学 位 論 文 の 要 旨

氏名　　乃木 章子

学 位 論 文 名　**Plasma n-3 Polyunsaturated Fatty Acid and Cardiovascular Disease Risk Factors in Japanese, Korean and Mongolian Workers**

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著 者 名　Akiko Nogi, Jianjun Yang, Limei Li, Masayuki Yamasaki, Mamiko Watanabe, Michio Hashimoto, Kuninori Shiwaku

論 文 内 容 の 要 旨

Introduction

The identification of major risk factors through epidemiological studies and the control of these risk factors have contributed to a drop in cardiovascular disease (CVD) mortality rates in almost all industrialized countries. Increasing levels of CVD risk factors in Asian developing countries appear to be related to adverse lifestyle changes accompanying industrialization and urbanization. Dietary fatty acids appear to be of significant importance in CVD. Epidemiological data strongly support the relationship between high n-3 polyunsaturated fatty acid (PUFA) intake and lower incidence of CVD. While, the favorable role of n-3 PUFA in CVD has been demonstrated in several animal experiments and in Western populations, it remains less clear in Asians populations. The use of n-3 PUFA supplements may induce greater preventative effects on CVD in Western populations, who have a low fish intake (1.4 g/day of α-linolenic acid and 0.1-0.2 g/day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the U.S.A.), while the effects of n-3 PUFA may be underestimated in the Japanese who consume a daily average of 2.4-2.9 g of n-3 PUFA. An observational study of Japanese, Koreans and Mongolians with extended histories of remarkably different frequencies of fish intake was conducted to examine whether differences in plasma n-3 PUFA affects CVD risk factors.

Materials and Methods

A total of 411 Japanese in Shimane Prefecture, in 1999 - 2002, 418 Koreans in Busan, in 2003, a total of 252 Mongolians in Ulaanbaatar, in 2003, aged 30 - 60 yr participated in this study. None of the participants was using prescription medications for diabetes, hyperlipidemia

or hypertension. The Ethics Committee of Shimane University School of Medicine approved all study protocols, and all subjects gave their written informed consent.

We conducted a cross-sectional study in workplace settings and determined body mass index (BMI), blood pressure, total cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglyceride (TG), glucose, insulin, homoeostasis model assessment-insulin resistance (HOMA-IR) and fatty acid composition in plasma. Fatty acid composition was determined using a modification of the one-step analysis for a good recovery for plasma fatty acid, rather than by the conventional Folch procedure. To 100 μl of plasma, 2.0 ml methanol containing 10 mg tricosanoic acid as an internal standard and 200 μl acetyl chloride were added. The mixture was incubated at 100 ℃ for 60 min and cooled, then octane 400 μl was added to samples and neutralized with 0.5 N aqueous NaOH containing 10% sodium chloride. The octane phase with the fatty acid methyl esters was directly subjected to gas chromatography. The gas chromatography separation was done on a Model 5890II (Hewlett-Packard, Avondale, PA, U.S.A.) equipped with a flame ionization detector and an automatic sampler Model 7673. A 30 m x 0.25 mm capillary column (DB-WAX P/N 122-7032, J & W Scientific, CA, U.S.A.) was initially maintained at 100 ℃ for 1 min, raised to 180 ℃ at 20 ℃/min, then raised to 240 ℃ at 2 ℃/min, and further raised to 260 ℃ at 4 ℃/min and maintained for 5 min. Fatty acid composition was expressed as molecular percentage/ml plasma. Several fatty acid indexes were derived from the primary data: the total percentage of saturated fatty acids, which was calculated as the sum of the percentages of palmitic acid (16:0) and stearic acid (18:0); the total percentage of monounsaturated fatty acids, which was represented as the percentages of oleic acid (18:1); the total percentage of n-3 PUFAs, which was calculated as the sum of the percentages of α-linolenic acid (18:3n-3), EPA (20:5n-3), docosapentaenoic acid (22:5n-3, DPA) and DHA (22:6n-3); and, the total percentage of n-6 PUFAs, calculated as the sum of the percentages of linoleic acid (18:2n-6) and arachidonic acid (20:4n-6). The unsaturation index (USI) for each group was calculated by taking the molecular percentage of each fatty acid, and multiplying it by the number of double bonds in the fatty acids. Information on each participant's lifestyle was obtained using a self-reported questionnaire, including habits on smoking, alcohol consumption, exercising for over 20 min twice a week, meat intake more than twice a day and frequency of fish intake per week.

Results and Discussion

The Japanese ate fish more frequently, followed by the Koreans, while the Mongolians consumed meat more frequently. The Mongolians had significantly higher values for BMI, followed by the Koreans, and then the Japanese. Similarly, the Mongolians had significantly higher values for blood pressure, followed by the Koreans and Japanese. Relative to the Japanese, metabolic parameters of the Koreans showed significantly lower values for HDL-C and higher values for LDL-C and TG. The Mongolians also had significantly higher values for insulin and HOMA-IR, followed by the Koreans, and then the Japanese.

In fatty acid composition, the Japanese showed remarkably higher values for EPA, DHA, n-3 PUFA and USI, and lower values for n-6 PUFA/n-3 PUFA, followed by the Koreans, and then the Mongolians. Plasma EPA, DHA and n-3 PUFA levels of the Koreans fell between those of the Japanese and Mongolians. A wide range of n-3 PUFA in the Japanese (2.35-20.96%) and Koreans (3.10-16.80%) was observed, while the Mongolians had a very narrow range of n-3 PUFA (2.89-7.90%). Plasma fatty acid composition is a reflection of the fatty acid composition of linoleic acid and n-3 PUFA in usual diet, but it does not reflect the fatty acid composition of saturated fatty acids or of monounsaturated fatty acids, because the metabolic conversion of other fatty acids that obscures the relationship of these fatty acids in the plasma and diet. The Japanese workers had three times the EPA and two times the DHA and n-3 PUFA levels did the Mongolians, with the values for the Koreans falling between the Japanese and Mongolians. These remarkably different values of plasma n-3 PUFA, particularly EPA and DHA, in the present study, appear to reflect the differences in marine fish consumption of the Japanese, Koreans and Mongolians.

To investigate n-3 PUFA effects, metabolic parameters were compared between tertiles of plasma n-3 PUFA for the three ethnic groups. The Japanese were categorized as 11.2% for the lowest tertile (2.35-5.81%), 29.9% for the intermediate (5.82-8.69%), and 59.1% for the highest tertile (8.70-20.96%). The Koreans and Mongolians, respectively, were rated as 20.8% and 88.9% for the lowest tertile, 48.6% and 11.1% for the intermediate, and 29.7% and 0.0% for the highest tertile of plasma n-3 PUFA. One-way ANOVAs showed n-3 PUFA in the Japanese to be associated with BMI, LDL-C, HDL-C and TG, while n-3 PUFA was not associated with any metabolic parameters in the Koreans, and solely with TG in the Mongolians. A significant negative correlation between n-3 PUFA and TG and a significant positive correlation between n-3 PUFA and HDL-C were observed for the Japanese and Mongolians, but not for the Koreans. General linear measurement multivariate analysis after adjustment for gender, age, smoking, drinking, exercise habits and BMI showed n-3 PUFA was associated with HDL-C and TG in the Japanese, while it was associated with systolic blood pressure in the Koreans, and TG in the Mongolians.

Conclusion

The remarkably different ratios of plasma n-3 PUFA in the three ethnic groups appear to reflect extended histories of significantly different frequencies of fish intake. The standard death rates from CVD in 2002 by WHO Global InfoBase Online were 44 per 100,000 population in the Japan, 112 in Korea and 194 in Mongolia. The mortality rate from CVD in these three populations was related to BMI, diastolic blood pressure, insulin, HOMA-IR and plasma n-3 PUFA levels, all of which were considered in the present study. An increase in n-3 PUFA was associated with HDL-C and TG in the Japanese and Mongolians, but these beneficial effects were not constant across the three Asian ethnic groups.