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Plasma polyunsaturated fatty acid profile and delta-5 desaturase activity are altered in patients with type 2 diabetes

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ABSTRACT

Objective. The association between imbalance of polyunsaturated fatty acids (PUFAs), especially low plasma n-3 to n-6 PUFA ratio, and risk of cardiovascular diseases is well known. A balance of plasma PUFAs is determined not only by dietary fatty acid intake, but also by the endogenous fatty acid metabolism, which could be dysregulated by diabetes. In this study, we investigated the plasma n-3 and n-6 PUFA profile and fatty acid desaturase activity in patients with type 2 diabetes (T2D).

Materials/Methods. The subjects were 396 patients with T2D and 122 healthy controls. Plasma eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and dihomo-γ-linolenic acid (DGLA) levels were measured by capillary gas chromatography.

Results. Plasma DHA, AA, and DGLA levels were significantly higher, and EPA levels tended to be lower in patients with T2D than in the controls. Patients with T2D also exhibited significantly lower EPA/AA, DHA/AA, and (EPA + DHA)/AA ratios, and a higher AA/DGLA ratio than the controls. Multiple regression analyses, including age, sex, body mass index, and metabolic parameters in the total population, revealed that the presence of T2D was independently associated with elevated plasma DHA, AA, and DGLA levels and decreased EPA/AA, DHA/AA, and (EPA + DHA)/AA ratios. Furthermore, T2D was independently and positively related to the AA/DGLA ratio, which serves as an estimate of delta (Δ)-5 desaturase activity.

Conclusions. Elevated plasma AA levels and decreased n-3 PUFA/AA ratios in T2D are attributable, at least partly, to Δ5 desaturase activation.

Abbreviations: PUFA, polyunsaturated fatty acid; T2D, type 2 diabetes; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; D5D, Δ5 desaturase; D6D, Δ6 desaturase; FPG, fasting plasma glucose; IRI, immunoreactive insulin; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate; SD, standard deviation; HOMA-R, insulin resistance index by homeostasis model assessment; BMI, body mass index.

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1. Introduction

Epidemiological evidence has demonstrated that consumption of fish oil or n-3 polyunsaturated fatty acids (PUFAs) is associated with a reduced risk of cardiovascular diseases [1–3]. Circulating n-3 PUFA levels that objectively reflect dietary consumption are also shown to be associated with a reduced risk of acute coronary events [4] and cardiac sudden death [5], and with a lower total mortality with fewer cardiovascular deaths [6]. Eicosanoids derived from n-6 PUFA arachidonic acid (AA) are pro-inflammatory, proaggregative, and vasoconstrictive, whereas ones derived from eicosapentaenoic acid (EPA) have cardioprotective effects by opposing the effects induced by AA [7,8]. In relation to these biological characteristics, a lower EPA/AA ratio in circulation has been found to be predictive against major cardiac events in the general population [9], as well as in patients with established coronary artery disease [10,11], and in those with chronic kidney disease on hemodialysis [12]. The EPA/AA ratio showed even better association with cardiac events than individual EPA, docosahexaenoic acid (DHA), or AA levels in some studies [10–12].

However, the effect of type 2 diabetes (T2D) on the PUFA profile is still controversial [13,14]. The PUFA profile in blood or tissue not only reflects dietary fatty acid intake, but is also determined by the endogenous fatty acid metabolism, including elongation and desaturation [15,16]. Both delta (Δ)-5 desaturase (D5D) and Δ6 desaturase (D6D) catalyze the synthesis of long-chain n-6 and n-3 PUFAs, the activity of which can be estimated using PUFA product-to-precursor ratios [15,16]. The D5D activity index expressed as AA to dihomo-γ-linoleic acid (DGLA) ratio in blood or tissue has been negatively associated with insulin resistance [16,17] and newly diagnosed T2D [18,19] in cross-sectional studies. To date, few studies have examined a balance of n-3 and n-6 PUFAs [20,21], and no study has assessed the D5D activity index, in association with diabetes for hospital-based subjects with T2D.

The purpose of this study was to investigate the association of T2D with PUFA profile, particularly the balance of n-3 PUFAs to AA and the D5D activity index.

2. Methods

2.1. Subjects

We consecutively enrolled 396 subjects with T2D (228 men and 168 women), who were admitted to the Diabetes Center of Osaka City University Hospital for the purpose of glycemic control, education, and/or evaluation of diabetic complications between January 2009 and June 2013. T2D was diagnosed based on criteria of the American Diabetes Association [22]. Subjects with type 1 diabetes and other types of diabetes were excluded from the present study. Smokers were defined as current or past smokers in our analyses. All subjects provided written informed consent, and the ethical review board of our institution approved this study protocol.

For comparison, we had 122 apparently healthy men (n = 72) and women (n = 50) as controls. They were selected for measurement of blood PUFA concentrations from participants of the 2005 health check program in Osaka, as described previously [12]. The control subjects provided written informed consent regarding use of their data and blood samples for research purposes. None had fasting hyperglycemia (glucose > 126 mg/dL) or proteinuria by dipstick. No control subject was taking medications for hypertension, diabetes mellitus, or dyslipidemia.

2.2. Laboratory measurements

Blood samples were collected from T2D patients after an overnight fast. Using an automated analyzer, the samples were tested the same day of collection for plasma concentrations of glucose (FPG), immunoreactive insulin (IRI), creatinine, uric acid, triglycerides (TG), total cholesterol, and high-density lipoprotein-cholesterol (HDL-C). Additional measurements, including PUFAs, were performed using freshly frozen samples kept at −30 °C. For healthy controls, venous blood was collected after an overnight fast and fresh serum samples were kept frozen before assays. Glycated hemoglobin A1c (HbA1c) levels were estimated as National Glycohemoglobin Standardization Program equivalent values (%) using the converting formula established by the Japan Diabetes Society [23]. An estimated glomerular filtration rate (eGFR) was calculated per the guidelines proposed by the Japanese Society of Nephrology [24]. Non-HDL cholesterol was calculated by subtracting HDL-C from the total cholesterol level.

2.3. Measurement of blood PUFA levels

Frozen plasma samples of T2D subjects were shipped to SRL (Tokyo, Japan), and EPA, DHA, DGLA, and AA concentrations were measured by capillary gas chromatography. In brief, total plasma lipids were extracted by the method of Folch, and fatty acids were transmethylated with 14% boron trifluoride-methanol. Then PUFAs were measured using the GC-2010 system (Shimadzu, Kyoto, Japan) equipped with the TC-70 column (GL Sciences, Tokyo, Japan). EPA, DHA, DGLA, and AA concentrations in serum for healthy controls were measured by the same methods as in T2D subjects [12].

2.4. Statistical analysis

Statistical analyses were performed using the JMP® 10 software (SAS Institute, Cary, NC). Data were expressed as number (%), mean ± standard deviation (SD) or median (interquartile range) as appropriate. For comparisons between the T2D and control groups, the following tests were used as appropriate: χ^2-test, Student's *t*-test, or Wilcoxon rank-sum test. Skewed parameters, such as TG, IRI, insulin resistance index by homeostasis model assessment (HOMA-R), plasma PUFA levels, and n-3/n-6 PUFA ratios, were logarithmically transformed before regression analyses. In multiple regression analyses, each PUFA level or n-3/n-6 PUFA ratio was the dependent variable, and the following were all independent variables: presence of diabetes, age, sex, body mass index (BMI), eGFR, TG level, HDL-C level, non HDL-C level, uric acid level, smoking status, and treatment with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins). In multiple