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Review

Postprandial hyperlipidemia as a potential residual risk factor

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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.

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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].

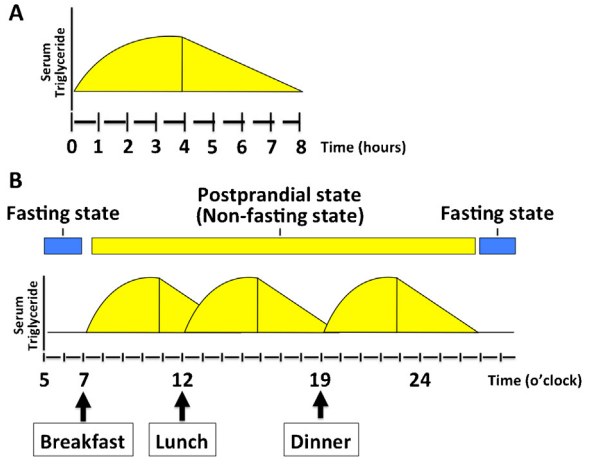

Fig. 1. Serum TG levels after the meal. (A) Serum TG levels reach a peak at 3–4 h after the meal and slowly return to initial levels at 6–8 h after the meal. (B) Most of the day is a nonfasting state (in other words a postprandial state) in people who eat at least three meals a day.

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

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TG is at the same time a lowering of remnant cholesterol levels. These findings indicate that nonfasting TG is an important and residual risk factor when LDL cholesterol is lowered to recommended levels.

Endothelial dysfunction

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 [23–25]. Remnant lipoproteins (or remnant-like lipoproteins) decrease nitric oxide (NO) released from the endothelium [26]. Remnant lipoproteins induce oxidative stress and production of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α [27], and depress the activity of endothelial nitric oxide synthase (eNOS) in endothelial cells [28]. Furthermore, CRP, a circulating inflammatory marker, inhibits eNOS activity [29,30] and TNF-α decreases eNOS protein expression [31].

Measurement of brachial artery flow-mediated dilation (FMD) using high-resolution ultrasonography is a sensitive method for detecting endothelial dysfunction. Shear stress via reactive hyperemia in the forearm induces NO release and subsequent vasodilatation. Postprandial hyperlipidemia (postprandial hypertriglyceridemia) causes endothelial dysfunction assessed by brachial artery FMD [5,25,32,33]. Acetylcholine (ACh)-induced vasodilatation is mediated by NO released from the endothelium in human coronary arteries. Kugiyama et al. reported that remnant lipoprotein levels were independently associated with abnormal endothelium-dependent vasomotor responses to ACh infusion, reflected by impaired dilation or constriction of the epicardial coronary arteries [34].

Diagnosis of postprandial hyperlipidemia

There is still no established method for diagnosis of postprandial hyperlipidemia. Epidemiologic studies conducted in Japan have shown that the incidences of myocardial infarction, exercise-induced angina, and sudden death increase when the nonfasting TG level is ≥165 mg/dL [8,35].

Examining the effects of oral fat loading on the magnitude and duration of hyperlipidemia is considered to be useful [5,13,15,36,37]. For fat loading, a cookie test and a cream test have been reported [13,37]. The cookie consisted of 75 g carbohydrate (flour starch and maltose), 28.5 g fat (butter), and 8 g protein for a total of 592 kcal a carton (SARAYA Corp, Osaka, Japan) [37] and the oral fat tolerance test (OFTT) cream consisted of 57% water, 33% lipid, 3% protein, and 7% carbohydrate (Jomo Food Industry, Takashi, Japan) [13]. Harano et al. recommend the use of the cookie containing 75 g carbohydrate in conjunction with a 75 g oral glucose tolerance test (OGTT) [37]. Serum TG and remnant-like particles-cholesterol (RLP-C) were elevated at 1 and 2 h after the cookie ingestion. At 1 or 2 h, levels exceeding 0.75 mmol/L (66 mg/dL) and 0.085 mmol/L for RLP-C above basal were defined as postprandial dyslipidemia.

An oral fat loading test, which takes over 4 h, can reveal postprandial lipid profiles including total cholesterol (TC), TG, LDL-C, HDL-C, Apo B-48, RLP-C, and RLP-TG [4,5,13,15]. After an overnight fast, subjects ingest 17 or 30 g fat/m^2 body surface area contained in a cookie or cream. Venous blood samples are obtained before and 2, 4, 6, and 8 h after the oral fat load to determine lipid profiles. Postprandial serum levels of TG, RLP-C, RLP-TG, and ApoB-48 significantly increase and reach peak levels at the 4th hour and return to baseline levels at the 8th hour in healthy subjects ($n = 20$) (Fig. 2A and B) [5,13]. Serum levels of TC, LDL-C, HDL-C, and ApoB-100 remain constant or show a minimal change throughout the 8-h period [4,5,13,15]. Blood glucose levels do not change during the fat loading test using the cream [13,15], but they are increased at 2 h after fat load using the cookie, which contains a larger amount of carbohydrate [5].

Interestingly, postprandial brachial artery FMD decreases and reaches the lowest level at the 4th hour after oral fat load (Fig. 2C). Linear regression analysis revealed that the maximum reduction in postprandial %FMD is associated with the maximum increases in postprandial TG and ApoB-48 levels [5]. A combination test of an oral fat loading test and brachial artery FMD is useful for evaluating the association of postprandial hyperlipidemia with endothelial dysfunction [5,6,32,38–40].

Treatment of postprandial hyperlipidemia

Diet and exercise

A diet that includes large amounts of fresh, unprocessed plants, with moderate levels of lean protein and beneficial fats, such as omega-3, will substantially improve postprandial glucose and lipid levels [38].

Abdominal (central) obesity contributes to insulin resistance. Exercise improves insulin sensitivity and acutely lowers glucose and TG levels [41].

Pharmacologic therapy for postprandial hyperlipidemia

Effective treatment has not been established till date. We will describe the available evidence and potential drugs.

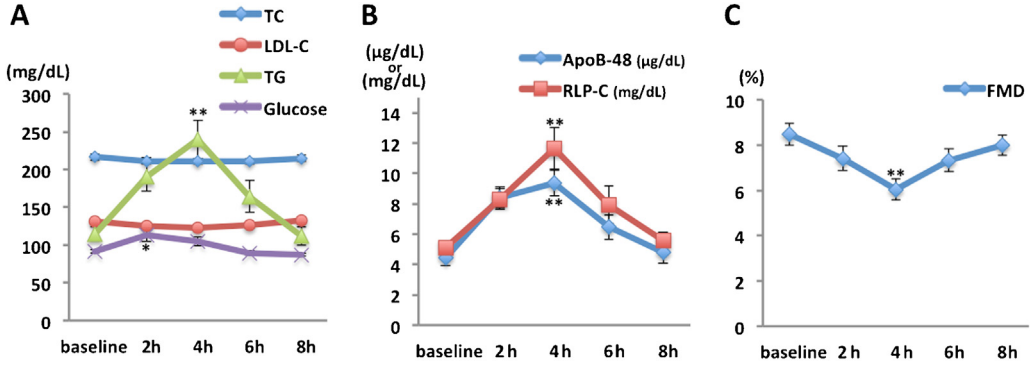

Fig. 2. Postprandial profiles of serum lipid, blood glucose, and FMD after the cookie test in healthy subjects. (A) Postprandial changes in TC, TG, LDL-C, and glucose. (B) Postprandial changes in Apo B-48 and RLP-C. (C) Postprandial brachial artery %FMD. $N = 20$. Data are expressed as mean ± SE. $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. baseline. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Apo, apolipoprotein; RLP-C, remnant-like particles-cholesterol; FMD, flow-mediated dilation.

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Statins

Statin treatment is a well-established therapy for reducing cardiovascular disease. The most prominent effects of statin treatment are its potent LDL-C-lowering properties, but it is also well known that statins significantly reduce TG levels. Statin therapy is recommended as the first pharmacological step to reduce elevated LDL-C and TG levels in high-risk subjects, particularly subjects with metabolic syndrome and diabetes. However, beneficial effects of statins on apoB48 plasma levels are debatable [42]. Therefore, add-on therapy for use with statins is needed to improve postprandial hyperlipidemia, a residual risk factor.

Ezetimibe

Ezetimibe inhibits intestinal cholesterol absorption by blocking Niemann-Pick C1-like 1 (NPC1L1) protein. Ezetimibe improves fasting and postprandial hyperlipidemia by suppression of intestinal chylomicron production in patients with type IIb hyperlipidemia and in healthy subjects [4,5]. Ezetimibe treatment suppresses postprandial elevation of TG, remnant lipoprotein cholesterol, and ApoB48. Postprandial hyperlipidemia is closely correlated with transient endothelial dysfunction assed by FMD, and ezetimibe improves postprandial hyperlipidemia and its induced endothelial dysfunction [5].

A recent clinical trial, IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), revealed that ezetimibe added to statin therapy after acute coronary syndrome resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes [43]. The PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) study also revealed that the treatment with the combination of a statin and ezetimibe resulted in greater coronary plaque regression than that with standard statin monotherapy [44]. These results might be attributed to lowering LDL cholesterol to levels below previous targets. Furthermore, the results of those studies showed that ezetimibe added to statin therapy reduced levels of TG (IMPROVE-IT) or RLP-C (PRECISE-IVUS). We previously reported that hypertriglyceridemia is independently associated with endothelial dysfunction in patients with CHD during statin therapy and that ezetimibe add-on therapy improves endothelial function along with reduction of TG in these high-risk populations [45]. Therefore, ezetimibe added to statin therapy achieves not only further reduction in LDL-C but also improvement in hypertriglyceridemia and results in good outcomes in patients with CHD.

Omega-3 fatty acids

Fish oil supplementation reduces TG levels. We previously reported that omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) significantly decreased postprandial TG elevation and postprandial endothelial dysfunction [6]. The JELIS (Japan EPA lipid intervention study) trial revealed that EPA added to statin therapy prevented major coronary events in hypercholesterolemic patients compared with standard statin monotherapy [46]. In that study, levels of TG reduction in patients who received the combination therapy of a statin plus EPA were significantly larger than those in patients who received the standard statin monotherapy.

Fibrates

Fibrates, peroxisome proliferator-activated receptor-alpha (PPAR-α) agonists, reduce postprandial lipemia. We previously reported that bezafibrate significantly reduced postprandial elevation of TG-rich lipoproteins and decreased postprandial endothelial dysfunction [40]. However, combination therapy of statins and fibrates has been restricted following early reports of rhabdomyolysis. K-877, a potent and selective PPAR-α modulator (SPPARMα) [47], significantly reduced TG concentrations in dyslipidemic patients on stable statin treatment and was well tolerated [48]. K-877 is expected to be useful for reducing residual risk factors during statin therapy.

Conclusions

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.

Conflicts of interest

Drs Nakamura, Miyoshi, and Ito have received lecturer fees from MSD. K. K, Mochida Pharmaceutical Co., LTD., and Takeda Pharmaceutical Company Limited.

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