International Journal of Nutrition and Food Sciences
2023; 12(1): 21-28
http://www.sciencepublishinggroup.com/j/ijnfs
doi: 10.11648/j.ijnfs.20231201.13
ISSN: 2327-2694 (Print); ISSN: 2327-2716 (Online)

Remnant Indices for Estimating Postprandial Lipidemia in Young Women

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To cite this article:
Erika Mizutani-Watanabe, Michitaka Naito. Remnant Indices for Estimating Postprandial Lipidemia in Young Women. *International Journal of Nutrition and Food Sciences*. Vol. 12, No. 1, 2023, pp. 21-28 doi: 10.11648/j.ijnfs.20231201.13

Received: January 19, 2023; **Accepted**: February 14, 2023; **Published**: February 24, 2023

Abstract: Postprandial hyperglycemia is well established as a major risk factor for prediabetes and type 2 diabetes. However, for postprandial hyperlipidemia, no definitive criteria exist, and fasting values of lipids and lipoproteins had limited efficacy for estimating postprandial lipidemia. In the present study, we performed a fat-ingestion test and aimed to propose indices for estimating postprandial lipoprotein metabolism. Methods: Healthy young Japanese women (n=54, age 21.1 ± 1.0 y) with apolipoprotein E phenotype 3/3 were enrolled. They ingested fat cream (OFTT cream™, Jomo, Japan; 1 g/kg as cream, 0.35 g/kg as fat). Venous blood samples were taken before (0 h) and at 0.5, 1, 2, 4, and 6 h after ingestion. Results: The serum triglyceride (TG) level peaked at 2 h and returned to below baseline at 6 h. The remnant-like particle-TG (RP-TG) level increased at 1 h, peaked at 2 h, and returned to baseline at 6 h. The remnant lipoprotein-cholesterol (RLP-C) level increased at 2 h, peaked at 4 h, and returned to baseline at 6 h. The apolipoprotein B48 level increased at 1 h, peaked at 4 h, and did not return to baseline at 6 h. The apolipoprotein B100 concentration slightly decreased at 2 h and increased at 6 h. TG−RP-TG did not change during 6 h, but RP-TG/TG rose at 2–6 h compared to the fasting value. RP-TG/RLP-C increased at 2–4 h and returned to baseline at 6 h. Conclusion: After fat ingestion, while the concentration of non-remnant TG was stable, remnant TG increased. The content of TG per remnant particle increased up to 2 h and decreased from 2 h to 6 h, and the size became smaller. The remnant indices, RP-TG/TG and RP-TG/RLP-C, may be useful for estimating postprandial lipidemia.

Keywords: Fat-Ingestion Test, Postprandial Lipidemia, Remnant, Index, Women, Apolipoprotein B48, Triglyceride

1. Introduction

Regarding the plasma triglyceride (TG) level, most of the time in a day is spent in the postprandial state, and the true fasting period may be only a few hours. It has been reported that small changes in the fasting plasma TG level can lead to large differences in the diurnal TG level [1]. However, different from the glucose tolerance test, although various fat-ingestion or tolerance tests have been devised, no standardized test protocol exists for postprandial lipidemia.

Greater postprandial TG and apolipoprotein B48 concentrations have been reported to be associated with coronary heart disease (CHD) in women [2–4]. The postprandial accumulation of TG-rich lipoproteins (TRL) in plasma was also a significant risk factor for CHD [5, 6]. Moreover, in large prospective cohort studies in women, nonfasting TG concentrations were significantly associated with increased CHD risk, even after adjustment for fasting TG or high-density lipoprotein-cholesterol (HDL-C) [2, 7, 8]. Also, non-fasting TG was reported to better reflect the presence of higher remnant lipoprotein concentrations [9].

Excessive postprandial lipidemia, namely postprandial hyperlipidemia, appears usually as one of the phenomena of so-called atherogenic dyslipidemia (AD) characterized by fasting plasma hypertriglyceridemia, low HDL-C, an increase in small dense low-density lipoprotein and excessive postprandial lipidemia and is frequently seen in individuals with high cardiovascular risks such as obesity/overweight, type 2 diabetes mellitus, and metabolic syndrome [10, 11], and the components of AD are closely linked to each other [12, 13].

The pathophysiology of AD is explained by the accumulation of TRL synthesized by the liver (very low-density lipoprotein, VLDL) [14] and the intestine (chylomicron, CM) [15] in the blood. This accumulation has been attributed to the overproduction of both VLDL and CM and to a defective TRL removal process [16]. Elevated fasting and postprandial blood TRL concentrations are considered a causal risk factor for atherosclerosis [12, 13].

Therefore, this study aimed to propose indices of postprandial lipid and lipoprotein metabolism in young women. This generation of women was enrolled because the highest consumers of high-fat fast food are adolescents and young adults [17].

2. Methods

2.1. Subjects

Healthy young Japanese women (n=54, age 21.0 ± 1.0 y) with a normal ovarian cycle and apolipoprotein E phenotype 3/3 were enrolled. They were non-smokers, were not suffering from any apparent acute or chronic illness, and were not taking any medication or dietary supplements. This study was approved by the Institutional Review Board of Sugiyama Jogakuen University School of Life Studies (Nos. 2013-3, 2014-2, -22, -23). The subjects provided written informed consent. The procedures were conducted in accord with the Helsinki Declaration of 1975 as revised in 1983.

2.2. Anthropometric and Body Composition Measurements

Body mass and height were measured according to standard methods. The waist circumference was assessed as the abdominal girth at the level of the umbilicus, and the hip circumference was measured at the level of the greater trochanters. The waist-to-hip (W/H) ratio was calculated. The body composition, including the visceral fat area (VFA), was analyzed using an 8-polar bioelectrical impedance method (InBody720, BioSpace, Tokyo, Japan).

2.3. Experimental Design

The subjects ingested fat cream (OFTT cream™, Jomo, Takasaki, Japan; 1 g/kg body mass as cream, 0.35 g/kg as fat). The OFTT cream was used as described [18]. The fat beverage was prepared by mixing 1 g/kg of OFTT cream with the same final amount of distilled water.

The subjects abstained from consuming alcohol on the day before the trial and ingested the beverage after a 12 h overnight fast. Venous blood samples were taken before ingestion (0 h) and at 0.5, 1, 2, 4, and 6 h after beverage ingestion. During the test, the subjects avoided exercise and eating but had free access to water 1 h after the ingestion. Blood samples were taken with the subject in a supine position.

2.4. Biochemical Analysis

Blood and serum samples were immediately refrigerated (4°C) or frozen (−80°C) until analysis. The concentration of glucose was measured using a mutarotase-glucose oxidase method (Wako, Osaka, Japan). Insulin was measured via chemiluminescent enzyme immunoassay (Fujirebio, Tokyo, Japan). Hemoglobin A1c (HbA1c) was measured using a latex agglutination method (Fujirebio) and was expressed as a National Glycohemoglobin Standardization Program (NGSP) value. Insulin resistance was evaluated using the homeostasis model assessment for insulin resistance (HOMA-IR) and calculated as HOMA-IR=$(I_0 \times G_0)/405$, where I_0 is the fasting insulin concentration (mU/L) and G_0 is the fasting glucose concentration (mg/dL) [19].

Total cholesterol (TC) was measured enzymatically (Sysmex, Hyogo, Japan). HDL-C was measured using a direct method (Fujirebio). LDL-C was calculated using the Friedewald formula [20]. TG was measured enzymatically (Sekisui Medical). Remnant-like particle-TG (RP-TG) was measured by an immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan) [21]. Briefly, remnant-like particles were isolated from the serum on an immunoaffinity mixed gel containing anti-ApoA-I and anti-ApoB100 monoclonal antibodies, and the concentration of TG in the unbound fraction was measured as RP-TG using the enzymatic method. Remnant lipoprotein-cholesterol (RLP-C) was measured via homogeneous assay (MetaboRead RemL-C, Kyowa Medex, Tokyo, Japan) [22]. Apolipoproteins (Apo) A-I, A-II, B, C-II, C-III, and E were measured using the immunoturbidimetric method (Sekisui Medical). ApoB48 was measured via chemiluminescent enzyme immunoassay (Fujirebio). The concentration of ApoB100 was calculated by subtracting the value of ApoB48 from the value of ApoB [23]. The ApoE phenotype was measured using the isometric electrophoresis method (Phenotyping ApoE IEF System, Joko, Tokyo, Japan).

Postprandial changes in the concentrations of glucose, insulin, TG, RP-TG, RLP-C, ApoB48, and ApoB100 were calculated as the difference from the baseline mean value (as 0 at 0 h) and were shown as *Δ*glucose, *Δ*insulin, *Δ*TG, *Δ*RP-TG, *Δ*RLP-C, *Δ*ApoB48, and *Δ*ApoB100, respectively. We also calculated TG−RP-TG, RP-TG/TG, and RP-TG/RLP-C as the indices of postprandial lipidemia.

2.5. Statistical Analyses

Statistical analyses were performed using SPSS ver. 25 software (IBM, Tokyo, Japan). Normal distribution of data was verified using the Shapiro-Wilk test for skewness and kurtosis of distribution. Non-normally distributed data were examined for a normal distribution when logarithmically transformed, and they were analyzed using parametric statistics. The data are presented as the mean ± SEM. The difference in the time course compared with the fasting value was analyzed by performing a repeated-measures analysis of variance (ANOVA), followed by the Dunnett test. For all data, $p<0.05$ was considered significant.

3. Results

3.1. Subject Characteristics

Anthropometric characteristics and fasting blood chemical data are shown in Table 1. The fat cream was tolerated well by all subjects, and no participant had symptoms, such as nausea, vomiting, or diarrhea. None of the subjects fell under the Japanese criteria for obesity (BMI≥25 kg/m^2), according to the definition by the Japan Society for the Study of Obesity, or metabolic syndrome, as defined by the Japan Atherosclerosis Society. The physique of the subjects was considered average for young Japanese women, similar to the values reported in the National Nutritional Survey [24].

Table 1. *Physical characteristics and fasting blood chemical data of the subjects.*

Age (years)	21.1	±	0.1
Height (cm)	158.3	±	0.6
Mass (kg)	50.6	±	0.8
BMI (kg/m^2)	20.2	±	0.3
% Body fat	25.4	±	0.6
W/H	0.78	±	0.01
VFA (cm^2)	26.1	±	1.9
HbA1c (%)	5.2	±	0.04
HOMA-IR	1.3	±	0.1
TC (mg/dL)	174.2	±	3.2
HDL-C (mg/dL)	65.0	±	1.4
LDL-C (mg/dL)	97.6	±	3.0
ApoA-I (mg/dL)	151.1	±	2.6
ApoA-II (mg/dL)	25.9	±	0.5
ApoC-II (mg/dL)	2.3	±	0.1
ApoC-III (mg/dL)	7.0	±	0.2
ApoE (mg/dL)	4.0	±	0.1

Values are the mean ± SEM.

Blood chemical data and calculated indices in the fat-ingestion test are presented in Table 2. The time courses for *Δ*glucose (A) and *Δ*insulin (B) are shown in Figure 1, and those for *Δ*TG (A), *Δ*RP-TG (B), *Δ*RLP-C (C), *Δ*ApoB48 (D), and *Δ*ApoB100 (E) are shown in Figure 2.

3.2. Glucose and Insulin

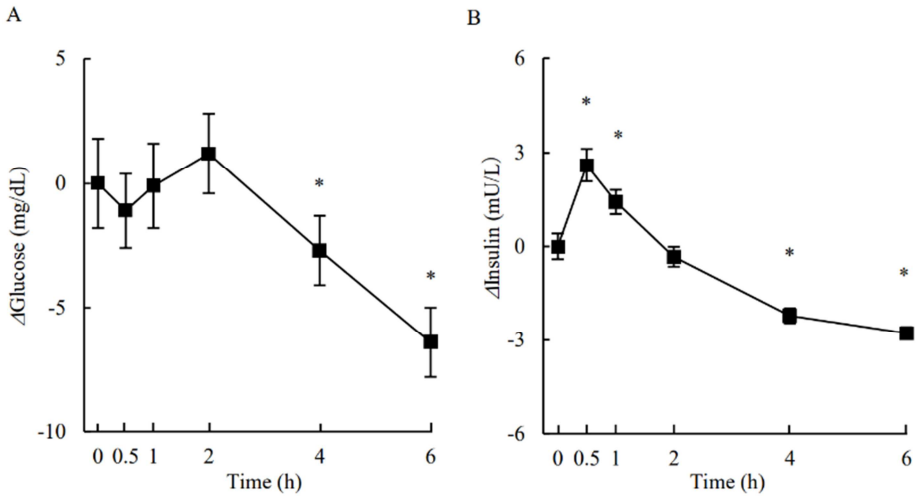
The serum glucose concentration did not increase after the fat ingestion compared to the fasting level, and it slightly but significantly decreased to below baseline at 4 and 6 h. The serum insulin concentration increased at 0.5 and 1 h and decreased to below baseline at 4 and 6 h.

3.3. TG, RP-TG, RLP-C, ApoB48, and ApoB100

The serum TG concentration peaked at 2 h and returned to lower than baseline at the end of the experiment (6 h). RP-TG increased at 1 h, peaked at 2 h, and returned to baseline at 6 h. The RLP-C level increased at 2 h, peaked at 4 h, and returned to baseline at 6 h. The ApoB48 concentration increased at 1 h, peaked at 4 h, and did not return to baseline even at 6 h. The postprandial change of ApoB100 was small, but the ApoB100 concentration significantly decreased at 2 h and increased at 6 h. Waist size, hip size, W/H ratio, and VFA were not significantly correlated with any of the total or incremental area under the curve items (data not shown).

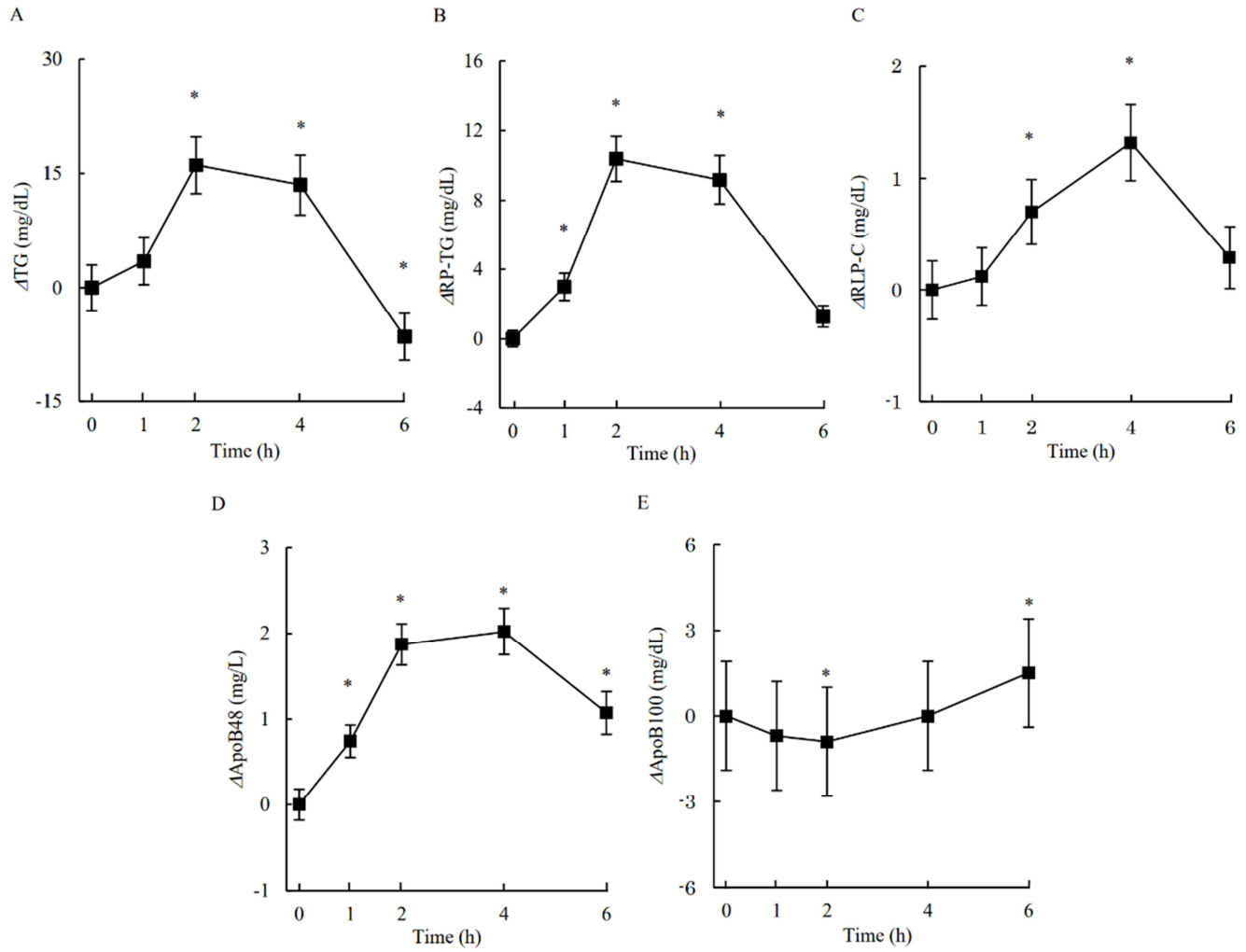
3.4. TG–RP-TG, RP-TG/TG, and RP-TG/RLP-C

The time courses for calculated indices TG−RP-TG (A), RP-TG/TG (B), and RP-TG/RLP-C (C) are shown in Figure 3. TG−RP-TG did not significantly change during 6 h. RP-TG/TG significantly rose at 2–6 h compared to the fasting value. RP-TG/RLP-C increased at 2–4 h and returned to baseline at 6 h.



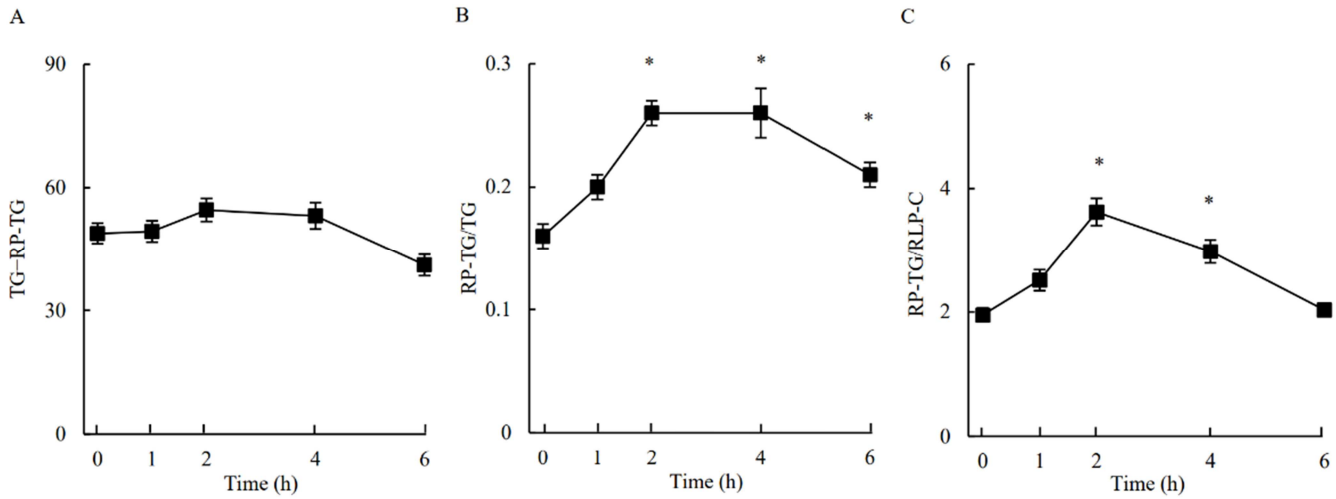
Values are the mean ± SEM. *p<0.05 vs. fasting value.

Figure 1. *Time courses for Δglucose (A) and Δinsulin (B) in the fat-ingestion test.*



Values are the mean ± SEM. *p<0.05 vs. fasting value.

Figure 2. *Time courses for ΔTG (A), ΔRP-TG (B), ΔRLP-C (C), ΔApoB48 (D), and ΔApoB100 (E) in the fat-ingestion test.*



Values are the mean ± SEM. *p<0.05 vs. fasting value.

Figure 3. *Time courses for the calculated indices TG−RP-TG (A), RP-TG/TG (B), and RP-TG/RLP-C (C).*

Table 2. *Blood chemical data and calculated indices in the fat-ingestion test.*

	0 h			0.5 h			1 h			2 h			4 h			6 h		
Glucose (mg/dL)	88.2	±	1.8	87.1	±	1.5	88.1	±	1.7	89.4	±	1.6	85.5	±	1.4*	81.8	±	1.4*
Insulin (mU/L)	5.93	±	0.41	8.53	±	0.52*	7.35	±	0.39*	5.60	±	0.33	3.71	±	0.24*	3.15	±	0.20*
TG (mg/dL)	57.8	±	3.0				61.3	±	3.1	73.9	±	3.8*	71.3	±	4.0*	51.3	±	3.1*
RP-TG (mg/dL)	8.9	±	0.5				11.9	±	0.8*	19.3	±	1.3*	18.1	±	1.4*	10.2	±	0.6
RLP-C (mg/dL)	4.90	±	0.26				5.02	±	0.26	5.60	±	0.29*	6.22	±	0.34*	5.19	±	0.28
ApoB48 (mg/L)	2.24	±	0.18				2.98	±	0.19*	4.11	±	0.24*	4.26	±	0.27*	3.31	±	0.25*
ApoB100 (mg/dL)	69.4	±	1.9				68.7	±	1.9	68.5	±	1.9*	69.4	±	1.9	70.9	±	1.9*
TG−RP-TG	48.9	±	2.7				49.4	±	2.6	54.6	±	2.8	53.2	±	3.2	41.1	±	2.6
RP-TG/TG	0.16	±	0.01				0.20	±	0.01	0.26	±	0.01*	0.26	±	0.02*	0.21	±	0.01*
RP-TG/RLP-C	1.95	±	0.11				2.51	±	0.17	3.62	±	0.22*	2.98	±	0.19*	2.03	±	0.08

Values are the mean ± SEM. *p<0.05 vs. fasting value.

4. Discussion

4.1. Major Findings

The major findings in this study are as follows: TG−RP-TG, namely TG contained in the lipoproteins other than remnants, did not significantly change during 6 h, but RP-TG/TG rose at 2–6 h compared to the fasting value, suggesting that the concentration of non-remnant TG was stable during the entire experiment, and the ratio of remnant TG to total TG increased. RP-TG/RLP-C increased at 2–4 h and returned to baseline at 6 h. Because RP-TG is hydrolyzed by lipoprotein lipase, releasing fatty acids and glycerol in the circulation, and then the concentration decreases to 6 h, but the cholesterol content in the remnant (RLP-C) does not decrease until the particle is taken up into the liver, the results indicate that the content of TG per remnant particle decreased, and the size became smaller from 2 h to 6 h. Because RP-TG and RLP-C contain both exogenous and endogenous remnants, it is difficult to clarify the relation to ApoB48, but it is supposed that the chylomicron remnant (CMR) remaining at the end of the experiment also became smaller.

The fat cream used in this study has a composition similar to butter fat, mainly consisting of saturated fatty acids. OFTT cream also does not contain carbohydrates. Therefore, the blood glucose level did not increase after the cream ingestion. However, a slight but significant increase in insulin was observed at 0.5–1 h, suggesting the effect of fat on incretin (GIP and/or GLP-1) release [18].

4.2. Analysis of Exogenous and Endogenous Lipoproteins

The method for measurement of remnant-like particle-cholesterol (RP-C) uses a monoclonal antibody to recognize all ApoB100-containing lipoproteins except for those that are ApoE enriched, and the contents of TG and cholesterol in the unbound remnant-like particles, which contain a subpopulation of ApoB48-containing TRL and remnant-like VLDL containing ApoB100, are measured [25, 26]. However, in the present study, only the TG in the fraction (RP-TG) was measured, because the cholesterol content is sometimes less than the lower limit of detection in young Japanese women [27]. RP-TG has been reported to be more sensitive to an exogenous remnant [28]. Meanwhile, the method for RLP-C is based on specific interactions of surfactants with lipoproteins and recognizes differences in the hydrated density, net charge, or size of lipoproteins [26] and more closely reflects the VLDL remnant [29], and RLP-C has been reported to be more suitable for an endogenous remnant [28].

In order to analyze postprandial lipidemia precisely, it is necessary to examine exogenous and endogenous lipoprotein metabolism separately. However, a single indicator is not sufficient for this purpose. That is why we used several indicators or markers, such as TG, RP-TG, RLP-C, ApoB48, ApoB100, and remnant indices. ApoB48 is the structural apolipoprotein of exogenous or intestinal lipoproteins, namely CM and its remnant, and is an index of the number of exogenous lipoproteins because every exogenous lipoprotein has one ApoB48 molecule. In the present study, the ApoB48 level did not return to baseline even at the end of experiment, suggesting that the postprandial exogenous lipoprotein metabolism was not complete 6 h after fat ingestion, even in healthy young women, consistent with our previous studies [30–32].

Meanwhile, ApoB100 is the structural apolipoprotein of endogenous or hepatic lipoproteins, namely VLDL and its remnant and LDL, and is an index of the number of endogenous lipoproteins because every endogenous lipoprotein has one ApoB100 molecule. However, because most of the ApoB100 molecules are contained in LDL, the postprandial change in ApoB100 concentration is small. In the present study, ApoB100 concentration showed a slight but significant change during the experiment, decreased at 2 h, and increased at 6 h. The results may indicate initial inhibition of VLDL secretion from the liver by the influx of CMR and an increase in VLDL secretion at a later phase.

4.3. Determinants of Postprandial Lipidemia

While delayed TRL clearance is an important determinant of postprandial lipidemia, the overproduction of intestinal ApoB48-containing lipoproteins also contributes [33]. Although the postprandial elevation in ApoB48 level is moderate, the increase in the capacity to transfer the ingested lipid is mainly due to enrichment of the lipid load, not an increase in the number of particles. About half of the TG in CM particles was unloaded through the course of remnant formation [34], and the residence time of ApoB48 in the

circulation was calculated to be 4.8 h [35]. The increase in the remnant cholesterol level was reported to be a better risk factor than the TG level, particularly in women [36, 37]. Women with android obesity, both with normal and high fasting TG, exhibit a more pronounced and deleterious postprandial TG response compared to women with gynoid obesity with normal fasting TG [38], supporting the influence of sex on postprandial lipoprotein metabolism via body-composition differences. Visceral fat obesity has been reported to be associated with impaired postprandial lipid metabolism [39, 40]. It was also reported that waist circumstance was a strong determinant of postprandial lipidemia or a diurnal TG profile in both females and males [41]. However, in the present study, the waist circumference or VFA was not significantly associated with postprandial lipid and lipoprotein markers, probably because the subjects were all healthy, non-obese young women.

4.4. Study Strengths and Limitations

This study has several strengths. First, a larger number of subjects were enrolled than in our previous studies, and novel indices for postprandial lipidemia were proposed. Second, previous postprandial studies utilized meals that are unrealistically high in calories or fat for Japanese women and were not standardized to body mass [26]. The typical daily intake of fat by a Japanese adult woman is about 50 g [24]. Accordingly, the amount of fat ingested in the present study (ca. 17–18 g) corresponds to about one-third of the daily fat consumption and is modest or moderate. Another strength of this study was the use of a fat amount scaled to body mass, unlike previous studies or the 75 g oral glucose tolerance test. Although it was reported that a low-fat (15 g) meal had no effect on postprandial lipidemia in healthy men [42], the amount of fat near the lower limit induced significant postprandial lipidemia in Japanese women.

This study also has some limitations. We measured several markers of lipids and lipoproteins, including ApoB48, RP-TG, and RLP-C. However, these methods of measurement cannot perfectly discriminate between exogenous and endogenous lipoproteins. Therefore, analysis of the postprandial lipoprotein metabolism may not be enough. Examinees were restricted to the ApoE3/3 phenotype. Although ApoE3 is the wild type (but not the prototype) [43] and the most common in Japan [44] and probably in most of the world, other types, such as E2 and E4, may be different with regard to the response to fat ingestion. Therefore, the present results may not be applicable for subjects with a phenotype other than E3. Lastly, because only healthy Japanese young women were examined, the present results should be interpreted with caution.

5. Conclusion

After fat ingestion, the concentration of non-remnant TG was stable, and remnant TG increased. The content of TG per remnant particle increased up to 2 h, then decreased to 6 h, and the size became smaller. The novel indices RP-TG/TG and RP-TG/RLP-C may be useful for estimating postprandial lipidemia. More studies will be needed to verify the clinical usability of these indices in the future.

Conflict of Interests

The authors declare that they have no competing interests.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (21300259, 24500874, and 15K00855).

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