Original Article

Differences in Serum Phospholipid Fatty Acid Compositions and Estimated Desaturase Activities between Japanese Men with and without Metabolic Syndrome

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***Aim*: This study was designed to clarify differences in serum phospholipid fatty acid compositions and estimated desaturase activities between Japanese men with and without metabolic syndrome (MetS).**
***Methods*: From among 227 males, 40 to 59 years of age, excluding those receiving treatment for lipid disorders, 165 subjects (including 27 with MetS) were selected for this study. Serum phospholipid fatty acid compositions were determined, and desaturase activities were estimated.**
***Results*: The C15:0 and C17:0 fatty acids associated with hepatic function were lower, while the C20:3n-6 and C20:4n-3 fatty acids were higher, in subjects with than without MetS ($p<0.05$). The estimated desaturase activity for D5D(n-6) was lower in subjects with than without MetS ($p<0.01$). Body fat percentage was an independent negative predictor of C17:0, and a positive predictor of log C20:3n-6 and log C20:4n-3 ($p<0.01$). HDL-C was an independent negative predictor of log C15:0 and of C17:0 ($p<0.01$).**
***Conclusion*: Decreases in minor saturated fatty acids, accumulation of C20:3n-6 and C20:4n-3 and low estimated D5D activitiy were confirmed to be associated with MetS.**

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Key words; Dihomo-γ-linolenic acid, Icosatetraenoic acid, Pentadecanoic acid, Heptadecanoic acid

Introduction

Metabolic syndrome (MetS) has been recognized as a constellation of multiple risk factors for cardiovascular disease, with dyslipidemia plus elevated glucose and blood pressure, which are widely regarded as targets for preventing the early stages of coronary artery disease. The predominant underlying risk factor is considered to be visceral obesity causing insulin resistance[1)].

There have been numerous reports on the relationships among dietary fat intake, serum fatty acids, and cardiovascular disease and its risk factors. Observations often made in studies measuring serum fatty acids include higher proportions of stearic acid (C18:0), dihomo-γ-linolenic acid (C20:3n-6) and total saturated fatty acids (SFA), and lower arachidonic acid (C20:4n-6) and total polyunsaturated fatty acids (PUFA), in subjects with coronary heart disease and its risk factors[2-7)].

In recent years, a relationship has been recognized between the development of coronary heart disease and decreased delta-5 desaturase (D5D) activity[8, 9)], which converts C20:3n-6 to C20:4n-6 and C20:4n-3 to icosapentaenoic acid (C20:5n-3) (**Fig. 1**). The endogenous fatty acid synthesis catalyzed by D5D reflects serum fatty acid composition, and D5D activity is also recognized as predicting MetS[10, 11)]. On the other hand, the effects of delta-6 desaturase (D6D)

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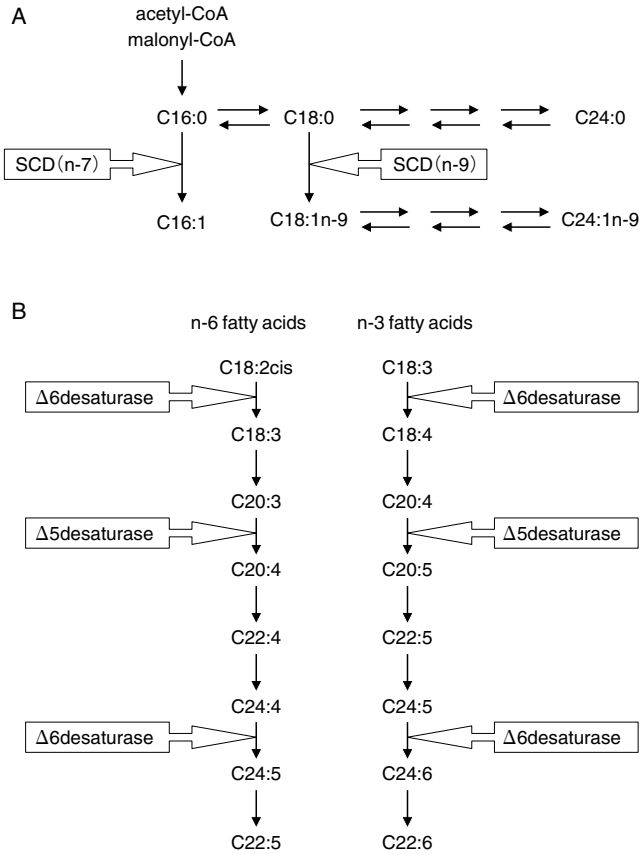

Fig. 1. Metabolic pathways of fatty acids.

(A) Mono unsaturated fatty acid synthesis by stearoyl CoA desaturase (SCD). (B) Both polyunsaturated fatty acid families, n-3 and n-6 fatty acids, share the same enzymes.

activity on the risk of ischemic heart disease are unknown. D6D is a rate-limiting enzyme in the PUFA biosynthetic pathway, converting the essential fatty acids linoleic (C18:2n-6) and alpha-linolenic (C18:3n-3) acid into gamma-linolenic acid (C18:3n-6) and octadecatetraenoic acid (C18:4n-3), respectively. According to *in vitro* and animal model studies, dietary PUFA reportedly decreases both the activity and the expression of D5D and D6D[12-14].

Stearoyl CoA desaturase (SCD) is also a rate-limiting enzyme catalyzing the synthesis of monounsaturated fatty acids, mainly palmitoleic (C16:1) and oleic (C18:1) acid, from the saturated fatty acids palmitic (C16:0) and stearic (C18:0) acid, respectively. SCD is known to be related to obesity and insulin resistance[11].

The fatty acid composition of serum phospholipids reflects dietary fatty acid intake over the prior few weeks, as well as endogenous fatty acid metabolism[15, 16]. Thus, phospholipids play various important roles not only as membrane components, but also as the source of fatty acids, serving as precursors for physiologically active substances affecting cell functions.

Fatty acid compositions and desaturase activities in Japanese subjects with MetS have not been documented, and habitual dietary fatty acid intake in Japan differs from that in Northern European populations. The purpose of this study was to examine differences in serum phospholipid fatty acid compositions and estimated desaturase activities between Japanese subjects with and without MetS.

Subjects and Methods

Subjects

The protocol was approved by Japan Women's University ethics committee. The 227 male subjects, ranging in age from 40 to 59 years, received a complete medical check-up at Mitsui Memorial Hospital, and provided written informed consent. Subjects receiving treatment for MetS or related disorders were excluded. Thus, data on 165 males were analyzed for this study. According to the definition of the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome (April 2005)[17], we defined MetS as the presence of 2 or more abnormalities involving serum lipids, glucose levels and blood pressure in addition to visceral obesity (umbilical circumference: 85 cm or more in men). The following were considered to be abnormal values: Triglyceride (TG) ≧150 mg/dL and/or HDL-cholesterol (HDL-C) <40 mg/dL, systolic blood pressure ≧130 mmHg and/or diastolic blood pressure ≧85 mmHg, fasting glucose ≧110 mg dL.

Anthropometric Measurements

Height and weight were measured, and body mass index (BMI) was calculated as: BMI=body weight (kg)/height (m)^2. Umbilical circumference was measured during the late exhalation phase in the standing position. Body weight and fat percentage were measured using bioelectrical impedance analysis at both heels (Body Fat Analyzer TBF-210, Tanita Co. Ltd, Tokyo). Blood pressure was measured using an automatic blood pressure manometer (Kentaro BP- 203RV Ⅲ B, Nihon Colin Co. Ltd, Tokyo), with the subject in the seated position.

Blood Sampling and Analysis

All serum and plasma samples were obtained in the fasting state and measurements were conducted in the laboratory of Mitsui Memorial Hospital. Serum total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-C and TG levels were measured enzymatically. Aspartate aminotransferase (AST), alanine aminotrans-

Table 1. Clinical characteristics of subjects with and without metabolic syndrome

	without metabolic syndrome	with metabolic syndrome	*p*
Number	138	27	
Age	50.5 ± 5.8	48.4 ± 6.7	0.091
Body mass index	23.2 ± 2.6	26.9 ± 2.9	< 0.001
Umbilical circumference (cm)	83.2 ± 6.6	92.9 ± 6.4	< 0.001
Body fat percentage (%)	21.6 ± 4.1	27.4 ± 3.9	< 0.001
Systolic blood pressure (mmHg)	128 ± 20	143 ± 13	< 0.001
Diastolic blood pressure (mmHg)	81 ± 11	89 ± 10	0.001
Aspartate aminotransferase (IU/L)	22 ± 7	23 ± 6	0.624
Alanine aminotransferase (IU/L)	25 ± 12	32 ± 15	0.009
γ-glutamyltransferase (IU/L)	50 ± 37	58 ± 29	0.280
Uric acid (mg/dL)	6.1 ± 1.1	6.8 ± 1.4	0.007
Hemoglobin A_{1c} (%)	5.3 ± 0.5	5.8 ± 0.8	0.012
Fasting plasma glucose (mg/dL)	95 ± 9	108 ± 23	0.007
Fasting insulin (μU/L)	6.4 ± 3.2	11.0 ± 5.4	< 0.001
HOMA-IR	1.5 ± 0.8	3.0 ± 1.7	< 0.001
Total Cholesterol (mg/dL)	207 ± 28	217 ± 38	0.201
LDL-Cholesterol (mg/dL)	128 ± 28	137 ± 38	0.240
HDL-Cholesterol (mg/dL)	60 ± 14	48 ± 7	< 0.001
Triglyceride (mg/dL)	114 ± 66	217 ± 87	< 0.001
TG/HDL-C	2.1 ± 1.6	4.7 ± 2.4	< 0.001

Values are expressed as the means ± SD.
HOMA-IR: homeostasis model assessment of insulin resistance, TG/HDL-C: triglyceride/HDL-cholesterol ratio

ferase (ALT) and gamma-glutamyltransferase (γ-GTP) were measured by UV and L-γ-glutamyl-3-carboxy-4-nitroanilide substrate methods. Uric acid was determined by the uricase method. These biochemical parameters were measured with a TBA-200FR (Toshiba Medical Co. Ltd., Tokyo, Japan). Plasma glucose was determined enzymatically using a fully automated glucose analyzer (GA-1170 Arkray, Inc., Kyoto, Japan) and HbA_{1c} was determined with a fully automated glycohemoglobin (HbA_{1c}) analyzer based on high performance liquid chromatography (HPLC) (ADAMS A1c, HA-8150 Arkray, Inc., Kyoto, Japan). Serum insulin was determined by chemiluminescence immunoassay with an automated immunoassay system, the ADVIA Centaur (Bayer Medical, NY, USA).

The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as: HOMA-IR = fasting plasma glucose (mg/dL) × fasting insulin (IRI) (μU/L) ÷ 405.

Fatty Acid Analysis

Serum lipids were extracted by the method of Folch *et al.*[18]. The phospholipid (PL) fraction was obtained with thin-layer chromatography and methylated as described in our previous report[19] with minor modifications. The fatty acid methyl esters were separated by gas-liquid chromatography (Shimadzu GC14B, Tokyo, Japan) using a 0.25 mm × 30 m capillary column containing DB-FFAP (J&W Scientific, CA, USA). The injector temperature was 230℃, and the column temperature rose 2℃/min from 160℃ to 200℃. Nitrogen was employed as the carrier gas, and the split ratio was 22.0.

Estimation of Desaturase Activities

Desaturase activities were estimated as the product to precursor ratio of individual fatty acids in serum phospholipids, as follows: SCD(n-7) = (C16:1n-7/C16:0), SCD(n-9) = (C18:1cis n-9/C18:0), D5D(n-6) = (C20:4n-6/C20:3n-6), D6D(n-3) = C18:4n-3/C18:3n-3, D5D(n-3) = (C20:5n-3/C20:4n-3).

Statistical Analysis

Statistical analysis was performed using the SPSS12.0J software package for Windows (SPSS Inc., Japan). Data are expressed as the means ± standard deviation. Between-group comparisons were made using the Mann-Whitney *U* test. *P* values < 0.05 were considered significant. Normality was assessed by the Kolmogorov-Smirnov test and skewed variables were log transformed. For all subjects, relations between variables were assessed by linear correlation analysis. Step-

wise multiple regression analysis was performed to explore determinants of fatty acids. Age, BMI, umbilical circumference, body fat percentage, SBP, DBP, AST, ALT, γ-GTP, uric acid, FPG, log IRI, HDL-C, LDL-C and logTG were included as predictors in the original model. *P* values <0.01 were considered significant for regression analysis.

Results

Prevalence of Metabolic Syndrome

The prevalence, in our 165 subjects, of an abnormally large umbilical circumference, high blood pressure, abnormal fasting plasma glucose, low HDL-cholesterolemia and hypertriglyceridemia was 76 (46%), 90 (55%), 17 (10%), 11 (7%) and 48 (29%), respectively. The prevalence of MetS in these subjects was 16.3% (27 cases).

Clinical Characteristics

The clinical characteristics of the subjects with and without MetS are shown in **Table 1**. In addition to the parameters indicative of MetS, body fat percentage, fasting insulin, HOMA-IR ($p<0.001$), ALT, uric acid ($p<0.01$) and HbA_{1c} ($p<0.05$) were higher in subjects with than without MetS. The TG/HDL-C ratio was also higher in subjects with MetS ($p<0.001$).

Fatty Acid Composition

Serum phospholipid fatty acid compositions are shown in **Table 2**. C15:0 and C17:0 fatty acids were lower, and C20:3n-6 and C20:4n-3 fatty acids higher in subjects with than without MetS ($p<0.05$).

Multiple Regression Analysis

The best predictors of fatty acid variations differing significantly between subjects with and without Mets, demonstrated by stepwise regression analysis of biological parameters, are shown in **Table 3**. Body fat percentage was an independent negative predictor of C17:0, and a positive predictor of log C20:3n-6 and log C20:4n-3 ($p<0.01$). HDL-C was an independent negative predictor of log C15:0 ($p<0.05$), and C17:0 ($p<0.01$). Log TG was an independent negative predictor of C17:0, and a positive predictor of log C20:3n-6 ($p<0.05$). γ-GTP was an independent negative predictor of log C15:0 ($p<0.01$). Significant independent explanatory variables were obtained; however, the adjusted R^2 values showed a contribution of less than 15% for each fatty acid. Thus, no independent relation of blood pressure or glycemic parameters was observed with any fatty acids.

Table 2. Serum phospholipid fatty acid compositions in subjects with and without metabolic syndrome

	without metabolic syndrome ($n=138$)	with metabolic syndrome ($n=27$)	*p*
	% of total fatty acids		
SFA			
12:0	0.16 ± 0.13	0.14 ± 0.09	0.495
14:0	0.59 ± 0.17	0.55 ± 0.14	0.325
15:0	0.17 ± 0.05	0.15 ± 0.04	0.024
16:0	28.45 ± 3.56	28.47 ± 2.65	0.978
17:0	0.37 ± 0.10	0.33 ± 0.10	0.026
18:0	14.50 ± 2.07	14.89 ± 2.03	0.365
20:0	0.53 ± 0.13	0.50 ± 0.09	0.289
22:0	1.19 ± 0.39	1.17 ± 0.23	0.813
24:0	1.07 ± 0.31	1.01 ± 0.19	0.186
MUFA			
14:1	0.11 ± 0.05	0.10 ± 0.05	0.493
16:1	0.45 ± 0.18	0.45 ± 0.16	0.929
17:1	0.07 ± 0.03	0.07 ± 0.02	0.281
18:1 cis	7.69 ± 1.42	8.04 ± 1.17	0.230
18:1 trans	1.58 ± 0.29	1.49 ± 0.21	0.119
20:1	0.25 ± 0.06	0.24 ± 0.05	0.548
22:1	0.07 ± 0.06	0.07 ± 0.05	0.799
24:1	1.95 ± 0.54	1.84 ± 0.59	0.352
n-6PUFA			
18:2 cis	17.12 ± 3.53	17.05 ± 2.24	0.902
18:2 trans	0.05 ± 0.02	0.05 ± 0.01	0.331
20:2	0.28 ± 0.09	0.29 ± 0.06	0.496
20:3	1.73 ± 0.53	1.99 ± 0.67	0.023
20:4	7.78 ± 1.64	7.67 ± 1.84	0.754
22:2	0.45 ± 0.13	0.42 ± 0.09	0.162
n-3PUFA			
18:3	0.18 ± 0.08	0.19 ± 0.05	0.574
18:4	0.15 ± 0.07	0.13 ± 0.07	0.170
20:4	0.16 ± 0.06	0.18 ± 0.07	0.045
20:5	2.93 ± 1.46	2.89 ± 1.60	0.899
22:5	1.01 ± 0.30	1.07 ± 0.34	0.401
22:6	7.09 ± 2.04	7.17 ± 1.97	0.843
unknown peak			
1	0.12 ± 0.07	0.13 ± 0.07	0.595
unknown peak			
2	1.61 ± 2.30	1.41 ± 1.74	0.671

Values are expressed as the means ± SD.
SFA: saturated fatty acid, MUFA: monounsaturated fatty acid, PUFA: polyunsaturated fatty acid

Estimated Desaturase Activity

As shown in **Table 4**, the estimated desaturase activity of D5D(n-6) was lower in subjects with than without MetS ($p<0.01$).

Table 3. Best predictors of variations in fatty acids in a stepwise backward regression analysis

	Predictor	beta coefficient	*p*	Adjusted R^2
log C15:0	γ-glutamyltransferase	−0.260	0.001	
	HDL-Cholesterol	−0.169	0.026	0.079 ($p=0.000$)
C17:0	HDL-Cholesterol	−0.281	0.002	
	Body fat percentage	−0.255	0.003	
	log Triglyceride	−0.236	0.014	0.108 ($p=0.000$)
log C20:3(n-6)	Body fat percentage	0.261	0.002	
	log Triglyceride	0.195	0.017	0.143 ($p=0.000$)
log C20:4(n-3)	Body fat percentage	0.298	0.000	0.083 ($p=0.000$)

$n=165$

Table 4. Estimated desaturase activities in subjects with and without metabolic syndrome

	without metabolic syndrome	with metabolic syndrome	*p*
number of subjects	138	27	
SCD(n-7)	0.02 ± 0.01	0.02 ± 0.01	0.915
SCD(n-9)	0.55 ± 0.18	0.55 ± 0.11	0.995
D5D(n-6)	4.77 ± 1.26	4.06 ± 1.08	0.006
D6D(n-3)	1.00 ± 0.69	0.78 ± 0.61	0.153
D5D(n-3)	19.54 ± 9.30	17.14 ± 9.30	0.202

$n=165$. Values are expressed as the means ± SD.
SCD-1(n-7) = C16:1(n-7)/C16:0, SCD-1(n-9) = C18:1cis(n-9)/C18:0, D5D(n-6) = C20:4(n-6)/C20:3(n-6), D6D(n-3) = C18:4(n-3)/ C18:3(n-3), D5D(n-3) = C20:5(n-3)/C20:4(n-3).

Table 5. Correlation coefficients between estimated desaturase activities

	SCD(n-7)	SCD(n-9)	log D5D(n-6)	log D6D(n-3)	log D5D(n-3)
SCD(n-7)					
SCD(n-9)	0.641**				
log D5D(n-6)					
log D6D(n-3)	−0.477**	−0.530**			
log D5D(n-3)			0.635**		

$n=165$, Values are significant correlation coefficients at $p<0.01$ (**).
SCD(n-7) = C16:1(n-7)/C16:0, SCD(n-9) = C18:1cis(n-9)/C18:0, D5D(n-6) = C20:4(n-6)/C20:3(n-6), D6D(n-3) = C18:4(n-3)/C18:3(n-3), D5D(n-3) = C20:5(n-3)/C20:4(n-3).

Correlations Among Estimated Desaturase Activities

Associations among estimated desaturase activities are shown in **Table 5**. There was a positive correlation between SCD(n-7) and SCD(n-9) ($p<0.01$). Log D6D(n-3) showed negative correlations with SCD(n-7) and SCD(n-9) ($p<0.01$). Log D5D(n-6) showed a positive correlation with log D5D(n-3) ($p<0.01$).

Discussion

To our knowledge, this is the first study to determine phospholipid fatty acid compositions and to estimate desaturase activities in Japanese men with MetS. The number of subjects is semi-epidemiological, as those with MetS in the present study received no medications or other treatments, such that the information obtained was unbiased. The prevalence of MetS in our subjects was essentially the same as that in the Japanese adult male population as a whole, i.e. approximately 15%[20, 21].

There have been numerous studies on serum fatty acids and coronary heart disease or atherogenic risk factors, although few focused on C15:0 and/or

C17:0 results[7, 10, 22]. C15:0 and C17:0 are contained in various plant and animal foods but only in small amounts. The percentages of C15:0 and C17:0 in adipose tissue and serum lipid esters have been proposed as biomarkers of dietary ruminant fat intake, especially dairy products[23], because the human body is unable to synthesize fatty acids with an uneven number of C atoms, unlike ruminal microbes of dairy cattle[24]. In this study, the levels of C15:0 and C17:0 were lower than in Western subjects who probably consume more animal fat and less fish oil; therefore, the results might partially reflect habitual dietary consumption. As no reports have been published on C15:0 and C17:0 fatty acid consumption in Japanese subjects, dietary reports designed to clarify the differences between those with and without MetS are now being investigated.

In MetS subjects, the percentages of C15:0 and C17:0 in phospholipids were lower than in subjects without MetS. Furthermore, C17:0 correlated negatively with HDL-C, body fat percentage and log TG, and is suggested to reflect fat storage and decreased effects of hepatic triglyceride lipase[25]. Warensjö *et al*. reported that the proportions of C15:0 and C17:0 in serum phospholipids were significantly and negatively correlated with serum concentrations of plasminogen activator inhibitor-1, tissue-type plasminogen activator, TG, insulin, specific insulin, pro-insulin and leptin, suggesting negative relationships with insulin-resistance syndrome and the risk of coronary heart disease; however, they did not measure HDL-C[26]. The mechanisms underlying these results have not been elucidated. Considering that C17:0 is a metabolite converted from PGH1, 8-iso-PGH, 13(S)-hydroxy-PGH2 and 15-keto-PGH2 by human platelet thromboxane synthase[27], further studies are needed to clarify the role of these minor saturated fatty acids in metabolism, and the involvement of decreased C15:0 and C17:0 in MetS.

One of the two rate-limiting steps in the production of biologically important PUFA, such as C20:4n-6, C20:5n-3 and C22:6n-3, is the desaturation of C20:3n-6 to C20:4n-6 and C20:4n-3 to C20:5n-3, determined by the activity of D5D. The other step, catalyzed by D6D, is the desaturation of C18:2n-6 to C18:3n-6 and C18:3n-3 to C18:4n-3.

As no data are available on the n-3 biosynthetic pathway in populations consuming fish and fish products daily, we aimed to clarify the significance of the PUFA level and to estimate desaturase activity in Japanese. We showed C20:3n-6 and C20:4n-3 fatty acid levels to be higher and estimated D5D(n-6) activity to be lower in our subjects with than in those without MetS. Essentially the same results were reported for n-6 fatty acids and D5D(n-6) by Zak *et al*. in the Czech Republic[28] and by Warenjö *et al*. in a Swedish[10] study population. We were not able to detect C18:3n-6, although its identification has been described in European reports. This was considered to be because of the difference in dietary n-6 and n-3 PUFA intake. Our subjects consumed fish and fish products 9.7 ± 5.0 times per week, and Japanese people generally consume about 90 g of fish and fish products per day[29]. Thus, a lower level of n-6 PUFAs and higher n-3 PUFA percentages were obtained in our subjects than is Western surveys. In addition, our results indicate that despite significantly higher C20:4n-3 fatty acid levels, the estimated D5D(n-3) activity did not differ between our subjects and those without MetS. As for the large intake of C20:5n-3 from fish and fish products, estimated D5D(n-3), calculated as C20:4n-3/C20:5n-3, does not precisely reflect the n-3 fatty acid biosynthetic state. Therefore, we should take into account the effects of dietary n-3 fatty acid intake when evaluating the appropriateness of the estimated D5D(n-3) activity. The C20:4n-3 fatty acid percentage might be a better parameter than the estimated D5D(n-3) activity for evaluating abnormal n-3 fatty acid synthesis.

Nevertheless, C20:3n-6 and C20:4n-3 fatty acid levels were higher and the estimated D5D(n-6) activity was lower in our subjects with than without MetS. Furthermore, weak but positive relationships were observed between the body fat percentage and log C20:3n-6 and log C20:4n-3. These results are similar to those obtained in obese children with a significantly elevated correlation between plasma C20:3n-6 and leptin[30]. These observations are supported by a report describing a negative correlation between C20:3n-6 and peripheral insulin sensitivity[31], as well as high SCD and D6D activities and low D5D activity, generally considered to be associated with an insulin-resistant status[32, 33]. SCD-1 expression has been found to be highly correlated with liver steatosis[34]. Under lipogenic conditions, when increased expression of hepatic PPARγ2 lead to elevated SCD, and SREBP-1 was activated with increased insulin resistance and hyperinsulinemia[35-37], newly synthesized fatty acids could be dominated by saturated or monounsaturated fatty acids and the availability of essential fatty acids might be limited. The negative correlation between SCD and D6D(n-3) indicates an augmenting reaction which maintains essential PUFA levels. In this study, estimated SCD did not differ between subjects with versus without MetS, and ALT was significantly higher, although within the normal range, in the MetS group.

This indicates that in our MetS group, the degree of hepatic steatosis is modest, although lipogenesis might be accelerated. Because of the higher consumption of fish and fish products by Japanese, n-3PUFA levels may still be within the normal range in subjects with Mets, possibly contributing to high C20:3n-6 and C20:4n-3 fatty acids via low D5D expression and/or activity, instead of increased SCD, since dietary PUFA reportedly decreases both the activity and expression of D5D and D6D[12-14].

The other reasons for increased these fatty acids are the high biochemical use of C20:4n-6 with less use of C20:3n-6. PUFA play important roles as precursors of eicosanoids, such as prostaglandins (PG), thromboxanes and leukotrienes, which help regulate blood pressure, heart rate, vascular dilation, blood clotting, lipolysis and immune responses. C20:3n-6 is the precursor of series 1 PG, such as PGG1, PGH1 and PGE1, which have anti-atherogenic functions. As the percentage of C20:4n-6 did not differ between subjects with and without MetS, we consider phospholipase A_2 activity, which generates platelet activating factor (PAF) and PAF-like phospholipids with release of C20:4n-6, to have been accelerated. PAF-like phospholipids are recognized in the atherogenic lipoproteins of small, dense LDL[38-41]. Zak *et al*. reported that the severity of MetS was associated with the progression of oxidative stress, as evaluated with conjugated dienes in LDL[28]. Their results are consistent with the high TG/HDL-C ratio in our subjects with compared to without MetS. We have found a TG/HDL-C ratio higher than 2.0 to be an easily measured parameter which indicates the presence of small, dense LDL in first-stage screening[42].

In conclusion, fatty acid compositions and estimated desaturase activities were confirmed to differ between Japanese male subjects with and without MetS, as in other study populations. Further study is needed to clarify whether altered fatty acid compositions are associated with MetS with atherogenic and thrombogenic mechanisms. The effects of dietary fatty acid intake must also be examined.

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References

1) World Health Organization Definition, diagnosis, and classification of diabetes and its complications: report of a WHO consultation. Part I: World Health Organization 1999
2) Maruyama C, Tsushima M, Kyotani S, Nakamori T, Fukushima S, and Maruyama T: Cerebral blood flow velocity and serum fatty acid composition. Nutr Metab Cardiovasc Dis, 1996; 6:81-89
3) Zheng ZJ, Folsom AR, Ma J, Arnett DK, McGovern PG, and Eckfeldt JH: Plasma fatty acid composition and 6-year incidence of hypertension in middle-aged adults: Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol, 1996; 150:492-500
4) Zák A, Zeman M, Tvrzická E: Fatty acid composition of phosphatidylcholine and levels of lipids and lipoproteins in hyperlipoproteinemia.I. Relation to HDL lipoprotein. Cas Lek Cesk, 1998; 137:368-371
5) Iso H, Sato S, Umemura U, Kudo M , Koike K, Kitamura A, Imano H, Okamura T, Naito Y, Shimamoto T: Linoleic acid, other fatty acids, and the risk of stroke. Stroke, 2002; 33:2086-2093
6) Wang L, Folsom AR, Eckfeldt JH: Plasma fatty acid composition and incidence of coronary heart disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Nutr Metab Cardiovasc Dis, 2003; 13:256-266
7) Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH; ARIC Study Investigators: Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr, 2003; 78:91-98
8) Byberg L, Smedman A, Vessby B, Lithell H: Plasminogen activator inhibitor-1 and relations to fatty acid composition in the diet and in serum cholesterol esters. Arterioscler Thromb Vasc Biol, 2001; 21:2086-2092
9) Ohrvall M, Berglund L, Salminen I, Lithell H, Aro A, Vessby B: The serum cholesterol ester fatty acid composition but not the serum concentration of alpha tocopherol predicts the development of myocardial infarction in 50-year-old men: 19 years follow-up. Atherosclerosis, 1996; 127:65-71
10) Warensjö E, Risérus U, Vessby B: Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. Diabetologia, 2005; 48:1999-2005
11) Warensjö E, Ingelsson E, Lundmark P, Lannfelt L, Syvänen AC, Vessby B, Risérus U: Polymorphisms in the SCD1 gene: associations with body fat distribution and insulin sensitivity. Obesity, 2007 (Silver Spring); 15:1732-1740
12) Cho HP, Nakamura T, and Clarke SD: Cloning, expression, and fatty acid regulation of the human Δ-5 desaturase. J Biol Chem, 1999; 274:37335-37339
13) Cho HP, Nakamura T, Clarke SD: Cloning, expression, and nutritional regulation of the mammalian Delta-6 desaturase. J Biol Chem, 1999; 274:471-477
14) Matsuzaka T, Shimano H, Yahagi N, Amemiya-Kudo M, Yoshikawa T, Hasty AH, Tamura Y, Osuga J, Okazaki H, Iizuka Y, Takahashi A, Sone H, Gotoda T, Ishibashi S, Yamada N: Dual regulation of mouse Delta(5)- and Delta(6)- desaturase gene expression by SREBP-1 and PPARalpha. J Lipid Res, 2002; 43:107-114
15) Ma J, Folsom AR, Shahar E, Eckfeldt JH: Plasma fatty acid composition as an indicator of habitual dietary fat

intake in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Am J Clin Nutr, 1995; 62:564-571
16) Vessby B, Gustafsson IB, Tengblad S, Boberg M, Andersson A: Desaturation and elongation of Fatty acids and insulin action. Ann N Y Acad Sci, 2002; 967:183-195
17) The committee for diagnostic criteria of Metabolic Syndrome: Definition and diagnostic criteria of Metabolic Syndrome. Intern Med, 2005; 94:1-16
18) FOLCH J, LEES M, SLOANE STANLEY GH: A simple method for the isolation and purification of total lipides from animal tissues. J Biol Chem, 1957; 226:497-509
19) Maruyama C, Kijimoto R, Ito K, Doi K, Imamura M, Nakamori T, Fukushima S, Maruyama T, and Tsushima M: Serum fatty acid composition in hyperlipidemic females. J Clin Biochem Nutr, 1993; 15:143-153
20) Urashima M, Wada T, Fukumoto T, Joki M, Maeda T, Hashimoto H, and Oda S: Prevalence of metabolic syndrome in 22,892 Japanese population and its association with life style. JMAJ, 2005; 48:441-450
21) Arai H, Yamamoto A, Matsuzawa Y, Saito Y, Yamada N, Oikawa S, Mabuchi H, Teramoto T, Sasaki J, Nakaya N, Itakura H, Ishikawa Y, Ouchi Y, Horibe H, Shirahashi N, Kita T: Prevalence of metabolic syndrome in the general Japanese population in 2000. J Atheroscler Thromb, 2006; 13:202-208
22) Warensjö E, Sundström J, Lind L, Vessby B: Factor analysis of fatty acids in serum lipids as a measure of dietary fat quality in relation to the metabolic syndrome in men. Am J Clin Nutr, 2006; 84:442-448
23) Wolk A, Furuheim M, Vessby B: Fatty acid composition of adipose tissue and serum lipids are valid biological markers of dairy fat intake in men. J Nutr, 2001; 131:828-833
24) Wu Z, Palmquist DL: Synthesis and biohydrogenation of fatty acids by ruminal microorganisms in vitro. J Dairy Sci, 1991; 74:3035-3036
25) Werner A, Havinga R, Bos T, Bloks VW, Kuipers F, Verkade HJ: Essential fatty acid deficiency in mice is associated with hepatic steatosis and secretion of large VLDL particles. Am J Physiol Gastrointest Liver Physiol, 2005; 288:1150-1158
26) Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B: Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarctioin. A prospective case-control study. Br J Nutr, 2004; 91:635-642
27) Hecker M and Ullrich V: On the mechanism of prostacyclin and thromboxane A2 biosynthesis. J Biol Chem, 1989; 264:141-150
28) Zák A, Tvrzická E, Vecka M, Jáchymová M, Duffková L, Stanková B, Vávrová L, Kodydková J, Zeman M: Severity of metabolic syndrome unfavorably influences oxidative stress and fatty acid metabolism in men. Tohoku J Exp Med, 2007; 212:359-371
29) The health and nutrition information study group. Ministry of Health, Labour and Welfare of Japan: The national Health and nutrition survey in Japan, 2003. pp38, Daiichi-shuppan, Tokyo, 2006
30) Okada T, Sato NF, Kuromori Y, Miyashita M, Tanigutchi K, Iwata F, Hara M, Ayusawa M, Harada K, Saito E: Characteristics of obese children with low content of arachidonic acid in plasma lipids. Pediatr Int, 2007; 49:437-442
31) Vessby B, Tengblad S, Lithell H: Insulin sensitivity is related to the fatty acid composition of serum lipids and skeletal muscle phospholipids in 70-year-old men. Diabetologia, 1994; 37:1044-1050
32) Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Campbell LV: The relation between insulin sensitivity and the fatty-acid composition of skeletel-muscle phospholipids. N Engl J Med, 1993; 328:238-244
33) Pan DA, Lillioja S, Milner MR, Kriketos AD, Baur LA, Bogardus C, Storlien LH: Skeletal muscle membrane lipid composition is related to adiposity and insulin action. J Clin Invest, 1995; 96:2802-2808
34) Miyazaki M, Kim YC, Ntambi JM: A lipogenic diet in mice with a disruption of the stearoyl-CoA desaturase 1 gene reveals a stringent requirement of endogenous monounsaturated fatty acids for triglyceride synthesis. J Lipid Res, 2001; 42:1018-1024
35) Horton JD, Shimomura I, Ikemoto S, Bashmakov Y, Hammer RE: Overexpression of sterol regulatory element-binding protein-1a in mouse adipose tissue produces adipocyte hypertrophy, increased fatty acid secretion, and fatty liver. J Biol Chem, 2003; 278:36652-36660
36) Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS, Goldstein JL: Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. Mol Cell, 2000; 6:77-86
37) Zhang YL, Hernandez-Ono A, Siri P, Weisberg S, Conlon D, Graham MJ, Crooke RM, Huang LS, Ginsberg HN: Aberrant hepatic expression of PPARgamma2 stimulates hepatic lipogenesis in a mouse model of obesity, insulin resistance, dyslipidemia, and hepatic steatosis. J Biol Chem, 2006; 281:37603-37615
38) Marathe GK, Prescott SM, Zimmerman GA, McIntyre TM: Oxidized LDL contains inflammatory PAF-like phospholipids. Trends Cardiovasc Med, 2001; 11:139-142
39) Tsoukatos DC, Liapikos TA, Tselepis AD, Chapman MJ, Ninio E: Platelet-activating factor acetylhydrolase and transacetylase activities in human plasma low-density lipoprotein. Biochem J, 2001; 357:457-464
40) Mayer K, Merfels M, Muhly-Reinholz M, Gokorsch S, Rosseau S, Lohmeyer J, Schwarzer N, Krüll M, Suttorp N, Grimminger F, Seeger W: Omega-3 fatty acids suppress monocyte adhesion to human endothelial cells: role of endothelial PAF generation. Am J Physiol Heart Circ Physiol, 2002; 28:H811-818
41) Androulakis N, Durand H, Ninio E, Tsoukatos DC: Molecular and mechanistic characterization of platelet-activating factor-like bioactivity produced upon LDL oxidation. J Lipid Res, 2005; 46:1923-1932
42) Maruyama C, Imamura K, Teramoto T: Assessment of LDL particle size by triglyceride/HDL-cholesterol ratio in non-diabetic, healthy subjects without prominent hyperlipidemia. J Atheroscler Thromb, 2003; 10:186-191