Acta Med. Okayama, 2014
Vol. 68, No. 1, pp. 27-34

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Association of Blood Pressure and Body Mass Index with Intraocular Pressure in Middle-aged and Older Japanese Residents: A Cross-sectional and Longitudinal Study

Masao Yoshida[a]*, Mamoru Ishikawa[a,b], Kanae Karita[a], Akatsuki Kokaze[a,c], Matsuko Harada[a,d], Shinichiro Take[a,e], and Hideki Ohno[a]

[a]*Department of Public Health, Kyorin University School of Medicine, Mitaka, Tokyo 181-8611, Japan,*
[b]*Ningen Dock Clinic Kashiwa, Kashiwa, Chiba 277-0841, Japan,*
[c]*Department of Public Health, Showa University School of Medicine, Shinagawa-ku, Tokyo 142-8555, Japan,*
[d]*Department of Living Science, Teikyo Junior College, Shibuya-ku, Tokyo 151-0071, Japan, and*
[e]*Saitama Kaisei Hospital, Yashio, Saitama 340-0825, Japan*

To clarify whether high blood pressure (BP) and high body mass index (BMI) are associated with elevated intraocular pressure (IOP), a cross-sectional and longitudinal study was conducted. This epidemiological study analyzed health examination data obtained between 2001 and 2005 from 896 Japanese individuals (aged 32-79 years) who had not undergone any ocular surgery or medical treatment for hypertension, ocular hypertension, or glaucoma. Multiple-regression analysis of our cross-sectional data showed that systolic and diastolic BP (SBP and DBP) and BMI had significant and near-significant positive associations with IOP in men ($p < 0.05$) and women ($p < 0.1$). Our longitudinal study from analyses of covariance found that the adjusted mean level of changes in IOP tended to increase with increased levels of SBP, DBP, and BMI in men ($p < 0.1$). In women also, changes in SBP and BMI tended to be positively related with that of IOP ($p < 0.1$). The results of this study suggested that BP and BMI were positively associated with IOP in middle-aged and older Japanese. Therefore, management of BP and improvement of obesity might be especially important to Japanese patients with open-angle glaucoma or ocular hypertension as they have a higher incidence of normal-tension glaucoma than Europeans and Americans.

Key words: intraocular pressure, blood pressure, body mass index, epidemiology, glaucoma

Glaucoma is the second-leading cause of blindness worldwide. It is estimated that the number of people with glaucoma will reach 80 million in 2020, and more than 70% of those will have open-angle glaucoma (OAG) [1]. Ocular hypertension, which is usually defined as intraocular pressure (IOP) higher than normal, IOP > 21 mmHg, in the absence of optic nerve damage or visual field loss [2], is one of the major risk factors for the development of OAG [3]. Several studies have reported that relatively high IOP can cause optic-nerve damage and visual-field abnormalities, even if the IOP is within the normal range [4, 5]. High IOP can also affect the progression of visual-field defects in patients with OAG, particularly those with normal tension glaucoma (NTG) [6, 7].

Many cross-sectional [8-20] and longitudinal [16,

Received March 26, 2013; accepted October 8, 2013.
*Corresponding author. Phone:+81-422-47-5511; Fax:+81-422-76-0366
E-mail:yohhy@ks.kyorin-u.ac.jp (M. Yoshida)

21, 22] epidemiological studies have investigated the risk factors associated with elevated IOP. We have previously conducted cross-sectional epidemiological studies and reported the positive associations of IOP with BP, BMI, and a smoking habit [23, 24]. Although these reports have suggested positive associations between IOP and blood pressure (BP) and several life-style related factors such as body mass index (BMI), drinking, smoking, and exercise habits, most of these reports conducted in Western [8-14] and Asian [15, 17-20] countries were examined cross-sectionally. Several epidemiological studies have examined this relationship longitudinally in Asian populations [16, 21, 22]. Given this background, we attempted to collect subjects from 2001 to 2005 and follow-up these individual subjects, and investigated whether high BP and high BMI were associated with elevated IOP, and whether the subsequent changes in systolic BP (SBP), diastolic BP (DBP), and BMI were associated with that of IOP from both cross-sectional and longitudinal analyses. We analyzed health examination data from middle-aged and older Japanese residents in a prefectural capital close to Tokyo. The results of this study might contribute to preventing the progression of IOP-related optic-nerve damage and visual-field defects.

Materials and Methods

Subjects. A total of 1,320 residents of the Ibaraki prefecture, Japan, underwent an annual health examination between April 2001 and March 2004 at a general hospital in Mito, which is the capital city of the prefecture. From this initial group, 1,113 individuals (829 men and 284 women), ranging in age from 28 to 79 years, who had not undergone any ocular surgery or medical treatment for hypertension, ocular hypertension, or glaucoma, were selected as candidates for the present study. If the subjects had consulted for health examinations 3 years or more during the 5-year follow-up period between 2001 and 2005, data from the first visit and the most recent visit of each subject were used for longitudinal analysis. As a result, 896 subjects (652 men and 244 women) were enrolled in this cross-sectional and longitudinal study (average follow-up period was 3.6 years). The age of the subjects ranged from 32 to 79 years at baseline. This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the human ethics review committees of Mito Red Cross Hospital and Kyorin University School of Medicine in Japan.

Health examination. The health examination consisted of a questionnaire that assessed demographic and lifestyle-related factors, along with the following measurements and tests: height, weight, BP, IOP, hematological and serum biochemistry, chest X-rays, electrocardiography, and fundus photography. All subjects were requested not to consume any food or alcohol after 21 : 00 h on the day before the examination.

The topics covered in the questionnaire included age, marital status, occupation, residence, current status and past history of medication, family medical history, smoking history and number of cigarettes smoked per day, drinking history, and exercise habits. Alcohol consumption was classified into the following 4 categories: never or seldom, several times per month, several times per week, and every day. BP was measured with a sphygmomanometer using the right arm; 2 consecutive measurements were taken after subjects had rested in a sitting position for at least 5 min. IOP was measured using a non-contact tonometer (NT-3000, Nidek, Japan) and 3 consecutive measurements were taken per eye.

Statistical analyses. SBP and DBP values for each subject were calculated as the mean of 2 measurements. For IOP, the mean of 3 measurements was calculated for each eye; however, as there was a strong correlation ($r = 0.84$) between the mean IOPs of the right and left eyes in each individual, the mean of these 2 values was used as a single measure of IOP. The associations of age with IOP, SBP, DBP, and BMI − calculated as weight (kg)/height squared (m^2) − were determined by comparing the mean values of these 4 parameters among 4 age groups (< 40 years, 40-49 years, 50-59 years, and ≥ 60 years) by gender, using the Bonferroni multiple-comparison method [25]. The Student's *t*-test was used to analyze differences in the mean IOP, SBP, DBP, and BMI between the 2 sexes by age group.

Cross-sectional associations between IOP and demographic and lifestyle-related factors were analyzed using a univariate regression analysis; then the partial regression coefficients and the standardized partial regression coefficients for IOP of the following independent variables were determined by multiple regression: age, SBP (model 1), DBP (model 2), BMI, number of cigarettes smoking per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1).

Longitudinal changes in BP, BMI, and IOP during the follow-up period were based on data obtained from the first visit and the most recent visit of each subject from 2001 to 2005. The associations of changes in age, SBP, DBP, and BMI with IOP over an average follow-up period of 3.6 years were analyzed using univariate regression analysis, then the multivariate partial regression coefficients and the standardized partial regression coefficients of changes in age, SBP, DBP, and BMI for IOP were determined by multiple-regression analyses. These were adjusted for age, SBP (model 1), DBP (model 2), BMI, number of cigarettes smoked per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) at baseline. Next, the adjusted mean levels of changes in IOP, calculated by analysis of covariance, were compared among the 3 categories stratified by changes in SBP, DBP, and BMI by tertile (subjects were divided to equalize the number of subjects in each category for both sexes into 3 categories). All analyses were conducted using the SAS statistical software package, version 9.3 [26].

Results

Cross-sectional analyses. The relationships between age and IOP, SBP, DBP, and BMI are shown in Table 1. The mean IOP was highest in the < 40 age group for both sexes. In both sexes, the highest mean SBP, DBP, and BMI values were found in the age groups of ≥ 60, 50–59, and 50–59, respectively. All parameters measured were significantly higher in men than in women ($p < 0.05$ for IOP and < 0.01 for SBP, DBP, and BMI). The Bonferroni multiple-comparison analysis revealed that the mean IOP was significantly lower in the ≥ 60 age group than in the < 40 age group in both sexes ($p < 0.05$).

Table 2 shows the univariate regression coefficients, the multivariate partial regression coefficients, and the standardized partial regression coefficients of demographic and lifestyle-related factors for IOP according to regression analyses, including SBP (model 1) or DBP (model 2) as independent variables, in the cross-sectional study. Age and regular exercise had a negative association with IOP in men ($p < 0.01$ and 0.16, respectively) and women ($p < 0.01$ and 0.08, respectively). On the other hand, SBP, DBP, BMI, and the number of cigarettes smoked per day had significant positive associations with IOP in men ($p \leq 0.01$ for SBP, DBP, and BMI, and 0.08 for cigarettes). In women, SBP, DBP, and BMI had significant positive associations with IOP ($p < 0.05$). After adjusting for the other independent variables, SBP, DBP, BMI, and the number of cigarettes smoked per day had significant positive associations with IOP in men ($p < 0.05$). In women, SBP, DBP, and BMI had significant positive associations with IOP ($p < 0.05$ for SBP and DBP, and < 0.1 for BMI). On the contrary, age had a significant negative association with IOP in both sexes ($p < 0.01$).

Longitudinal analyses. Table 3 shows the

Table 1 Baseline characteristics of IOP, SBP, DBP, and BMI by sex and age in middle-aged and older Japanese men and women

Age Group (years)	Number of Subjects		Mean ± SD							
			IOP (mmHg)		SBP (mmHg)		DBP (mmHg)		BMI (kg/m^2)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
< 40	110	53	14.3 ± 2.6[d]	14.1 ± 2.7[d]	119.5 ± 13.7[c,d]	111.7 ± 12.8[c,d]*	71.1 ± 9.5[c]	65.7 ± 7.7[c]*	22.9 ± 2.9	21.7 ± 3.2
40–49	183	63	13.9 ± 2.4	13.6 ± 2.6	122.9 ± 13.5[c,d]	120.1 ± 13.0	72.1 ± 9.1[c]	69.4 ± 8.1	23.4 ± 2.6	22.6 ± 3.0**
50–59	241	72	13.7 ± 2.8	13.5 ± 2.8	127.8 ± 14.1[a,b,d]	124.0 ± 13.1[a]*	75.6 ± 9.0[a,b]	71.4 ± 8.2[a]**	23.9 ± 2.5	23.1 ± 3.0
≥ 60	118	56	13.4 ± 2.5[a]	13.1 ± 2.7[a]	134.4 ± 16.0[a,b,c]	129.3 ± 15.6[a]	74.1 ± 9.6	70.0 ± 8.4	22.7 ± 2.8	22.1 ± 2.9
Total/Mean	652	244	13.9 ± 2.6	13.6 ± 2.7*	126.1 ± 14.3	122.3 ± 14.0**	74.0 ± 9.3	70.3 ± 8.2**	23.6 ± 2.7	22.8 ± 3.1**

IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.
Significant differences at the 0.05 level on the basis of Bonferroni multiple comparison: [a]versus age group < 40; [b]versus age group 40–49; [c]versus age group 50–59; [d]versus age group ≥ 60. *P* values for difference between males and females: *$p < 0.05$; **$p < 0.01$.

Table 2 Cross-sectional associations of demographic and lifestyle-related factors with IOP at baseline according to univariate and multivariate regression analyses

	Univariate regression coefficients				Multivariate regression coefficients					
	Regression coefficients		*P* Value		Partial regression coefficients		Standardized partial regression coefficients		*P* Value	
Variables†	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Model 1										
Age (years)	−0.093	−0.081	<0.01	<0.01	−0.112	−0.104	−0.322	−0.301	<0.01	<0.01
SBP (mmHg)‡	0.049	0.041	<0.01	0.02	0.048	0.050	0.204	0.205	<0.01	0.02
BMI (kg/m²)	0.181	0.209	0.01	0.04	0.140	0.173	0.142	0.191	0.02	0.04
Number of cigarette smoking per day	0.040	0.051	0.08	0.17	0.035	0.062	0.143	0.150	0.04	0.18
Alcohol consumption	0.182	0.175	0.10	0.21	0.299	0.266	0.123	0.102	0.11	0.25
Regular exercise	−0.089	−0.103	0.16	0.08	0.121	−0.207	0.021	−0.050	0.58	0.39
Model 2										
Age (years)	·	·	·	·	−0.104	−0.095	−0.309	−0.297	<0.01	<0.01
DBP (mmHg)‡	0.061	0.076	0.01	0.03	0.074	0.079	0.260	0.271	0.02	0.04
BMI (kg/m²)	·	·	·	·	0.133	0.155	0.136	0.165	0.03	0.07
Number of cigarette smoking per day	·	·	·	·	0.030	0.066	0.151	0.162	0.04	0.20
Alcohol consumption	·	·	·	·	0.294	0.244	0.122	0.090	0.08	0.21
Regular exercise	·	·	·	·	0.132	−0.251	0.019	−0.064	0.49	0.33

IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.
†Age, SBP (model 1) or DBP (model 2), number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) were added as independent variables.
‡Age, BMI, number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) were added as independent variables.

Table 3 Longitudinal associations of age, SBP, DBP, and BMI with IOP according to univariate and multivariate regression analyses

	Univariate regression coefficients				Multivariate regression coefficients					
	Regression coefficients		*P* Value		Partial regression coefficients		Standardized partial regression coefficients		*P* Value	
Variables	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Model 1										
Age (years)†	−0.081	−0.080	<0.01	<0.01	−0.092	−0.085	−0.234	−0.210	<0.01	<0.01
SBP (mmHg)‡	0.041	0.036	0.01	0.04	0.040	0.041	0.190	0.194	0.02	0.06
BMI (kg/m²)*	0.143	0.174	0.03	0.06	0.128	0.159	0.129	0.175	0.03	0.05
Model 2										
Age (years)†	−0.069	−0.067	<0.01	<0.01	−0.088	−0.079	−0.221	−0.199	<0.01	<0.01
DBP (mmHg)‡	0.049	0.058	0.08	0.10	0.052	0.057	0.224	0.238	0.10	0.17
BMI (kg/m²)*	0.133	0.153	0.06	0.07	0.118	0.138	0.120	0.151	0.04	0.08

IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.
†SBP (model 1) or DBP (model 2), BMI, number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) at baseline were added as independent variables.
‡Age, BMI, number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) at baseline were added as independent variables.
*Age, SBP (model 1) or DBP (model 2), number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) at baseline were added as independent variables.

univariate regression coefficients, the multivariate partial regression coefficients, and the multivariate standardized partial regression coefficients of age, SBP, DBP, and BMI for IOP according to regression analyses, including SBP (model 1) or DBP (model 2) as independent variables in the longitudinal study. After adjusting for age, SBP, DBP, BMI, the number of cigarettes smoked per day, alcohol consumption, and regular exercise at baseline, both changes in SBP and BMI had significant positive associations with IOP in men ($p < 0.05$) and women ($p < 0.1$). On the other hand, changes in age had a significant negative association with IOP in both sexes ($p < 0.01$).

In Table 4, the adjusted mean levels of changes in IOP obtained by analyses of covariance were compared among tertile categories stratified by changes in SBP, DBP, and BMI. The adjusted mean level of changes in IOP increased significantly in men with increased levels of the 3 SBP categories ($p < 0.01$) and BMI categories ($p = 0.01$) with a tendency for increase in DBP categories ($p = 0.08$). In women, the adjusted mean level of changes in IOP increased significantly with increased levels of the 3 SBP categories ($p = 0.03$) and tended to increase with BMI categories ($p = 0.07$).

Discussion

The mean IOP across the group as a whole in the present cross-sectional study, measured using a non-contact tonometer, was 13.9 ± 2.6 mmHg for men and 13.6 ± 2.7 mmHg for women; the mean IOP was significantly higher in men than in women ($p < 0.05$). In both sexes, the mean IOP decreased with age, and subjects ≥ 60 years of age showed the lowest mean IOP. Several previous studies of Europeans and

Table 4 Adjusted mean levels of changes in IOP stratified by changes in SBP, DBP, and BMI by tertile

Variables	Number (%) of subjects	Mean ± SE Changes in IOP (mmHg)	*P* value for the difference from the lowest group	*P* for trend
SBP†				
Men				
SBP increased by > 5.8 mmHg	217 (33.3)	0.16 ± 0.03	0.01	<0.01
SBP stayed within +5.8 ~ −3.7 mmHg	219 (33.6)	−0.07 ± 0.02	0.04	
SBP decreased by > 3.7 mmHg	216 (33.1)	−0.18 ± 0.04	·	
Women				
SBP increased by > 5.4 mmHg	79 (32.4)	0.15 ± 0.04	0.04	0.03
SBP stayed within +5.4 ~ −4.0 mmHg	83 (34.0)	−0.08 ± 0.02	0.11	
SBP decreased by > 4.0 mmHg	82 (33.6)	−0.15 ± 0.05	·	
DBP†				
Men				
DBP increased by > 3.6 mmHg	218 (33.4)	0.13 ± 0.03	0.07	0.08
DBP stayed within +3.6 ~ −2.7 mmHg	218 (33.4)	−0.09 ± 0.02	0.33	
DBP decreased by > 2.7 mmHg	216 (33.1)	−0.14 ± 0.03	·	
Women				
DBP increased by > 3.7 mmHg	81 (33.2)	0.11 ± 0.04	0.16	0.13
DBP stayed within +3.7 ~ −2.9 mmHg	83 (34.0)	−0.09 ± 0.03	0.56	
DBP decreased by > 2.9 mmHg	80 (32.8)	−0.12 ± 0.04	·	
BMI*				
Men				
BMI increased by > 1.2 kg/m²	216 (33.1)	0.10 ± 0.03	0.02	0.01
BMI stayed within +1.2 ~ −0.8 kg/m²	220 (33.7)	0.06 ± 0.02	0.07	
BMI decreased by > 0.8 kg/m²	216 (33.1)	−0.25 ± 0.04	·	
Women				
BMI increased by > 1.3 kg/m²	80 (32.8)	0.09 ± 0.03	0.09	0.07
BMI stayed within +1.3 ~ −1.1 kg/m²	83 (34.0)	0.06 ± 0.02	0.12	
BMI decreased by > 1.1 kg/m²	81 (33.2)	−0.24 ± 0.06	·	

IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

† Age, BMI, number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) at baseline were added as independent variables.

* Age, SBP, number of cigarettes consumed per day, alcohol consumption (never or seldom = 0; several times per month = 1; several times per week = 2; everyday = 3), and regular exercise (no = 0; yes = 1) at baseline were added as independent variables.

Americans have reported an increase in IOP after the age of 40 years [10, 13, 14, 27] and a decrease in IOP among elderly populations [28-31], while IOP was found to decrease with age in cross-sectional studies conducted among Asian populations [17, 19, 20, 32, 33].

The association of IOP with age observed in the present cross-sectional study was consistent with that found in several Asian countries. However, when the association between age and IOP were analyzed longitudinally, the inverse age-IOP association appeared to be controversial. The results of this study from both cross-sectional and longitudinal analyses showed that age had a significant negative association with IOP. Nakano's 10-year longitudinal analysis in young and middle-aged Japanese men [22] also reported that IOP decreased with age in all age groups. On the other hand, Nomura [16] reported that though IOP decreased with age in cross-sectional analysis, there was a tendency for IOP to increase with age in longitudinal analysis. This tendency may reflect the Westernization of the Japanese diet with higher cholesterol levels [16]; a positive correlation between IOP and cholesterol levels has been reported previously [13]. Further investigations will be necessary to clarify the association between aging and IOP.

In the present study, a positive association with IOP was observed in both sexes for SBP, DBP, and BMI in the cross-sectional analysis, and for SBP and BMI in longitudinal analysis. Previous epidemiological studies [8-22, 31, 34, 35] have shown similar results. Many cross-sectional studies [8-20] have observed a positive association of IOP with SBP [8-19] and BMI [8, 14, 16-20], and others have found a positive association between IOP and both SBP and DBP [12, 13, 15, 17, 18], or between IOP and mean BP (1/3SBP + 2/3DBP) [20]. These results from cross-sectional studies have been confirmed by longitudinal studies in Japanese [16, 21, 22] and Western [31, 34, 35] populations. These reports have suggested positive associations of changes in IOP with that of SBP and DBP [31, 34, 35], SBP and BMI [16, 22], and BMI [21].

Our findings of the positive BP-IOP and the positive BMI-IOP associations from cross-sectional and longitudinal analyses are in agreement with other cross-sectional and longitudinal studies. However, we should point out the important limitations that our study might have had, because the distribution of IOP might not correspond to that in the general population. All the subjects in this study were clients who had consulted a general hospital for an annual health check; we excluded all subjects receiving medical treatment for hypertension, ocular hypertension, or glaucoma, in order to evaluate the association of BP and BMI with IOP in the absence of the effects of medication. Such selection bias might have led to the skewness of the distribution of IOP in this study compared with that in the general population. Furthermore, the IOP values in this study were obtained using a non-contact tonometer, rather than the more accurate Goldmann applanation tonometer, which is less likely to be affected by central corneal thickness [36].

Previous reports on the mechanism of the BP-IOP association [37, 38] have suggested that high BP, especially elevated SBP, might elevate IOP by increasing ultrafiltration of the aqueous humor through the elevation of ciliary artery pressure. Elevated SBP might have a more important role than elevated DBP in this process, because SBP forms a pressure peak. Results from our longitudinal study also showed that there was a significantly stronger positive association of changes in IOP with SBP than DBP in both sexes, whereas both the positive SBP-IOP and the positive DBP-IOP associations reached statistical significance in the cross-sectional study. The strong positive correlation between SBP and IOP could therefore be responsible for the apparent positive relationship between DBP and IOP. Studies of the BMI-IOP association have also indicated that this association might be caused by a reduction in aqueous-humor outflow caused by elevated intraorbital pressure associated with excessive intraorbital fatty tissue, or by an increase in the outflow resistance of the episcleral vein due to an increase in blood viscosity associated with weight gain [8, 15, 39].

According to the nationwide glaucoma survey in Japan [28] and the US Collaborative Normal-Tension Glaucoma Study [29, 30], it was clarified that the prevalence of visual-field abnormalities gradually increased at over 15 mmHg of IOP and that the progression of visual-field defects was significantly reduced among the NTG group, which showed a 30% decrease in IOP compared with the untreated control group. Therefore, management of BP and BMI in addition to prohibition of smoking might be especially important to Japanese patients with OAG or ocular hypertension as they have a higher incidence of NTG than Europeans and Americans.

Acknowledgments. This study was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 22790570).

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