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Abstract

Background

Varenicline has been reported to achieve high rates of smoking cessation. It remains undetermined whether varenicline therapy improves vascular function in smokers.

Methods

Consecutive Seventy-two smokers (age 57±12 years) who succeeded in complete smoking cessation and 46 normal healthy volunteers (age 24±3 years) with no cardiovascular risk factors were enrolled into this study. Vascular function and structure were assessed by flow-mediated dilation (FMD), nitroglycerin-induced vasodilation, and brachial artery intima-media thickness (baIMT) at baseline and 20 weeks after the initiation of varenicline therapy in smokers. FMD and baIMT were measured simultaneously using a semi-automatic vessel wall-tracking software program. 75 μg dose of a nitroglycerin tablet were sublingually administered for the nitroglycerin-induced vasodilation measurement.

Results

Exhaled-carbon monoxide concentration decreased significantly (20.0±11.1 ppm at baseline vs 1.9 ±1.5 ppm after 20 weeks, $p<0.001$). FMD was significantly improved after 20 weeks (4.09%±1.83% at baseline vs 4.77%±2.33% after 20 weeks, $p=0.010$), whereas nitroglycerin-induced vasodilation and baIMT were not significantly changed.

Conclusions

Smoking cessation with varenicline therapy significantly increased FMD without significant

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changes of nitroglycerin-induced vasodilation or baIMT from baseline to 20 weeks. It appears to improve vascular function in smokers, which depends on endothelial function rather than on vascular smooth muscle function or changes in vascular structure.

Key Words: Smoking cessation; Endothelial function; Vascular function; Atherosclerosis; Varenicline

Introduction

Smoking annually accounts for about 1.2 million deaths worldwide. Smoking causes ischemic heart disease as well as impairment of endothelial function in the general circulation, including the coronary circulation. Ischemic heart disease accounts for about 40% of all smoking-related deaths[1]. Therefore, smoking cessation remains the most important intervention in preventive and preemptive medicine.

Varenicline, which is a partial agonist and antagonist of the α4β2 nicotinic acetylcholine receptor, has been reported to be safe and to achieve high rates of smoking cessation[2]. Although 1 meta-analysis reported that the use of varenicline in smoking cessation significantly increases the risk of cardiovascular disease (CVD)[3], another meta-analysis did not find such an increase of risk[4]. It remains controversial whether varenicline therapy increases the risk of cardiovascular events[5].

Smoking cessation is often associated with an increase in body weight and body mass index (BMI)[6]. Body weight gain per se increases the risk for CVD; thus, an increase in body weight following smoking cessation may consequently lead to vascular dysfunction and CVD[7].

Flow-mediated dilation (FMD), an index of vascular endothelium-dependent vasodilation[7,8], has been shown to be a useful parameter in predicting cardiovascular events[10-12]. Nitroglycerin-induced vasodilation, a parameter of vascular endothelium-independent vasodilation, is impaired in subjects with cardiovascular risk factors and coronary heart disease[13] and is thought to be associated with alterations in smooth muscle cells as a result of atherosclerosis. Brachial artery intima-media thickness (baIMT), a morphologic parameter, has also been associated with risk factors[14,15] and coronary endothelial functionality[16] in subjects with coronary artery disease. Therefore, FMD, nitroglycerin-induced vasodilation, and baIMT have been used as measures to assess vascular disorders associated with cardiovascular risks including smoking.

We sought to determine whether smoking cessation using varenicline therapy improves FMD, nitroglycerin-induced vasodilation, and baIMT as surrogate parameters of cardiovascular events.

Methods

Study population

We enrolled consecutive 91 subjects who visited the smoking cessation outpatient department at Osaka City University Hospital from April 2010 to November 2013. 13 subjects who received smoking cessation therapy with other pharmacotherapies and 6 subjects who failed to stop smoking with varenicline were excluded. 72 subjects who received smoking cessation therapy with varenicline, and completed smoking cessation and 46 normal healthy volunteers with no cardiovascular risk factors including smoking were enrolled. All 72 subjects fulfilled the following criteria; 1) Brinkman index (number of cigarettes per day×years of smoking) ≧200, 2) Tobacco Dependence Screener score ≧5[17], and 3) motivation to quit smoking immediately, 4) provision of written agreement to undergo smoking cessation therapy. The study was approved by the Ethics Committee of Osaka City University and

written informed consent was obtained from all subjects.

Baseline and follow-up clinical investigations

The medical records of each of the 72 subjects were comprehensively reviewed to obtain clinical data at baseline prior to and 20 weeks after the initiation of varenicline therapy. The definitions of CVD, peripheral artery disease, and carotid artery disease were as per standard clinical diagnoses. Cardiovascular risk factors were defined as follows: hypertension was considered as systolic blood pressure ≧140 mm Hg and/or diastolic blood pressure ≧90 mm Hg based on the average of 2 or more readings taken on each of 2 or more different days or as the current use of antihypertensive drugs[18]. Subjects with plasma low-density lipoprotein cholesterol levels >140 mg/dL or those receiving cholesterol-lowering therapy were defined as hypercholesterolemic subjects[19]. Subjects were regarded as diabetic if they were receiving treatment with insulin or oral hypoglycemic agents or if their hemoglobin A1c (HbA1c) level was more than 6.5%[20]. Personal and family histories of CVD were obtained.

Ultrasound system

The ultrasound system was described in detail in our previous study[21]. Briefly, the ultrasound system with a semi-automatic vessel wall-tracking software program (UNEXEF; Unex Co. Ltd., Nagoya, Japan) provided 1 longitudinal, 2 short-axis and 1 processed A-mode line images of the brachial artery using a 10-MHz newly developed H type probe with a stereotactic probe holder, which was used for positioning the transducer at an optimal position on the brachial artery proximal to the bifurcation of the radial and ulnar arteries. Two short-axis images with an automated positioning software program enabled to keep the transducer at a constant position.

The echo signals reflected by the interfaces between the endothelium and blood on 1 side and between the blood and endothelium on the other side could be identified for the vessel lumen on the processed A-mode line, and their displacement could be monitored. After selection of the desired interfaces on the display, the exact position of each interface was determined using the peak point of the A mode and was tracked continuously. The electrocardiogram was used for detecting each R wave, allowing recording of the vessel diameter to be synchronized with end diastole. The inner vessel diameter at the end diastolic period was continuously measured for each pulse automatically. The measurement result was shown on the screen. All images during measurement were stored on the hard disk for off-line analysis.

Vascular tests

All subjects were instructed to fast for at least 12 hours, to stop heavy exercise for at least 24 hours, to abstain from smoking and consumption of alcohol, caffeine, and antioxidant vitamins for at least 6 hours, and to sleep soundly for at least 6 hours before testing. If the subjects were premenopausal women, the tests were performed at the menstrual period. All drugs were withdrawn at least 12 hours before testing. After recording of height, weight, and abdominal circumference, all subjects were asked to rest in a sitting position in a quiet temperature-controlled room (22℃ to 25℃) for 15 minutes. Then, after the subjects had rested again for at least 15 minutes in a supine position in the same room, ultrasound assessment of the brachial artery was performed between 7:00 AM and 11:59 AM, according to the guidelines[22] for ultrasound assessment of the FMD of the brachial artery. Suprasystolic compression (at least 50 mm Hg above systolic blood pressure) was performed at the forearm for 5 minutes. Longitudinal images of the brachial artery were continuously recorded from 0 seconds after cuff inflation to 5 minutes after cuff release and were stored on the hard disk for off-line

assessment. The lumen diameter of the brachial artery both at the baseline and at maximum dilation and baIMT at baseline were automatically measured simultaneously using the software program. The FMD measurement was used for assessment of endothelium-dependent vasodilation.

After at least 15 minutes of FMD measurement, another image was acquired to document the recovery of baseline conditions. When baseline rest images were procured, 75 μg of nitroglycerin were administered sublingually. Subsequently, images of the brachial artery were recorded continuously for at least 8 minutes until the dilation reached a plateau. Subjects' mouths were carefully checked to confirm that nitroglycerin had been dissolved and absorbed 1 minute after its administration. Nitroglycerin-induced vasodilation was automatically calculated as a percent change in peak vessel diameter from the baseline value. Nitroglycerin-induced vasodilation was used for assessment of endothelium-independent vasodilation.

The measurements of FMD, baIMT at baseline, and nitroglycerin-induced vasodilation were performed by an experienced examiner who was blinded to the status and/or diagnoses of subjects.

Protocol

All 72 subjects completed questionnaires and interviews. Measurements of anthropometric data, the vascular tests as described above, and venous blood collection after overnight fasting were performed at baseline and 20 weeks after the initiation of varenicline therapy. The concentrations of fasting plasma glucose and immunoreactive insulin (IRI), HbA1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglycerides were measured before initiation and after 20 weeks. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as an index of insulin resistance using the following formula: HOMA-IR= fasting IRI×fasting plasma glucose/405.

Varenicline therapy

Varenicline was initiated after initial vascular tests and venous blood collection in all 72 enrolled subjects. The starting dose was 0.5 mg once daily. This was titrated up to 1.0 mg twice daily as follows: 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, then 1.0 mg twice daily for 11 weeks, in accordance with the Japanese manual of anti-smoking therapy. All subjects visited the smoking cessation outpatient department at our institute 2, 4, 8, and 12 weeks after the initiation of varenicline. Questionnaires regarding smoking status and adverse events were completed and exhaled-carbon monoxide concentration and body weight were assessed at each visit.

Statistical analysis

All values are expressed as mean±standard deviation (SD) (range) or as frequencies (percentage) or as median (interquartile range). The Wilcoxon signed-rank test was used to compare clinical variables at baseline and 20 weeks after the initiation of varenicline therapy. The Mann-Whitney test was used to compare variables between the normal healthy volunteers and the smoker subjects at baseline or at 20 weeks. Univariate and multivariate linear regression analyses were used to examine associations between changes in FMD from baseline to 20 weeks after varenicline therapy and clinical variables and between FMD level prior to varenicline therapy and clinical variables. Statistical significance was set at a value of $p<0.05$.

All calculations were performed using SPSS software (Version 20, SPSS, Inc., Chicago, Illinois).

Results

The 46 normal healthy volunteers were predominantly male clustered near (24.4±3.2) years of

Table 1. Normal healthy volunteer characteristics

	Baseline
n	46
Male (%)	41 (89.1)
Age (years)	24.4±3.2
Height (cm)	169.8±7.2
Weight (kg)	62.1±8.6
BMI (kg/m^2)	21.5±2.1
SBP (mm Hg)	108.4±9.1
DBP (mm Hg)	63.2±5.6

BMI, body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Data are shown as mean±SD.

Table 2. Patient characteristics

	Baseline	20 weeks	Change	p value (Baseline vs 20 weeks)
n	72			
Male (%)	52 (72.2)			
Age (years)	58 (50-66)			
Height (cm)	166.6 (159.7-172.6)			
Weight (kg)	66.0 (55.9-76.1)	67.0 (57.3-77.7)	1.7 (1.0-3.7)	<0.001
BMI (kg/m^2)	23.7 (21.3-26.0)	24.3 (21.7-26.9)	0.6 (0.4-1.4)	<0.001
HTN (%)	28 (38.9)			
HCL (%)	26 (36.1)			
DM (%)	26 (36.1)			
Brinkman index	780 (458-1185)			
TDS	8 (7-9)			
FTND	6 (4-8)			
CO (ppm)	18 (11-26)	2 (1-2)	−16 (−24-9)	<0.001
SBP (mm Hg)	116 (107-129)	120 (109-128)	3 (−3-11)	0.020
DBP (mm Hg)	77 (68-83)	76 (72-85)	2 (−1-6)	0.004
LDL-C (mg/dL)	116 (98-143)	116 (96-142)	1 (−14-17)	0.466
HDL-C (mg/dL)	46 (40-58)	50 (43-57)	2 (−1-7)	0.005
TG (mg/dL)	124 (77-208)	134 (79-196)	1 (−44-44)	0.492
FPG (mg/dL)	96 (88-114)	102 (94-121)	6 (−1-16)	<0.001
HbA1c (%)	5.9 (5.4-6.9)	5.8 (5.5-7.0)	0.0 (−0.2-0.2)	0.532
IRI (μU/mL)	5.1 (3.5-7.4)	6.6 (4.8-10.6)	1.3 (−0.2-3.3)	<0.001
HOMA-IR	1.2 (0.9-2.0)	1.7 (1.2-3.0)	0.4 (−0.3-0.9)	<0.001

BMI, body mass index; HTN, hypertension; HCL, hypercholesterolemia; DM, diabetes mellitus; TDS, tobacco dependence screener; FTND, Fagerstrome test for nicotine dependence; CO, carbon monoxide concentration of the expired air; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, serum triglycerides; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IRI, immunoreactive insulin; and HOMA-IR, homeostasis model assessment of insulin resistance. Data are shown as median (interquartile range). (Wilcoxon signed-rank test)

age and the 72 subjects were predominantly male clustered near 57 years of age. Characteristics of the normal healthy volunteers were shown in Table 1 and clinical characteristics of the subjects at baseline and 20 weeks after the initiation of varenicline therapy are shown in Table 2. Brinkman index, exhaled-carbon monoxide concentration, Tobacco Dependence Screener and Fagerstrom test for

Table 3. FMD, NTG-induced Vasodilation and BaIMT Data

	Volunteers	Patients		p value (Volunteer vs Baseline)	p value (Volunteer vs 20 weeks)
		Baseline	20 weeks		
FMD (%)	5.5 (3.5-8.2)	4.0 (2.8-5.3)	4.7 (3.0-6.1)	0.002	0.058
NTG-induced vasodilation (%)	20.2 (17.1-27.5)	14.5 (9.8-20.0)	15.4 (10.5-18.9)	<0.001	<0.001
BaIMT (mm)	0.23 (0.20-0.25)	0.29 (0.25-0.34)	0.30 (0.27-0.37)	<0.001	<0.001

FMD, flow-mediated dilation; NTG, nitroglycerin; and BaIMT, brachial artery intima-media thickness. Data are shown as median (interquartile range). (Mann-Whitney test)

nicotine dependence[23,24] before varenicline therapy were 831.7±471.3, 20.0±11.1 ppm, 7.7±1.5, and 5.7±2.5, respectively. The proportion of hypertension, hypercholesterolemia and diabetes mellitus were 38.9%, 36.1%, and 36.1%. There were significant increases in body weight ($p<0.001$) and BMI ($p<0.001$) from baseline to 20 weeks post-initiation. There was a significant decrease in exhaled-carbon monoxide concentration from baseline to 20 weeks ($p<0.001$). There were significant changes in systolic blood pressure ($p=0.020$) and diastolic blood pressure ($p=0.004$) during the study. There were significant increases in HDL-C ($p=0.005$), IRI ($p<0.001$), and HOMA-IR ($p<0.001$). No significant increase in HbA1c was noted from baseline to 20 weeks.

Table 3 shows FMD, nitroglycerin-induced vasodilation and baIMT in the 46 normal healthy volunteers and those at baseline and 20 weeks after the initiation of varenicline therapy in the 72 subjects. FMD and nitroglycerin-induced vasodilation were significantly lower in the subjects than those in the normal healthy volunteers and baIMT was significantly higher in the subjects than that in the normal healthy volunteers. FMD increased from baseline to 20 weeks and there were no significant difference between FMD in the normal healthy volunteers and that in the subjects at the 20-week time point.

Univariate regression shows that change in FMD from baseline to 20 weeks was significantly associated with FMD level prior to varenicline therapy ($t=-2.988$, $p=0.004$), change in BMI ($t=-2.011$, $p=0.048$), and change in systolic blood pressure ($t=2.354$, $p=0.021$). Using age, sex, Brinkman index, and factors that showed $p<0.10$ in univariate regression analyses, multivariate regression analysis were performed and showed that changes in FMD from baseline to 20 weeks was independently associated with FMD level prior to varenicline therapy ($t=-2.668$, $p=0.010$) (Table 4).

FMD level prior to varenicline therapy was negatively correlated with changes in FMD level from baseline to 20 weeks ($r=-0.336$, $p=0.004$).

Univariate regression shows that FMD level prior to varenicline therapy was significantly associated with hypertension ($t=-1.374$, $p=0.001$), and systolic blood pressure ($t=-0.026$, $p=0.046$). Using age, sex, Brinkman index, and factors that showed $p<0.10$ in univariate regression analyses, multivariate regression analysis were performed and showed that FMD level prior to varenicline therapy was independently associated with hypertension ($t=-1.642$, $p<0.001$) (Table 5).

Figure 1 displays changes of FMD in individual subjects. There was a significant mean increase in FMD from baseline to 20 weeks ($p=0.017$).

Figure 2 demonstrates changes of nitroglycerin-induced vasodilation over the treatment period for individual subjects. No significant overall difference was observed. ($p=0.699$).

Figure 3 depicts changes in baIMT over the study term for individual subjects. Overall baIMT remained constant between baseline and the 20-week time point ($p=0.137$).

Table 4. Prediction of change in flow-mediated dilation by regression analysis

Variable	Univariate analysis		Multivariate analysis	
	t	p value	t	p value
Sex	−0.844	0.402	−0.136	0.892
Age	−1.728	0.088	−1.045	0.300
BMI	−1.860	0.067	−1.917	0.060
Brinkman index	−0.757	0.452	0.310	0.758
HTN	0.405	0.527		
HCL	2.488	0.119		
DM	1.803	0.184		
TDS	0.040	0.969		
FTND	0.247	0.806		
CO	−1.267	0.209		
SBP	−0.853	0.397		
DBP	−0.422	0.674		
LDL-C	−0.058	0.954		
HDL-C	0.889	0.377		
TG	−0.969	0.336		
FPG	−0.633	0.529		
HbA1c	0.023	0.981		
IRI	−0.059	0.953		
HOMA-IR	−0.320	0.750		
FMD	−2.988	0.004	−2.668	0.010
NTG-induced vasodilation	0.660	0.512		
BaIMT	−0.765	0.447		
Brachial arterial diameter	−1.086	0.281		
Change in BMI	−2.011	0.048	−0.764	0.448
Change in SBP	2.354	0.021	1.927	0.058
Change in DBP	1.790	0.078		
Change in LDL	0.000	1.000		
Change in HDL	0.116	0.908		
Change in TG	−0.892	0.376		
Change in FPG	0.761	0.449		
Change in HbA1c	−1.085	0.282		
Change in IRI	−0.209	0.835		
Change in HOMA-IR	0.247	0.806		
Change in NTG-induced vasodilation	1.884	0.064		
Change in baIMT	−0.962	0.340		

BMI, body mass index; HTN, hypertension; HCL, hypercholesterolemia; DM, diabetes mellitus; TDS, tobacco dependence screener; FTND, Fagerstrome test for nicotine dependence; CO, carbon monoxide concentration of the expired air; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, serum triglycerides; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment of insulin resistance; FMD, flow-mediated dilation; NTG, nitroglycerin; and BaIMT, brachial artery intima-media thickness.

Discussion

Our data demonstrate that smoking cessation using varenicline therapy significantly improves FMD regardless of body weight gain, but does not improve nitroglycerin-induced vasodilation or baIMT from baseline to 20 weeks after the initiation of varenicline.

Smoking decreases FMD, a parameter of endothelial function, as well as promoting atherogenesis,

Table 5. Prediction of baseline flow-mediated dilation by regression analysis

Variable	Univariate analysis		Multivariate analysis	
	t	p value	t	p value
Sex	0.093	0.926	0.030	0.949
Age	0.779	0.438	0.027	0.156
BMI	−0.994	0.324		
Brinkman index	0.607	0.546	0.000	0.489
HTN	−1.374	0.001	−1.642	<0.001
HCL	−0.373	0.412		
DM	−0.648	0.151		
TDS	−0.011	0.940		
FTND	0.028	0.748		
CO	0.008	0.697		
SBP	−0.026	0.046		
DBP	0.000	0.985		
LDL-C	−0.003	0.631		
HDL-C	0.017	0.333		
TG	0.000	0.870		
FPG	−0.013	0.157		
HbA1c	−0.260	0.201		
IRI	−0.084	0.188		
HOMA-IR	−0.300	0.129		

BMI, body mass index; HTN, hypertension; HCL, hypercholesterolemia; DM, diabetes mellitus; TDS, tobacco dependence screener; FTND, Fagerstrome test for nicotine dependence; CO, carbon monoxide concentration of the expired air; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, serum triglycerides; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IRI, immunoreactive insulin; and HOMA-IR, homeostasis model assessment of insulin resistance.

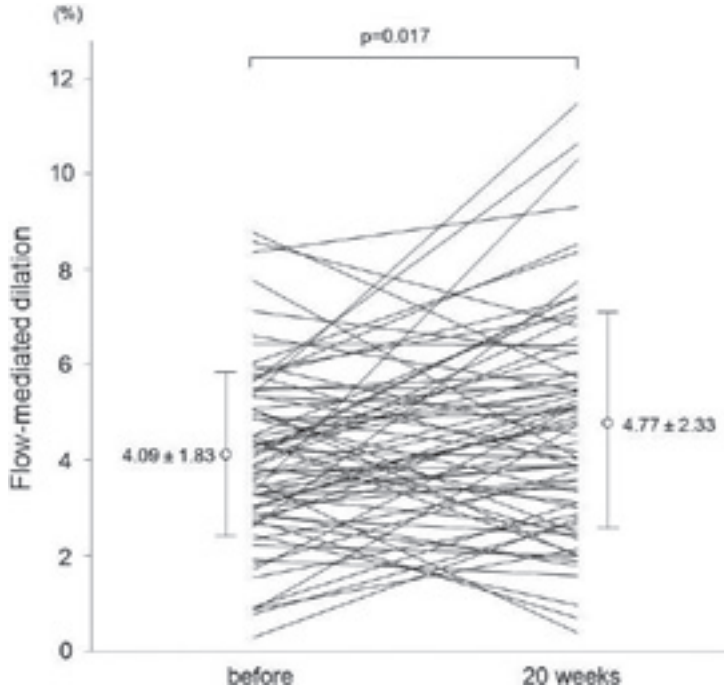

Figure 1. Flow-mediated dilation (FMD) was measured at baseline and at 20 weeks after therapy commenced. Individual changes are plotted for each subject. The overall level of FMD increased over the course of the study (p=0.017).

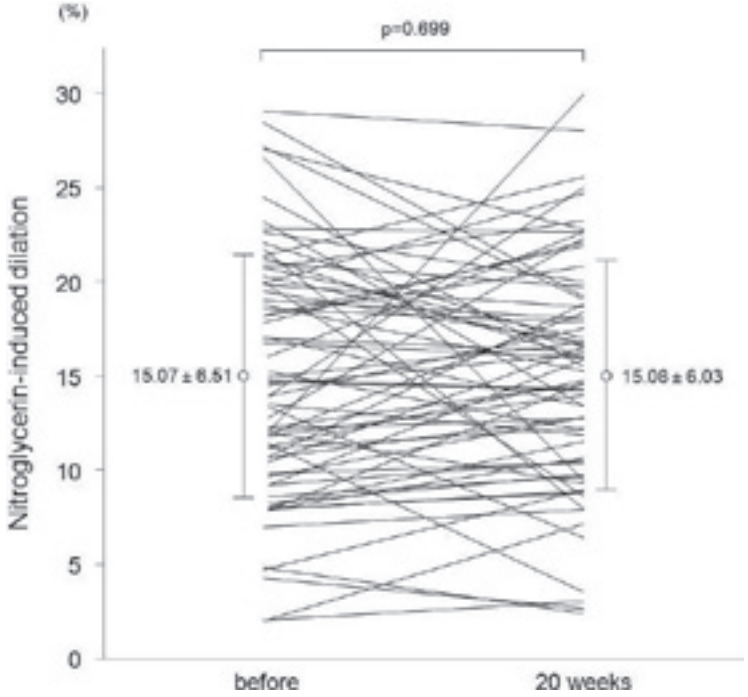

Figure 2. Nitroglycerin-induced vasodilation was measured at baseline and at 20 weeks after therapy commenced. Individual changes are plotted for each subject. No significant overall change was observed (p=0.699).

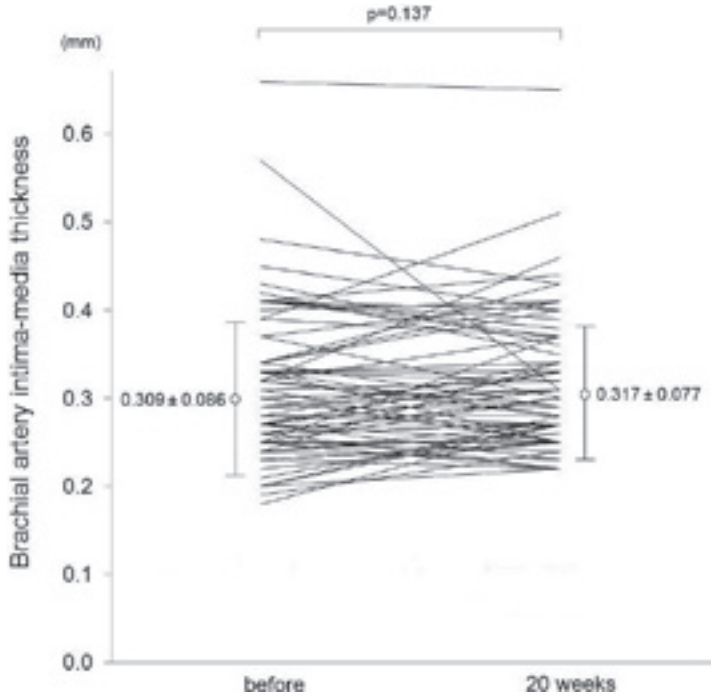

Figure 3. Brachial artery intima-media thickness (baIMT) was measured at baseline and at 20 weeks after therapy commenced. Individual changes are plotted for each subject. No significant overall change was observed (p=0.137).

and increasing the risk of CVD. Several mechanisms, including vasomotor and neurohormonal dysfunction and increased oxidative stress, have been proposed, although the exact mechanisms are not fully clarified[25]. Smoking cessation has been reported to increase FMD and decrease the risk of

CVD. Both endothelium-independent vasodilation using a direct smooth muscle relaxant such as nitroglycerin and baIMT, a morphologic parameter, should be assessed simultaneously. This allows the origin of FMD decrease to be assigned specifically to endothelial dysfunction, vascular smooth muscle dysfunction, or changes in vascular structure[23]. We used an ultrasound system with a semi-automatic vessel wall-tracking software program that enabled us to evaluate FMD, nitroglycerin-induced vasodilation, and baIMT simultaneously. The results imply that the increase in FMD may attribute to improvement of endothelial function, not changes in vascular smooth muscle function or vascular structure in this 20-week period.

Recently, nitroglycerin-induced vasodilation has been shown to have a significant relationship with FMD and correlation with Framingham risk score and to be a marker of atherosclerosis grade[27]. However, the impact of smoking cessation using varenicline on this parameter has not been fully examined. BaIMT has been reported to be associated with risk factors and to be correlated with carotid intima-media thickness[26]. While several studies have examined the influence of smoking cessation on carotid intima-media thickness during 2-6 year follow-up periods[28-30], the effect of smoking cessation using varenicline therapy on baIMT has not been previously reported. Endothelial dysfunction, the first step in atherosclerosis, leads to compensatory responses that firstly alter the properties of the endothelium, secondly stimulates proliferation of smooth-muscle cells and causes smooth-muscle dysfunction, and finally thickens the artery wall, which compensates by gradual lumen dilatation. This gradual atherogenetic process may suggest that nitroglycerin-induced vasodilation and baIMT have not been changed in this 20-week period. Longer-term follow-up periods would be necessary to determine the influence of smoking cessation using varenicline on nitroglycerin-induced vasodilation and baIMT.

The endothelium is a monolayer of cells that covers the vascular lumen throughout the body. It is directly exposed to chemical substances absorbed during smoking and easier to be impaired than the vascular smooth muscles or other vascular structures. Therefore, it may be more rapid to restore its function than the other vascular structures once chemical substances are eliminated by smoking cessation.

Patients who have risk factors such as hypertension, diabetes mellitus, dyslipidemia are known to have impaired endothelial function and reduced FMD. Multivariate regression analysis showed that changes in FMD from baseline to 20 weeks independently correlated with FMD levels prior to varenicline therapy. Baseline markers of smoking intensity as well as baseline CVD risk factors did not predict changes in FMD over the course of the study (Table 4). Our data indicate that smoking cessation using varenicline therapy significantly improves FMD in smokers who have both reduced baseline FMD and increases in BMI, diastolic blood pressure, insulin resistance indices, including HOMA-IR, after 20 weeks of varenicline therapy. This would suggest that the effect of smoking cessation using varenicline therapy may more than offset the effects of increases in BMI, diastolic blood pressure, insulin resistance indices, and reduce risk of cardiovascular disease through FMD improvements.

Changes in FMD from baseline to 20 weeks were negatively correlated with FMD levels prior to varenicline therapy. FMD level prior to varenicline therapy were negatively correlated with hypertension. This implies that smokers with low FMD which can be attributed to hypertension may yet undergo vascular functional recovery and should therefore strive to quit smoking despite low vascular function.

Study limitations

We enrolled consecutive subjects who visited the smoking cessation outpatient department, received smoking cessation therapy using varenicline, and completed smoking cessation. There were no control subjects who stopped smoking using other smoking cessation pharmacotherapies or without drug therapy or failed to stop smoking using varenicline. There were also no age-matched healthy nonsmokers. In addition, there were no previous reports that examined changes in FMD in subjects with self-motivating smoking cessation and no drug therapy. Pharmacotherapies other than smoking cessation therapy that the enrolled subjects received were not changed from baseline to 20 weeks and hence might not have been significantly related with changes in FMD over the course of the study.

Measurement of FMD at baseline and 20 weeks after the initiation of varenicline indicated that FMD increased approximately 0.7%. Extended follow-up would be necessary to evaluate the relationship between FMD improvement in the first 20 weeks after smoking cessation using varenicline therapy and future cardiovascular events.

Conclusions

Smoking cessation using varenicline therapy improves FMD without changes in nitroglycerin-induced vasodilation and baIMT, regardless of significant increases in BMI, diastolic blood pressure and insulin resistance indices. Smoking cessation using varenicline therapy appears to improve vascular function in a manner dependent on endothelial function, but independent of vascular smooth muscle function and changes in vascular structure.

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