Original Article

Associations of Fibrinogen with Metabolic Syndrome in Rural Chinese Population

Jixiang Ma[1], Aiqiang Xu[1], Chongqi Jia[2], Longjian Liu[3], Zhentao Fu[1], Jing Dong[1], Xiaolei Guo[1], Junying Su[1], and Zhenqiang Bi[1]

[1]Institution of Non-Communicable Disease Prevention, Shandong Centre for Disease Control and Prevention, China
[2]Department of Epidemiology and Health Statistics, Shandong University, China
[3]Department of Epidemiology and Biostatistics, School of Public Health, Drexel University, U.S.

***Aim*: Metabolic syndrome (MS) comprises a constellation of various metabolic abnormalities, but insulin resistance is considered the basis of the syndrome. The relationship of plasma fibrinogen with MS and insulin resistance remains inconclusive. The aim of this study was to assess whether plasma fibrinogen levels were associated with MS and insulin resistance in a rural population of China.**

***Methods*: Participants were selected using a multi-stage random-sampling method. A standardized interview was conducted by trained personnel, and "metabolic syndrome" was defined according to the Chinese Diabetes Association. Insulin resistance was assessed by fasting insulin and HOMA-IR. Associations of fibrinogen levels with components of MS and insulin resistance were determined using correlation analysis and multiple linear regression analyses.**

***Results*: A total of 1,792 participants (M: 815, W: 977) aged 15 to 85 years was studied. Adjusted mean fibrinogen concentration increased with increases in the number of MS components ($p<0.001$). Multiple linear regression analyses showed that fibrinogen concentration was significantly and positively associated with age, DBP and negatively with physical exercise and HDL-C in males and females, and positively with WHR, LogTG, and FPG in females. No statistically significant association between fibrinogen and insulin resistance was observed.**

***Conclusions*: Fibrinogen was significantly associated with MS, independent of major confounders. Insulin resistance showed an inconsistent association with fibrinogen.**

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Key words; Fibrinogen, Metabolic syndrome, Insulin resistance, Inflammation

Introduction

Metabolic syndrome (MS) comprises a constellation of various metabolic abnormalities related with a high risk of diabetes and cardiovascular disease (CVD), including obesity, dyslipidemia, hyperglycemia, and hypertension[1, 2]. A number of studies have reported the substantial role of insulin resistance in the pathogenesis of the syndrome[3-5]. It has also been frequently demonstrated that MS is related to the activation of hemostasis (coagulation and fibrinolysis) and inflammation[6-8]. Increased risk of CVD associated with insulin resistance or MS is thought to be mediated in part by the enhanced potential for acute thrombosis through hypercoagulability, impaired fibrinolysis and inflammation[9-11].

Fibrinogen, an acute-phase protein, is synthesized in the liver and plays an essential role in blood coagulation. It strongly affects hemostasis, blood rheology, platelet aggregation, and endothelial function[12-15]. Many studies have demonstrated that a high plasma fibrinogen level is an independent risk factor for CVD, including coronary heart disease, ischemic stroke, and peripheral thromboembolism[16-20].

Previous studies have demonstrated a positive association between fibrinogen and the presence of

Address for correspondence: Zhenqiang Bi, Shandong Centre for Disease Control and Prevention, P.O. Box 250014, 16992 Jingshi Road, Jinan, P.R. China
E-mail: zhenqiangbi@gmail.com
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MS and various components[8, 21-24]; however, the relationships between fibrinogen and specific components of MS remain inconclusive[6, 8]. In addition, no study has examined specifically the association between fibrinogen and MS in a Chinese population. The aim of this study was thus to examine the association between fibrinogen and metabolic syndrome and insulin resistance in a population-based baseline survey on cardiovascular risks in Wulian county, Shandong, China.

Materials and Methods

Wulian is a rural county in Shandong Province, located in the east of China and has a population of about 500,000. A survey was carried out in 2002, which aimed to explore CVD risk factor prevalence in the local population. Participants were selected using a multi-stage random-sampling method, by which 2,837 men and women aged 15–90 were recruited, with a participation rate of 90%. They were interviewed at home and invited for a clinical examination at the clinical center. The study was approved by the Ethics Committee of the Shandong Centre for Disease Control and Prevention. Informed consent was obtained from all subjects.

Plasma fibrinogen and other laboratory tests were performed in a random subset of 1,878 subjects selected by a systematic sampling method. Subjects ($n=86$) with acute illness or evidence of coronary or cerebral disease were excluded from the study. Ultimately, 1,792 subjects were included in the study.

Data Collection

A standardized interview conducted by trained personnel, with detailed information was collected on demographic factors, medical history, and lifestyle characteristics, including dietary habits, smoking habits, alcohol consumption, and physical exercise. Information on medication for hypertension, diabetes and dislipidemia was also aquired at the interview. Blood pressure was measured three times on the right arm using a mercury sphygmomanometer of appropriate cuff size with the participant in a seated position after 5-min rest. Participants were advised to avoid smoking cigarettes, consuming alcohol or caffeinated beverages and exercise for at least 30 min prior to the blood pressure measurement.

Height, weight, waist and hip circumferences were measured twice, with subjects wearing light clothing and no shoes. The second measurement was recorded. Waist circumference (WC) was measured 1 cm above the navel at minimal respiration, and hip circumference at the level of maximum extension of the buttocks. Waist-to-hip ratio (WHR) was used as an index of fat distribution. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Participants were classified as smokers or nonsmokers according to the definition provided by the World Health Organization (WHO)[25]. Alcohol consumption and physical exercise were defined alcohol consumption or exercise at least twice a week.

An overnight fasting blood sample was taken from individual participants, with vacuum tubes prefilled with EDTA and centrifuged at room temperature for 15 min. Plasma aliquots were frozen at −70℃ for fibrinogen, insulin, and lipid measurements. All blood sample analyses were performed with standard procedures in the laboratory of the Shandong Center for Disease Control and Prevention.

Glucose was determined immediately in fresh plasma using a glucose oxidase method. Total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), triglycerides (TG), and low density lipoprotein-cholesterol (LDL-C) (only for those with triglyceride higher than 4.52 mmol/L) were determined enzymically, using an automatic biochemistry analyzer (OLYMPUS600; Olympus, Tokyo, Japan). LDL-C was calculated by Friedewald's formula for participants who had less than 4.5 mmol/L TG: LDL-C = TC − HDL-C − TG/5[26]. All lipid reagents were manufactured by the Biosino Biotechnology Company Ltd (Beijing, China). Plasma fibrinogen concentrations were analyzed using the immunonephelometric method[27], whose coefficient of variation was 3.7% at a mean level of 3.4 g/L. The plasma insulin concentration was determined using a radioimmunoassay[28], with a coefficient of variation of 4.1% at a mean level of 8.9 μIU/mL. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the formula described by Matthews *et al.*[29]: Fasting Insulin [μIU/mL] × FPG[mmol/L]/22.5.

MS was defined as the clustering of two or more of the following criteria according to the Chinese Diabetes Association[30]: 1) obesity (BMI ≥ 25 kg/m^2), 2) high blood pressure (≥ 140/90 mmHg), 3) dyslipidemia (TG ≥ 1.7 mmol/L and/or HDL-C < 0.9 mmol/L (male) and/or < 1.0 mmol/L (female)), and 4) hyperglycemia (fasting plasma glucose (FPG) ≥ 6.1 mmol/L).

Statistical Analyses

Males and females were compared using the *t*-test and chi-square test for continuous and categorical variables, respectively. The *t*-test was used to exam-

Table 1. Characteristics of study subjects

	Male ($n=815$)	Female ($n=977$)	p
Age (years)	48.4 (12.4)	47.2 (12.0)	NS
Fibrinogen (g/L)	3.4 (0.8)	3.4 (0.7)	NS
Systolic blood pressure (mmHg)	134 (21)	132 (23)	<0.05
Diastolic blood pressure (mmHg)	84 (12)	82 (11)	<0.001
Body mass index (kg/m^2)	23.4 (3.5)	24.0 (3.5)	<0.01
Waist circumference (cm)	79.7 (9.2)	79.2 (8.9)	NS
HOMA	2.1 (1.9)	2.2 (2.7)	NS
Log HOMA	0.2 (0.2)	0.3 (0.2)	NS
Waist-hip ratio	0.9 (0.1)	0.8 (0.1)	<0.001
Glucose (mmol/L)	5.3 (1.1)	5.2 (0.9)	NS
TG (mmol/L)	1.3 (1.3)	1.2 (0.9)	<0.05
Log TG	0.04 (0.24)	0.02 (0.22)	<0.05
TC (mmol/L)	5.1 (0.9)	5.0 (0.9)	<0.01
HDL-C (mmol/L)	1.6 (0.3)	1.6 (0.4)	NS
LDL-C (mmol/L)	2.9 (0.6)	2.9 (0.6)	NS
Insulin (μIU/mL)	8.7 (7.0)	9.2 (7.6)	NS
Log Insulin	0.89 (0.20)	0.91 (0.19)	<0.05
Smoking (%)	69.2	13.1	<0.001
Drinking (%)	63.2	8.5	<0.001
Physical exercise (%)	18.1	14.1	NS

Differences were tested by Student's t-test for continuous variables and by the chi-square test for category variables; unless otherwise indicated, values are shown as the means (SD).

ine differences in mean fibrinogen concentrations according to cigarette smoking, alcohol consumption and physical exercise. Pearson correlation coefficients were calculated for continuous variables to examine correlations between the study variables and fibrinogen. To assess whether there was an association between the severity of MS and fibrinogen, subjects were grouped into five subgroups according to MS components (i.e, 0, 1, 2, 3, or 4 represents the number of metabolic abnormalities). Adjusted means of fibrinogen concentration were calculated for each cluster using a multiple linear regression model that considered age, gender, physical exercise, smoking and alcohol consumption status as covariates. The trend of adjusted mean fibrinogen levels with an increasing number of metabolic abnormalities was also examined.

As several variables had a strong correlation, we performed collinearity diagnosis. Step-wise forward multiple linear regression analyses – with the plasma fibrinogen level as the dependent variable and age, BMI, WHR, SBP, DBP, FPG, insulin, Log TG, TC, HDL-C, LDL-C, Log HOMA, physical exercise, alcohol-drinking, smoking and medication as independent variables – were performed after excluding identified factors with collinearity.

All tests were performed with a significance level of 0.05 and were analyzed using Stata 8.0 software (Stata Corporation, College Station, TX, USA).

Results

We successfully recruited 1,792 participants (815 men and 977 women) aged 15 to 85 years. **Table 1** shows the characteristics of the participants by gender. There were significant differences in BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), WC, WHR, FPG, TG, LogTG and Loginsulin, while there were no significant differences in age, fibrinogen, HDL-C, LDL-C, and insulin between men and women.

Significant differences (Male: 3.14 ± 0.77, 3.41 ± 0.77, $p<0.01$; Female: 3.15 ± 0.65, 3.43 ± 0.70, $p<0.01$) in mean fibrinogen concentrations were observed between subjects with and without physical exercise in both genders while no significant differences were observed between smokers and non-smokers (Male: 3.38 ± 0.77, 3.32 ± 0.74, $p<0.05$; Female: 3.54 ± 0.80, 3.37 ± 0.67, $p<0.05$), and between those with and without alcohol consumption (Male: $3.35 \pm$

Table 2. Correlation coefficients of fibrinogen with age and individual components of metabolic syndrome

Metabolic factors	Male (n=815)	Female (n=977)	Total (n=1,792)
Age (years)	0.139**	0.277**	0.208**
BMI (kg/m^2)	−0.047	0.092**	0.027
WC (cm)	0.028	0.210**	0.120**
WHR	0.126**	0.239**	0.172**
SBP (mmHg)	0.183**	0.253**	0.219**
DBP (mmHg)	0.146**	0.185**	0.163**
Insulin (μIU/mL)	0.045	0.088*	0.068**
Log Insulin	0.024	0.061	0.044
Log HOMA	0.046	0.084*	0.058*
HOMA	0.029	0.086*	0.069**
TG (mmol/L)	0.486**	0.445**	0.463**
Log TG	0.437**	0.471**	0.452**
Glucose (mmol/L)	0.027	0.116**	0.068**
HDL-C (mmol/L)	−0.022	−0.102**	−0.064*
LDL-C (mmol/L)	0.218**	0.079*	0.148**
TC (mmol/L)	0.169**	0.177**	0.171**

Pearson correlation coefficients were calculated.
**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

0.82, 3.38±0.64, $p>0.05$; Female: 3.35±0.71, 3.40±0.69, $p>0.05$) in both genders.

Fibrinogen was correlated positively with age, WHR, SBP, DBP, TG, LogTG, TC, and negatively with physical exercise in both genders, and positively with BMI, WC, insulin, LogHOMA, HOMA, glucose, smoking, and negatively with HDL-C in females, and negatively with alcohol consumption and positively with LDL-C in males. Triglycerides had the highest correlation coefficient in males (r=0.465, $p<$0.01) and females (r=0.435, $p<0.01$) (**Table 2**).

To examine the association between fibrinogen and MS, plasma fibrinogen levels were compared across the number of MS components. Adjusted mean fibrinogen levels increased with an increased number of MS components (p for trend <0.001, **Table 3**). A significant difference in mean fibrinogen levels was also observed between subjects with and MS without.

In multiple linear regression analyses, TC, HDL-C, and insulin were excluded because of collinearity. Significant and independent associations were shown between fibrinogen and age and DBP positively, HDL-C and physical exercise negatively in both males and females, and WHR, LogTG, and FPG positively in females. Fibrinogen did not show a significant association with insulin resistance (**Table 4**).

Table 3. Adjusted mean fibrinogen (g/L) by the number of metabolic abnormalities

Metabolic abnormalities[@]	N	%	Multi-adjusted[§] mean fibrinogen (SD)
0	688	38.4	3.2 (0.6)
1	614	34.3	3.4 (0.7)
2	354	19.8	3.5 (0.8)
3	112	6.3	3.7 (0.8)
4	24	1.3	4.0 (1.2)
			Test for trend, $p<0.01$
Non-MS	1,656	92.4	3.4 (0.7)
MS	136	7.4	3.8 (0.9)
			$p<0.01$

[@]Metabolic abnormalities were defined as follows, according to the Chinese Diabetes Association: 1) obesity (BMI ≥25 kg/m^2), 2) high blood pressure (≥140/90 mmHg), 3) dyslipidemia (TG ≥1.7 mmol/L and/or HDL-C <0.9 mmol/L (male) and/or <1.0 mmol/L (female)), 4) hyperglycemia (FPG ≥6.1 mmol/L).
[§]Data were adjusted for age, gender, physical exercise, smoking, and alcohol-consumption

Table 4. Multivariate stepwise linear regression analysis of fibrinogen in relation to age and other significant variables

Independent variables	Dependent variable: Fibrinogen		
	B	SE	p
Male			
Age (Years)	0.010	0.002	<0.001
DBP (mmHg)	0.004	0.002	<0.001
HDL-C (mmol/L)	−0.184	0.079	<0.001
Physical exercise (Yes/No)	−0.244	0.061	<0.05
Medication (Yes/No)	−0.238	0.102	<0.001
Female			
Age (Years)	2.225	0.309	<0.001
DBP (mmHg)	0.010	0.002	<0.001
WHR	0.004	0.002	<0.05
HDL-C (mmol/L)	−0.125	0.060	<0.05
FPG (mmol/L)	0.760	0.355	<0.05
Log TG	1.332	0.095	<0.001
Physical exercise (Yes/No)	−0.243	0.056	<0.001
Medication(Yes/No)	−0.188	0.083	<0.05

Discussion

Our study demonstrated that fibrinogen levels are significantly associated with MS in a population-based sample in China. MS is a clustering of cardiovascular risk factors, such as obesity, hypertension, hyperglycemia, and dyslipidemia[1)], and it is typically accompanied with insulin resistance. Several studies

have examined the relationship between individual components of MS and fibrinogen concentration; since MS represents a cluster of simultaneously occurring components, it may not be appropriate to examine only the relation of fibrinogen to each variable. Indeed, we observed an increasing trend of fibrinogen concentrations across a number of metabolic abnormalities. This is consistent with previous studies of non-diabetic[23] and diabetic patients[24].

Inflammation is now thought to play a key role in the pathophysiology of cardiovascular disease[31] and has also been proved to be associated with MS[8, 32, 33]. A central role has been attributed to proinflammatory cytokines tumor necrosis factor-α (TNF-α)[34] and interleukin-6[35], and this role is supported by the fact that both are produced in substantial amounts by human adipose tissue. TNF-α impairs insulin-stimulated glucose uptake in a variety of cells and decreases lipoprotein lipase activity. Both cytokines increase hepatic lipogenesis[36, 37] and elicit a systemic acute-phase response[38]. Furthermore, various aspects of the acute-phase response, such as C-reactive-protein[33], fibrinogen[23], plasminogen activator inhibitor 1 levels[39, 40], and white blood cell count[41-43], have recently been found to correlate positively with MS. Fibrinogen, on binding to its integrin receptor on the surface of leukocytes, also facilitates a chemotactic response that supposedly plays a vital role in the process of inflammation[44].

Insulin resistance is considered to be the basis of MS. Evaluated by insulin concentration and HOMA, it was related to fibrinogen in females in univariate analysis in our study. Previous studies examining this issue remain inconclusive. In a pooled sample of 22 normotensive and untreated mildly hypertensive patients[45], fibrinogen was found to be related to the insulin-mediated glucose disposal rate but not with insulin concentration. In the Atherosclerosis Risk in Communities Study[46], fibrinogen was associated with serum insulin concentrations in women, but not in men. In 62 non-diabetic and non-hypertensive patients, a highly significant negative correlation between fibrinogen and insulin sensitivity, and a positive correlation between fibrinogen and fasting insulin, was confirmed[47]. In a previously mentioned cross-sectional study among 1,252 non-diabetic men, hyperfibrinogenemia was significantly associated with high insulin levels[23].

The controversy regarding the association between fibrinogen and insulin resistance might be explained by their indirect relationship. Plasma fibrinogen levels rise acutely in response to various stimuli, including the release of cytokines, such as TNF-α, during the inflammation process. Recent studies have shown that TNF-α is implicated in insulin resistance in human obesity[48, 49]; it is also known that TNF-α has a procoagulant effect on the human haemostatic mechanism[50, 51]. For these reasons, fibrinogen might be related to inflammation.

Plasma fibrinogen is influenced by many other factors, increasing with age, BMI, smoking, diabetes, and post-menopause, and related to fasting serum insulin, LDL-C, and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical exercise, and increased HDL-C[46, 52].

Our study demonstrated that fibrinogen was related to age, WHR, SBP, DBP, TG, Log TG, TC positively, and physical exercise negatively in both men and women, to BMI, WC, insulin, LogHOMA, HOMA, glucose, smoking positively and HDL-C negatively in females, and to alcohol-drinking negatively and LDL-C positively in males. Multiple regression analysis showed significant and independent associations between fibrinogen and age, SBP positively, physical exercise and HDL-C negatively in both males and females, and WHR, Log TG and FPG positively in females. Fibrinogen did not show a significant association with insulin resistance.

Sex differences were observed in our study in several metabolic factors and relations of fibrinogen with Log TG, FPG, and WHR. A similar result in another study indicated that WHR may be a more robust risk factor of CVD in female than in male obese patients[53]. This might be attributed to the greater rate of subcutaneous fat deposition as a result of increasing weight in females[54]. Gender differences in metablic syndrome components need further study of the possible determinants.

Our study illustrated the association between fibrinogen and MS in an Asian population. Similar findings have been found in Indian and Italian population studies[23, 24]; however, the association between fibrinogen and insulin resistance is still controversial in Western and populations Asian[45-47]. Recent studies showed no significant racial difference in fibrinogen concentration between Europeans and South Asians[55].

In conclusion, our study, using a large population-based random sample of a Chinese population, demonstrates that fibrinogen is significantly associated with MS, independent of major covariates. Fibrinogen showed an inconsistent relation with insulin resistance, which may indicate an inflammatory process with a high fibrinogen level rather than insulin resistance in the pathogenesis of MS. Further studies are needed to examine the potential role of fibrinogen in the pathogenesis of MS to determine the appropriate

intervention for this syndrome.

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