Association between fibrinogen and carotid intima-media thickness by smoking status

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ABSTRACT

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Fibrinogen may be associated with carotid intima-media thickness (CIMT). But some studies did not show the significant association between fibrinogen and CIMT. Smoking is one of the risk factors for atherosclerosis and also related with increasing the level of fibrinogen. Thus, our hypothesis is that the association between fibrinogen and CIMT can be modified by smoking status.

Fibrinogen was measured in 277 men who were aged 40-87 years, without history of myocardial infarction and cerebrovascular diseases. Maximum and three point mean values (defined as IMTmax and IMTtpm, respectively) of CIMT measured by ultrasonography were used as continuous variables. Plaque was defined when IMTmax > 1.0 mm or an area of focal wall thickening was 100% greater than the neighboring sites. Independent association between fibrinogen and CIMT by smoking status was assessed by

linear regression analysis and logistic regression analysis.

Fibrinogen was positively associated with CIMT even after adjustment for potential confounders such as age, body mass index, systolic blood pressure, fasting glucose, and ratio of total cholesterol to high-density lipoprotein cholesterol in current smokers (Standardized ß for IMTmax = 0.25, $p = 0.021$; Standardized ß for IMTtpm = 0.21, $p = 0.038$). But there is no significant association between fibrinogen and CIMT in former (Standardized ß for IMTmax = -0.07, $p = 0.421$; Standardized ß for IMTtpm = -0.04, $p = 0.605$) and never smokers (Standardized ß for IMTmax = -0.01, $p = 0.955$; Standardized ß for IMTtpm = -0.04, $p = 0.692$). Odds ratio for having plaque that increased per 1 standard deviation of fibrinogen was 2.04 (95% CI, 1.08 - 3.85) in current smokers when adjusted for potential confounders, but not significant in former smokers (OR = 0.68, 95% CI = 0.42-1.09), or never smokers (OR = 0.98, 95% CI = 0.55-1.77).

Our findings suggest that cigarette smoking may role as an effect modifier to the association between fibrinogen and CIMT.

Keywords: Fibrinogen, smoking, atherosclerosis, carotid intima-media thickness

I. INTRODUCTION

Fibrinogen

Fibrinogen is a 340kDa soluble plasma glycoprotein and composed of six chains (two Aα-, two Bß-, and two γ-chains) (Sorensen et al., 2012). Fibrinogen is synthesized in liver and the concentration of fibrinogen in plasma is 200 to 400 mg/dl (Kampoli et al., 2012). Fibrinogen plays a major role in hemostasis and promotes platelet aggregation. It is also an acute phase protein that is increased by inflammatory reactions and an important determinant of blood viscosity (Sorensen et al., 2011, Danesh et al., 2005). Many epidemiological studies have been shown that fibrinogen increased the risk of cardiovascular diseases. A meta-analysis of 31 prospective studies, involving about 6,944 myocardial infarction or stroke events and 13,210 deaths, indicated the hazard ratio per 1 g/l increase in fibrinogen level for coronary heart disease was 2.42 (95% confidence interval [CI] 2.24-2.60), for stroke was 2.06 (95% CI 1.83-2.33) and for other vascular mortality was 2.76 (95%CI 2.28-3.35) (Danesh et al., 2005). These results are explained by several mechanisms such as enhancing lipid deposition, increasing smooth muscle cell proliferation, promoting inflammation and the formation of foam cells (de Moerloose et al., 2010).

Carotid intima-media thickness

The carotid arterial wall consists of the intima, the media, and the adventitia. Atherosclerosis starts with focal thickening of the intima. During progression of the atherosclerosis, arterial wall is changed by thickening of the intima and media. Thus intima-media thickness, defined as the thickness between the intimal-luminal and the medial-advential, is used as a non-invasive marker of early atherosclerosis (Devine et al., 2006) that is associated with prevalence of cardiovascular disease (Lorenz et al., 2007). A systematic review and meta-analysis from 37,197 participants showed the association between carotid intima-media thickness (CIMT) and the relative risk for myocardial infarction and stroke. From this study, the age- and sex- adjusted relative risk of myocardial infarction was 1.26 (95%CI 1.21-1.30) per 1 standard deviation CIMT difference and the age- and sex- adjusted relative risk of stroke was 1.32 (95% CI 1.27-1.38) (Lorenz et al., 2007).

Association between fibrinogen and atherosclerosis

Several studies have suggested a positive association between fibrinogen and atherosclerosis. The case-control analysis of the ARIC study showed a significant positive association between plasma fibrinogen level and atherosclerosis in the carotid arteries (Wu et al., 1992). Similarly, the CARDIA study showed the results that elevated levels of fibrinogen in participants aged 25-37 were associated with increased mean of CIMT after

13 years of follow-up (Green et al., 2009). However some studies failed to show the significant relationship between fibrinogen and CIMT in different study population. One study which was composed by 64 normotensive volunteers and 122 hypertensive patients among Korean did not show the significant positive correlation between fibrinogen and CIMT (Choi et al., 2004). The other study consisted 100 atherosclerotic patients among Japanese also did not revealed the positive association between fibrinogen and CIMT (Hayashi, 2010).

Smoking as an effect modifier

Cigarette smoking is related with increasing the level of fibrinogen. The Framingham study showed that the values of fibrinogen were significantly increased in smokers than in non smokers (Kannel et al., 1987). Smoking is also an established risk factor for atherosclerosis (Erhardt, 2009). The explained mechanism for the association between smoking and atherosclerosis include endothelial dysfunction, vessel wall injury, oxidative stress, platelet activation and inflammation (Leone, 2007, Unverdorben et al., 2009). Most of these mechanisms are also related to the association between fibrinogen and cardiovascular disease (Borissoff et al., 2011). In this context, some studies have suggested that smoking may influence the association between fibrinogen and cardiovascular risk (Ernst, 1993, Woodward et al., 1998, Kannel, 2005, Tuut and Hense, 2001, Fowkes et al., 1996). The WHO

MONICA study suggested that the association between fibrinogen and cardiovascular risk factors included hypertension, dyslipidemia and diabetes mellitus was stronger in smokers than non-smokers (Tuut and Hense, 2001). However, to the best of our knowledge, the association between fibrinogen and CIMT according to smoking status has not been assessed.

II. OBJECTIVES

The purpose of this study was to assess the association between fibrinogen and CIMT as a marker of atherosclerosis by smoking status.

Specifically,

(1) To assess the linear association between fibrinogen and CIMT by smoking status

(2) To assess whether elevated levels of fibrinogen are associated with the risk of carotid atherosclerosis by smoking status

III. PARTICIPANTS AND METHODS

1. Participants

The participants in this cross-sectional study were from a community-based prospective cohort in Kangwha Island, South Korea. Total 1253 participants were recruited in 2010. Fibrinogen assay was assessed only in part, for 796 participants (311 men, 485 women) as an ancillary study. There are very few current smokers in women for the participants (2.08%), thus we limited to men for this investigation. Among 311 men who were assessed the fibrinogen, we excluded 34 participants due to following reasons: absence of CIMT measurement (n=6), history of myocardial infarction or stroke (n=28). Finally, 277 men were eligible for this study. The characteristics, such as age, blood pressure, body mass index, cholesterol and fasting plasma glucose, were similar to those of the larger parent study.

Two or 3 days before the examination, participants were received the notice by phone call to remind them to bring identification and not to eat or drink anything except water from 21:00 the day before the examination to the end of the examination. Hypertensive patients were informed that they were allowed to take hypertension medicine.

The protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine.

2. Data collection

Anthropometrics

Standing height was measured to the nearest 0.1 cm using a stadiometer (SECA-225, Germany). Participants stood on the floor with the heels of both feet together and toes pointed slightly outward at approximately a 60º angle. The position of the heels, buttocks, shoulder blades, and back of the head was checked for contact with the vertical backboard. Once correctly positioned, participants took a deep breath and the headboard was lowered and positioned firmly on top of the head with sufficient pressure to compress the hair and height was recorded by the examiners. Body weight was measured to the nearest 0.1 kg on a digital scale (SECA-225, Germany) with participants wearing underwear and examination gowns. Participants stood still in the center of the scale platform with their hands at their sides and looked straight ahead. Weight was recorded by the examiners when the digital readout was stable. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Blood pressure

Blood pressure was measured by an automatic sphygmomanometer (Dinamap 1846 SX/P; GE Healthcare, USA). Before blood pressure measurements were acquired, participants were asked to sit and rest in the examination room for at least 5 min. After rest, an appropriate-sized cuff was

applied snugly around the upper arm at the heart level. Appropriate cuff size was chosen for each subject according to mid-arm circumference. Two readings with at least 5 min intervals were obtained and averaged to determine systolic and diastolic blood pressure. If the 2 readings differed by more than 10 mmHg, additional readings were obtained and the last 2 readings were averaged.

Questionnaires

The participants' age, sex, medical history and smoking status were interviewed using a standardized questionnaire by trained interviewers. Personal medical history of hypertension, diabetes mellitus, angina, myocardial infarction, stroke, and cancer were obtained. Current smokers were defined as those who had smoked more than 100 cigarettes in a life time and reported presently smoking. Former smokers were those who had smoked greater than 100 cigarettes in a life but not smoke recently and who had smoked fewer than 100 cigarettes were defined as never smoker.

Laboratory test

Blood samples were taken after at least an 8 hour fast. Glucose, alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride (TG) were measured by enzymatic methods (ADVIA 1800; Siemens Corp, USA). Low-density

lipoprotein (LDL) cholesterol was calculated using Friedewald's formula (Friedewald et al., 1972). C-reactive protein was measured by turbidimetric immunoassay assay (ADVIA 1800; DenKa Seiken, Japan). White blood cell (WBC) was measured by impedance method using automatic analyzers (ADIVA120; Siemens Corp, USA) and d-dimer was measured by enzyme linked fluorescent assay (Mini vidas; BioMerieux SA, France).

Fibrinogen was measured by turbidimetric immunoassay (Sta-R; DIAGNOSTICA STAGO S.A.S, France). Both intra-assay and inter-assay coefficients for fibrinogen were <5%.

Carotid intima-media thickness

Both common carotid arteries were measured with high-resolution B-mode ultrasonography (SSAD-3500SV; Aloka, Japan) using a 7.5 MHz linear array transducer. For the measurement, participants were lying in the supine position and with their head turned 45° contralateral to the scanning side. Images were taken in the 20 mm proximal to the origin of the bulb at the far wall of the both common carotid arteries (Yanase et al., 2006). CIMT was measured the vertical distance between the leading edge of the first and second echogenic lines of both common carotid arteries' far wall at the end-diastolic phase using appropriate software (IntimaScope; MediaCross, Japan). Three-point measurement refers to the mean value of 3-point CIMT, including both end points and the median point in the 20 mm region. Evaluation for

maximal value was obtained by the CIMT value at a maximal point of the region (Yanase et al., 2006).

For using outcome variables, the IMTtpm was the mean between average value of right and left side of the mean value of 3 point CIMT. The IMTmax was the highest value among both CIMT. Increased IMT was defined as upper 25% of IMTtpm and Plaque was defined as the IMTmax > 1.0 mm or an area of focal wall thickening was 100% greater than the CIMT of neighboring sites.

3. Statistical analysis

The mean and median values of collected variables were computed by smoking status. Differences of values between smoking statuses were assessed by analysis of variance for continuous variables, chi-square tests for dichotomous variables and Kruskal wallis test for skewed variables. Fisher's exact test was applied if the number of observations per cell was fewer than five. Linear regression analysis was performed to assess the linear relationship between fibrinogen and CIMT. We performed logistic regression analysis to assess the risk for carotid atherosclerosis as increase 1 standard deviation of fibrinogen. Additionally, the risk for carotid atherosclerosis was estimated by analyzing fibrinogen as tertile group within each category of smoking status. All regression analysis was performed additionally with adjustment for age, BMI, systolic blood pressure (SBP), fasting glucose and ratio of total cholesterol to HDL cholesterol. All statistical tests were performed with the SAS version 9.2 (SAS Inc., Cary, NC, USA) and all analysis were two-sided and p values < 0.05 were regarded as statistically significant.

IV. RESULTS

1. Characteristics of participants by smoking status.

The overall mean age was 60.4 ± 10.1 year and mean fibrinogen level was 2.9 ± 0.6 g/l.

Table 1 shows the characteristics of study participants according to smoking status. Former smokers were older than current or never smokers and fibrinogen level was highest in former smokers. In current smokers, the mean value for BMI was lowest and the mean value for AST was highest. There were no significantly differences for blood pressure, cholesterol, glucose and C-reactive protein between smoking statuses.

Table 1. Characteristics of participants.

	Never smokers (N=80)	Former smokers (N=122)	Current smokers (N=75)	p value
Age, year	59.5±10.4	63.4±9.7	56.6±9.0	<.0001
BMI, kg/m^2	24.6±3.0	24.8±3.0	23.6±3.1	0.016
SBP, mmHg	117.9±16.2	119.7±14.6	118.4±18.3	0.704
DBP, mmHg	73.1±9.6	73.8±9.5	75.6±10.8	0.276
Total cholesterol, mg/dL	189.2±24.6	189.3±33.5	185.5±34.4	0.673
HDL cholesterol, mg/dL	41.0±7.9	40.7±8.7	41.8±11.6	0.715
Triglycerides, mg/dL	125.5 (98.5-183)	137.5 (100-181)	146 (99-213)	0.560*
LDLcholesterol, mg/dL	118.9±24.0	118.2±28.6	109.5±33.3	0.076
AST, IU/L	24.0±6.5	25.1±7.4	33.3±40.0	0.012
ALT, IU/L	24.1±10.1	24.1±10.3	29.0±32.1	0.159
Fasting glucose, mg/dL	92.5 (86-106)	92 (88-103)	92 (85-99)	0.356*
C-reactive protein, mg/L	0.68 (0.38-1.32)	0.88 (0.50-1.74)	0.81 (0.58-1.69)	0.067*
WBC,Thous/uL	5.3±1.3	5.9±1.6	6.4±1.6	<.0001
Fibrinogen, g/L	2.72±0.5	2.94±0.7	2.88±0.6	0.044
D-dimer, μg/mL	0.27 (0.20-0.42)	0.31 (0.24-0.54)	0.3 (0.21-0.51)	0.227*
Hypertension	24 (30.0)	41 (33.6)	14 (18.7)	0.074†
Diabetes mellitus	8 (10.0)	13 (10.7)	4 (5.3)	0.421†
Dyslipidemia	0 (0.0)	6 (4.9)	2 (2.7)	0.111‡

Data are expressed mean ± SD, median (inter-quartile range) or number (%).

LDL cholesterol was assessed only in triglyceride < 400 mg/dl.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL Cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; WBC, white blood cell

* Kruskal-Wallis Test, † chi-square test, ‡ Fisher exact test

2. Carotid intima-media thickness of participants by smoking status

Table 2 shows the mean value for carotid intima-media thickness and the prevalence for increased IMT or plaque of participants according to smoking status. The IMTtpm and IMTmax were highest in former smokers, but the differences were not significant. Similarly, increased IMT and plaque were more prevalent among former smokers then current smokers or never smokers, but differences were not significant.

Table 2. Carotid intima-media thickness of participants.

	Never smokers (N=80)	Former smokers (N=122)	Current smokers (N=75)	p value
IMTtpm, mm	0.72±0.14	0.76±0.18	0.72±0.17	0.084
IMTmax, mm	0.97±0.30	1.04±0.46	0.98±0.32	0.36
Increased IMT	13 (16.3)	38 (31.2)	19 (25.3)	0.059†
Plaque	40 (50.0)	72 (59.0)	37 (49.3)	0.301†

Data are expressed mean ± SD, median (inter-quartile range) or number (%).

† Chi-square test

Because age is one of the strong determinants for both fibrinogen and CIMT (Krobot et al., 1992, Salonen and Salonen, 1990), we assessed the value for fibrinogen, IMTtpm and IMTmax after age adjustment. When age adjusted, values for fibrinogen level, IMTtpm and IMTmax were highest in current smokers, although the differences between smoking statuses were not statistically significant.

Table 3. Age adjusted value for fibrinogen and CIMT by smoking status

	Never smokers (N=80)	Former smokers (N=122)	Current smokers (N=75)	p value
Fibrinogen, g/L	2.73 (2.59-2.86)	2.91 (2.79-3.02)	2.93 (2.78-3.07)	0.046
IMTtpm, mm	0.73 (0.69-0.76)	0.74 (0.71-0.77)	0.75 (0.72-0.78)	0.305
IMTmax, mm	0.98 (0.90-1.06)	1.00 (0.94-1.07)	1.04 (0.95-1.12)	0.358

Data are expressed age adjusted mean (95% confidence limits).

3. The relationship between fibrinogen and CIMT by smoking status

We assessed the relationship between fibrinogen and CIMT by plotting the values of fibrinogen and IMTtpm according to smoking status.

Figure 1, 2 and 3 show the relationship between fibrinogen and IMTtpm in never smokers, former smokers and current smoker, respectively.

The horizontal axis represents fibrinogen and the vertical axis represents IMTtpm. We can see different results of the relationship between fibrinogen and IMTtpm in figure 1, 2 and 3. In current smokers, IMTtpm was the largest increased by rising fibrinogen, compared with never or former smokers

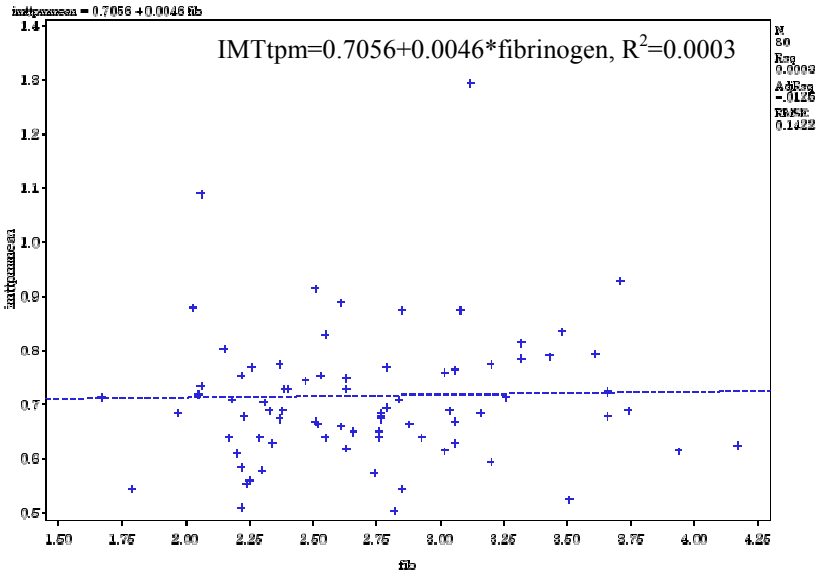


Figure 1. The relationship between fibrinogen and IMTtpm in never smokers.

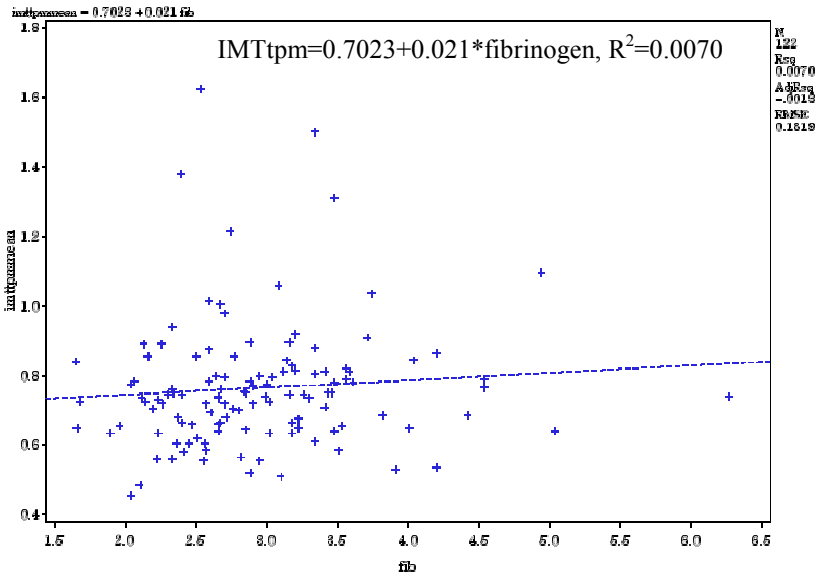


Figure 2. The relationship between fibrinogen and IMTtpm in former smokers.

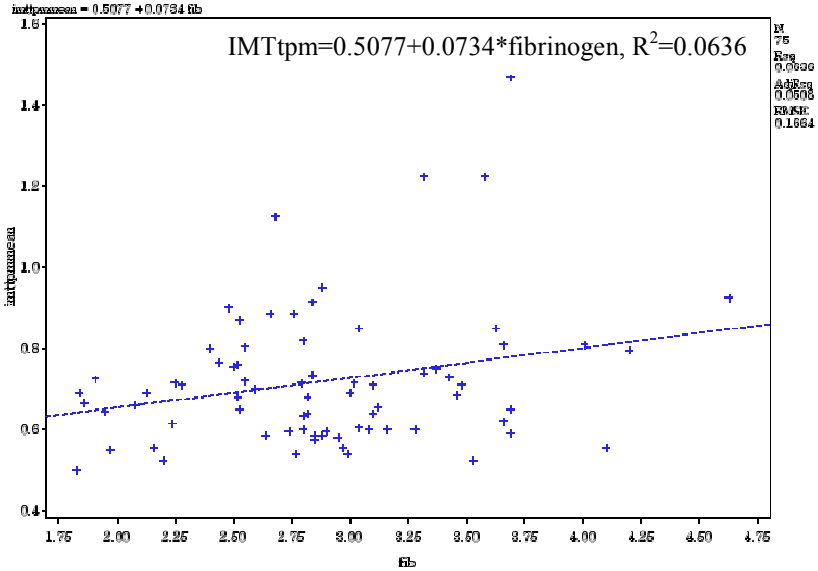


Figure 3. The relationship between fibrinogen and IMTtpm in current smokers.

We also plotted the values of fibrinogen and IMTmax by smoking status. Figure 4, 5 and 6 shows the relationship between fibrinogen and IMTmax in never smokers, former smokers and current smoker, respectively. The horizontal axis represents fibrinogen and the vertical axis represents IMTmax. Similarly to the relationship between fibrinogen and IMTtpm, we can see these different results of the relationship between fibrinogen and IMTmax by smoking status. IMTmax was increased by rising fibrinogen level in current smokers but this aspect was not observed in former and never smokers.

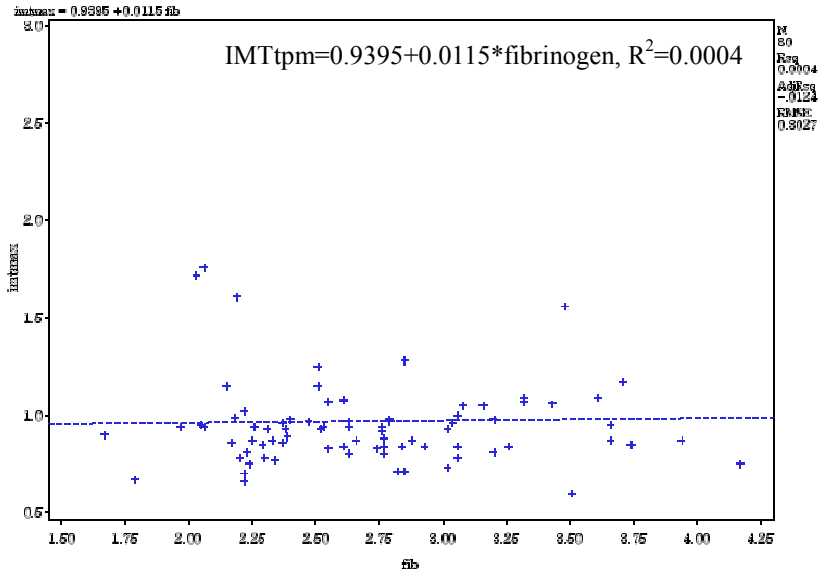


Figure 4. The relationship between fibrinogen and IMTmax in never smokers.

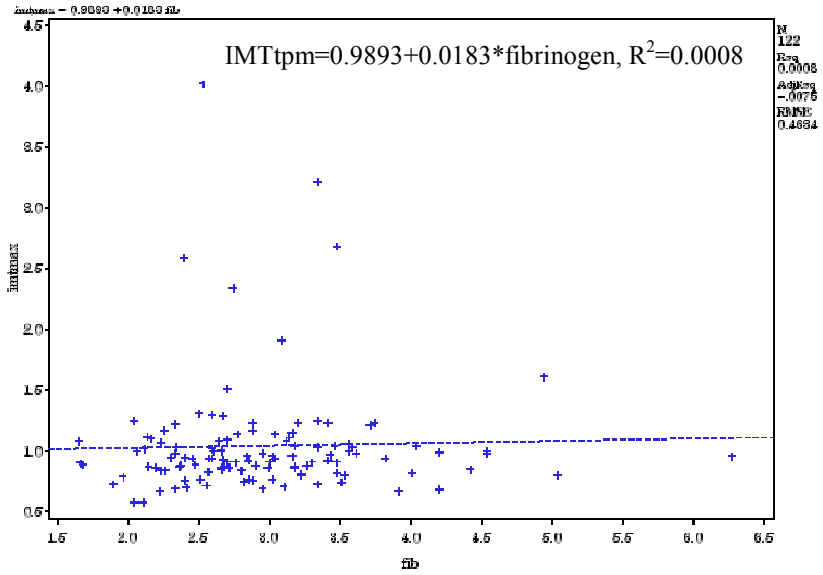


Figure 5. The relationship between fibrinogen and IMTmax in formersmokers.

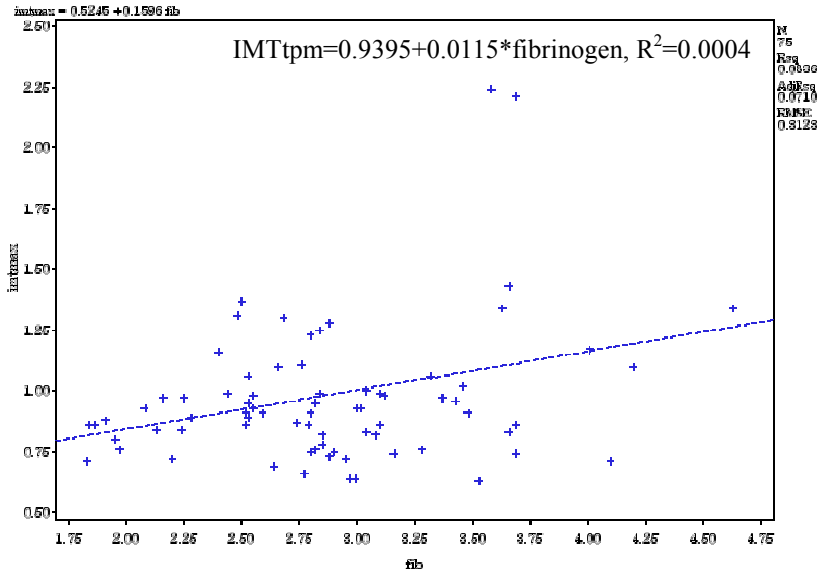


Figure 6. The relationship between fibrinogen and IMTmax in current smokers.

4. The linear association between fibrinogen and CIMT by smoking status

Table 4 shows the linear association between fibrinogen and CIMT by smoking status. In current smokers, fibrinogen has significant positive association with IMTtpm and IMTmax. This significant association was not disappeared even after adjusting potential confounding variables such as age, BMI, SBP, fasting glucose and ratio of total cholesterol to HDL cholesterol. However, there was no significant association between fibrinogen and CIMT in former and never smokers. Additionally, in current smokers, fibrinogen explained the IMTtpm, and IMTmax about 6% and 8% respectively but in former and never smokers, fibrinogen explained the IMTtpm and IMTmax only less than 0.1%.

Table 4. Linear association between Fibrinogen and CIMT by smoking status

	IMTtpm			IMTmax		
	S(ß)[†]	R^2	p-value	S(ß)[†]	R^2	p-value
Never smokers (N=80)						
Unadjusted	0.017	0.0003	0.880	0.020	0.0004	0.859
Age adjusted	-0.063	0.149	0.557	-0.030	0.059	0.788
Multiple adjusted[*]	-0.043	0.208	0.692	-0.006	0.196	0.955
Former smokers (N=122)						
Unadjusted	0.084	0.007	0.359	0.029	0.001	0.753
Age adjusted	-0.005	0.253	0.952	-0.037	0.137	0.669
Multiple adjusted[*]	-0.044	0.285	0.605	-0.074	0.168	0.421
Current smoker (N=75)						
Unadjusted	0.252	0.064	0.029	0.029	0.001	0.753
Age adjusted	0.160	0.305	0.114	0.210	0.263	0.045
Multiple adjusted[*]	0.207	0.394	0.038	0.245	0.325	0.021

[*]Adjusted for age, BMI, SBP, fasting glucose, total cholesterol/HDL cholesterol

[†] S(ß) displays the standardized regression coefficients.

5. The association between the risk of carotid atherosclerosis and fibrinogen by smoking status

Table 5 shows the risk of carotid atherosclerosis per 1 standard deviation increase in fibrinogen by smoking status. Carotid atherosclerosis was presented using increased IMT or plaque.

At this analysis, only in current smokers, the risk of carotid atherosclerosis was significantly increased as 1 standard deviation increase of fibrinogen. These results were remained significantly after adjustment for potential confounders such as age, BMI, SBP, fasting glucose and ratio of total cholesterol to HDL cholesterol.

Table 5. The risk of carotid atherosclerosis* per 1 standard deviation increase in fibrinogen by smoking status

	Increased IMT		Plaque	
	No. of case	Odds ratio (95% CI)	No. of case	Odds ratio (95% CI)
Never smokers (N=80)				
Unadjusted	13	1.07 (0.59-1.93)	40	1.24 (0.79-1.93)
Age adjusted	13	0.89 (0.45-1.75)	40	1.04 (0.63-1.70)
Multiple adjusted†	13	0.86 (0.42-1.79)	40	1.06 (0.60-1.87)
Former smokers (N=122)				
Unadjusted	38	1.18 (0.81-1.72)	72	0.995 (0.69-1.43)
Age adjusted	38	0.78 (0.64-1.49)	72	0.78 (0.51-1.20)
Multiple adjusted†	38	0.93 (0.58-1.50)	72	0.68 (0.42-1.10)
Current smoker (N=75)				
Unadjusted	19	2.01 (1.14-3.55)	37	2.00 (1.17-3.40)
Age adjusted	19	1.95 (1.02-3.71)	37	1.90 (1.06-3.43)
Multiple adjusted†	19	3.59 (1.41-9.12)	37	2.06 (1.09-3.89)

Standard deviation for Fibrinogen = 0.525 (in never smoker), 0.724 (in former smoker), 0.587 (in current smoker)

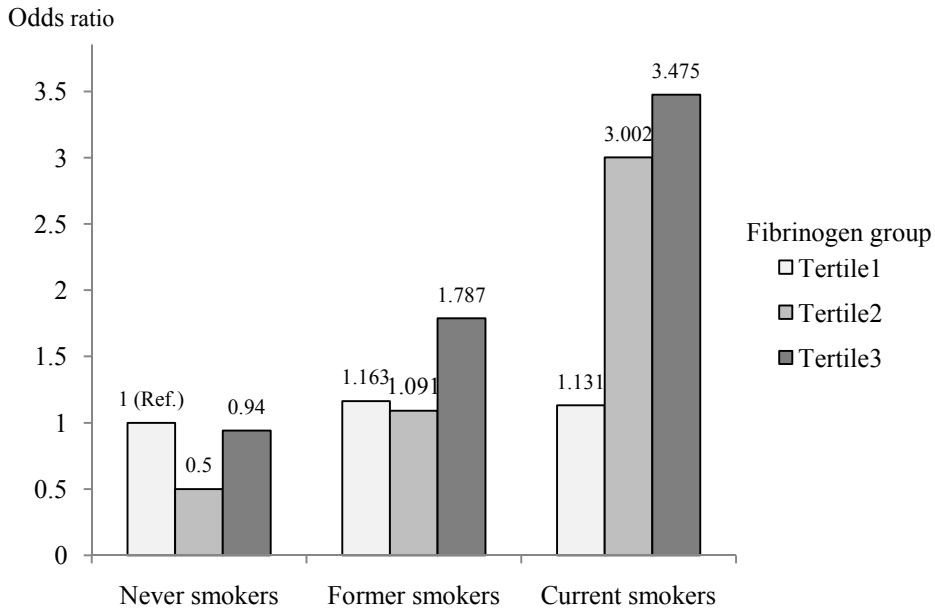
* Carotid atherosclerosis was presented using increased IMT or plaque.

†Adjusted for age, BMI, SBP, fasting glucose, total cholesterol/HDL cholesterol

6. Risk for increased IMT by tertile of fibrinogen and smoking status

Figure 7 shows the risk for increased IMT by tertile of fibrinogen and smoking status. Although the odds ratios of increased IMT for all group were not statistically significant compared with individuals with a lowest tertile of fibrinogen and nonsmoker, we can see the trend to increase the risk for increased IMT according to tertile of fibrinogen in current smokers. This trend was not shown in former or never smokers.

Figure 7. The risk for increased IMT by tertile of fibrinogen and smoking status



All values were adjusted for age, BMI, SBP, fasting glucose, total cholesterol/HDL cholesterol.

V. DISCUSSION

In this community-based study, the association between fibrinogen and CIMT was different by smoking status. Among current smokers, we can see the significant positive association between fibrinogen and CIMT even after adjusting the potential confounders. But we cannot see the significant results for the association between fibrinogen and CIMT in former smokers or never smokers.

Although some previous studies have suggested a positive association between fibrinogen and CIMT (Green et al., 2009, Paramo et al., 2004, Grebe et al., 2010), this positive association has been inconsistent in the literature (Hayashi, 2010, Sekikawa et al., 2007, Choi et al., 2004). Our results suggest that the smoking act as an effect modifier on the association between fibrinogen and CIMT and this suggestion can partially explain the inconsistent results of previous studies for the association between fibrinogen and CIMT. It has been proposed that the association between fibrinogen and cardiovascular disease (Fowkes et al., 1996) or cardiovascular risk factors (Tuut and Hense, 2001) are may be affected in part through interaction with smoking. Similarly, some studies showed different association with atherosclerosis and inflammatory markers according to smoking status (Thakore et al., 2007, Nguyen et al., 2011).

Smoking as an effect modifier in the relation between fibrinogen and atherosclerosis can be explained by several mechanisms.

First, oxidative stress from smoking can be directly associated with a modification in function of fibrinogen and fibrin architectures. In a study with 68 young healthy male participants, a function of the contribution of fibrinogen to clot strength was significantly higher in postsmoking sample than in presmoking sample. Authors suggested that this functional change can contribute to the increasing clot strength which is related the kinetics of clot formation, the rapidity of fibrin build up, and clot strength. When measured the clot-shear elasticity using the thromboelastography (TEG), postsmoking samples displayed different parameter for TEG as compared to nonsmoking and presmoking smaples. Additionally, postsmoking fibrin clots had thinner fibrin fibers and had more fibrin fibers per 1-μm^2 compared to nonsmoking and presmoking fibrin clots. And postsmoking fibrin clot had more uniform fibrin fiber distribution compared to nonsmoking and presmoking fibrin clot (Barua et al., 2010). These alteration of fibrin that fibrin is thinner and more numerous is related premature coronary atherothrombosis (Collet et al., 2006). And clot with a high fiber density would cause delayed clot lysis and thrombotic disease (Lord, 2011).

Second, smoking effects on fibrinolysis by alteration of plasminogen activator inhibitor type 1 (PAI-1) (Yanbaeva et al., 2007). The Caerphilly study showed that smokers had higher level of PAI-1 than nonsmokers.

Additionally, the participants who smoked more than 25 cigarettes per day had a higher level of PAI-1 compared to the participants who smoked less than 25 cigarettes per day (Yarnell et al., 2000). PAI-1 inhibits the fibrinolytic pathway by binding both urinary-type plasminogen activator and tissue plasminogen activator (t-PA) which are activators of plasminogen for lysis of fibrin clot. In addition, PAI-1 bind to fibrin and it retains the inhibitory activity against t-PA and urinary-type plasminogen activator, when it bound to fibrin. Thus, due to the action of PAI-1 such as the inhibitor of fibrinolysis, it has been suggested that high plasma PAI-1 level might be related to the formation of a thrombus (Kohler and Grant, 2000). In this context, the alteration of PAI-1 level due to smoking can be related the carotid atherosclerosis.

Finally, previous studies have been shown that smoking is related with increasing the level of fibrinogen. The Framingham study showed that age adjusted fibrinogen values were higher in smokers then in nonsmokers and this result was statistically significant (Kannel et al., 1987). The Northwick park heart study reported similar results. This study showed that the level of fibrinogen was higher in current smokers than in ex-smokers. And the level of fibrinogen was higher according to the smoking duration (Meade et al., 1987). Also, cigarette smoking associate with increased CIMT. The ARIC study's results demonstrated the relationship between smoking and CIMT and that increasing dose for cigarette smoking was related to increased IMT

(Howard et al., 1994). These actions of smoking can be effect on the association between fibrinogen and CIMT.

Our study has the following limitations. First, we could not see the time dependent change of fibrinogen level or CIMT because of the cross-sectional study design. Thus the causal relationship between fibrinogen and CIMT by smoking status was not evaluated in this study. Another limitation is that our sample size was relatively small. Thus non significant results in former or never smokers can be due to small sample size. In addition, we assessed only in men and our results cannot be applied in women.

VI. CONCLUSION

This study showed that the increased fibrinogen level in current smokers have more linked to the CIMT than the increased fibrinogen level in former smokers or never smokers. We confirmed the different association between fibrinogen and CIMT by smoking status both in continuous analysis and categorical analysis, even after adjustment for potential confounders such as age, BMI, SBP, fasting glucose and ratio of total cholesterol to HDL cholesterol. These results suggest that the association between fibrinogen and CIMT can be modified by smoking status.

Further, lager cohort studies are necessary to confirm this interaction between fibrinogen, smoking and CIMT.

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ABSTRACT (IN KOREAN)

흡연 상태에 따른 섬유소원과 경동맥 내중막 두께와의 관련성

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조혜민

서론: 흡연은 죽상경화증의 위험인자로 알려져 있으며 또한 섬유소원(Fibrinogen)의 증가와도 관련이 있는 것으로 보고되고 있다. 한편, 선행 연구들에서 섬유소원과 경동맥 내중막 두께와의 관련성이 제기되고 있지만, 일부 연구에서는 이들간의 유의한 관련성을 보이지 않았다. 따라서 흡연이 섬유소원과 경동맥 내중막 두께의 관련성에 어떠한 영향을 미치는지 연구하였다.

방법: 이 연구는 강화도에서 진행되는 지역 기반 전향적 코호트 연구의 일부로, 2010년 전체 대상자 1253 명 중 40-87 세의 심근경색 및 뇌혈관 질환이 없고, 섬유소원 및 경동맥 내중막 두께를 측정한 277명의 성인 남성을 대상으로 시행되었다. 경동맥 내중막 두께는 초음파(Aloka, Japan)를 이용하여 최대값(IMTmax)과 세 지점의 평균값(IMTtpm)을 측정하였다. 플라크는 IMTmax가 1.0 mm 보다 큰 경우 또는 주변보다 100% 이상 혈관벽이 두꺼워져 있는 것으로 정의 하였다. 흡연상태에 따른 섬유소원과 경동맥 내중막 두께와의 독립적인 연관성은 선형회귀분석과 로지스틱 회귀분석으로 평가하였다.

결과: 현재 흡연자에서 섬유소원은 잠재적 혼란변수인 연령, 체질량 지수, 수축기 혈압, 공복 혈당, 총 콜레스테롤과 고밀도 지단백 콜레스테롤의 비를 보정한 후에도 통계적으로 유의한 양의 관련성을 보였다(IMTmax $ß_{sd}$ = 0.25, p = 0.021; IMTtpm $ß_{sd}$ = 0.21, p = 0.038). 그러나 과거 흡연자와 비흡연자에서는 이러한 관련성을 확인할 수 없었다. 현재 흡연자에서 잠재적 혼란변수를 보정한 후 섬유소원이 1 표준편차 증가할 때마다 플라크를 가질 위험은 2.04 배 (95% CI, 1.08-3.85) 증가 하였다. 하지만 이러한 관련성은 과거 흡연자와 비흡연자에서는 확인할 수 없었다.

고찰: 이 연구에서는 흡연이 섬유소원과 경동맥 내중막 두께와의 관련성에 있어 효과 변경 인자(effect modifier)로 작용하였다. 이들의 인과적인 관계에 대한 평가를 위하여 추후 전향적인 연구가 뒷받침 되어야 할 것이다.

핵심 되는 말: 섬유소원, 흡연, 죽상경화증, 경동맥 내중막 두께