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ORIGINAL ARTICLE

Pitavastatin prevents postprandial endothelial dysfunction via reduction of the serum triglyceride level in obese male subjects

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Abstract Obesity is a well-established risk factor for the development and progression of coronary heart disease. Moreover, endothelial dysfunction is an early event in atherosclerosis and is known to be associated with postprandial hypertriglyceridemia. The purpose of this study was to determine whether a statin might have an effect on postprandial hypertriglyceridemia, and thereby on endothelial function in obese subjects. Twenty-four obese male subjects were recruited for this study. They were randomly assigned to receive pitavastatin (2 mg/day) or placebo for 2 weeks. The oral fat loading test using OFTT cream was performed pre- and post-treatment, in which the lipid profile and flow-mediated dilation (FMD) were assessed before and 4 h after an oral fat load. In the oral fat loading test conducted pretreatment, the oral fat load induced a marked increase of the serum triglyceride (TG) level and decrease in FMD in the pitavastatin and placebo group. In the test conducted post-treatment, the increase in postprandial TG was attenuated (+183 vs. +81 mg/dL, $P < 0.001$) and decrease in postprandial FMD was completely abolished (−1.1 vs. +0.1%, $P < 0.01$) by pitavastatin treatment. Moreover, there was a good correlation between the change in postprandial TG and the change in postprandial FMD after the 2 weeks of treatment ($r = -0.737$, $P < 0.001$). Pitavastatin might prevent endothelial dysfunction caused by postprandial hypertriglyceridemia within 2 weeks of therapy in obese subjects.

Keywords Endothelial function · Triglycerides · Postprandial response · Pitavastatin

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Introduction

Although measurement of the lipid profile is routinely performed in the early morning in the fasting state, recent studies have revealed that the postprandial lipid profile might be more relevant for the determination of cardiovascular risk [1, 2]. This study group has also previously demonstrated that the intimal-medial thickness of the carotid artery was increased in diabetic patients with postprandial hypertriglyceridemia [3]. However, these studies addressing the significance of the postprandial lipid profile have in common the clinical limitation that the main contributor cannot be precisely determined, as not only lipids but also other parameters, such as the serum glucose level, change in the postprandial state.

Various reports have shown that an acute lipid load produces a marked increase of the serum triglyceride (TG) or remnant-like particle cholesterol (RLP-C) level, and also a consistent onset of endothelial dysfunction [4, 5], which reaches its maximum by 4 h after a standard fat load [5]. In these studies, investigators have used various oral fat tolerance tests with various materials, some of which induce the change of glucose as well as lipid metabolism [6]. OFTT cream is used in oral fat tolerance tests, and can cause postprandial hypertriglyceridemia without change in glucose metabolism [7]. OFTT cream, therefore, seems

appropriate for use as a test substance to evaluate the influence of lipids on endothelial function. However, there are few studies examining the effect of statins on postprandial endothelial dysfunction using OFTT cream.

HMG-CoA reductase inhibitors (statins), thought to be one of the candidate drugs for improving endothelial function, exert this beneficial effect via lowering of the serum lipid levels and/or their pleiotropic effects. Some studies suggested that statin therapy prevented postprandial endothelial dysfunction in healthy volunteers and in diabetic patients [4, 8], but the contributions of lipid-modifying effects of statins on postprandial endothelial function have not yet been well demonstrated.

In the present study, we performed an oral fat loading test using OFTT cream to assess the effects of statins on both endothelial function and lipid profile in the postprandial state.

Materials and methods

Subjects and study design

Twenty-four obese male subjects (mean age 44 years; range 29–68 years) were recruited for the present study. Obesity was defined as a body mass index of $\geq$25 kg/m^2, as proposed by the Japanese Society for the Study of Obesity [9]. All of the subjects were thought to need lifestyle modification and/or medication for obesity; however, none had received any medication until enrollment in the study. The subjects were advised not to change their diet from 2 weeks prior to the start and throughout the present study. They were randomly assigned to receive pitavastatin (Kowa, Nagoya, Japan) at 2 mg/day or placebo, using the sealed-envelope method, for 2 weeks. To induce the postprandial state relevant to our study, we performed an oral fat loading test using OFTT cream, and the serum lipid profile and endothelial function was evaluated by flow-mediated dilation (FMD) measured before and 4 h after the oral fat load. The decision to limit the sampling time to 4 h after the oral fat load was based on a report that the serum TG and RLP-C levels reached their peak at 4 h after an oral fat load [4, 10].

This study was conducted with the approval of our institutional Ethics Committee and in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from each of the participants.

Oral fat loading test

The composition of the test cream (OFFT cream; Jomo, Takasaki, Japan) is shown in Table 1. OFTT cream was developed as a fat load test to obtain data fundamental to establish a method for the evaluation of postprandial hypertriglyceridemia. This formula contains 74 mg of cholesterol per 100 g. The oral fat loading test was performed as previously described [10]. After each subject had fasted overnight for 12 h, he was given 70 g of OFTT cream. The serum lipid profile and FMD were measured before and 4 h after the oral fat load.

Table 1 Composition of oral fat tolerance test cream

Energy (kcal)	342
Casein Na (%)	1.5
Sucrose esters of fatty acid (%)	0.5
Lecithin (%)	0.36
Glycerin fatty acid ester (%)	0.25
Stevia sweetener (%)	0.02
Water (%)	62.4
Butter fat (%)	35.0
Saturated fatty acid (%)	22.5
Monounsaturated fatty acid (%)	1.2
Polyunsaturated fatty acid (%)	11.3

Values per 100 g of OFTT cream are shown

Lipid parameters

The serum lipid profile, including the serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG, was measured by standard laboratory procedures. Serum low-density lipoprotein cholesterol (LDL-C) was quantified by a direct homogeneous assay method [11].

FMD assessment

The brachial arterial diameter was measured on B-mode ultrasound images with the EnVisor (Philips Medical Systems, Bothell, WA, USA) and a 3.0–12.0 MHz linear-array transducer. The artery was scanned longitudinally and the center of the artery was identified at the point where the clearest view of the anterior and posterior intimal layers could be obtained. After a resting scan (baseline), a pneumatic tourniquet tied around the forearm was inflated to a pressure of 250 mmHg for 5 min and then released, to produce rebound increase of blood flow. A second scan was performed continuously from 30 s before to 90 s after the deflation of the cuff. Subsequently, 10–15 min were allowed for recovery of the blood flow and then an additional scan was performed. Finally, 3–4 min later, a sublingual nitroglycerin (NTG) spray (300 mg) was administered and the scanning was repeated. The sonographer was blinded to the treatment given to the subjects. The vessel diameters were measured by two independent

observers, with FMD and NTG-induced dilatation being calculated as a percent change from the baseline diameter, and the results were averaged.

Statistical analysis

Statistical analysis was performed using the JMP software (SAS Institute, Cary, NC, USA). Data are shown as mean ± standard deviation (SD), or as indicated. Comparisons of continuous variables between two groups were performed by two-sample *t*-test or Wilcoxon's rank sum test. The effects of the oral fat load and drug treatment were evaluated by the one-sample *t*-test or Wilcoxon's signed rank test, according to their distribution. General linear models were used to assess the relationships between the nominal changes in the postprandial FMD and nominal changes in postprandial serum lipids following the treatment. Univariate and multivariate regression analysis were used to identify independent predictors of improvement of the postprandial FMD after the treatment. Variables used in the univariate analysis were the nominal changes in the serum LDL-C, HDL-C, and TG after the treatment, and the same variables were entered into the multivariate model. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics of the subjects

Twenty-four male subjects were enrolled for evaluation of the endothelial function after an oral fat load. All the subjects were middle-aged and obese. About 50% of the subjects were diagnosed as having metabolic syndrome according to the Japanese criteria [12]. The clinical characteristics at the baseline, except for age, were comparable between the placebo group ($n = 12$) and the pitavastatin group ($n = 12$) (Table 2).

Postprandial responses at baseline

Before treatment, the oral fat load induced a marked increase of the serum TG from 194.4 ± 107.2 to 373.5 ± 184.5 mg/dL ($P < 0.001$), while the serum HDL-C was slightly, but significantly, reduced from 50.8 ± 7.9 to 49.2 ± 8.3 mg/dL ($P < 0.001$) in all patients; no significant change of the serum LDL-C was observed (138.1 ± 35.6 vs. 139.4 ± 34.7 mg/dL, $P = 0.11$). With regard to the endothelial function, a significant decrease of FMD was observed after an oral fat load in all the subjects (10.7% ± 2.4% vs. 9.5% ± 2.8%, $P < 0.001$), while no significant change of endothelium-independent vasodilatation mediated by NTG was observed (data not shown). Similar changes were observed in both placebo and pitavastatin groups (Table 3; Fig. 1a), in which the increases in postprandial serum TG (+175.7 ± 141.3 vs. +182.6 ± 88.0 mg/dL, $P = 0.89$) and the decreases in postprandial FMD (−1.3 ± 1.6 vs. −1.1 ± 1.2%, $P = 0.84$) were comparable, although these two groups were different in age at baseline.

Effects of pitavastatin in the fasting state

Both placebo and pitavastatin were tolerated well by the subjects. No adverse events were observed. The effects of pitavastatin on the lipid profile and FMD in the fasting state are shown in Table 3 and Fig. 1a. In the pitavastatin group, significant decreases of the serum TC, LDL-C, and TG by −16.4%, −19.5%, and −17.6%, respectively, were

Table 2 Baseline patient characteristics

	Placebo ($n = 12$)	Pitavastatin ($n = 12$)	*P*
Age (years)	39.8 ± 9.2	48.4 ± 8.7	0.03
Male, *n* (%)	12 (100)	12 (100)	–
Body mass index (kg/m^2)	29.4 ± 1.7	28.5 ± 2.7	0.34
Waist circumference (cm)	97.6 ± 6.6	95.5 ± 5.0	0.41
Systolic blood pressure (mmHg)	136.0 ± 14.6	140.8 ± 19.9	0.50
Diastolic blood pressure (mmHg)	88.3 ± 8.4	92.3 ± 13.9	0.41
Glucose (mg/dL)	95.9 ± 9.2	114.3 ± 32.8	0.08
Hypertension, *n* (%)	7 (58)	8 (67)	0.67
Diabetes mellitus, *n* (%)	0 (0)	2 (17)	0.14
Metabolic syndrome, *n* (%)[a]	5 (42)	7 (58)	0.41
TC (mg/dL)	217.4 ± 54.2	231.8 ± 52.2	0.51
LDL-C (mg/dL)	130.6 ± 30.6	145.7 ± 39.9	0.31
HDL-C (mg/dL)	48.6 ± 5.6	53.0 ± 9.5	0.19
TG (mg/dL)	195.3 ± 121.3	193.6 ± 96.5	0.97
FMD (%)	11.1 ± 2.3	10.4 ± 2.4	0.47

Data are expressed in numbers (percentage) unless otherwise specified. Continuous variables are represented by mean ± SD

TC total cholesterol; *LDL-C* low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol; *TG* triglycerides; *FMD* flow-mediated dilation

[a] Metabolic syndrome was diagnosed in accordance with the Japanese criteria

Table 3 Changes in postprandial lipid parameters following treatment

	Placebo			*P* value compared with baseline	Pitavastatin			*P* value compared with baseline
	Baseline	2 weeks	% Change		Baseline	2 weeks	% Change	
TC (mg/dL)								
Fasting	217.4 ± 54.2	212.2 ± 47.0	−1.9 ± 7.1	0.37	231.8 ± 52.2	192.8 ± 41.0	−16.4 ± 6.4	<0.001
Postprandial	218.1 ± 53.5	213.7 ± 46.6	−1.5 ± 6.2	0.42	232.1 ± 50.0	195.0 ± 41.5	−15.7 ± 6.2	<0.001
Nominal change	0.7 ± 5.0	1.5 ± 4.0	–	0.75[b]	0.3 ± 5.5	2.3 ± 3.8	–	0.33[b]
P value compared with fasting	0.83[a]	0.21[a]			0.81[a]	0.07[a]		
LDL-C (mg/dL)								
Fasting	130.6 ± 30.6	130.8 ± 33.0	−0.1 ± 7.9	0.97	145.7 ± 39.9	116.6 ± 31.5	−19.5 ± 8.0	<0.001
Postprandial	131.6 ± 31.6	131.5 ± 33.8	−0.2 ± 7.0	0.91	147.2 ± 37.4	115.8 ± 30.5	−21.1 ± 7.5	<0.001
Nominal change	1.0 ± 3.9	0.7 ± 3.9	–	0.98[b]	1.5 ± 3.7	−0.8 ± 4.2	–	0.06[b]
P value compared with fasting	0.47[a]	0.67[a]			0.19[a]	0.60[a]		
HDL-C (mg/dL)								
Fasting	48.6 ± 5.6	47.9 ± 5.6	−1.0 ± 9.1	0.71	53.0 ± 9.5	54.1 ± 9.0	2.5 ± 6.1	0.19
Postprandial	46.8 ± 5.3	47.3 ± 6.4	1.6 ± 11.3	0.64	51.6 ± 10.1	54.1 ± 9.5	5.7 ± 9.9	0.07
Nominal change	−1.8 ± 1.7	−0.6 ± 1.6	–	0.10[b]	−1.4 ± 2.0	0 ± 2.3	–	0.22[b]
P value compared with fasting	0.01[a]	0.33[a]			0.03[a]	1.00[a]		
TG (mg/dL)								
Fasting	195.3 ± 121.3	186.7 ± 111.5	−8.5 ± 20.2	0.30	193.6 ± 96.5	150.8 ± 68.3	−17.6 ± 15.6	0.003
Postprandial	370.9 ± 226.2	382.7 ± 216.2	5.0 ± 9.8	0.11	376.2 ± 141.3	231.9 ± 97.0	−36.2 ± 15.8	<0.001
Nominal change	175.7 ± 141.3	195.9 ± 135.4	–	0.01[b]	182.6 ± 88.0	81.2 ± 48.9	–	<0.001[b]
P value compared with fasting	<0.001[a]	<0.001[a]			<0.001[a]	<0.001[a]		

Continuous variables are represented by mean ± SD. Abbreviations are as given in Table 1

[a] Wilcoxon's signed rank test

[b] Wilcoxon's rank sum test

observed. In addition, FMD increased significantly from 10.4% ± 2.4% to 11.2% ± 2.1%. On the other hand, no such changes were detected in any of the subjects of the placebo group.

Effects of pitavastatin in postprandial state

Significant decreases of the postprandial serum TC and LDL-C by pitavastatin treatment were observed, similar to the case in the fasting state. Postprandial serum TG was markedly decreased (−36%), indicating that the increase in postprandial serum TG was attenuated by pitavastatin treatment ($P < 0.001$) (Table 3). Concomitantly, the decrease in postprandial FMD noted pretreatment was also completely abolished following pitavastatin treatment (−1.1% ± 1.2% vs. 0.1% ± 1.0%, $P < 0.001$) (Fig. 1b). No significant changes were noted in the placebo group.

Relationship between change in postprandial FMD and change in the serum TG during the 2 weeks of treatment

The nominal change in postprandial FMD from baseline to the 2-week treatment with pitavastatin and placebo had a significant inverse correlation with the nominal change in postprandial serum LDL-C ($r = -0.449$, $P = 0.028$) and TG ($r = -0.737$, $P < 0.001$, Fig. 2), and no correlation with the nominal change in postprandial serum HDL-C

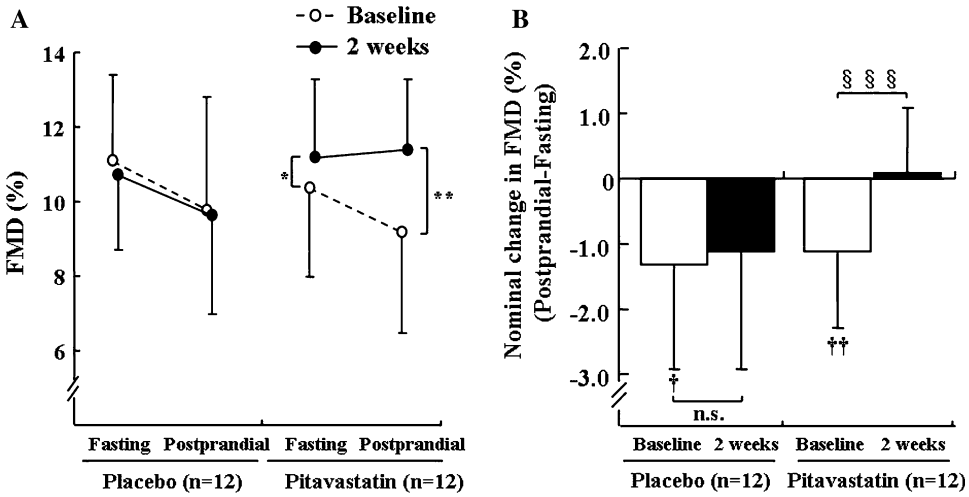

Fig. 1 Changes in flow-mediated dilation (*FMD*) in response to an oral fat load in the pitavastatin group and placebo group before and after 2 weeks of treatment. Effects of pitavastatin on fasting and postprandial value of FMD (**A**) or change in postprandial FMD (**B**) are shown. Data are presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. baseline; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ versus fasting; $^{\S\S\S}P < 0.001$ versus baseline. $P < 0.05$ was considered statistically significant

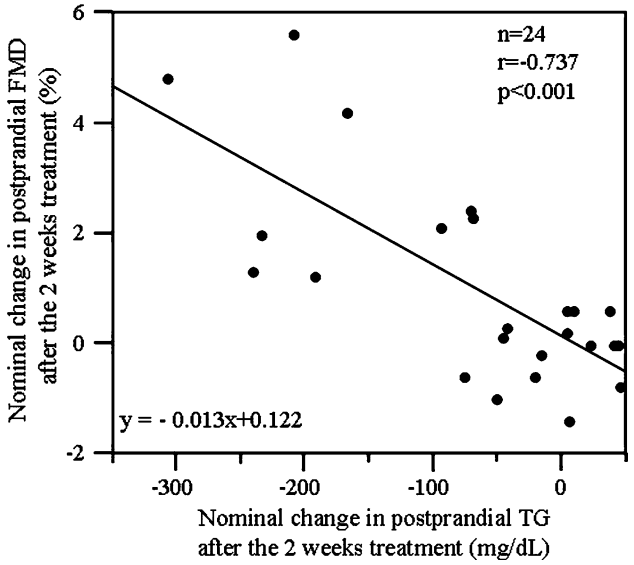

Fig. 2 Association of the change in postprandial flow-mediated dilation (*FMD*) with the change in postprandial triglyceride (*TG*) after 2 weeks of pitavastatin or placebo treatment

($r = 0.081$, $P = 0.706$) in univariate linear regression analysis. Moreover, in multivariate linear regression analysis, nominal change in postprandial serum TG remained significantly correlated with nominal change in postprandial FMD among the covariates, including nominal change in postprandial serum LDL-C, TG, and HDL-C (standardized regression coefficient = −0.040, $P < 0.001$).

Discussion

Previous studies have reported higher postprandial serum TG levels in coronary artery disease (CAD) subjects than in control subjects, and also that postprandial serum TG levels were more closely related to the risk of CAD than the fasting serum TG levels [13, 14]. Endothelial dysfunction, characterized by decreased synthesis, release, and activity of nitric oxide (NO), is known to be an early event in atherosclerosis, and acutely impaired endothelium-dependent vasodilation after a high-fat meal has found to be associated with postprandial hypertriglyceridemia [4].

Similar to previous studies [15], it was demonstrated that postprandial endothelial dysfunction was induced by an ingestion of OFTT cream, associated with a marked increase of the serum TG, with no significant change of the serum LDL-C. Although ages at baseline were different between the placebo and pitavastatin groups (39.8 vs. 48.4 years, $P = 0.03$) in this study, the effects of an oral fat load on TG and FMD were comparable. Therefore, it is suggested that this difference of ages minimally influences the present results. It is known that not only postprandial hypertriglyceridemia but also postprandial hyperglycemia induces endothelial dysfunction [8]. OFTT cream is one of the agents used in oral fat tolerance tests, and can cause a transient increase of serum TG without change in glucose metabolism [7]. It has a composition similar to that of fresh dairy cream, and it includes stevia as an artificial sweetener, which has no calories. Using stevia as sweetener, the secondary response of lipid to insulin and glucose fluctuations can be avoided. In this aspect, the impairment of postprandial FMD in our study could be caused primarily by a dramatic increase of the serum TG level.

Triglyceride-rich lipoproteins (TRLs) have been shown to induce oxidative stress and to be involved in the endothelial dysfunction caused by an oral fat load [16]. Under this condition, oxidative stress may be increased by excessive generation of superoxide anions (O_2^-) at the mitochondrial level, which in turn inactivate nitric oxide to produce peroxynitrite, a potent long-lived oxidant [17]. Therefore, treatment strategies aimed at lowering the

postprandial serum TG levels may lead to a reduction in the risk of coronary events.

On the other hand, this study demonstrated a minor, but nonetheless significant, reduction of the serum HDL-C after an oral fat load. Hajer et al. [18] have shown that cholesterol ester transfer (CET) increases after an oral fat load, resulting in a decrease of the serum HDL-C level. HDL metabolism may also be influenced after a fat meal, but whether postprandial decrease of the serum HDL-C might affect the endothelial function or risk of coronary events is still unclear.

Measurement of FMD is a very useful method to estimate the curative effects of treatments on atherosclerosis. Kitta et al. [19] reported that persistent impairment of FMD despite optimal therapy to reduce risk factors had an adverse impact on the outcome in patients with CAD. Statins are one of the representative drugs known to improve endothelial function due to lipid-lowering or its pleiotropic actions. In agreement with previous reports [4, 20], this study demonstrated that pitavastatin completely prevented postprandial impairment of FMD, and correlated with decreased postprandial TG level. Of note, this reduction of postprandial TG (−36.2%) was stronger than that of fasting state (−17.6%). Moreover, the improvement in postprandial FMD was closely associated with the reduction in postprandial TG level. Considering these results, the prevention of postprandial endothelial dysfunction by pitavastatin is expected to be caused at least in part by its TG-lowering actins. Wilmink et al. [4] suggested that lowering of RLP-C, rather than total TG levels, may contribute to the prevention of endothelial dysfunction after an oral fat load during statin use. Evidence has accumulated that within the total TG fraction the RLPs, derived from exogenous (chylomicron remnants) and endogenous origin (very-low-density lipoprotein [VLDL] and intermediate-density lipoprotein), may be of pivotal importance for the adverse vascular effects. Statins are known to upregulate LDL receptors [21]. Since the LDL receptor is important for removal of remnant particles, statins can improve RLP clearance. Moreover, statins decrease hepatic VLDL secretion [22]. These effects of statins may contribute the reduction of postprandial TG level, thereby preventing endothelial dysfunction.

Besides lipid-lowering effects, the statin-associated prevention of FMD impaired after a fat load could also be related to its pleiotropic actions, which we could not evaluate in the present study. Simvastatin, but not ezetimibe, a novel cholesterol absorption inhibitor, improved endothelium-dependent vasodilation in patients with chronic heart failure despite a similar change in LDL-C [23]. Ceriello et al. [8] showed that 3 days of simvastatin treatment ameliorated postprandial endothelial dysfunction in diabetic patients, a phenomenon independent of the lipid-lowering effect of the drugs. These 'direct' effects of statins include attenuation of oxidative and proinflammatory pathways, and upregulation of antiatherosclerotic mechanisms [24, 25]. The finding that statins exert pleiotropic effects on fasting and postprandial endothelial function may have important clinical implications.

This study had several limitations. Only obese male subjects were enrolled; therefore, the results cannot be generalized to the entire population of both sexes. Although postprandial change of the serum TRLs is thought to be more important than that of the serum total TG, TRLs such as RLP-C, VLDL-C, and apoB-48 were not measured directly in this study. Finally, it should be noted that the oral fat load used for this study represented a nonphysiological load of TG.

In conclusion, this study demonstrated that pitavastatin prevented the impairment in FMD after an ingestion of OFTT cream in obese male subjects. In addition, the improvement of postprandial FMD was associated with the attenuation of increased TG level. In the postprandial state, TG-lowering effects of pitavastatin contribute at least in part to the prevention of the endothelial dysfunction. These effects could represent additional beneficial effects of statins in the prevention of atherosclerotic diseases.

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