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Original Article

Postprandial Paraoxonase 1 Activity Following Consumption of Recommended Amounts of Mixed Meals in Healthy Males

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***Aim*: Postprandial lipid level increases induce oxidative stress, which is involved in atherogenesis. The antioxidant properties of paraoxonase 1 (PON1) have attracted attention. However, changes in postprandial PON1 levels differ across prior studies, and changes in PON1 lactonase activity, potentially relevant to PON1 physiology, after the consumption of ordinary meals are unknown. Herein we evaluated postprandial serum lipid levels and PON1 changes following mixed-meal consumption of the amounts recommended for ordinary meals.**

***Methods*: Nine healthy male volunteers consumed three different meals in a randomized cross-over design. The test meals were as follows: S, white rice; SMF, S with fat-containing protein-rich main dishes; and SMFV: SMF with vegetable dishes. The serum lipid concentrations and PON1 lactonase and arylesterase activities were determined during a three-hour period after the consumption of these meals.**

***Results*: The postprandial triglyceride levels were higher after consuming the SMF and SMFV meals than after consuming the S meal. Despite postprandial high-density lipoprotein cholesterol being unchanged, PON1 lactonase activity was decreased, while PON1 arylesterase activity was increased in the postprandial state after all test meals. Postprandial changes in lactonase and arylesterase activities did not differ among the test meals.**

***Conclusions*: Inverse changes in PON1 lactonase and arylesterase activities were observed after consuming recommended ordinary meals. This observation provides useful information for choosing PON1 species as postprandial markers.**

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Key words: Paraoxonase 1, Lactonase activity, Postprandial, Triglyceride, Oxidative stress marker

Introduction

A postprandial increase in lipid levels, particularly triglycerides (TG), is an independent risk factor for atherosclerosis[1-3)], as postprandially elevated TG causes oxidative stress, which leads to the production of atherogenic lipoproteins[4, 5)]. Conversely, high-density lipoprotein (HDL) particles exert protective effects against the oxidative modification of various molecules/substances, including low-density lipoprotein (LDL) particles[6, 7)]. Paraoxonase 1 (PON1) has attracted great interest as a major enzyme responsible for the antioxidant properties of HDL particles[8, 9)].

Several studies have demonstrated postprandial changes in PON1 arylesterase activity in both animal models[10)] and humans[11-13)], including healthy subjects[11, 12)]. However, earlier studies produced controversial results, with both increased[11, 13)] and decreased[11, 12)] PON1 levels. Of note, in earlier studies focusing on postprandial PON1 response, the amounts of fat and antioxidants in the experimental diets were much

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greater than those contained in routinely eaten meals. Therefore, the postprandial PON1 response to actual meals eaten on a daily basis is yet to be elucidated. Given the importance of PON1[8, 9] and the aforementioned controversial findings[11-13], determining postprandial changes in PON1 levels under ordinary dietary conditions would clearly be worthwhile.

PON1 hydrolyzes a large number of compounds and shows different activities depending on the substrates[14]. Although not all physiologically relevant substrates of PON1 have been confirmed to date, we can reasonably speculate that lactones are physiological substrates[15, 16]. In most earlier human studies, the activities of arylesterase and/or paraoxonase, the substrates of which may not necessarily reflect the physiological activity of PON1, were measured to assess PON1 levels, and no nutritional research study has evaluated postprandial lactonase activity in human subjects to date. Hence, it is our view that measuring PON1 lactonase activity would provide novel information regarding postprandial PON1 responses that may have a physiological relevance.

We investigated the postprandial responses of serum PON1 lactonase and arylesterase activities following the consumption of recommended amounts of mixed meals in healthy males. Our primary goal was to obtain information regarding postprandial changes in PON1 activities, including lactonase activity, under real-life dietary conditions.

Subjects and Methods

Ethics Statement

This study was conducted according to the guidelines established in the Declaration of Helsinki, and all procedures involving human subjects were approved by the ethical committee for experimental research involving human subjects of Japan Women's University (No.48). Written informed consent was obtained from all participants.

Subjects

Because postprandial PON1 lactonase activity had not previously been evaluated in human studies, we employed a sample size calculated based on a prior postprandial study (in this context, the sample size was estimated to be seven subjects)[17]. The inclusion criteria were male gender, age between 30 and 49 years, and body mass index (BMI) between 18.5 and 25 kg/m^2. Baseline data on health and lifestyle factors, including habitual food intake, were assessed using a questionnaire. Subjects were excluded if any disease and/or glucose or lipid metabolism abnormalities were detected at their most recent medical check-up or if they had a family history of diabetes mellitus and/or dyslipidemias. Nine healthy Japanese males volunteered to participate in the present study conducted at Japan Women's University, Tokyo, Japan.

Test Meals

Three test meals were designed using boiled white rice as the staple food, with or without side dishes (**Table 1**). The test meals were as follows: staple food alone (S) as a control meal; the staple food with a main dish and a fat-rich food item (SMF) as a model of a meal containing a recommended amount of fat; and the staple food with a main dish, a fat-rich food item, and a vegetable dish (SMFV) as a model of a meal containing vegetables along with the other components. The SMFV meal conformed to the recommendations for standard meals for the Japanese population[18]. Two hundred grams of boiled white rice (aseptic packed Sato Rice; Sato Foods Co., Ltd., Niigata, Japan) served as the staple food. The main dishes consisted of a boiled egg and tofu (soybean curd) (*momen-tofu*; Takanofoods Co., Ltd., Ibaraki, Japan). Mayonnaise (Kewpie Corporation, Tokyo, Japan) was used as the fat-rich food item. The vegetable dishes consisted of boiled spinach (frozen spinach; Kewpie Corporation) and boiled broccoli (frozen broccoli; Kewpie Corporation). Each test meal was seasoned with 3 g of soy sauce (Kikkoman Corporation, Chiba, Japan) and was served with 200 mL of hot water. All test meals were prepared as previously described[17] just before the experiment. The detailed composition, calculated energy, and nutrient content of the test meals, based on standard tables for food components in Japan, are shown in **Table 1**.

Protocol

This study was conducted using a randomized, single-blind, cross-over design. All subjects consumed each type of meal, and the wash-out period was at least one week. Randomization of the order of consuming each test meal was individually generated using random numbers. While the subjects and staff members who served the test meals knew which test meal was consumed, data analysts and assessors were blinded to the order of test meal consumption.

The subjects were instructed to maintain their habitual dietary and physical activities during the study period and record their daily meals, health status, and physical activity. The day prior to each test day, the subjects recorded their food intake by keeping detailed 24-h food diaries. Each participant was instructed to finish consuming the same dish before

Table 1. Compositions and the nutrient and energy contents of the three test meals

			Test meals		
			S	SMF	SMFV
〈Dishes〉	〈Foods〉				
Staple food	Boiled white rice*	(g)	200	200	200
Main dish	Tofu (soybean curd)†	(g)	–	100	100
	Boiled egg	(g)	–	50	50
Fat-rich food item	Mayonnaise‡	(g)	–	13	13
Vegetable dish	Boiled spinach‡	(g)	–	–	60
	Boiled broccoli‡	(g)	–	–	60
Seasoning	Soy sauce§	(g)	3	3	3
Drink	Hot water	(mL)	200	200	200
〈Energy and Nutrients〉					
Energy		(kJ)	1414	2397	2527
Energy		(kcal)	338	573	604
Protein		(g)	5.2	18.6	22.3
Fat		(g)	0.6	19.2	19.7
Carbohydrate		(g)	73.9	75.5	76.1
Total dietary fiber		(g)	0.6	1.0	5.4
Soluble dietary fiber		(g)	0.0	0.1	1.0
Insoluble dietary fiber		(g)	0.6	0.9	4.4
α-tocopherol		(mg)	0.0	1.9	4.5
Ascorbic acid		(mg)	0	0	44

S, staple food; SMF, staple food, main dish, and fat-rich food item; SMFV, staple food, main dish, fat-rich food item, and vegetable dish
*Aseptic packed Sato Rice; Sato Foods Co., Ltd., Niigata, Japan
†*Momen-tofu*; Takanofoods Co., Ltd., Ibaraki, Japan
‡Kewpie Corporation, Tokyo, Japan
§Kikkoman Corporation, Chiba, Japan

21:00 the day before each of the test days and then fast overnight.

On the test morning, the subjects arrived at Japan Women's University by 09:00. Anthropometric measurements were obtained, and fasting blood was collected after the aforementioned overnight fast. Immediately after providing a blood sample, each subject began to consume the test meal. To exclude any effects of the order of eating the dishes, the subjects were instructed to eat alternately the boiled white rice and side dishes, masticate each mouthful of food 20 times before swallowing, and finish eating the entire amount of food in just 15 min. The test meals were consumed under supervision. Venous blood samples were drawn via venipuncture before and 30, 60, 120, and 180 min after meal ingestion. The subjects remained seated throughout the test under the supervision of research staff members.

Measurements

Height, weight, and waist circumference were measured. BMI was calculated employing the formula: weight (kg)/height $(m)^2$. The visceral fat area was measured according to the dual impedance analysis method using HDS-2000 DUALSCAN (Omron Healthcare Co., Ltd., Kyoto, Japan).

The collected blood samples were allowed to clot for 30 min at room temperature and were then centrifuged at 1,200 ×g for 10 min at 15℃. Separated serum samples were stored at −80℃ until the analysis. The serum total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and TG con-

Table 2. Characteristics and anthropometric parameters of the participants at the first visit

Age (years)	38.1 ± 1.8
Body mass index (kg/m^2)	23.1 ± 0.5
Waist circumference (cm)	81.1 ± 1.4
Visceral fat area (cm^2)	54.9 ± 6.1

The values are presented as means ± SEM; $n = 9$

Table 3. Body weights and fasting values of serum lipid parameters and paraoxonase 1 activities in healthy males prior to consuming the three test meals (median with interquartile ranges in parentheses, $n=9$)

	Test meals			*p*-value
	S	SMF	SMFV	
Body weight (kg)	66.8 (65.4, 69.6)	67.9 (64.2, 69.9)	66.7 (64.3, 69.7)	0.972
TG (mmol/L)	0.88 (0.60, 1.32)	0.78 (0.54, 1.87)	0.91 (0.64, 1.02)	0.717
HDL-C (mmol/L)	1.60 (1.28, 1.73)	1.55 (1.31, 1.82)	1.47 (1.31, 1.77)	0.814
LDL-C (mmol/L)	2.87 (2.26, 3.78)	2.87 (2.41, 3.09)	2.97 (2.44, 3.26)	0.819
PON1 lactonase activity (U/L)	74 (53, 95)	73 (57, 100)	78 (54, 93)	0.459
PON1 arylesterase activity (U/L)	178 (140, 193)	168 (158, 205)	154 (146, 180)	0.050

P-values were calculated using the Friedman test for comparisons among the three test meals.
S, staple food; SMF, staple food, main dish, and fat-rich food item; SMFV, staple food, main dish, fat-rich food item, and vegetable dish
TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PON1, paraoxonase 1

centrations were measured using enzymatic methods in the laboratory at Saitama Social Insurance Hospital, Saitama, Japan.

Serum PON1 lactonase activity was kinetically determined at 37℃ using 5-(thiobutyl)butyrolactone, a lactone substrate, by recording absorbance changes at 405 nm on a microplate reader, as previously described[19]. Five-(thiobutyl)butyrolactone is analogous to γ-nonanoic lactone that is released upon hydrolysis of the γ-butyrolactone ring. Serum PON1 arylesterase activity was kinetically determined at 37℃ using phenylacetate as a substrate by recording absorbance changes at 270 nm[19].

Statistical Analysis

All statistical analyses were performed using the SPSS software package for Windows (version 16.0J, SPSS Japan Inc., Tokyo, Japan). The values are shown as the median and interquartile range, unless stated otherwise. The statistical significance of differences in parameters between the test meal values and those obtained after fasting and at each measurement time point were assessed using the nonparametric Friedman's test followed by the Wilcoxon signed-ranks test for pair-wise comparisons with the Bonferroni correction. The carry over and period effects were evaluated by applying the nonparametric Friedman's test. A *p*-value of <0.05 was considered to indicate a statistically significant difference.

Results

All subjects completed the study and fully consumed all test meals without problems. No adverse events, such as abdominal pain or diarrhea, occurred during the test period.

The characteristics of the subjects are shown in **Table 2**. The subjects' body weights did not change during the study period, and there were no significant differences in fasting lipid parameters or PON1 lactonase activity among the three test meals (**Table 3**).

Serum Lipid Responses

The postprandial serum TG responses to each meal are shown in **Fig. 1A**. The postprandial serum TG concentration did not change after the consumption of the S meal compared with that observed in the fasted state. Following the consumption of the SMF and SMFV meals, postprandial serum TG concentrations significantly increased compared with those measured in the fasted state ($p<0.05$) and after the consumption of the S meal ($p<0.05$). The median (interquartile range) values of the percent changes in TG with the S, SMF, and SMFV meals at 180 min were −6.1 (−13.7−30.7), 46.8 (32.2−98.1), and 73.8 (24.8−107.4), respectively. In contrast, the postprandial serum HDL-C (**Fig. 1B**), LDL-C, and TC concentrations did not change after the consumption of any of the test meals compared with those at the fasted state. Hence, these lipid parameters did not significantly differ among the test meals (data not shown).

Serum PON1 Lactonase and Arylesterase Activities in Response to the Test Meals

PON1 lactonase activity decreased after the consumption of each of the test meals compared with that in the fasted state ($p<0.05$) (**Fig. 2A**). In contrast to PON1 lactonase activity, postprandial PON1 arylesterase activity increased after each of the test meals compared with that in the fasted state ($p<0.05$) (**Fig. 2B**). No significant differences in postprandial responses were observed in either PON1 lactonase activity or arylesterase activity among the three test meals.

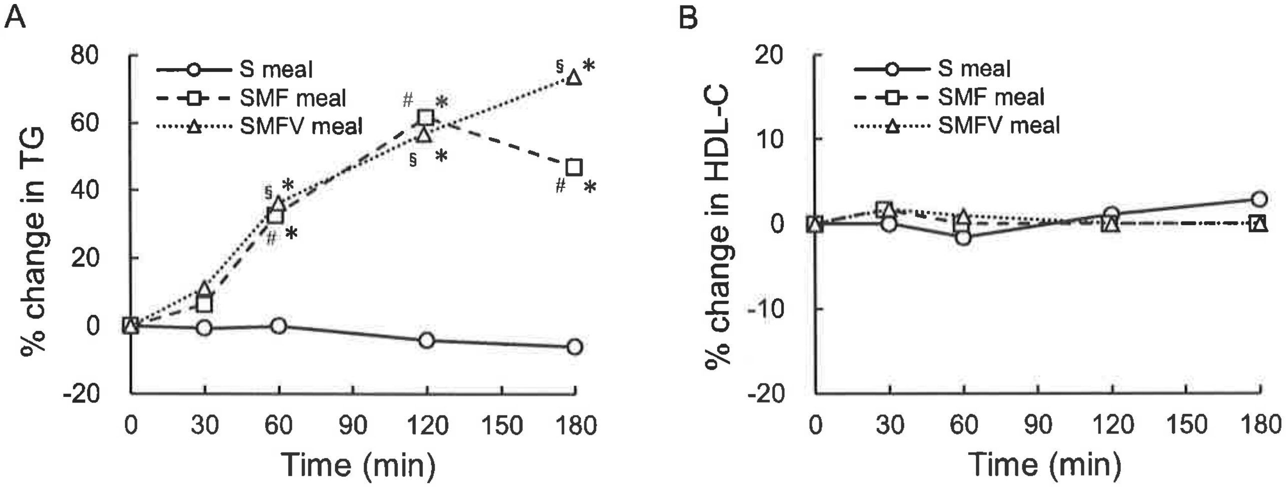

Fig. 1. Postprandial lipid responses after the consumption of the three test meals

Postprandial percent changes in serum triglyceride (TG) concentrations (A) and serum high-density lipoprotein cholesterol (HDL-C) concentrations (B) in healthy males during a 180-min period after consuming one of the three test meals containing the same amount of boiled white rice with or without side dishes. S meal, staple food; SMF meal, staple food, main dish, and fat-rich food item; SMFV meal, staple food, main dish, fat-rich food item, and vegetable dish. The values are presented as medians ($n=9$). *, significant difference from the S meal at $p<0.05$. #, significant difference from 0 min after consuming the SMF meal at $p<0.05$. §, significant difference from 0 min after consuming the SMFV meal at $p<0.05$. ($p<0.05$; the Wilcoxon signed-ranks test with the Bonferroni correction).

Discussion

To our knowledge, this is the first study to measure postprandial PON1 activities, with particular emphasis on lactonase, after the consumption of routine mixed meals in amounts corresponding to ordinary dietary intake levels. The present study demonstrated that postprandial PON1 lactonase activity was decreased, while PON1 arylesterase activity was increased, with no apparent change in the postprandial HDL-C concentration. In addition, the postprandial changes in PON1 lactonase and arylesterase activities exhibited similar trends regardless of the test meals. The finding would be noteworthy as basic information regarding the postprandial PON1 responses under real-life dietary conditions.

Changes in postprandial PON1 arylesterase activity have been studied with respect to oxidative stress conditions[14, 20], which are associated with postprandial increases in both TG and glucose levels[4, 5]. PON1 arylesterase activity was reportedly decreased after consuming a massive volume of fat and carbohydrate[12] or meals rich in used cooking fat[11]. However, it was reported to be increased after the consumption of meals containing unused fat[11] or non-oxidized oil[13], observations consistent with the results of this study. The S meal contained little fat, and the SMF and SMFV meals had only 13 g of fresh mayonnaise with almost the same volume of carbohydrates from boiled white rice. Although we are unable to fully explain the present study finding of increased postprandial PON1 arylesterase activity after the consumption of the fat-containing SMF and SMFV meals as well as the S meal, the controversial results for postprandial changes in PON1 arylesterase activity obtained in earlier studies may, at least to some degree, have been influenced by differences in meal contents, which are possibly associated with different oxidative stress levels. The postprandial TG concentrations did not markedly increase after the consumption of the fat-containing SMF and SMFV meals, and postprandial plasma glucose after the SMFV meal was lower than that after the S meal as reported previously[17]; thus, it is reasonable to speculate that oxidative stress might not largely be induced by meals of the size recommended for the Japanese population.

PON1 lactonase has the potential to be physiologically relevant to the oxidation of fatty acid products, and a consensus is emerging regarding the PON1 function of lactonase activity[16], though no prior studies have examined PON1 lactonase activity in the postprandial context. An *in vitro* study demonstrated that the incubation of serum or HDL obtained from healthy subjects with elevated concentrations of very-low-density lipoproteins (VLDL) decreased PON1 lactonase activity in a VLDL dose-dependent man-

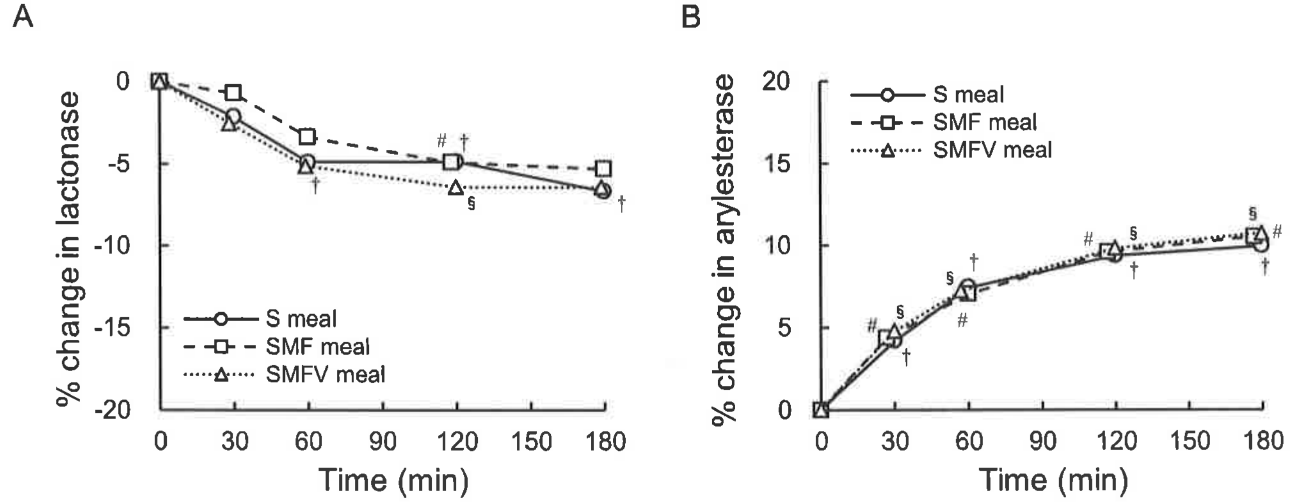

Fig. 2. Postprandial paraoxonase 1 (PON1) lactonase and arylesterase activities after the consumption of the three test meals

Postprandial percent changes in serum PON1 lactonase activities (A) and PON1 arylesterase activities (B) in healthy males during a 180-min period after consuming one of the three test meals containing the same amount of boiled white rice with or without side dishes. S meal, staple food; SMF meal, staple food, main dish, and fat-rich food item; SMFV meal, staple food, main dish, fat-rich food item, and vegetable dish. The values are presented as medians ($n=9$). †, significant difference from 0 min after consuming the S meal at $p<0.05$. $^{\#}$, significant difference from 0 min after consuming the SMF meal at $p<0.05$. §, significant difference from 0 min after consuming the SMFV meal at $p<0.05$. ($p<0.05$; the Wilcoxon signed-ranks test with the Bonferroni correction)

ner[21]. This finding indicates that PON1 lactonase activity responds to lipid oxidation, whereas no information is available regarding lactone metabolites derived from carbohydrates. A physiologically relevant PON1 level could, at a minimum, be decreasingly affected by the consumption of ordinary meals. While it is important to note the new insight of lactonase activity that adds to current knowledge in the postprandial PON1 field, further accumulation of data is required before solid conclusions can be drawn regarding these findings.

Furthermore, for inverse changes in phenylacetate (arylesterase) activity and physiological lactonase activity, we can offer an additional explanation for these seemingly paradoxical observations. This phenomenon may be due to differences in active site conformations; that is, the lactonase activity exploits one active site conformation and the esterase activity exploits another[15, 16]. The hydrolysis of aromatic esters and the lactone dihydrocoumarin employed in this study has also been determined by an alternate catalytic mode that uses only a part of the active site residues utilized for lactone hydrolysis[15, 16]. The active site of PON1 exhibits versatility; that is, multiple residues share the same function, and individual active site residues perform multiple tasks[15, 16]. Competition may ensue, explaining the inverse relationship. These observations also highlight the significance of exploring lactonase activity in studies aiming to elucidate the effects of PON1 on cardiometabolic risks.

This is the first investigation to focus on the effects of vegetable consumption on changes in postprandial PON1 levels. The consumption of vegetables[22, 23] or meals supplemented with vitamins[24, 25] reportedly increases the amount of lipid soluble antioxidants in postprandial TG-rich lipoproteins. Therefore, colored vegetable consumption is expected to decrease postprandial oxidative stress and increase PON1 activity by protecting PON1 enzymes from oxidative stress-induced inactivation. Although spinach and broccoli are rich in antioxidants such as α-tocopherol and carotenoids, the changes in neither PON1 lactonase nor arylesterase activity differed between the mixed meal with vegetables (SMFV meal) and that without vegetables (SMF meal) in this study. Therefore, changes in PON1 activity with the consumption of vegetables following ordinary meals may not occur in the postprandial state, as was in case of a study with blackcurrant juice, which is rich in water-soluble antioxidant polyphenols and ascorbic acid[26]. On the other hand, prior reports on human studies have shown that the intake of antioxidants exerts beneficial effects on PON1 activity[27-31]. Further research is required to determine the optimal quality and quantity of vegetables, duration of intervention, and health status of subjects.

The present study has several limitations. We evaluated the effects of consuming mixed type of meals, while the degree of postprandial PON1 activity is implied to vary depending on fatty acid composition[10)] and/or the antioxidant capacities of different types of vegetables[32, 33)]. More studies are needed to assess the effects of other types of fat-rich food items and/or vegetables. We did not measure markers related to oxidative status and/or remnant lipoproteins. With the primary aim of observing the effects of real-life dietary conditions in the present study, the amount of added fat was smaller than that supplied in earlier studies[5, 34, 35)] and changes in such markers may not be marked in healthy subjects. However, as this can give an important consideration of postprandial PON1 pathology, these measurements must be included as the next challenge. In addition, postprandial PON1 arylesterase and paraoxonase activities of patients with diabetes are lower than those of healthy subjects[36, 37)]. Future studies are also needed to evaluate individual or population differences, including diabetes, dyslipidemia, and PON1 polymorphisms, on postprandial PON1 responses including lactonase activities in particular. Although we acknowledge these limitations, to date, we do not know changes in postprandial PON1 (particularly lactonase) activities following the consumption of recommended amounts of fat-containing mixed meals; thus, the present results offer potentially useful insights for clarifying the effects of consuming an ordinary diet on postprandial PON1 activities.

In conclusion, the present study demonstrated a postprandial decrease in PON1 lactonase and an increase in PON1 arylesterase activities in healthy males who consumed meals containing amounts of fat recommended for ordinary meals. This provides useful information for choosing PON1 species as postprandial markers. More studies are warranted to confirm our findings in relation to the prevention of atherosclerosis in clinical practice.

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Author Contributions

Conceived and designed the study: N.K., C.M. Conducted the study: N.K., C.M., S.M., R.A., T.M. Analyzed the data: N.K. Performed the assays: K.K., G.A., R.C. Wrote the paper: N.K., C.M., K.K. Critically reviewed the paper: G.A, R.C. Approved the final version: all authors.

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None of the authors have any conflicts of interest to declare.

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