Introduction

Trans fatty acids (TFAs) are a type of unsaturated fatty acid that contains double bonds in a trans configuration. Unsaturated fatty acids are classified into two forms, trans and cis, based on the orientation of the hydrogen atoms forming the double bonds; the majority of natural unsaturated fatty acids exist in the cis form. However, TFAs are produced from cis-unsaturated fatty acids by partial hydrogenation during the industrial process of manufacturing hydrogenated oil from vegetable oil. Hydrogenated oil manufactured by this process is widely used to produce margarine, shortening, and other products because of its commercial value and convenience.

Many cohort studies conducted in Europe and the United States have shown that increased TFA intake increases the risk of developing coronary heart disease. However, whether TFA intake is directly associated with the development of diabetes mellitus (DM) remains unknown.

Methods: We performed the 75-g oral glucose tolerance test in two Japanese cohorts: a cohort of 454 native Japanese living in Hiroshima, Japan, and a cohort of 426 Japanese-Americans living in Los Angeles, USA, who shared identical genetic predispositions but had different lifestyles. Serum elaidic acid concentration was measured and compared, and its association with insulin resistance was assessed.

Results: Serum elaidic acid concentrations were significantly higher in the Japanese-Americans (median, 18.2 µmol/L) than in the native Japanese (median, 11.0 µmol/L). The serum elaidic acid concentrations in the native Japanese DM group (16.0 µmol/L) were significantly higher compared with those in the normal glucose tolerance (10.8 µmol/L) and impaired glucose tolerance (11.7 µmol/L) groups. Multiple linear regression analyses showed that serum elaidic acid concentrations were significantly positively associated with homeostasis model assessment for insulin resistance (HOMA-IR) values after adjusting for various factors.

Conclusions: These results suggest that excessive TFA intake worsens insulin resistance and increases the risk of developing DM even in the native Japanese, whose intakes of animal fat and simple carbohydrates were presumed to be lower than those of the Japanese-Americans.
associated with the development of diabetes mellitus (DM) remains unknown. Although four long-term observational studies on the association between the development of DM and TFA intake have been reported, the results vary. Short-term interventional studies in humans have demonstrated no significant changes in glucose tolerance or insulin resistance in healthy adults consuming TFAs, whereas TFA intake adversely affected insulin resistance in obese adults with a history of DM. In other words, the results of these studies suggest that TFA intake may aggravate insulin resistance in certain types of individuals.

The World Health Organization (WHO) recommends a mean TFA intake of less than 1% of the total energy intake. Europe and the United States, where significant amounts of TFAs are consumed, have started restricting the use of TFAs because of their potential to cause arteriosclerotic diseases. In California, USA, the use of oil, shortening, or margarine containing artificial TFAs within a food facility has been banned since 2010. In contrast, no food containing TFAs are regulated in Japan, where TFA intake is reportedly less. However, a recent report indicated that the estimated TFA intake by some groups of Japanese, mainly young adults living in cities, exceeded the amount recommended by the WHO.

In 1970, we started an epidemiological study targeting Japanese-Americans, titled the Hawaii-Los Angeles-Hiroshima Study, and conducted medical surveys in Hawaii and Los Angeles every few years, totaling 24 surveys until 2015. Comparing the native Japanese in Hiroshima, Japan with a Japanese lifestyle and Japanese-Americans in the United States with an American lifestyle and who shared identical genetic predispositions, we have reported that the prevalence rates of obesity, type 2 DM, and metabolic syndrome are significantly higher in the Japanese-Americans than in the native Japanese. However, as observed globally, the prevalence of DM in Japan has been increasing in recent years, suggesting that even the eating habits of native Japanese are increasingly becoming westernized.

### Aim

After observing increased TFA intake in Japan, we compared the concentrations of serum elaidic acid, which is most commonly found in processed food among the many subtypes of TFAs, in the native Japanese living in Hiroshima and the Japanese-Americans living in Los Angeles, California, using a 2010 medical survey. Then, we investigated the association between serum elaidic acid concentrations and insulin resistance.

### Table 1. Clinical characteristics of the study subjects

| Parameter                  | Native Japanese | Japanese-Americans | P value |
|----------------------------|-----------------|--------------------|---------|
| N (men/women)              | 454 (159/295)   | 426 (182/244)      |         |
| NGT/IGT/DM                 | 341/97/16       | 323/70/33          |         |
| Age (years)                | 57.7 ± 15.1     | 59.4 ± 14.4        | 0.089   |
| BMI                        | 22.8 ± 3.0      | 22.3 ± 3.7         | 0.018   |
| SBP (mmHg)                 | 126 ± 18        | 131 ± 18           | <0.001  |
| DBP (mmHg)                 | 77 ± 11         | 82 ± 11            | <0.001  |
| FSG (mg/dL)                | 93.0 ± 9.6      | 90.3 ± 11.6        | <0.001  |
| 2-h SG (mg/dL)             | 121.3 ± 36.2    | 118.1 ± 45.6       | 0.262   |
| FIRI† (µU/mL)              | 3.89 (3.16-5.55)| 4.76 (3.49-8.66)   | <0.001  |
| 2-h IRI† (µU/mL)           | 42.18 (27.24-64.92)| 50.72 (29.43-80.25)| 0.007   |
| HOMA-IR†                   | 0.89 (0.71-1.28)| 1.07 (0.74-2.02)   | <0.001  |
| HOMA-β†                    | 52.0 (40.3-75.5)| 77.7 (51.6-120.0)  | <0.001  |
| TG† (mg/dL)                | 86.5 (62.0-120.0)| 108.5 (75.8-150.3) | <0.001  |
| HDL-C (mg/dL)              | 62.5 ± 14.2     | 61.2 ± 16.1        | 0.195   |
| LDL-C (mg/dL)              | 126.6 ± 31.6    | 129.0 ± 36.2       | 0.289   |
| Elaidic acid† (µmol/L)     | 11.0 (9.5-13.5) | 18.2 (14.1-24.5)   | <0.001  |

Data are expressed as the means ± SD, median (interquartile range) or number. Parameters were transformed logarithmically before analysis. P values were calculated by t-test. DBP, Diastolic blood pressure; DM, Diabetes mellitus; FIRI, Fasting immunoreactive insulin; FSG, Fasting serum glucose; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function; IGT, Impaired glucose tolerance; LDL-C, low-density lipoprotein-cholesterol; NGT, Normal glucose tolerance; SBP, Systolic blood pressure; TG, Triglyceride; 2-h IRI, Immunoreactive insulin at two hours after an oral glucose load; 2-h SG, Serum glucose at two hours after an oral glucose load.
Methods

Research Design and Methods

This study was a cross-sectional analysis of data collected as part of the Hawaii-Los Angeles-Hiroshima Study. Our study included 552 native Japanese living in Hiroshima who underwent a medical checkup in 2009 and 608 Japanese-Americans living in Los Angeles who underwent a medical checkup in 2010. All participants, except for those under treatment for DM, underwent a 75-g oral glucose tolerance test (OGTT) and were divided according to OGTT results into the following three groups: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and DM. NGT was defined as a fasting serum glucose level of <110 mg/dl and a serum glucose level of <140 mg/dl at 2 h after OGTT. DM was defined as a fasting serum glucose level of ≥126 mg/dl and/or a serum glucose level of ≥200 mg/dl at 2 h after OGTT or as treatment of previously diagnosed diabetes. IGT was diagnosed in participants who did not meet the criteria of either NGT or DM. After excluding the participants under treatment for dyslipidemia and those with a fasting serum glucose levels ≥140 mg/dl, 454 native Japanese and 426 Japanese-Americans were ultimately included in this study. All participants received an explanation of the study procedures and provided written informed consent. This study was approved by the ethics committee of Hiroshima University.

Biochemical Analysis

Blood samples were collected from all participants after overnight fasting, and serum samples were stored at −80°C until analysis. Serum glucose was measured using the hexokinase method. Immunoreactive insulin (IRI) levels were measured using the double-antibody radioimmunoassay. Homeostasis model assessment was used to estimate β-cell function (HOMA-β) and insulin resistance (HOMA-IR). Triglyceride (TG) levels were measured using an enzymatic method. High-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were measured using a homogeneous assay (MetaboLead HDL-C and Determiner L LDL-C, respectively, Kyowa Medex, Tokyo, Japan).

Measurement of Serum Elaidic Acid Concentrations

Elaidic acid concentrations were measured by gas chromatography/mass spectrometry (GC–MS QP2010; Shimadzu, Kyoto, Japan) at the Integrated Center for Mass Spectrometry at Kobe University Graduate School of Medicine, according to a previously reported procedure.

Statistical Analysis

Data were expressed as means with standard devi-
sure (SBP) and diastolic blood pressure (DBP) were significantly higher in the Japanese-Americans. Body mass index (BMI) and fasting serum glucose levels were higher in the native Japanese, whereas FIRI, 2-h IRI, HOMA-IR, HOMA-β, and TG levels were significantly higher in the Japanese-Americans. The median serum elaidic acid concentrations were 11.0 µmol/L in the native Japanese and 18.2 µmol/L in the Japanese-Americans, significantly higher in the Japanese-Americans than in the native Japanese. The distribution of serum elaidic acid concentrations showed that the concentrations in the Japanese-Americans tended to be higher overall and more varied compared with those of the native Japanese (Fig. 1).

Next, serum elaidic acid concentrations were analyzed according to glucose tolerance status (Fig. 2). In the native Japanese, the median serum elaidic acid concentrations were 11.0 µmol/L in the NGT group, 15.7 µmol/L in the IGT group, and 16.0 µmol/L in the DM group, with no significant differences between the three groups. However, in the Japanese-Americans, the median serum elaidic acid concentrations were 18.4 µmol/L in the NGT group, 18.3 µmol/L in the IGT group, and 17.9 µmol/L in the DM group, with a significantly higher median in the DM group compared with the other groups. The distribution of serum elaidic acid concentrations showed that the concentrations in the Japanese-Americans tended to be higher overall and more varied compared with those of the native Japanese (Fig. 1).

The associations between insulin resistance and serum elaidic acid concentrations were assessed by regression analyses. The results showed that there was a significant positive correlation between HOMA-IR and serum elaidic acid concentrations in the Japanese-Americans. In the native Japanese, there was no significant correlation between HOMA-IR and serum elaidic acid concentrations. The differences in parameters between two groups were analyzed by unpaired t-tests, while the differences in parameters between three groups were analyzed by the one-way analysis of variance (ANOVA). The correlation between elaidic acid concentration and each parameter was assessed by Pearson’s coefficient.

Results

The characteristics of the study participants are shown in Table 1. No significant difference was observed in age between the two cohorts. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in the Japanese-Americans. Body mass index (BMI) and fasting serum glucose levels were higher in the native Japanese, whereas FIRI, 2-h IRI, HOMA-IR, HOMA-β, and TG levels were significantly higher in the Japanese-Americans. The median serum elaidic acid concentrations were 11.0 µmol/L in the native Japanese and 18.2 µmol/L in the Japanese-Americans, significantly higher in the Japanese-Americans than in the native Japanese. The distribution of serum elaidic acid concentrations showed that the concentrations in the Japanese-Americans tended to be higher overall and more varied compared with those of the native Japanese (Fig. 1).

Fig. 2. Comparisons of serum elaidic acid concentrations by glucose tolerance status in native Japanese (A) and Japanese-Americans (B). Parameters were transformed logarithmically before analysis. Statistical analyses were performed by ANOVA followed by Bonferroni’s test for multiple comparisons.
had higher concentrations even in the native Japanese whose serum elaidic acid concentrations were lower compared with those of the Japanese-Americans; the native Japanese showed an independent positive association between concentration and insulin resistance. Although two of the four prospective studies showed no significant association between TFA intake and the incidence of DM9, 10), another study that followed 84,204 female nurses for 14 years showed a significant association8). In these three studies, the total TFA intake was estimated based on the results of dietary surveys. The different results may have reflected errors in the estimation of TFA intake or variations in

Discussion

In this study, we first revealed that in a 2010 survey, the absolute serum elaidic acid concentrations differed significantly between native Japanese living in Japan and Japanese-Americans living in the United States, who shared identical genetic predispositions but had different lifestyles. Furthermore, the DM group

![Fig. 3](image)

**Table 2.** Relationships between HOMA-IR and other parameters in native Japanese

| Parameter          | β    | P value |
|--------------------|------|---------|
| Age (years)        | 0.285| <0.001  |
| Sex                | 0.035| <0.001  |
| BMI                | 0.159| 0.001   |
| SBP (mmHg)         | 0.355| <0.001  |
| DBP (mmHg)         | 0.164| <0.001  |
| TG (mg/dL)         | 0.111| 0.018   |
| HDL-C (mg/dL)      | 0.021| <0.001  |
| LDL-C (mg/dL)      | 0.029| <0.001  |
| Elaidic acid (µmol/L) | 0.075| 0.120   |

β, Standardizes regression coefficients. Parameters were transformed logarithmically before analysis. Data were analyzed by a simple linear regression analysis.

Fig. 3. Correlations of serum elaidic acid concentrations and HOMA-IR in 454 native Japanese (A) and 426 Japanese-Americans (B). Parameters were transformed logarithmically before analysis. Pearson’s correlation coefficients (r) and P values are given.
TFA intake during the follow-up period. Wang et al. assessed the association between TFA intake and the incidence of DM while simultaneously estimating the intake of each TFA subtype and measuring blood TFA concentrations to complement these limitations. They reported that blood concentrations of t-16:1n7 and t-18:1 (elaidic acid) TFAs were significantly positively correlated with the incidence of DM\(^{11}\). However, blood TFA concentrations were analyzed as a ratio to blood total fatty acid concentration. Because this ratio is affected by other intrinsic fatty acids, Wang et al. recommended additional studies using absolute blood TFA concentrations, which may more accurately reflect TFA intake. In the present study, we measured absolute serum concentrations of elaidic acid among TFA subtypes and observed significantly lower concentrations in native Japanese living in Hiroshima than those in Japanese-Americans living in Los Angeles. Because TFAs are not intrinsically synthesized, serum TFA concentrations seem to reflect dietary intake. Presumably, great differences in lifestyles, especially the contents of meals, still existed between Japan and the United States in 2010.

Next, we demonstrated that the DM group of the native Japanese cohort had serum elaidic acid concentrations as high as those observed in the Japanese-Americans. Furthermore, this study revealed that serum elaidic acid concentrations were significantly positively associated with HOMA-IR values in the native Japanese. These results suggested that excessive TFA intake might be one of the factors that worsen insulin resistance in this population. Although the mechanism of how TFAs aggravate insulin resistance remains unknown in many aspects, studies with animal models reported the following. A study in rats indicated that the consumption of a high-TFA diet weakens insulin sensitivity in adipocytes, changes the adipocyte plasma membrane fatty acid composition and fluidity\(^{25}\), increases the expression of resistin messenger RNA, and decreases the expression of peroxisome proliferator-activated receptor \(\gamma\) and lipoprotein lipase messenger RNA\(^{26}\). Moreover, excessive TFA intake in mice also reportedly increases the expression of genes associated with lipogenesis in the liver, including those for sterol regulatory element-binding proteins, consequently inducing insulin resistance and fatty liver\(^{27}\).

However, there were no significant differences in serum elaidic acid concentrations between the NGT, IGT, and DM groups in the Japanese-Americans. Moreover, no significant correlations between serum elaidic acid concentrations and HOMA-IR values were observed in the Japanese-Americans. The HOMA-IR values of the IGT and DM groups were significantly higher than those of the NGT group in the Japanese-Americans (Supplemental Fig. 1). This result indicates that the worsening of insulin resistance is an important factor for the development of DM in Japanese-Americans. We previously reported that Japanese-Americans have higher insulin resistance than native Japanese\(^{19}\) and that the intakes of animal fat and simple carbohydrates were markedly higher in Japanese-Americans than in native Japanese\(^{28, 29}\). Accordingly, the effect of TFA intake on the development of DM is presumed to be relatively greater in native Japanese whose intake of animal fat and simple carbohydrates are lower compared with that of Japanese-Americans.

This study has several limitations. First, in the native Japanese, an independent significant positive association was observed between serum elaidic acid concentrations and HOMA-IR values, but this association was not observed after adjusting for TG levels. A possible reason for this may be that, because fatty acid is a major component of TG, an increase in TG leads to an increase in total fatty acids, including elaidic

| Table 3. Relationships of serum elaidic acid concentrations in native Japanese by regression analysis with HOMA-IR as the dependent variable |
|------------------------------|---------|---------|
| β, Standardized regression coefficients. \(^1\)Parameters were transformed logarithmically before analysis. Data were analyzed by each multiple regression model. |
| Not adjusted | 0.111 | 0.018 |
| Adjusted for age, sex | 0.131 | 0.006 |
| Adjusted for age, sex, and BMI | 0.089 | 0.033 |
| Adjusted for age, sex, and SBP | 0.135 | 0.004 |
| Adjusted for age, sex, and DBP | 0.108 | 0.019 |
| Adjusted for age, sex, and NGT/IGT/DM | 0.113 | 0.018 |
| Adjusted for age, sex, and HDL-C | 0.114 | 0.014 |
| Adjusted for age, sex, and LDL-C | 0.100 | 0.036 |
| Adjusted for age, sex, and TG \(^1\) | -0.031 | 0.538 |

\(\beta\)
acid. In fact, a regression model showed a linear association between TG and elaidic acid (data not shown). Second, this study is a cross-sectional study that was conducted in 2010, and data were collected from Japanese-Americans living in Los Angeles when the partial regulation on TFAs was implemented in California. Further studies are needed to collect data on serum elaidic acid concentrations in Japanese-Americans under the current regulations.

**Conclusion**

The results of the present study demonstrated that serum elaidic acid concentrations in the native Japanese were significantly lower compared with those in the Japanese-Americans living in the United States and observed an independent significant positive association between serum elaidic acid concentrations and HOMA-IR values in the native Japanese. In the native Japanese, TFA intake may have aggravated insulin resistance and increased the risk of developing DM. Similar to the United States, regulation of TFAs may also become an important policy for the future prevention of DM in Japan.

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The authors received no specific funding for this article.

**Conflicts of Interest**

None.

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Supplemental Fig. 1. Comparison of HOMA-IR by glucose tolerance in native Japanese (A) and Japanese-Americans (B). Parameters were transformed logarithmically before analysis. Statistical analyses were performed by ANOVA followed by Bonferroni’s test for multiple comparisons.