



Progression of Carotid Atherosclerosis in Two Japanese Populations with Different Lifestyles

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Aim: We have conducted medical surveys on two Japanese populations (Japanese Americans living in the US and native Japanese living in Japan) to investigate the impact of westernization of lifestyles on diseases in Japanese people. A 1998 survey revealed that the progression of carotid intima-media wall thickness (IMT) was faster by approximately 20 years in Japanese Americans than in native Japanese. In this study, we compared the progression of atherosclerosis in native Japanese versus that in Japanese Americans using carotid IMT data from medical examinations conducted in the 2010s.

Methods: This study included 115 native Japanese living in Hiroshima who underwent a medical examination in 2014 and 112 Japanese Americans living in Hawaii who underwent a medical examination in 2012, excluding those receiving medication for diabetes mellitus (DM) or dyslipidemia. Carotid IMT was compared between the two Japanese populations.

Results: Serum total and low-density lipoprotein cholesterol levels were significantly higher in native Japanese than in Japanese Americans. The median carotid IMT was significantly greater in Japanese Americans than in native Japanese [median (25th-75th percentile): 1.27 (0.86-2.02) mm vs. 1.00 (0.80-1.30) mm, $P=0.001$]. Regression curves showed that the age at which IMT exceeded 1.1 mm was estimated at >50 years in Japanese Americans and at approximately 60 years in native Japanese.

Conclusions: According to surveys conducted in 2012 and 2014, carotid IMT was still greater in Japanese Americans than in native Japanese. However, a comparison with data from the 1998 survey showed that current native Japanese had higher serum lipid levels and more advanced atherosclerosis.

Key words: Intima-media wall thickness, Atherosclerosis, Westernization of lifestyle

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Introduction

Since 1970, we have been conducting medical surveys and an epidemiological study on Japanese Americans living in Hawaii and Los Angeles, called the Hawaii–Los Angeles–Hiroshima Study¹. Japanese Americans are defined as Japanese immigrants in the US and their descendants. Japanese Americans share identical genetic predispositions with native Japanese,

but have been exposed to westernized lifestyles, including dietary and exercise habits. By comparing survey results of this population of Japanese Americans with those of native Japanese with a Japanese lifestyle in Hiroshima, we investigated the impact of changing environmental factors associated with westernization of lifestyles on diseases in Japanese people. Surveys conducted from 1978 to 1988 showed that compared with native Japanese, Japanese Americans consumed a Western-style diet that was higher in animal fat and simple carbohydrates but lower in complex carbohydrates², which remained the same as in the survey conducted from 1992 to 1995³. We have reported that Japanese Americans have higher insulin resistance, which is a risk factor for atherosclerosis, than native Japanese⁴ and that the prevalence of dys-

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lipidemia²), DM⁵), obesity, and metabolic syndrome^{6, 7}) is higher in Japanese Americans than in native Japanese.

Furthermore, the survey conducted in 1998 showed that carotid intima-media wall thickness (IMT), which is useful for detecting subclinical atherosclerosis⁸), was greater in Japanese Americans than in native Japanese in every age group. The age at which IMT exceeded 1.1 mm, an indicator of atherosclerosis⁹), was estimated at approximately 70 years in native Japanese, but approximately 50 years in Japanese Americans. We reported that the rate of IMT progression was faster by approximately 20 years in Japanese Americans than in native Japanese¹⁰).

As more than 10 years have passed since this survey, it is expected that lifestyles of native Japanese living in Japan have been westernized and that the progression of atherosclerosis is comparable with that in Japanese Americans. There is also another report that carotid IMT was greater in Japanese Americans than in native Japanese in the survey conducted from 2002 to 2006¹¹). Besides, in other Japanese cohorts from 2005 to 2010, compared with Nagano residents, carotid IMT was higher in Okinawa residents who consumed high-fat, Western-style diets¹²).

The objective of the present study was to assess the association between westernization of lifestyles and atherosclerosis in Japanese people through comparison of carotid IMT in native Japanese living in Hiroshima and Japanese Americans living in Hawaii in the 2010s.

Methods

Study Group

The study population consisted of two groups: 115 native Japanese [42 men and 73 women, mean age 60.3 ± 1.3 years (mean \pm S.E)] who participated in the medical examination in 2014 in Hiroshima and 112 Japanese Americans (49 men and 63 women, mean age 62.8 ± 1.8 years) who participated in the medical examination in 2012 on Hawaii Island. We excluded subjects who were using medication for DM and dyslipidemia. We also excluded subjects who had fasting triglyceride (TG) levels of more than 400 mg/dl. The glucose tolerance status was ascertained by a 75-g oral glucose tolerance test (OGTT) in individual subjects as follows: normal glucose tolerance (NGT), a fasting serum glucose (FSG) level of <110 mg/dl and a 2-h SG level of <140 mg/dl after an oral glucose load; DM, a FSG level of ≥ 126 mg/dl or a 2-h SG level of ≥ 200 mg/dl; and impaired glucose tolerance (IGT), except for NGT and DM¹³). We defined the glucose intolerance group as the combined IGT and DM groups. The smoking status was assessed

using standard interview procedures. Each subject received an explanation of study procedures and provided written informed consent. This study was approved by the ethics committee of Hiroshima University.

Biochemical Analysis

After overnight fasting, each participant was interviewed and underwent a physical examination and venous blood collection. Body measurements were taken in the standing position. Body mass index (BMI) was calculated as weight (kg)/height (m)². Collected blood samples were centrifuged, and obtained serum samples were immediately frozen and stored until analysis. SG was measured using the hexokinase method. Serum total cholesterol (TC) and TG levels were measured by enzymatic methods (Kyowa Medex, Tokyo, Japan). High-density lipoprotein cholesterol (HDL-C) levels were measured by a homogenous assay (Kyowa Medex, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation¹⁴).

Measurements of Atherosclerotic Lesions

Carotid artery IMT was measured by B-mode ultrasonography (MyLab Five, Hitachi, Tokyo, Japan) with 10-MHz probe using a technique developed by Pignoli *et al.*¹⁵). In particular, we examined the far wall of the left and right common carotid arteries and internal carotid arteries. Examinations were made from three different longitudinal projections (i.e., anterior-oblique, lateral, and posterior-oblique). At each pre-defined angle of projection, the physician performing the scans visually identified the thickest arterial wall site, and the identified thickest IMT was defined as IMT in this study¹⁶). All measurements were performed by the same physician. The coefficient of variation was 5.8%–7.8% for repeated scans.

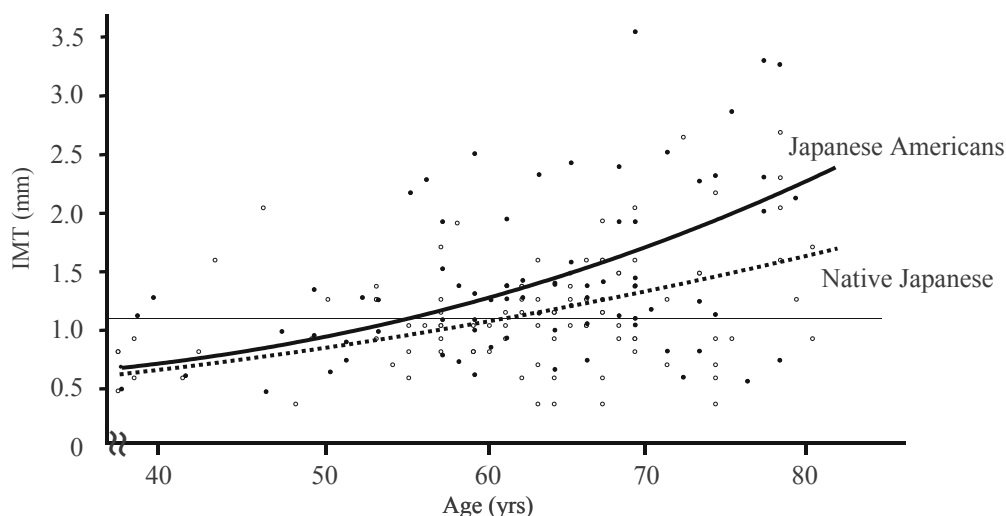
Statistical Analysis

Data are expressed as the mean \pm S.E or median (25th–75th percentile), depending on data distribution. Because of skewed distribution of data, TG and IMT values were logarithmically transformed and analyzed. Differences in continuous variables between native Japanese and Japanese Americans were analyzed using Student's *t*-test. Categorical variables were analyzed using χ^2 test. *P* values <0.05 were considered statistically significant. All analyses were performed using the software package SPSS version 20 (IBM Co. Ltd., Armonk, NY, USA).

Table 1. Baseline characteristics of subjects

	Native Japanese	Japanese Americans	<i>P</i>
<i>N</i> (Men/Women)	115 (42/73)	112 (49/63)	0.267
Age, years	60.3 ± 1.3	62.8 ± 1.8	0.269
BMI, kg/m ²	23.1 ± 0.3	24.0 ± 0.4	0.068
Systolic BP, mmHg	121.7 ± 1.7	134.0 ± 1.6*	<0.001
Diastolic BP, mmHg	72.3 ± 1.0	79.4 ± 0.9*	<0.001
TC, mg/dl	207.5 ± 2.8	195.3 ± 3.1*	0.004
LDL-C, mg/dl	125.3 ± 2.6	110.6 ± 2.7*	<0.001
HDL-C, mg/dl	62.9 ± 1.3	63.0 ± 1.6	0.984
TG [†] , mg/dl	87 (66-114)	96 (64-128)	0.108
Fasting glucose, mg/dl	93.6 ± 0.8	88.7 ± 0.9*	<0.001
2-h glucose, mg/dl	121.3 ± 3.0	122.2 ± 4.1	0.860
NGT/IGT/DM	83/28/4	82/20/10	0.144
Smoking, <i>n</i> (%)	40 (34.8)	38 (33.9)	0.223
Alcohol drinking, <i>n</i> (%)	51 (44.3)	44 (39.3)	0.440
Treatment for hypertension, <i>n</i> (%)	20 (17.4)	28 (25.0)	0.160
IMT [†] , mm	1.00 (0.80-1.30)	1.27 (0.86-2.02)*	0.001

BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; IMT, intima-media wall thickness. Data are presented as number, mean ± S.E. or median (25th-75th percentile levels). **P* < 0.05 native Japanese vs Japanese Americans. Data were analyzed by χ^2 test or by Student's *t*-test. [†]Parameters were transformed logarithmically before analysis.

**Fig. 1.** Age-related changes in IMT in native Japanese and Japanese Americans

Estimated IMT increases with age in native Japanese (○) and Japanese Americans (●). Lowest regression lines for native Japanese (dotted line) and Japanese Americans (solid line) are shown. The lateral straight line indicates IMT of 1.1 mm.

Results

Subject characteristics are shown in **Table 1**. There were no significant differences between native Japanese and Japanese Americans with respect to sex, age, BMI, or smoking status. Systolic blood pressure

(BP) and diastolic BP were significantly higher in Japanese Americans than in native Japanese. Although no significant differences in HDL-C or TG levels were observed between the two groups, TC and LDL-C levels were significantly higher in native Japanese than in Japanese Americans. The carotid IMT was signifi-

cantly greater in Japanese Americans than in native Japanese [median (25th-75th percentile): 1.27 (0.86-2.02) vs. 1.00 (0.80-1.30) mm, $P=0.001$].

Fig. 1 shows regression curves of carotid IMT plotted on the vertical axis against age on the horizontal axis for the two groups. The regression curve of IMT for Japanese Americans was plotted above that for native Japanese. The age at which the regression curve crossed the line for IMT of 1.1 mm, an indicator of advanced atherosclerosis⁹⁾, was at >50 years in Japanese Americans and at approximately 60 years in native Japanese.

Next, carotid IMT in both groups was assessed according to the presence or absence of an abnormal 75-g OGTT (**Fig. 2A**). Carotid IMT in subjects with NGT was 1.00 (0.70-1.30) mm in native Japanese ($n=83$) and 1.27 (0.82-1.86) mm in Japanese Americans ($n=82$) ($P<0.001$), whereas that in subjects with glucose intolerance (IGT + DM) was 1.05 (0.90-1.40) mm in native Japanese ($n=32$) and 1.31 (0.85-2.28) mm in Japanese Americans ($n=30$) ($P=0.043$). In subjects with either glucose condition, IMT was significantly higher in Japanese Americans than in native Japanese.

Finally, carotid IMT in both groups was assessed by age stratification (**Fig. 2B**). In subjects aged ≤ 49 years, IMT was 0.63 (0.54-0.80) mm in native Japanese ($n=22$) and 0.65 (0.56-0.78) mm in Japanese Americans ($n=22$), showing no significant difference between the two groups ($P=0.856$). However, IMT in subjects aged 50–69 years was 1.05 (0.90-1.26) mm in native Japanese ($n=66$) and 1.26 (0.99-1.38) mm in Japanese Americans ($n=44$), showing slightly but significantly higher IMT in Japanese Americans than in native Japanese ($P=0.044$). Furthermore, IMT in subjects aged ≥ 70 years was 1.40 (0.90-1.90) mm in native Japanese ($n=27$) and 2.02 (1.33-3.06) mm in Japanese Americans ($n=46$), showing extremely and significantly higher IMT in Japanese Americans than in native Japanese ($P=0.006$).

Discussion

In the 2010s, carotid IMT was still higher in Japanese Americans living in Hawaii than in native Japanese living in Hiroshima in all age groups. With aging, differences between the two groups increased and became significant. In other words, the longer Japanese people were exposed to westernized lifestyles, the greater was the impact on progression of atherosclerosis. However, when data were compared with those from the 1998 survey¹⁰⁾, the rate of IMT progression showed little change in Japanese Americans, whereas that in native Japanese advanced and was

accelerated by 10 years. This suggested that the progression of atherosclerosis in native Japanese was comparable with that in Japanese Americans.

According to a 2012 nutritional survey conducted on Japanese Americans living in Hawaii, who were also included in the present study, total daily energy intake was 1,987 kcal, with protein accounting for 12.1%, fat for 35.5%, and carbohydrate for 52.4%. These results were compared with data on consumed nutrients from the National Health and Nutrition Survey in Japan in the same year, which reported daily intake of 1,874 kcal, with protein accounting for 14.5%, fat for 26.4%, and carbohydrate for 59.1%¹⁷⁾; therefore, Japanese Americans consumed diets with higher fat content than those consumed by native Japanese. While this finding is consistent with the findings of the 1978-1988²⁾ and 1992-1995³⁾ surveys, Japanese Americans living in Hawaii still appeared to remain on high-fat, Western-style diets in the 2010s.

In this 2012–2014 survey, carotid IMT was still higher in Japanese Americans than in native Japanese, although average age, BMI, and proportion of smokers were similar, as shown in **Table 1**. Japanese Americans showed higher BP than native Japanese, and proportion of treatment for hypertension in Japanese Americans tended to be higher, which may affect the increase in carotid IMT in Japanese Americans.

On the other hand, it has been reported since the 1970s that Japanese lifestyles have been westernized and that serum lipid levels have been increasing in native Japanese in Japan^{18, 19)}. Our medical surveys also showed that serum lipid levels in Japanese Americans had consistently been higher or abnormal compared with those in native Japanese up to the 1980s^{1, 2)}. However, because the serum TC, TG, and LDL-C levels had increased in native Japanese but decreased in Japanese Americans since then, the 1998 survey showed no differences in these levels between the two groups¹⁰⁾. In this 2012-2014 survey, despite its small sample size, TC and LDL-C levels were significantly higher in native Japanese than in Japanese Americans, showing a reversal in the association. In the present study, although carotid IMT is still higher in Japanese Americans than in native Japanese, this reversal seems to have contributed to the increase in IMT in native Japanese and a decrease in the difference in IMT between the two groups.

In conclusion, the present study indicated again that atherosclerosis can progress in Japanese people if they are exposed to westernized lifestyles for a long period. However, because serum lipid levels have worsened in native Japanese, the progression of atherosclerosis was definitely faster than that shown in

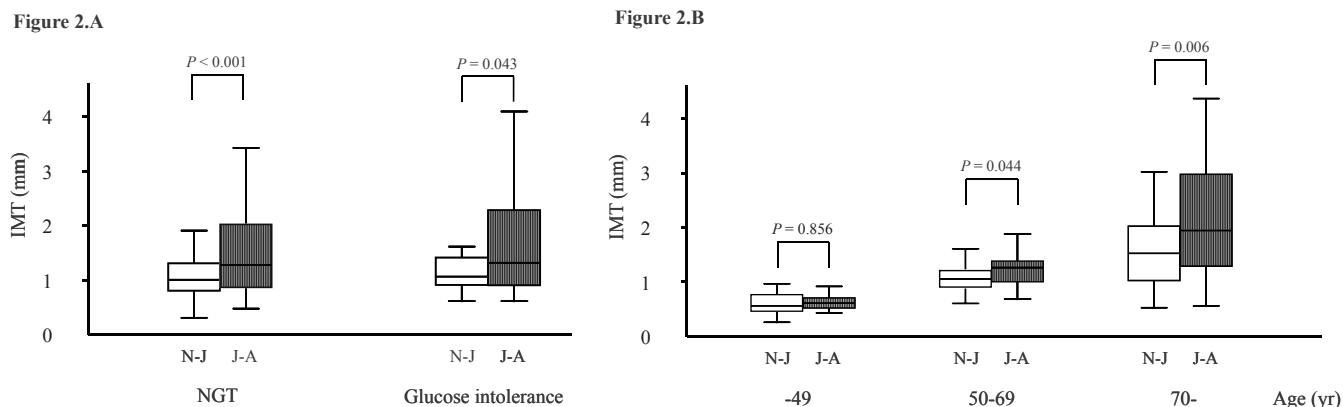


Fig. 2. IMT in the categories of subjects with NGT and glucose intolerance (A) or of age stratification (B) in native Japanese (N-J: white) and Japanese Americans (J-A: stripes)

A N-J; NGT: $n=83$, glucose intolerance: $n=32$ and J-A; NGT: $n=82$, glucose intolerance: $n=30$. B N-J; age ≤ 49 years: $n=22$, 50 years \leq age ≤ 69 years: $n=66$, 70 years \leq age: $n=27$, and J-A; age ≤ 49 years: $n=22$, 50 years \leq age ≤ 69 years: $n=44$, 70 years \leq age: $n=46$. NGT, normal glucose tolerance. The line in the middle of the box is plotted at the median, and the box extends from the 25th to 75th percentiles.

the 1998 survey¹⁰) and has become comparable to that in Japanese Americans. Even in Japanese people, in whom cardiovascular diseases are less prevalent than in Europeans and Americans, aggressive interventions to lower serum lipid levels with statins and other drugs appear to be important for prevention of atherosclerosis progression.

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None.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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