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Effects of a westernized lifestyle on the association between fasting serum nonesterified fatty acids and insulin secretion in Japanese men

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Abstract

The effects of the prolonged elevation of nonesterified fatty acid (NEFA) levels on insulin secretion have been controversial and thought to be sex-specific. To investigate the association between a westernized lifestyle and the effects of NEFA on insulin secretion in Japanese men, we examined 67 nondiabetic Japanese-American men and 220 nondiabetic native Japanese men who underwent a 75-g oral glucose tolerance test (OGTT). Most Japanese Americans we surveyed are genetically identical to Japanese living in Japan, but their lifestyle is more westernized. Sets of multiple regression analyses were performed to evaluate the relationship between the sum of the immunoreactive insulin (IRI) levels during the OGTT (ΣIRI) and clinical parameters. Japanese Americans had higher levels of fasting IRI, ΣIRI, and a higher insulin resistance index (homeostasis model assessment for insulin resistance [HOMA-IR]) than native Japanese, whereas there were no significant differences in fasting NEFA and triglyceride levels. A multiple regression analysis adjusted for age, fasting triglycerides, and body mass index (BMI) demonstrated that the fasting NEFA level was an independent determinant of the ΣIRI only in Japanese-American men (P = .001), but not in native Japanese men (P = .054). Even when HOMA-IR was included in models instead of BMI, the NEFA level was a significant variable of ΣIRI only in Japanese Americans (P < .001), and not in native Japanese (P = .098). In addition, a multiple regression analysis adjusted for age, fasting triglycerides, and BMI demonstrated that the fasting NEFA level was the only independent determinant of ΣC-peptide in Japanese-American men (P = .041). In conclusion, NEFA seems to be associated with insulin secretion independent of obesity or HOMA-IR. A westernized lifestyle may increase the effects of serum fasting NEFA levels on total insulin secretion after a glucose load in Japanese men.

1. Introduction

The high plasma nonesterified fatty acid (NEFA) concentration has been reported to be a risk factor in the deterioration of glucose tolerance in some longitudinal studies [1-3]. There is no doubt that NEFAs participate in the development of type 2 diabetes, although the role of NEFAs has not been entirely elucidated [4,5]. It is well established that a physiological elevation of the NEFA concentration induces peripheral and hepatic insulin resistance [4,6], and that an acute increase in NEFA levels stimulates glucose-stimulated insulin secretion (GSIS) [7-9]. However, the effects of a prolonged elevation of NEFA levels on GSIS have been controversial. There are some reports in which NEFAs desensitize GSIS in vitro [10] and in vivo [11]. Other studies have shown that prolonged exposure to saturated fatty acids enhanced GSIS, whereas unsaturated fatty acids impaired GSIS in rats [12]. In human beings, Boden et al [13] reported that the prolonged elevation of NEFA levels increased GSIS, but others reported that it decreased GSIS [7,14,15]. At least, the prolonged elevation of NEFAs is certainly associated with an absolute increase in GSIS [7,13-15].

In addition, NEFA-induced peripheral and hepatic insulin resistance seemed to be sex-specific [16,17]. Although it has

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been reported that NEFAs induced peripheral and hepatic insulin resistance to a similar degree in men and women [18], others reported that a NEFA elevation did not cause insulin resistance in female rats [16] and in women [17], or that the feminine hormonal milieu played a protective role against the detrimental effects of NEFA on insulin sensitivity in human beings [19]. A difference in susceptibility to NEFAs between the sexes cannot be excluded. It is possible that the effects of NEFAs on glucose metabolism, determined by both insulin sensitivity and insulin secretion, can be more readily observed in male subjects than females.

Most Japanese Americans living in Hawaii are genetically identical to Japanese living in Japan, but their dietary habits are more westernized; when compared with native Japanese, Japanese Americans consume more animal fat and saturated fatty acids [20-22]. The prevalence of diabetes in the Japanese Americans living in Hawaii exceeds that of Japanese living in Hiroshima by 3-fold [23,24]. In addition, Japanese Americans show higher levels of serum insulin than native Japanese with the same degree of obesity [23]. We have previously reported that these metabolic changes influenced by westernization differed by sex. For example, when obesity becomes obvious, the Trp64Arg variant of the β_3-adrenergic receptor gene is considered to be associated with visceral obesity only in men, and not in women [25]. Furthermore, the effect of fatty acid–binding protein 2 polymorphism on serum triglyceride levels was found only in men, and not in women [26]. Thus, a westernized lifestyle may affect men more strongly than women.

In the present study, we examined the associations between the serum levels of fasting NEFA and absolute total insulin secretion after a glucose load among native Japanese men in Hiroshima and Japanese-American men in Hawaii. Furthermore, we discussed whether the effects of these NEFA levels on GSIS might explain the difference in insulin secretion between native Japanese men and Japanese-American men.

2. Materials and methods

2.1. Subjects

The participants were Japanese-American men of full Japanese ancestry enrolled in a medical survey conducted on the island of Hawaii in 2002, and Japanese men living in Hiroshima who underwent similar medical examinations in 2002. The survey (Hawaii–Los Angeles–Hiroshima study) has been continued since 1970 and described in detail elsewhere [20-29]. The study population consisted of 124 Japanese-American men and 289 native Japanese men. With the exception of those previously diagnosed with diabetes, all participants underwent a 75-g oral glucose tolerance test (OGTT). Subjects who had been diagnosed with diabetes previously or by the results of OGTT, those taking medications known to affect glucose or lipid metabolism, and those subjects with a postgastrectomy status were excluded. A total of 67 Japanese-American men and 220 native Japanese men were examined. This study was approved by the Ethics Committee of Hiroshima University and the Council of the Hiroshima Kenjin-kai Association in Hawaii. Written informed consent was obtained from each participant.

2.2. Methods

The participants' physical measurements such as height, weight, and waist girth were recorded according to standard methods. The proportion of body fat was measured by a bioelectric impedance analysis method using a TBF-305 (Tanita, Tokyo, Japan). All participants were given a 75-g OGTT in the morning after a 12-hour fast, and venous blood samples were obtained at 0, 60, and 120 minutes. The blood was centrifuged and the serum was immediately frozen at −80°C. The frozen samples were subsequently brought back to Japan and analyzed together in the same laboratory with the samples obtained in Japan. The serum glucose levels were measured by the hexokinase method. Serum insulin (immunoreactive insulin [IRI]) and C-peptide were measured using commercially available radioimmunoassay (RIA) kits (Shionogi, Osaka, Japan). Serum C-peptide was measured only in the Japanese-American samples. Serum total cholesterol, triglyceride, and NEFA levels were measured using an enzymatic method. High-density lipoprotein cholesterol was determined using an immunoinhibition method, and low-density

Table 1
Clinical of characteristics of study subjects

	Native Japanese	Japanese Americans	*P* value[a]
No.	220	67	–
Glucose tolerance (normal/IFG, IGT)	173/47	50/17	NS
Age (y)	52.2 ± 0.9	64.6 ± 2.0	<.001
BMI (kg/m^2)	23.7 ± 0.2	25.1 ± 0.5	<.001
Waist girth (cm)	83.7 ± 0.5	89.0 ± 1.1	<.001
Body fat (%)	22.7 ± 0.3	24.0 ± 0.8	<.001
Fasting glucose (mmol/L)	5.33 ± 0.03	4.93 ± 0.06	<.001
Fasting IRI (pmol/L)	45.7 ± 1.7	64.8 ± 8.5	<.001[b]
ΣIRI (pmol/L)	770.0 ± 33.6	101.85 ± 92.8	.002[b]
HOMA-IR	1.53 ± 0.06	1.97 ± 0.26	.002[b]
Total cholesterol (mmol/L)	5.28 ± 0.05	5.17 ± 0.09	NS
LDL-C (mmol/L)	3.23 ± 0.05	3.30 ± 0.08	NS
HDL-C (mmol/L)	1.42 ± 0.02	1.31 ± 0.03	.037
NEFA (mmol/L)	0.405 ± 0.011	0.488 ± 0.022	NS[b]
Triglycerides (mmol/L)	1.49 ± 0.06	1.71 ± 0.17	NS[b]
AST (IU/L)	24.6 ± 0.49	26.1 ± 1.26	NS[b]
ALT (IU/L)	28.2 ± 1.04	23.8 ± 2.46	NS[b]
γ-GTP (IU/L)	67.3 ± 5.70	45.3 ± 6.84	0.043[b]

Data are means ± SE unless otherwise indicated. IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase.

[a] *P* values are determined by χ^2 test for glucose tolerance, Student unpaired *t* test for age, and analysis of covariance–adjusted age for continuous variables comparing native Japanese to Japanese Americans.

[b] Parameters are transformed logarithmically before analysis.

Table 2
Factors correlated with serum fasting NEFA determined by regression analysis

	Native Japanese (n = 220)			Japanese Americans (n = 67)		
	β	SE	P	β	SE	P
BMI (kg/m^2)	.0181	0.0107	.091	.0009	0.0155	.954
Waist girth (cm)	**.0081**	**0.0036**	**.026**	.0012	0.0062	.845
Body fat (%)	**.0144**	**0.0057**	**.012**	.0031	0.0099	.753

All data are from the regression analyses adjusted for age. Fasting NEFA is transformed logarithmically before analyses. Values in boldface type are statistically significant.

lipoprotein cholesterol (LDL-C) was determined by an enzymatic selective protection method. Aspartate aminotransferase and alanine aminotransferase levels were measured by a UV method, and γ-glutamyl transpeptidase (γ-GTP) levels were measured by an enzymatic method. The classification of glucose tolerance was diagnosed according to the 1998 World Health Organization criteria [30]. The insulin resistance index was assessed by a homeostasis model assessment for insulin resistance (HOMA-IR) [31]. ΣIRI was defined as the sum of the IRI levels during the OGTT (0-120 minutes), and ΣC-peptide was defined as the sum of the C-peptide levels.

2.3. Statistical analysis

The distributions of continuous data, such as age, body mass index (BMI), and biochemical variables were summarized with means ± SE. The mean age was compared by Student unpaired t test and the other continuous variables were compared by an age-adjusted analysis of covariance. The statistical significance of the difference in glucose tolerance was analyzed by a χ^2 test. Regression analysis adjusted for age was used to assess the association between the clinical parameters and fasting NEFA, fasting triglycerides, ΣIRI, or ΣC-peptide levels. Multiple regression analysis was performed to evaluate the relationship between ΣIRI or ΣC-peptide levels and the clinical parameters. Because strong nonnormality for the distributions of IRI, C-peptide, HOMA-IR, triglyceride, and NEFA levels were detected, those variables were statistically analyzed after logarithmic transformation. For data analysis, SAS package version 8.2 (SAS Institute, Cary, NC) and NLREG version 3.20 (RIRBM, Hiroshima University, Japan) software were used.

Table 3
Factors correlated with serum fasting triglycerides determined by regression analysis

	Native Japanese (n = 220)			Japanese Americans (n = 67)		
	β	SE	P	β	SE	P
BMI (kg/m^2)	.0616	0.0129	<.001	.0616	0.0199	.003
Waist girth (cm)	.0203	0.0044	<.001	.0238	0.0081	.004
Body fat (%)	.0326	0.0070	<.001	.0448	0.0124	.001

All data are from the regression analyses adjusted for age. Fasting triglycerides are transformed logarithmically before analyses. All values are statistically significant.

Table 4
Multiple regression model with ΣIRI and clinical parameters (model 1)

Explanatory variable	Native Japanese (n = 220)			Japanese Americans (n = 67)		
	β	SE	P	β	SE	P
Fasting NEFA (mmol/L)	.3669	0.1894	.054	**1.1290**	**0.3329**	**.001**
Fasting triglycerides (mmol/L)	**.0962**	**0.0338**	**.005**	−.0355	0.0451	.435
Age (y)	**.0047**	**0.0023**	**.040**	−.0031	0.0038	.417
BMI (kg/m^2)	**.0910**	**0.0117**	**<.001**	**.0691**	0.0164	**<.001**
R^2	0.3129			0.3390		

β is the estimated coefficient of each explanatory variable and R^2 the coefficient of determination for the model. ΣIRI is transformed logarithmically before the analysis. Values in boldface type are statistically significant.

3. Results

The clinical characteristics of the study participants are shown in Table 1. The mean age of the Japanese Americans was significantly higher than that of the native Japanese. Accordingly, all of the analyses performed were adjusted for age. BMI, waist girth, and body fat proportion were significantly higher in Japanese Americans than in native Japanese. The fasting glucose level was significantly higher in the native Japanese group, but fasting IRI, ΣIRI, and HOMA-IR levels were higher in the Japanese-American group. No significant differences were observed in the total cholesterol, LDL-C, NEFA, or triglyceride levels between the groups.

The fasting NEFA levels were correlated with waist girth or body fat only in native Japanese, but not in Japanese Americans (Table 2). On the other hand, the serum levels of fasting triglycerides had a strong correlation with these obesity indices in both groups (Table 3). The regression analyses with adjustment for age showed that BMI, waist

Table 5
Multiple regression model with ΣIRI and clinical parameters (model 2)

Explanatory variable	Native Japanese (n = 220)			Japanese Americans (n = 67)		
	β	SE	P	β	SE	P
Fasting NEFA (mmol/L)	.2797	0.1683	.098	**1.0427**	**0.2687**	**<.001**
Fasting triglycerides (mmol/L)	**.0725**	**0.0300**	**.017**	−.0127	0.0358	.724
Age (y)	**.0052**	**0.0020**	**.009**	−.0019	0.0031	.527
HOMA-IR	**.3734**	**0.0321**	**<.001**	**.1800**	**0.0234**	**<.001**
R^2	0.4600			0.5642		

β is the estimated coefficient of each explanatory variable and R^2 the coefficient of determination for the model. ΣIRI is transformed logarithmically before the analysis. Values in boldface type are statistically significant.

Table 6
Multiple regression model with ΣC-peptide and clinical parameters in Japanese Americans

Explanatory variable	Model 1			Model 2		
	β	SE	P	β	SE	P
Fasting NEFA (mmol/L)	**.5120**	**0.2453**	**.041**	**.4908**	**0.2265**	**.034**
Fasting triglycerides (mmol/L)	−.0048	0.0333	.885	.0007	0.0302	.982
Age (y)	−.0045	0.0028	.111	−.0037	0.0026	.155
BMI (kg/m^2)	.0220	0.0121	.073	–	–	–
HOMA-IR	–	–	–	**.0731**	**0.0198**	**<.001**
R^2	0.1720			0.2854		

β is the estimated coefficient of each explanatory variable and R^2 the coefficient of determination for each model. ΣC-peptide is transformed logarithmically before the analysis. Values in boldface type are statistically significant.

girth, body fat, HOMA-IR, and fasting NEFA levels had a significant correlation with ΣIRI in both groups (data not shown). The fasting triglyceride levels were a significant variable for ΣIRI only among native Japanese ($P < .001$).

Multiple regression analyses were performed to evaluate whether the correlation between fasting NEFA and ΣIRI was dependent on obesity or HOMA-IR (Tables 4 and 5). The model including age, BMI, fasting triglyceride levels, and fasting NEFA levels (Table 4, model 1) demonstrated that the triglyceride levels were an independent determinant of ΣIRI among native Japanese, and that NEFA levels were an independent determinant of ΣIRI among Japanese Americans. When HOMA-IR was included instead of BMI (Table 5, model 2), the determinant for each group remained the same. The analyses with models including waist girth or body fat instead of BMI showed a significant correlation between the fasting NEFA levels and ΣIRI in Japanese Americans, but not in native Japanese men (data not shown). These results indicate that the fasting NEFA levels were positively correlated with total insulin levels independently of obesity indices or HOMA-IR only in Japanese-American men, but not in native Japanese men.

To investigate whether elevated ΣIRI levels are due to elevated total insulin secretion, the relationship between the ΣC-peptide levels and the clinical parameters was evaluated. The regression analyses of ΣC-peptide levels with adjustment for age in Japanese Americans showed that waist girth ($P = .029$), body fat ($P = .003$), and HOMA-IR ($P = .001$) levels were significant determinants (data not shown). The multiple regression analysis model including age, BMI, fasting NEFA, and fasting triglycerides as the explanatory variables demonstrated that the fasting NEFA level was the only independent determinant of ΣC-peptide levels in Japanese-American men (Table 6).

4. Discussion

Westernized dietary habits may accelerate the effects of NEFA on insulin secretion after a glucose load in men. This study is the first to describe the association between lifestyle and the effects of NEFA on insulin secretion. We have previously reported that the intake of total fat and saturated fatty acids was higher in Japanese Americans than in native Japanese [20-22]. Although all of the Japanese Americans we surveyed were genetically identical to the native Japanese living in Japan [20,21], they were characterized by higher levels of serum insulin than native Japanese, even when they had the same degree of obesity [23]. In this report, we examined the relationship between NEFA levels and insulin concentration in Japanese-American men.

As shown in Table 1, fasting IRI, ΣIRI, and HOMA-IR levels were higher in Japanese Americans. These results are compatible with our previous observation [23,24], although neither fasting NEFA nor triglyceride levels were different between native Japanese men and Japanese-American men. However, the fasting NEFA level was associated with waist girth and the amount of body fat only in native Japanese, but not in Japanese Americans (Table 2). Because Japanese Americans consume more saturated fatty acids [20-22], it is conceivable that the ratio of polyunsaturated fatty acids to saturated fatty acids in the serum was lower in the Japanese Americans than in the native Japanese. This dissimilarity in dietary fat composition may have caused the discrepancy in the effects of the serum NEFA levels on insulin secretion after glucose load between the 2 groups, which contributed to the insulin hypersecretion in the Japanese-American men. It was reported in animal experiments that the insulinotropic potency of fatty acids was influenced by their chain length and their degree of saturation [32], and prolonged exposure to saturated fatty acids enhanced GSIS, whereas unsaturated fatty acids impaired GSIS [12], which is consistent with our hypothesis.

Our study demonstrated that the fasting NEFA level was a significant determinant of ΣIRI independent of BMI or HOMA-IR only in Japanese-American men (Tables 4 and 5). We suspect that NEFA can directly stimulate pancreatic beta cells, which leads to acceleration of GSIS especially in Japanese-American men. For example, Itoh et al [33] recently reported the direct effects of specific NEFAs on pancreatic beta cells through GPR40, which is an orphan G-protein–coupled receptor. Although the correlation between NEFA and ΣIRI levels might have been caused by a suppression of hepatic insulin clearance by NEFA partially [34,35], increased pancreatic insulin secretion should be present because NEFA was the significant explanatory variable of ΣC-peptide levels among Japanese Americans in the present study (Table 6).

Many reports suggested that an insulin hypersecretion caused by prolonged NEFA elevation was not sufficient to compensate for NEFA-induced insulin resistance [36]. We postulated that a prolonged elevation of serum NEFA levels and the increased saturated fatty acid ratio caused by westernized dietary habits might have contributed to postprandial insulin hypersecretion as long as the

pancreatic beta cells could compensate. When the beta cells could not compensate sufficiently for the peripheral insulin resistance, type 2 diabetes could occur. This hypothesis is supported by the report that total and saturated fat intake were risk factors for the development of type 2 diabetes in men [37].

There were several limitations in this study. First, we did not measure the actual NEFA profiles of the participants. To understand the effects of a specific NEFA (eg, palmitic acid) on insulin secretion, the chromatographic determination of the serum fatty acid composition is needed in the future. Second, we examined only male subjects. From the preliminary data, we could not find any apparent differences in the effects of NEFAs on insulin secretion after a glucose load between native Japanese women and Japanese-American women (data not shown). It is possible that the effects of a westernized lifestyle on NEFAs and insulin secretion differ based on sex. Further study is needed to clarify the difference in susceptibility to NEFAs or a westernized lifestyle between the sexes.

In summary, NEFA levels seem to be positively associated with insulin secretion independent of obesity or HOMA-IR. A westernized lifestyle may increase the effects of serum fasting NEFA levels on total insulin secretion after a glucose load in Japanese men.

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