

Westernization of lifestyle markedly increases carotid intima-media wall thickness (IMT) in Japanese people

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Abstract

To illustrate the impact of westernization of lifestyle on the development of pre-clinical atherosclerosis in Japanese people, we compared risk factors for atherosclerosis such as serum lipids, blood pressure, BMI, insulin resistance, and smoking habits between non-diabetic native Japanese and non-diabetic Japanese Americans. Two hundred and twenty two non-diabetic Japanese Americans living in Hawaii and 271 non-diabetic Japanese living in Hiroshima, Japan were studied. Carotid intima-media wall thickness (IMT) was measured in all subjects by one physician. For all measurements the same ultrasound instrumentation was used. Although no significant differences were seen in serum total cholesterol (TC), triglycerides, or LDL-cholesterol (LDL-C) levels between the two groups in the 1998 study, previous to 1998 these three parameters were significantly higher in Japanese Americans than native Japanese in our study which has spanned the past 20 years. IMT was significantly greater in Japanese Americans than native Japanese (1.20 ± 0.03 mm vs. 0.98 ± 0.03 mm, (mean \pm S.E.) respectively; $P < 0.0001$). Moreover Japanese Americans reach an IMT of 1.1 mm at age 50, whereas the native Japanese reach this value at age 70. These observations indicate more rapid atherosclerosis progression in Japanese Americans. Based on our IMT measurements, the status and the estimated progression of atherosclerosis in Japanese Americans is increased. Since IMT is a validated endpoint for assessment of atherosclerotic disease risk, it can be concluded that Japanese Americans are at increased risk for cardiovascular disease.

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1. Introduction

Previous immigrant studies have pointed out an association between westernization of lifestyle, and increased mortality and incidence of atherosclerotic disease, particularly coronary heart disease (CHD) [1–4]. Yano et al. compared the incidence of mortality due to CHD between native Japanese and Japanese immigrants in Hawaii, and found a 1.4-fold higher incidence in the latter, showing the impact of environmental factors on the development of CHD in Japanese [5]. However, no immigrant study has been performed to investigate pre-clinical atherosclerosis.

Evaluation of carotid intima media wall thickness (IMT) using ultrasonography is a validated quantitative method for assessing atherosclerosis [6], that is closely correlated with pathological findings observed in the carotid artery [7]. In addition, the appearance of atherosclerosis in the carotid artery has been highly associated with atherosclerosis in the aorta [8], and a close relationship has been observed between IMT and the incidence of CHD [9–11].

The development of CHD involves plaque formation, plaque rupture, and formation of thrombi [12,13]. Risk factors for atherosclerosis influence these characteristic developments in a complex manner. Thus investigation of pre-clinical atherosclerosis may be used in epidemiological studies to determine the impact of westernization of lifestyle on the development of atherosclerosis. In the present study, we investigated the association of risk

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factors for atherosclerosis with pre-clinical atherosclerosis as evaluated by IMT in native Japanese and Japanese Americans living in the United States.

2. Methods

2.1. Study group

Subjects were members of the Japanese American community in Hawaii who were enrolled in the Hawaii–Los Angeles–Hiroshima study. This is a long-term epidemiological study of risk factors for diabetes and cardiovascular disease, in which subjects are limited to a population genetically identical to the Japanese. This community has 1279 members. We examined a total of 1026 subjects from 1970 to 1998. The current analysis, utilized data obtained over the period from 1981 to 1998. We informed all community members of this examination, and administered the tests indicated below to members who participated voluntarily. With the exception of previously diagnosed diabetics, all participants underwent a 75 g oral glucose tolerance test (OGTT). Subjects diagnosed with diabetes, elevated fasting triglycerides (TG) (≥ 400 mg/dl), hyperlipidemia, and liver or kidney dysfunction were excluded. The number of non-diabetic Japanese Americans who were enrolled in this study was 287 in 1998, 352 in 1995, 394 in 1992, 420 in 1988, 467 in 1984, and 443 in 1981. In a similar examination in Hiroshima, Japan, the number of non-diabetic Japanese enrolled in this study was 490 in 1998, 485 in 1995, 683 in 1992, 465 in 1988, 756 in 1984, and 605 in 1981. We measured the IMT in 222 subjects in Hawaii, aged 66.6 ± 0.9 (mean \pm S.E.) years, who were randomly selected from the participants in the 1998 examination, and 271 subjects in Hiroshima, Japan, aged 60.9 ± 0.8 years. All of the subjects gave informed consent to participate in the examination. This study was approved by the Ethics Committee of Hiroshima University, and the Council of Hiroshima Kenjin-kai Association in Hawaii. The details of this study have been described elsewhere [14–16].

2.2. Measurements

Venous blood was obtained from each subject after overnight fasting, and an OGTT was performed. The serum samples were rapidly separated and frozen at -80°C . Frozen samples were brought back to Japan and analyzed together in the same laboratory with the samples obtained in Japan. Serum glucose was measured by the glucose oxidase method and immunoreactive insulin (IRI) by the double antibody method. Diabetes was diagnosed according to the 1998 WHO criteria [17]. Serum total cholesterol (TC) and triglyceride (TG) levels were measured using an enzymatic method with a 736-

60E Auto Analyzer (Hitachi, Tokyo, Japan) [18]. HDL-cholesterol (HDL-C) was determined using a precipitation method [19]. LDL-cholesterol (LDL-C) was calculated using the Friedewald's equation [20].

Carotid IMT was measured by B-mode ultrasonography (EUB-405X, Hitachi, Tokyo, Japan) with a 10-MHz probe using the technique by Pignoli et al [7]. 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 doing the scans visually identified the thickest arterial wall site. An image showing an automated contour detection of the given arterial wall from 1 cm upstream to at least 1 cm downstream of the thickest site was saved (Fig. 1, ultrasound image). The images were analyzed off-line by specifically designed software (IntimaScope, MEDIA CROSS Co., Ltd, Japan). The greatest value among the six averaged IMTs (three from the left and three from the right) was used as the representative value for each individual [21,22]. All measurements (scans and image analyses) were performed by one physician and using the same equipment. To measure the IMT of Japanese Americans living in Hawaii, transported the ultrasound instrumentation across the ocean, and calibrated the machine after moving. To assess variability in the IMT measurements, repeated scans of five subjects were performed 1 and 2 weeks apart. The coefficient of variation was 3.6–4.7% for repeated scans.

2.3. Statistical analysis

Data were analyzed using SAS Version 8.0 (SAS Institute, Cary, NC) and given as the mean \pm S.E. Mean values were compared by Student's unpaired *t*-test or by age, sex-adjusted analysis of covariance (ANCOVA), as appropriate. During analysis, values for TG were converted to logarithms when they did not fit a normal distribution.

3. Results

As shown in Table 1, the mean age, the proportion of females, and subjects with impaired glucose tolerance were higher in Japanese Americans than the native Japanese. Accordingly, all of the analyses performed were adjusted for age, sex, and glucose tolerance. BMI, insulin resistance as evaluated by homeostasis model assessment (HOMA) [23] were significantly higher in Japanese Americans. No significant difference was observed in TC, TG, HDL-C, or LDL-C levels between the two groups in the 1998 study (Table 1A). On the other hand, Japanese Americans had previously dis-

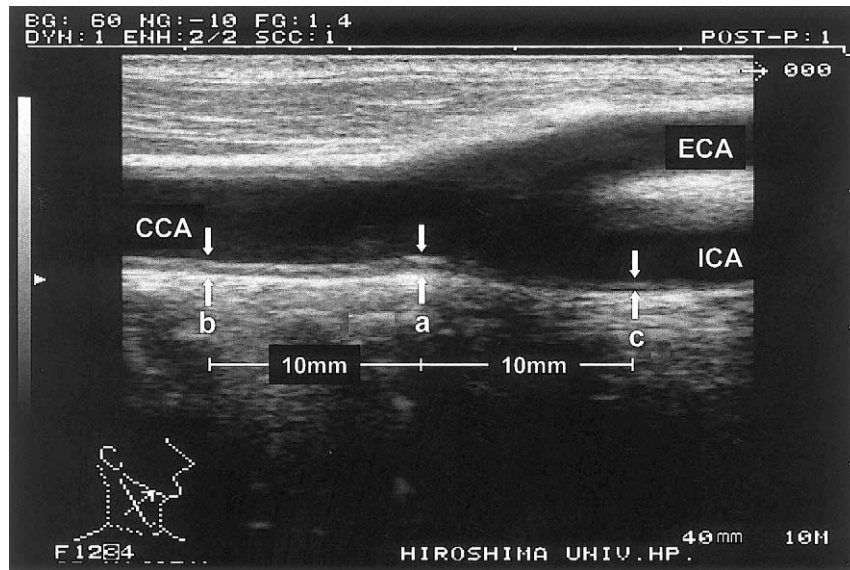


Fig. 1. High-frequency B-mode ultrasound imaging of the common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA). Three determinations of IMT were conducted at the site of greatest thickness (a) and at two other points, 1 cm downstream (b) and 1 cm upstream (c) from this site. These three determinations were averaged for evaluation.

Table 1
Characteristics of study subjects in the 1998 study

	Native Japanese	Japanese Americans	P value
A			
N (M/F)	271(197/74)	222(81/141)	
Age (years)	60.9±0.78	66.6±0.86	< 0.0001
BMI (kg/m ²)	22.8±0.26	24.9±0.27	< 0.0001
SBP (mmHg)	128.1±1.2	128.9±1.3	N.S.
DBP (mmHg)	77.2±0.8	75.3±0.9	N.S.
TC (mmol/l)	5.32±0.06	5.40±0.07	N.S.
TG (mmol/l)	1.56±0.05	1.66±0.06	N.S.
HDL-C (mmol/l)	1.48±0.03	1.51±0.03	N.S.
LDL-C (mmol/l)	3.15±0.06	3.27±0.06	N.S.
Smoking (%)	30.6	22.0	< 0.05
IGT (%)	33.1	55.3	< 0.05
HOMA	1.45±0.10	2.14±0.08	< 0.0001
IMT (mm)	0.98±0.03	1.20±0.03	< 0.0001
B			
Σ TC (mmol/l)	31.0±0.8	34.8±0.7	< 0.001
Σ TG (mmol/l)	7.46±0.30	9.21±0.44	< 0.001
Σ HDL-C (mmol/l)	8.21±0.28	8.68±0.26	N.S.
Σ LDL-C (mmol/l)	19.9±0.4	22.5±0.6	< 0.001

All risk factors were adjusted for age and sex except age. Values are means±S.E. SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, Triglycerides; HOMA, homeostasis model assessment; IMT, Carotid intima-media wall thickness. Σ TC, Σ TG, Σ HDL-C and Σ LDL-C were sum of TC, TG, HDL-C and LDL-C levels during six examinations between 1981 and 1998.

played higher serum levels of TC, TG and LDL-C than native Japanese prior to the 1995 study (Fig. 2A, B and D). Serum HDL-C levels were also marginally higher in Japanese Americans until 1998 (Fig. 2C). The sum of TC, TG, LDL-C but not HDL-C levels in six examina-

tions during the period from 1981 to 1998 was significantly higher in Japanese Americans than in native Japanese (Table 1B; Fig. 2). Thus previously observed differences have diminished recently, due to a rapid increase in serum TC (4.97 ± 0.04 in 1981 vs. 5.58 ± 0.09 in 1992, (mean±S.E.) $P < 0.0001$), TG (1.20 ± 0.03 in 1995 vs. 1.56 ± 0.05 in 1998, n.s.), HDL-C (1.18 ± 0.01 in 1981 vs. 1.48 ± 0.03 in 1998, $P < 0.0001$), and LDL-C (3.26 ± 0.04 in 1981 vs. 3.62 ± 0.04 in 1992, $P < 0.01$) levels in native Japanese, and gradual decrease in Japanese Americans (TC: 5.90 ± 0.05 in 1981 vs. 5.40 ± 0.07 in 1998, $P < 0.0001$, LDL-C: 3.93 ± 0.05 in 1981 vs. 3.27 ± 0.06 in 1998, $P < 0.0001$) (Fig. 2). This trend remained after adjustments for age, sex, BMI, blood pressure, smoking, and insulin resistance.

Compared with native Japanese however, Japanese Americans exhibited significantly higher IMT in values in 1998 (1.20 ± 0.03 vs. 0.98 ± 0.03 mm, (mean±S.E.) $P < 0.0001$). Stepwise regression analysis performed in 120 subjects who enrolled in both 1998 and 1988 examination showed that, having used IMT as dependent variable, only age and sex were significant independent variables in Japanese Americans in the 1998 study group (Table 2). The 1988 data, however, showed that age, smoking, and LDL-C were significant as independent variables in Japanese Americans (Table 2). Moreover, the 1981 and 1984 data similarly showed that LDL-C was a significant independent variable (data not shown).

An age related regression curve of IMT between the two groups indicated that Japanese Americans reach an IMT of 1.1 mm at age 50, whereas the native Japanese reach this value at age 70 (Fig. 3). Thus westernized

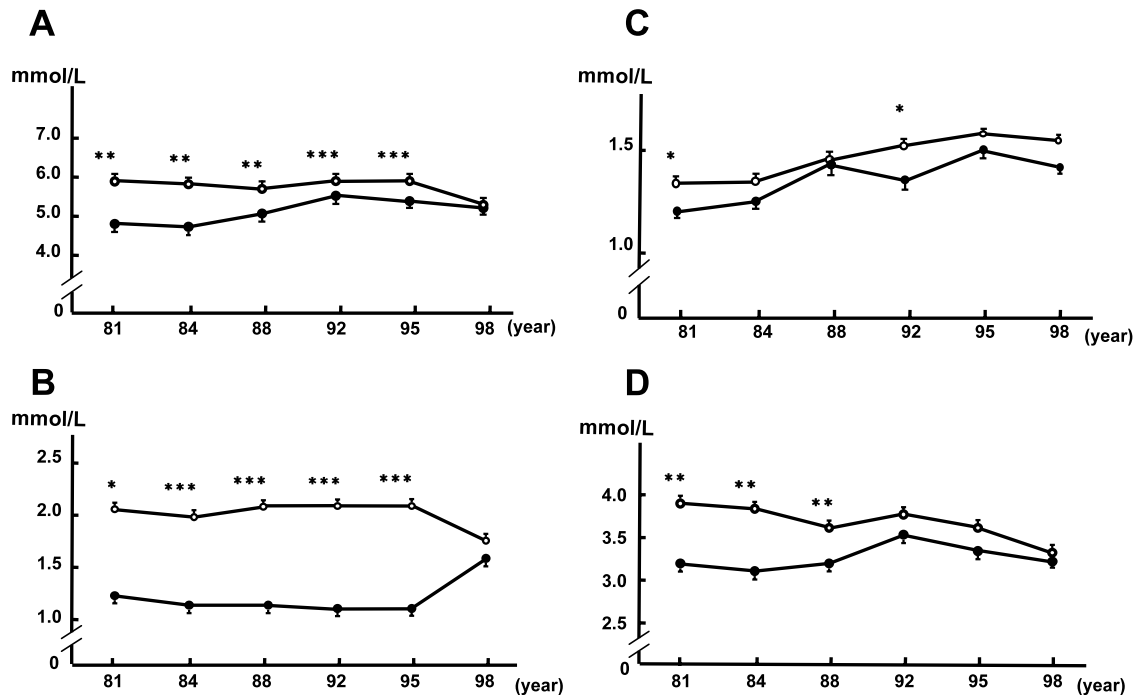


Fig. 2. Chronological changes in serum total cholesterol (A), TG (B), HDL cholesterol (C) and LDL cholesterol (D) levels during the last 20 years in native Japanese (●) and Japanese Americans (○). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 2
Determinants of IMT by stepwise regression analysis

	1988		1998	
	β	S.E.	β	S.E.
Age	0.205*	0.0045	0.480*	0.0040
Sex	0.045*	0.1061	0.234*	0.1035
SBP	not entered	not entered	not entered	not entered
BMI	0.018	0.0156	0.025	0.0158
LDL-C	0.044*	0.0015	not entered	not entered
Smoking	0.071*	0.0002	not entered	not entered

1988: BMI, BP, TC, TG, HDL-C, LDL-C, smoking, blood glucose, and IRI measured in 1988 were used as predictor variables. IMT values measured in 1998 were used as the dependent variable. $N = 120$, 1998: This analysis was performed using the data in 1998. $N = 120$.

* $P < 0.05$.

lifestyle has import to progress pre-clinical atherosclerosis 20 years' earlier in Japanese subjects.

4. Discussion

The present study shows that the average IMT of Japanese Americans was significantly higher than that of native Japanese. Westernization of lifestyle has advanced the degree of atherosclerosis in middle aged Japanese Americans by as much as 20 years in comparison to Japanese.

We observed higher mean IMT levels in Japanese Americans than native Japanese even in aged 40 or less,

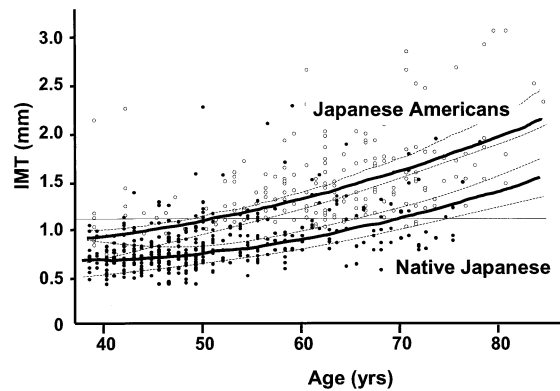


Fig. 3. Age related changes in IMT in non-diabetic native Japanese and Japanese Americans. Estimated IMT increase with age in native Japanese (●) and Japanese Americans (○). Lowess regression lines and 95% confidence intervals are shown.

although difference was small as compared with aged subjects (Fig. 3). This might be due to many of second or more later Japanese Americans, whose life style have been more westernized than the first generation Japanese Americans, consists of younger age subjects in our study.

The mortality rate of Japanese Americans due to CHD was approximately 50% that of Caucasians during the 1950s, but has gradually increased thereafter. During the 1970s, the mortality rate of Japanese Americans due to CHD became similar to that of Caucasians [24]. The incidence of CHD is affected by many factors such as genetic background, the level of medical care, disease

prevention strategies, and the degree and duration of exposure to risk factors for atherosclerosis [25,26]. Since it is difficult to evaluate the impact of environmental factors on coronary risk factors and atherosclerosis, it is important to assess the signs of pre-clinical atherosclerosis instead of focusing on coronary events alone.

As causes of changes in coronary risk factors, altered environmental factors such as eating habits and the degree of physical activity should be considered. The lifestyle of Japanese Americans, with an identical genetic background to that of native Japanese, has been rapidly westernized to a higher degree [3,14–16]. We have previously illustrated that the eating habits of Japanese Americans differed not in quantity but in quality [16]. Although total energy consumption was similar between the two groups, Japanese Americans consumed 1.6 times as much animal fat. The intake of saturated fatty acids (1.6 times) and cholesterol (1.4 times) was also significantly higher among Japanese Americans [16]. The intake of simple carbohydrates also increased to 1.6 times greater than that of native Japanese. Moreover, assessment of physical activity through interviews showed that strenuous physical activity was less common in Japanese American subjects [3,14].

In this medical survey, we also reported that Japanese Americans are more frequently exposed to risk factors for atherosclerosis such as diabetes mellitus, hyperlipidemia, and obesity than native Japanese [27]. However recently, the lifestyle of the native Japanese has changed, and their serum lipids have increased quite rapidly. Over the past 20 years, Japanese Americans have displayed significantly higher levels of serum TC, TG and LDL-C levels than Japanese. However, this trend has diminished recently due to the rapid increases in serum TC, TG, and LDL-C levels in native Japanese, and gradual decreases in some Japanese Americans (Fig. 2). Indeed, no significant differences were observed in serum TC, TG HDL-C, and LDL-C levels between the two groups in 1998 (Table 1A). The low rate of smoking among Japanese Americans as compared with native Japanese may be a factor related to the higher HDL-C levels seen in Japanese Americans (Table 1A).

Among the Japanese Americans, stepwise regression analysis showed that only age and sex were significant independent variables for IMT in 1998. However, the data from 1981 to 1988 showed that LDL-C was a significant independent variable in Japanese Americans (Table 2). Furthermore, the sum of TC, TG and LDL-C levels from 1981 to 1998 was significantly higher in Japanese Americans than in native Japanese (Table 1B). Thus exposure to coronary risk factors such as hypercholesterolemia for a longer duration and to a higher degree may be a potent factor explaining the differences in the IMT values of native Japanese and Japanese Americans.

We have previously reported that insulin resistance among Japanese Americans is greater and their insulin concentration is higher than that of the native Japanese [14,15] (Table 1A). Higher insulin concentrations and insulin resistance promote atherosclerosis [28]. However, the relationship of insulin concentration and insulin resistance to pre-clinical atherosclerosis remains unclear. Further study is needed to clarify whether metabolic disturbances associated with insulin resistance or insulin resistance per se is important to the progression of pre-clinical atherosclerosis.

In conclusion, westernization of lifestyle promotes the development of pre-clinical atherosclerosis in Japanese. Since IMT is a validated endpoint for atherosclerotic disease risk, it can be concluded that Japanese Americans are at increased risk for cardiovascular disease.

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