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Review

# Postprandial hyperlipidemia as a potential residual risk factor

Kazufumi Nakamura (MD, FJCC)[a,*], Toru Miyoshi (MD, FJCC)[a], Kei Yunoki (MD)[b], Hiroshi Ito (MD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[b] Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

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ABSTRACT

Statin therapy targeting reduction of low-density lipoprotein cholesterol (LDL-C) decreases the risk of coronary heart disease (CHD) and all-cause mortality. However, a substantial number of cases of CHD are not prevented and residual risk factors remain unsettled. A high triglyceride (TG) level is considered to be an important and residual risk factor. Postprandial hyperlipidemia is a condition in which TG-rich chylomicron remnants are increased during the postprandial period and hypertriglycedemia is protracted. Postprandial hyperlipidemia evokes atherogenesis during the postprandial period. Several prospective studies have revealed that nonfasting serum TG levels predict the incidence of CHD. Values of TG, remnant lipoprotein cholesterol, and remnant lipoprotein TG after fat loading were significantly higher in diabetes patients with insulin resistance than in diabetes patients without insulin resistance.

Endothelial dysfunction is an initial process of atherogenesis and it contributes to the pathogenesis of CHD. Postprandial hyperlipidemia (postprandial hypertriglyceridemia) is involved in the production of proinflammatory cytokines, recruitment of neutrophils, and generation of oxidative stress, resulting in endothelial dysfunction in healthy subjects, hypertriglyceridemic patients, or type 2 diabetic patients.

Effective treatment has not been established till date. Ezetimibe or omega-3 fatty acids significantly decrease postprandial TG elevation and postprandial endothelial dysfunction. Ezetimibe or omega-3 fatty acids added to statin therapy reduce serum TG levels and result in good outcomes in patients with CHD.

In conclusion, postprandial hyperlipidemia is an important and residual risk factor especially in patients with insulin resistance syndrome (metabolic syndrome) and diabetes mellitus. Further studies are needed to establish effective treatment.



**Contents**



* Corresponding author at: 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. Tel.: +81 86 235 7351; fax: +81 86 235 7353.
*E-mail address:* ichibun@cc.okayama-u.ac.jp (K. Nakamura).

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## Introduction

Many clinical trials and meta-analyses have revealed that statin therapy targeting reduction of low-density lipoprotein cholesterol (LDL-C) decreases the risk of coronary heart disease (CHD) and all-cause mortality [1,2]. However, a substantial number of cases of CHD are not prevented and residual risk factors remain unsettled. In particular, a low high-density lipoprotein cholesterol (HDL-C) level and a high triglyceride (TG) level are considered to be important and residual risk factors [3].

Serum TG level gradually increases after a meal, reaches a peak at 3–4 h after the meal, and then slowly returns to its initial level at 6–8 h after the meal [4–6]. Therefore, most of the day is a nonfasting state (in other words a postprandial state) for people who eat at least three meals a day (Fig. 1). The body is exposed to circulating lipids throughout most part of the day. A fasting state occurs for only a short period of the day. Thus, postprandial hyperlipidemia needs to be treated strictly.

## Significance of postprandial hyperlipidemia

Postprandial hyperlipidemia is a condition in which TG-rich chylomicron remnants are increased during the postprandial period and hypertriglycedemia is protracted. Postprandial hyperlipidemia evokes atherogenesis during the postprandial period [7].

Several prospective studies have revealed that nonfasting serum TG levels predict the incidence of CHD [8–11]. Iso et al. reported that the incidence of CHD was greater in a dose–response manner across increasing quartiles of nonfasting TG levels [8]. Eberly et al. reported that the prevalence of hypertriglyceridemia (200 mg/dL or more) in nonfasting values was higher than that in fasting values and that nonfasting and fasting TG levels were similarly predictive of nonfatal or fatal CHD [10]. Nonfasting LDL-C also has a prognostic value similar to that of fasting LDL-C [12]. Considering that the period of a fasting state in one day is short, the nonfasting lipid profile may be more useful than the fasting lipid profile for risk stratification [13].

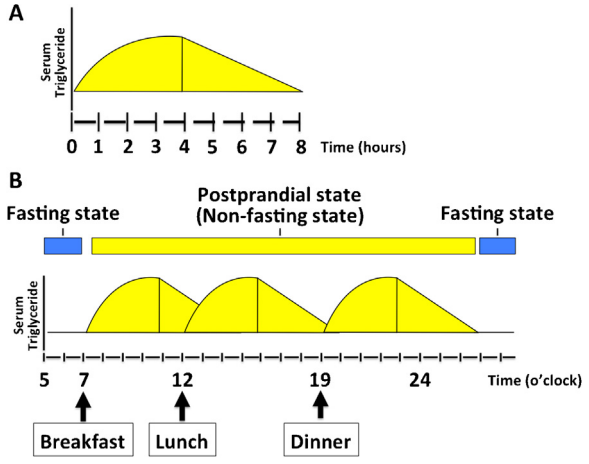


**Fig. 1.** Serum TG levels after the meal. (A) Serum TG levels reach a peak at 3–4 h after the meal and slowly return to initial levels at 6–8 h after the meal. (B) Most of the day is a nonfasting state (in other words a postprandial state) in people who eat at least three meals a day.

In patients with diabetes mellitus, remnant lipoprotein cholesterol levels remain high throughout the day except for a few hours before breakfast [14]. Therefore, measurement of nonfasting lipid profiles is necessary for evaluating coronary risk in patients with diabetes mellitus. Furthermore, values of TG, remnant lipoprotein cholesterol, and remnant lipoprotein TG after fat loading were shown to be significantly higher in diabetes patients with insulin resistance than in diabetes patients without insulin resistance [15]. Kim et al. also reported that postprandial accumulation of remnant lipoproteins is accentuated in insulin-resistant, postmenopausal women [16]. These results indicate that measurement of nonfasting lipid profiles is important for evaluating coronary risk in patients with insulin resistance syndrome (metabolic syndrome).

## Atherosclerosis and postprandial hyperlipidemia

### *Atherogenesis*

Lipoprotein particle metabolism is divided into two pathways, exogenous and endogenous pathways.

*Exogenous pathway*

Chylomicrons, lipoprotein particles that consist of TG (85–92%), phospholipids (6–12%), cholesterol (1–3%), and proteins (1–2%) including apolipoprotein (Apo) B-48 [17], transport dietary lipids from the intestines to the water-based solution of the bloodstream. When TG cores have been hydrolyzed by lipoprotein lipase, which is an enzyme on endothelial cells, chylomicron remnants are formed and are taken up by the liver.

*Endogenous pathway*

In the liver, triacylglycerols and cholesteryl ester are assembled with Apo B-100 to form very low-density lipoprotein (VLDL) particles, and VLDL particles are released into the bloodstream. VLDL is also hydrolyzed by lipoprotein lipase, and VLDL remnants or intermediate-density lipoprotein (IDL) is formed. VLDL remnants or IDL are hydrolyzed by hepatic lipase, and LDL is formed.

Chylomicrons, chylomicron remnants, VLDL, and IDL (VLDL remnants) contain large amounts of TG (chylomicrons: 85%, VLDL: 55%, and IDL: 25%). They are called TG-rich lipoproteins. In postprandial hyperlipidemia, TG-rich chylomicron remnants are increased and hypertriglycedemia is prolonged. Not only LDL and TG-rich VLDL remnants (IDL) derived from the endogenous pathway but also TG-rich chylomicron remnants derived from the exogenous pathway are taken up by macrophages and contribute to the foaming of macrophages [18–20].

Remnant cholesterol causes low-grade inflammation. Interestingly, Varbo et al. reported a causal association between elevated nonfasting remnant cholesterol (which is nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol) and low-grade inflammation assessed by C-reactive protein (CRP) elevation, together with increased risk of ischemic heart disease (IHD) and no causal association between elevated LDL cholesterol and low-grade inflammation [21]. Remnant cholesterol and nonfasting TG are highly correlated ($R^2$ = 0.96) [22] because remnant cholesterol is the cholesterol content of TG-rich lipoproteins including VLDL and VLDL remnants (IDL) in the fasting state and chylomicron remnants in the nonfasting state. Therefore, lowering of nonfasting