BMI, kg/m^2	25.08 ± 3.36	25.01 ± 3.35	0.857
Smoking, n (%)	106 (50.0)	45 (51.1)	0.858
Hypertension, n (%)	153 (72.2)	68 (77.3)	0.361
Heart rate, bpm	75.45 ± 14.68	78.5 ± 15.00	0.412
Diabetes, n (%)	60 (28.3)	22 (25.0)	0.559
Statins using, n (%)			
≥ 1 m	109 (51.4)	21 (23.9)	0.000
without & < 1 m	103 (48.6)	67 (76.1)	0.000
TG, mmol/L	1.50 (1.07, 2.25)	1.40 (1.09, 1.99)	0.454
TC, mmol/L	3.85 ± 1.00	4.04 ± 0.97	0.096
LDL-C, mmol/L	2.34 ± 0.89	2.55 ± 0.84	0.020
HDL-C, mmol/L	1.02 ± 0.24	1.01 ± 0.23	0.939
hs-CRP, mg/L	1.05 (0.53, 1.88)	5.76 (4.25, 5.75)	0.000

Notes: The levels of blood lipids and hs-CRP were measured in fasting state. Age, body mass index (BMI), heart rate, TC, LDL-C, HDL-C were expressed as mean ± standard deviation (M ± SD). TG and hs-CRP were expressed as median with 25th and 75th percentiles. Others were expressed as numbers and percentages.

There was no significant difference in fasting levels of TG, TC and HDL-C between two groups. CHD patients with fasting hs-CRP ≤ 3mg/L had a significantly lower fasting level of LDL-C than those with hs-CRP > 3mg/L ($P < 0.05$), which could be related to a higher percentage of long-term statins using (Table 1).

Non-fasting Changes in Levels of Blood Lipids in Two Groups

Levels of TC, HDL-C and LDL-C significantly decreased while level of TG significantly increased after a daily meal in two groups ($P < 0.05$). The changes in HDL-C levels after a daily meal were relatively slight in two groups (Fig. 1).

CHD patients with fasting hs-CRP ≤ 3mg/L had significantly lower levels of LDL-C after a daily meal than those with hs-CRP > 3mg/L ($P < 0.05$). However, there was no significant difference in non-fasting levels of TC, TG and HDL-C between two groups (Fig. 1).

Non-fasting Changes In Levels Of Hs-crp In Two Groups

Level of hs-CRP increased after a daily meal in two groups ($P < 0.05$). Non-fasting hs-CRP level at 4h was significantly higher than fasting hs-CRP level in CHD patients with fasting hs-CRP > 3mg/L ($P < 0.05$). Non-fasting hs-CRP levels at both 2h an 4h were significantly higher than fasting hs-CRP level in those with fasting hs-CRP ≤ 3mg/L ($P < 0.05$). CHD patients with fasting hs-CRP level > 3mg/L had significantly higher levels of hs-CRP before and after a daily meal than those with fasting hs-CRP level ≤ 3mg/L ($P < 0.05$) (Fig. 2A).

In either fasting or non-fasting state, the percentage of patients with hs-CRP level ≤ 3mg/L was higher than those with hs-CRP level > 3mg/L. Interestingly, the percentage of patients with hs-CRP level ≤ 3mg/L decreased from fasting 70.7% to around 60% after a daily meal. However, the percentage of patients with hs-CRP level > 3mg/L increased from fasting 29.3% to about 40% after a daily meal (Fig. 2B).

Source Analysis of Patients with Different Hs-CRP Levels in the Non-fasting State

Around 95% of CHD patients with non-fasting hs-CRP ≤ 3mg/L at 2h and 4h derived from those with fasting hs-CRP ≤ 3mg/L. Only about 5% of patients with non-fasting hs-CRP ≤ 3mg/L at 2h and 4h came from those with fasting hs-CRP > 3mg/L.

Around 68% of CHD patients with non-fasting hs-CRP > 3mg/L at 2h and 4h derived from those with fasting hs-CRP > 3mg/L. About 32% of patients with non-fasting hs-CRP > 3mg/L at 2h and 4h came from those with fasting hs-CRP ≤ 3mg/L (Table 2).

Table 2
Source analysis of patients with different hs-CRP levels in the non-fasting state.

Fasting hs-CRP level (mg/L)	Time	Non-fasting hs-CRP level (mg/L)	
		≤ 3	> 3
≤ 3	2 h	94.4	**31.2**
	4 h	95.3	**32.6**
> 3	2 h	5.6	68.8
	4 h	4.7	67.5

Notes: Data were the percentage of CHD patients with non-fasting hs-CRP levels ≤ 3mg/L or not after a daily meal deriving from those with different levels of fasting hs-CRP.

Effect of Statins Using on Non-fasting Changes in Hs-CRP Levels

According to the condition of statins using, all CHD patients were divided into two groups (i.e., ≥ 1m statins using, n = 130 vs. without & < 1m statins using, n = 170). After a daily meal, hs-CRP levels at 2h and 4h significantly increased when compared with the fasting hs-CRP level in each group ($P < 0.05$). Taking all patients as a whole, persons with statins using ≥ 1m had significantly lower hs-CRP levels in the fasting and non-fasting states than those without & < 1m statins using ($P < 0.05$) (Fig. 3A).

According to the condition of statins using, patients with fasting hs-CRP level ≤ 3mg/L were divided into two groups (i.e., ≥ 1m statins using, n = 109 vs. without & < 1m statins using, n = 103). The hs-CRP levels elevated significantly both in patients with statins using ≥ 1m and those without & < 1m statins using (Fig. 3B).

Interestingly, in hs-CRP > 3mg/L group, although the hs-CRP level of inpatients with statins using ≥ 1m slightly elevated at 2h and 4h, there is no significant difference between fasting and non-fasting state. However, the hs-CRP level of inpatients without & < 1m statins using elevated significantly after meal at 4h ($P < 0.05$) (Fig. 3C).

When taking all patients as a whole (n = 300), correlation analysis showed that there was no significant relationship between total AUC of hs-CRP and BMI, total AUC of TG or LDL-C (data were not showed).

Discussion

Elevated hs-CRP level is an important factor predicting the increased CHD risk. It was found that hs-CRP level after a high-fat meal significantly increased in patients with high cardiovascular risk but not in healthy subjects[16]. The present study showed that CHD patients even after a daily breakfast could also cause non-fasting increase in hs-CRP level, regardless of the conditions of statins using and fasting hs-CRP level. It suggested that the non-fasting increase in hs-CRP level could be related not only to the content of meal[17], but also to the underlying diseases of the individuals and the associated cardiovascular risk. More importantly, more than one-third of CHD patients with non-fasting high hs-CRP (i.e., > 3mg/L) came from those without high hs-CRP levels in the fasting state. It indicated that postprandial phase is the key period of atherosclerosis when considering humans are in the postprandial state for most of the day.

Hs-CRP is a kind of hypersensitive detection technology used in clinical laboratory, which can accurately detect low concentration CRP and improve the sensitivity and accuracy of the test. CRP is a nonspecific inflammatory marker secondary to the stimulation of interleukins (IL), including IL-1, IL-6 and IL-17, and the activation of NF-κB plays an important role in regulating CRP production[18, 19]. CRP can be secreted by many cells, such as artery smooth muscle cells, aortic endothelial cells, inflammatory cells, pyramidal neurons, renal cortical tubular epithelial cells and so on, but it mainly comes from hepatocytes in vivo[18, 20–22]. Liver connects with gastrointestinal tract directly via portal vein, and is sensitive to food intake. The gastrointestinal tract delivers lipids to liver through the portal vein when western food which is characterized of high sugar and lipid is digested[23]. Under the stimulation of hyperlipidemia, the liver anti-

inflammatory state could be turned to inflammatory state. No matter what the level of fasting hs-CRP is, the two groups of CHD patients with showed significant and similar increase in TG level after a daily meal. Thus, it can be considered that food intake induced the production of hs-CRP from liver.

In addition, diet-induced systemic inflammation accelerates IL production and release in other cells, which might also promote the production of CRP in the non-fasting state. It has been reported that IL-1β increased significantly in metabolic syndrome patients with central obesity after a high-fat meal, accompanied by significant postprandial hypertriglyceridemia which represents the increased number of triglyceride-rich lipoproteins and their remnants[24]. Chylomicron remnants promoted the expression of IL-1β in monocytes[25]. Moreover, we found that postprandial triglyceride-rich lipoproteins promoted premature aging of mouse subcutaneous adipose derived mesenchymal stem cells through oxidative stress mechanism, accompanying by IL-1α, IL-6 and other inflammatory factors[26]. As a key inflammatory factor in the upstream of inflammatory signaling pathway, IL-1β up-regulation or increased release can trigger a cascade of downstream inflammatory factors, including CRP.

In the present study, there was no significant relationship between total AUC of hs-CRP and BMI or total AUC of TG, which may be due to the influence of lipid-lowering drugs. Because a considerable number of enrolled patients with CHD took statins, which could have an impact on the level of hs-CRP. It was reported that statins play an antiinflammation role in hepatocytes via limiting proinflammatory genes expression, such as limiting NF-κB nuclear accumulation and DNA binding[27]. Additionally, clinical trials also showed the antiinflammatory role of statins[13, 28, 29]. It was consistent with the finding of the present study that statins using ≥ 1m significantly reduced both fasting and non-fasting hs-CRP in CHD patients.

However, statins using ≥ 1m was not able to completely antagonize the rise of hs-CRP level caused by a daily breakfast, even in those with fasting hs-CRP level ≤ 3mg/L. There was no deliberate diet control in this study. A daily breakfast could be a high-fat meal or not for different patients. Dietary habits could be a factor that reduces the effectiveness of drugs in non-fasting state. The Centers for Disease Control and the American Heart Association defined that hs-CRP level ≤ 3mg/L indicated lower or average cardiovascular events risk while hs-CRP level > 3mg/L indicated higher cardiovascular events risk[30]. Under the influence of food intake, the non-fasting hs-CRP elevated to a higher level of hs-CRP (> 3mg/L) in approximately 30% patients with a lower level of fasing hs-CRP (≤ 3mg/L). It indicated that about 30% of CHD patients in higher cardiovascular events risk group in the non-fasting state derived from lower or average cardiovascular risk group in the fasting state. Considering that humans are in the postprandial state in the most of a day, thus the detection of fasting hs-CRP level is not enough to reflect the real state of hs-CRP throughout a day. It was confirmed that intermittent fasting was responsible to reducing risk factors of cardiovascular disease, such as LDL-C, TG and fat mass[31, 32]. However, it was still uncertain whether it will influence the cardiovascular risk deriving from hs-CRP elevation in the non-fasting state.

Elevated hs-CRP act as both inducer and indicator of CHD, patients with CHD showed increased hs-CRP despite LDL-C < 70mg/dL and consequently benefited from antiinflammation therapy[33]. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) proved that reducing hs-CRP

though the IL-1β and downstream IL-6-receptor signaling pathway without reducing LDL-C level significantly lower incidence of recurrent cardiovascular events[14]. Interestingly, the Cardiovascular Inflammation Reduction Trail (CIRT) using Methotrexate to antiinflammation showed a completely contrary result compared with CANTOS[15]. According to CANTOS, antiinflammation therapy can independently reduce hs-CRP and cardiovascular events without LDL-C level changed. However, CIRT concluded patients with stable atherosclerosis did not reduce levels of IL-1β, IL-6, or hs-CRP and did not result in fewer cardiovascular events exposure to low-dose methotrexate, a kind of anti-inflammation drug probably reflects adenosine-mediated anti-inflammatory effects. A possible explanation is that the baseline CRP level in CANTOS (4.2mg/L) is significantly higher than in CIRT (1.6mg/L), indicating only patients with high baseline CRP level can benefit from statins anti-inflammation therapy.

Our study result is accord with the result of CANTOS and CIRT studies, statins play a role in non-fasting hs-CRP level decrease in CHD patients with higher fasting hs-CRP level. In our study, in fasting hs-CRP level ≤ 3mg/L group, hs-CRP level elevated significantly in both subgroups regardless of statins duration after meal in 2h and 4h. Interestingly, it is completely different in fasting hs-CRP > 3mg/L group, the hs-CRP level of inpatients with statins using ≥ 1m didn't elevated significantly after meal, but the inpatients without & < 1m statins using whose hs-CRP level gradually elevated after meal, especially in 4h, and it is significantly higher than hs-CRP level in fasting state. Therefore, we hypothesis statins can reduce non-fasting hs-CRP level when fasting level of hs-CRP > 3mg/L.

Conclusions

In conclusion, hs-CRP levels increased significantly in CHD patients after a daily meal. About 32% of patients with non-fasting hs-CRP > 3mg/L at 2h and 4h came from those with fasting hs-CRP ≤ 3mg/L. Statins using ≥ 1m can improve the non-fasting inflammatory response effectively only in patients with fasting hs-CRP > 3mg/L, however, it was not able to completely antagonize the rise of hs-CRP level caused by a daily breakfast in both group.

Limitations

There were several limitations in this study. First, the investigation on the effect of statins using on hs-CRP level was a cross-sectional one rather than a prospective one. Second, the breakfast contents of patients were not recorded and analyzed in detail.

Methods

Subjects

A total of 300 inpatients at the Department of Cardiovascular Medicine in the Second Xiangya Hospital of Central South University were recruited in this study from August 2015 to October 2019. The cohort included 300 patients with CHD. CHD was defined as a history of myocardial infarction (MI) and/or

angiographically proven coronary atherosclerosis in patients with angina pectoris (AP)[34]. Contemporaneous subjects who had no clinical history and manifestation of CHD were excluded. According to fasting level of hs-CRP > 3 mg/L or not, patients with CHD were divided into two groups, i.e., group with fasting hs-CRP > 3 mg/L or not.

The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University and conformed to the 1975 Declaration of Helsinki. Informed consent was gained from all subjects.

Laboratory Examinations

After fasting for at least 8h, venous blood samples were collected in all persons at fasting state and at 2h, 4h after a daily breakfast. Serum levels of total cholesterol (TC) and triglyceride (TG) were measured by automated enzymatic assays, and those of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by a commercially available direct method (Wako, Japan), i.e., selective protection method and antibody blocking method, respectively, on a HITACHI 7170A analyzer (Instrument Hitachi Ltd., Tokyo, Japan) by a laboratory technician who had no idea of this study[35]. Hs-CRP was analyzed from samples with a latex turbidimetric immunoassay (Medicalsystem, Ningbo, China). The analytical detection limit for this method is 0.5 mg/L.

Statistical Analysis

Statistical analysis was performed on SPSS 24.0. Data drawing was completed by Graphpad Prism 7.0 software. Quantitative variables were expressed as mean ± standard deviation, and qualitative variables were expressed as numbers and percentages. Fasting TG and hs-CRP levels not conforming to a normal distribution were log transformed for comparison and presented as median with 25th and 75th percentiles. Differences between the intra- and intergroup means were analysed by student's *t*-test. The statistical differences of non-normal distribution data were tested by Mann-Whitney nonparametric test. Categorical variables were compared using chi-squared statistic tests. All *P* values were 2-tailed, and $P < 0.05$ was considered statistically significant.

Declarations

Acknowledgments

We are grateful to all patients for their participating in this study.

Author contributions

QLin, YX and LL designed and conducted of this study. QLin, YX, YF and XWen participated in the collection and analysis of the data. YX and QLin contributed to the preparation of the manuscript. LL and QLiu conducted the literature review. All authors read the study and approved the manuscript for publication.

Funding

This project was supported by the National Natural Science Foundation of China [grant numbers. 81270956, 81470577] and the Fundamental Research Funds for the Central Universities of Central South University [grant number 2020zzts289].

Conflict of interests

The authors reported no relationship that could be construed as a conflict of interest.

Ethics statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The data collection procedure was discussed and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University.

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Figures

Figure 1

Comparisons of changes in levels of blood lipids after a daily meal between two groups. (A-D) The changed levels of TC (A), TG (B), LDL-C (C) and HDL-C (D) in two groups (i.e., CHD patients with fasting hs-CRP level ≤ 3mg/L or not). *P < 0.05 when compared with fasting hs-CRP ≤ 3mg/L group at the same time point, #P < 0.05 when compared with the fasting concentration in the same group.

Figure 2

Comparisons of changes in hs-CRP levels after a daily meal between two groups. (A) Changes of postprandial hs-CRP level in two groups (i.e., CHD patients with fasting hs-CRP level ≤ 3mg/L or not). (B) Comparisons of the percentages of patients with hs-CRP ≤ 3mg/L and > 3mg/L at different time points. *P < 0.05 when compared with fasting hs-CRP ≤ 3mg/L group at the same time point, # P < 0.05 when compared with the fasting level within each group.

Figure 3

Comparisons of the changes in hs-CRP levels after a daily meal between CHD patients with different terms of statins using. (A) Comparisons of the changes in hs-CRP after a daily meal between patients with different terms of statins using in all subjects (i.e., ≥ 1m statins using, n = 130 vs. without & < 1m statins using, n = 170). (B) Comparisons of the changes in hs-CRP after a daily meal between patients with different terms of statins using in those with fasting hs-CRP level ≤ 3mg/L (i.e., ≥ 1m statins using, n = 109 vs. without & < 1m statins using, n = 103). (C) Comparisons of the changes in hs-CRP after a daily meal between patients with different terms of statins using in those with fasting hs-CRP level > 3mg/L (i.e., ≥ 1m statins using, n = 21 vs. without & < 1m statins using, n = 67). * P < 0.05 when compared with CHD patietns without or with statins using < 1m at the same time point. # P < 0.05 when compared with the fasting level within each group.