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Association of metabolic syndrome with atherogenic index of plasma in an urban Chinese population: A 15-year prospective study

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Abstract *Background and aims:* The metabolic syndrome(Mets) is a multiplex risk factor for atheroselerotie cardiovascular disease. The aims of the study were to assess the association of the Mets with atherogenic index of plasma(AIP) and other atherogenic parameters in an urban Chinese population.
Methods and results: The data were collected in 1992 and then again in 2007 from the same group of 582 individuals(359 men and 223 women) without Mets in 1992. During 15 years' follow-up, AIP was the lipid parameter that was most strongly associated with Mets, with an unadjusted odds ratio of 5.66 (95% CI:1.76–18.23, P = 0.004) in the univariate logistic regression analysis. Multivariate logistic regression analyses also revealed that AIP was an independent risk factor for Mets. AIP significantly predicted Mets in men, with an unadjusted odds ratio of 30.73 (95% CI: 5.62, 168.12 P = 0.012) in a univariate model. Associations remained significant after adjustment for smoking, drinking, physical exercise and components of Mets. The incidences of Mets adjusted for age according to the quartiles of AIP showed a statistical linear trend in men(P for trend = 0.007) rather than in women(P for trend = 0.529).
Conclusions: AIP might be a strong and independent predictor for Mets in an urban Chinese population. The incidence of Mets increased with AIP elevated in men while not in women.

Metabolic syndrome(Mets) is a cluster of metabolic abnormalities characterized by abdominal obesity, hypertension, dyslipidemia, abnormal glucose metabolism, or previously diagnosed type 2 diabetes [1]. Lipid metabolism disorder is a common metabolic abnormality in patients with Mets, and closely related to atherosclerosis, significantly increased the risk of cardiovascular diseases [2]. Current guidelines indicate that first-line therapy should focus on lowering low-density lipoprotein cholesterol (LDL-C) [3,4]. However, according to the current guidelines and treatment standards, even if LDL-C is up to the standard, patients with dyslipidemia still have a high risk of cardiovascular events, so it is not enough to focus on the level of LDL-C.

In recent years, researchers have focused on the new atherogenic indices such as total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C), non-HDL (TC minus HDL-C), triglyceride to high-density lipoprotein cholesterol(TG/HDL-C) and LDL-C/HDL-C as well as their ability to predict the risk of cardiovascular events [5,6]. Recently, Dobiasova and Frohlich have referred to the logarithm of TG/HDL-C as the atherogenic index of plasma (AIP) [7]. The AIP value has a stronger sensitivity that reflects the interaction between atherogenic and protective lipoprotein. In a cross-sectional study conducted in Iran,

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the value of AIP was positively correlated with waist circumference and body mass index and was inversely correlated with physical activity [8]. In a prospective cohort study, Altan Onat et al. found that high AIP can predict diabetes and high blood pressure in both sexes after 7.8 years' follow-up in the Turkish population [9]. However, there is no prospective study to explore the relationship between AIP, atherogenic indices and Mets in an urban Chinese population. This study was therefore aimed to prospectively determine the predictive value of AIP and atherogenic indices for the Mets in an urban Chinese population.

Study population

The study population was obtained from a Chinese Multiprovincial Cohort Study(CMCS) in an urban community located in Chengdu, Sichuan province, China. A baseline examination was conducted on 711 participants in 1992 using a risk factor survey developed by the World Health Organization-Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (WHO-MONICA) [10]. The data were again collected in 2007 from the same group. Detailed information of these participants has been already reported [11–13]. In 1992, each patient's history of hypertension, diabetes mellitus, hyperlipidemia, heart disease(coronary artery disease, heart failure or arrhythmia), current smoking and current alcohol consumption, as well as their physical exercise habits, was determined by self-administered questionnaires and confirmed by a physician's interview. After at least 5-min of rest in seated position, blood pressure (BP) was measured in the sitting position twice at 2-min interval using an upright standard sphygmomanometer. Waist, height, weight, and body mass index (BMI) were measured. BMI was calculated as body weight (kg) divided by the height squared (m2). Blood was drawn from the antecubital vein in the morning after a 12-h fast for determinations of fasting plasma glucose (FPG), fasting serum TC, LDL-C, HDL-C, and TG. These chemistries were measured at West China Hospital laboratory. Since 114 participants were diagnosed with Mets, 7 participants with heart disease and 8 participants with diabetes mellitus in 1992, they were excluded from the analysis. Therefore, only 582 participants with complete data were available and analysed. This study was approved by Ministry of Health of China, as well as by the Ethics Committee of West China Hospital of Sichuan University. All participants provided written informed consent. In 2007, we repeated those measurements with the same methods.

Related definitions

Mets was defined as the new joint interim statement [1], and the presence of any 3 of 5 after mentioned risk factors constituted a diagnosis of MetS: (1) elevated TG was defined as 1.7 mmol/L or greater; (2) BP was defined as systolic BP (SBP) $\geq$ 130 and/or diastolic BP (DBP) $\geq$85 mmHg and/or those receiving antihypertensive medications; (3) reduced HDL-C was defined as a level less than 1.0 mmol/L for men and a level less than 1.3 mmol/L for women; (4) elevated FPG was defined as 5.6 mmol/L or greater; (5) for Asians, elevated WC was defined as 80 cm or greater for women and 90 cm or greater for men [1,14]. Smoking: average cigarette consumption $\geq$ one/day. Alcohol intake: average intake of alcohol $\geq$50 g/day. Physical activity: exercise one or more times per week, at least 20 min for each time.

Statistical analysis

Data are presented as the mean $\pm$ SD for normally continuous variables and as frequency(%)for categorical variables by gender. Additionally, to explore the relationship between the lipid parameters and risk of Mets, both univariate and multivariate logistic regression analyses were used to estimate the odds ratios (ORs) and 95% CI values. Similarly, the ORs and 95% CIs for the risk of Mets in various lipid parameters across each subgroup were estimated and their interactions were tested. After that, subjects were categorized into four groups according to the baseline AIP in different genders. Trend tests of Mets incidences across the four categories of AIP were conducted in both men and women. A 2-tailed $p < 0.05$ was considered significant in all analysis. Date were analyzed with the use of the statistical packages R(The R Foundation; https://www.r-project.org/; Version 3.1.2 2014-10-31) and Empower(R) (www.empowerstats.com; X & Y Solutions Inc.).

Results

Baseline characteristics of mets patients and controls

Table 1 shows the baseline characteristics of the involved population classified by genders. A total of 582 subjects were included in our study, including 359 (61.68%) male and 223 (38.32%) female. The mean age of male was older than that of female. The male had higher SBP, DBP, Hight, Weight, Waist circumference, waist hip rate(WHR) as well as rate of smoking and alcohol intake. Compared with female, male had higher levels of TG. By contrast, the level of HDL-C was lower in the male. Values of TG/HDL-C and AIP were significantly higher in the male than in the female.

Logistic regression analyses for AIP with mets risk

In the univariate logistic regression analysis, AIP was the lipid parameter that was most strongly associated with Mets with an unadjusted OR of 5.66(95% CI:1.76–18.23, P = 0.004). This association persisted after adjustments for some Mets risk factors (age, gender, smoking, drinking, physical exercise, components of Mets) (Table 2).

To determine the consistency of the relationship between various lipid parameters and risk of Mets, we conducted stratified analyses (Table 3). For non-adjusted

Table 1 Baseline characteristics of the involved population classified by genders.

	Men	Women	P-value
N	359	223	
Age	48.84 ± 5.71	45.95 ± 6.16	<0.001
EH	41 (11.42%)	18 (8.07%)	0.193
FBG(mmol/l)	4.24 ± 0.70	4.21 ± 0.65	0.654
Height(cm)	165.13 ± 5.70	154.57 ± 5.44	<0.001
Weight(cm)	62.64 ± 8.02	55.02 ± 6.75	<0.001
Waist(cm)	77.46 ± 7.41	72.30 ± 6.29	<0.001
Hip(cm)	91.19 ± 5.39	91.70 ± 5.29	0.267
WHR	0.69 ± 0.06	0.60 ± 0.05	<0.001
BMI	22.97 ± 2.72	23.00 ± 2.40	0.880
SBP(mmHg)	113.47 ± 12.81	110.07 ± 13.01	0.002
DBP(mmHg)	73.24 ± 8.43	71.42 ± 8.34	0.011
TG(mmol/L)	2.04 ± 0.86	1.87 ± 0.73	0.016
TC(mmol/L)	4.42 ± 0.71	4.50 ± 0.80	0.206
HDL-C(mmol/L)	1.24 ± 0.22	1.31 ± 0.24	<0.001
LDL-C(mmol/L)	2.23 ± 0.76	2.31 ± 0.81	0.231
non-HDL-C	3.18 ± 0.72	3.19 ± 0.80	0.891
TG/HDL-C	1.71 ± 0.81	1.48 ± 0.67	<0.001
LDL-C/HDL-C	1.89 ± 0.78	1.84 ± 0.77	0.543
TC/HDL-C	3.68 ± 0.86	3.54 ± 0.84	0.054
AIP	0.19 ± 0.18	0.14 ± 0.16	<0.001
Smoking	225 (62.67%)	1 (0.45%)	<0.001
Drinking	207 (57.66%)	6 (2.69%)	<0.001
Exercise	77 (21.45%)	46 (20.63%)	0.814

Data are presented as means ± SD or number (percentage).
EH, essential hypertension; FPG, fasting plasma glucose; WHR, waist hip rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AIP, atherogenic index of plasma.

model, the AIP was most strongly associated with Mets the OR for Mets was 30.73 in male ($P < 0.001$) and 2.58 in female ($P = 0.297$); a difference that was statistically significant(P interaction = 0.048). In Model 2, after adjusting for age and components of Mets including FPG, SBP, DBP, hypertension and Waist circumference, we found AIP was the most strongly associated with Mets, the OR for Mets was 10.94 in male ($P = 0.009$) and 2.07($P = 0.472$) in female(P interaction = 0.218). This association persisted after adjustments for more Mets risk factors include smoking, drinking and physical exercise. The adjusted OR for Mets in male was 11.75 ($P = 0.009$) compared with 2.35($P = 0.405$) in female (P interaction = 0.240).

Age-adjusted incident Mets according to the quartiles (Q) of AIP at baseline classified by genders

As shown in Fig. 1, the age-adjusted incident Mets over the 15 year follow-up period in male according to the quartiles of baseline AIP were 5.4, 9.9, 18.1 and 18.1%, in 74, 81, 99 and 105 participants respectively, and there was statistical linear trend through the four groups (P for trend = 0.007) for the 15-year period. In addition, age-adjusted incident Mets over the 15-year follow-up period in female according to the baseline AIP categories were 22.7, 23.5, 42.6 and 21.4%, in 66, 68, 47 and 42 participants respectively. There was no statistical linear trend through the four groups(P for trend = 0.460).

Discussion

In this 15-year prospective follow-up study, we found that compared with other lipid ratios, AIP was considered to be better predictors for Mets. Furthermore, this study demonstrated that AIP in the baseline is correlated to the development of Mets in the follow-up in men rather than in women independent of age, smoking, drinking, physical exercise and any of Mets components. The incidence of Mets increased with AIP elevated in men while not in women. Our findings were not fully consistent with previous study results.

A growing body of evidence indicates that dyslipidemia may contribute to the progression of atherosclerotic cardiovascular disease and stroke [15,16]. It is currently believed that the abnormal atherogenic dyslipidemia in patients with Mets is mainly characterized by elevated serum TG, decreased HDL-C, and many small, dense LDL-C(sdLDL). TG accelerates the oxidation of LDL-C, causes endothelial dysfunction, and promotes the formation of foam cells [17]. HDL-C is a blood lipid metabolism index against atherosclerosis in the body. It can transport excess cholesterol to the liver, inhibit the adhesion of LDL-C to the blood vessel wall, and thus exert anti-atherosclerosis effect

Table 2 Logistic regression analyses for the relationship between various atherogenic parameters at baseline and incident Mets at follow-up in different models.

	Model 1		Model 2		Model 3	
	OR(95% CI)	P-value	OR(95% CI)	P-value	OR(95% CI)	P-value
AIP	5.66 (1.76, 18.23)	0.004	5.22 (1.38, 19.82)	0.015	5.70 (1.46, 22.30)	0.012
non-HDL-C	1.25 (0.95, 1.63)	0.108	1.09 (0.81, 1.47)	0.565	1.12 (0.83, 1.51)	0.471
TG/HDL-C	1.52 (1.19, 1.94)	<0.001	1.48 (1.12, 1.94)	0.005	1.50 (1.13, 1.98)	0.005
LDL-C/HDL-C	1.18 (0.91, 1.54)	0.208	1.18 (0.89, 1.56)	0.243	1.19 (0.90, 1.58)	0.229
TC/HDL-C	1.33 (1.05, 1.68)	0.017	1.31 (1.02, 1.69)	0.037	1.33 (1.02, 1.72)	0.032

Model 1: non-adjusted model.
Model 2: adjusted for age, gender and components of Mets (included FPG, SBP, DBP, EH and Waist).
Model 3: adjusted for age, gender, smoking, drinking, physical exercise and components of Mets (included FPG, SBP, DBP, EH and Waist).
AIP, atherogenic index of plasma; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; Mets, metabolic syndrome; FPG, fasting plasma glucose; SBP, systolic blood pressure,; DBP, diastolic blood pressure; EH, essential hypertension.

Table 3 Hazards ratios with 95% confidence intervals for incident Mets increase in various atherogenic parameters in subgroups of gender.

	Model 1			Model 2			Model 3		
	HR(95%CI)	P value	P value for interaction	HR(95%CI)	P value	P value for interaction	HR(95%CI)	P value	P value for interaction
AIP									
Men	30.73 (5.62, 168.12)	<0.001	0.048	10.94 (1.82, 65.95)	0.009	0.218	11.75 (1.86, 74.12)	0.009	0.240
Women	2.58 (0.43, 15.35)	0.297		2.07 (0.29, 15.04)	0.472		2.35 (0.32, 17.52)	0.405	
non-HDL-C									
Men	1.51 (1.02, 2.24)	0.042	0.200	1.31 (0.86, 2.00)	0.209	0.200	1.37 (0.89, 2.11)	0.148	0.205
Women	1.06 (0.73, 1.53)	0.759		0.92 (0.61, 1.38)	0.695		0.93 (0.62, 1.41)	0.741	
TG/HDL-C									
Men	2.06 (1.48, 2.86)	<0.001	0.044	1.31 (0.86, 2.00)	0.209	0.200	1.37 (0.89, 2.11)	0.148	0.205
Women	1.19 (0.78, 1.83)	0.421		0.92 (0.61, 1.38)	0.695		0.93 (0.62, 1.41)	0.741	
LDL-C/HDL-C									
Men	1.30 (0.89, 1.88)	0.170	0.584	1.24 (0.85, 1.82)	0.258	0.690	1.24 (0.84, 1.83)	0.271	0.748
Women	1.12 (0.77, 1.63)	0.561		1.11 (0.73, 1.68)	0.622		1.13 (0.75, 1.72)	0.561	
TC/HDL-C									
Men	1.66 (1.19, 2.30)	0.003	0.142	1.24 (0.85, 1.82)	0.258	0.690	1.24 (0.84, 1.83)	0.271	0.748
Women	1.16 (0.82, 1.64)	0.405		1.11 (0.73, 1.68)	0.622		1.13 (0.75, 1.72)	0.561	

Model 1: non-adjusted model.
Model 2: adjusted for age, components of Mets (included FPG, SBP, DBP, EH and Waist).
Model 3: adjusted for age, smoking, drinking, physical exercise and components of Mets (included FPG, SBP, DBP, EH and Waist).
AIP, atherogenic index of plasma; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; Mets, metabolic syndrome; FPG, fasting plasma glucose; SBP, systolic blood pressure,; DBP, diastolic blood pressure; EH, essential hypertension.

[18]. In the early pathological state, although various lipid parameters are still in the normal range, the proportion of each single lipid parameter has changed, and the use of lipid ratios can reflect these changes, so the lipid ratios can predict the risk of cardiovascular events earlier than the traditional single lipid parameter. In our study, multivariate logistic regression analysis found that TG/HDL-C and TC/HDL-C were independently associated with Mets, suggesting that lipid ratios can be used as a reliable predictor of the risk of Mets.

sdLDL is a sub-component of low-density lipoprotein with smaller particles and higher density. The reasons that sdLDL has stronger atherosclerosis(AS)-probability may include: First, sdLDL particles are more easily exposed on the surface, which makes sdLDL easier to penetrate the vascular endothelium, bind to glycoprotein on the artery wall, and gradually develop lipid deposition, which is transformed into foam cells, leading to AS. Secondly, sdLDL is easy to be oxidized into oxidized LDL-C [19]. Oxidized LDL-C aggregates chemokines and adhesion molecules, thereby inducing the conversion of monocytes into macrophages [19]. Under the further action of cholesterol, a large number of foam cells will be generated to induce AS. In addition, sdLDL can also reduce the production of antioxidants such as vitamin E, which can not effectively prevent iron and copper ion-mediated oxidation in the body, thereby accelerating the progress of AS [20]. AIP has been suggested to be as a surrogate of sdLDL particles [7]. Studies have demonstrated that AIP might be a strong marker for predicting the risk of atherosclerosis and cardiovascular disease [21,22]. Other studies revealed that AIP was strongly associated with DM risk and increased with body weight [23,24]. Recently, Zhu et al. found that AIP is a strong marker to predict the risk of obesity [25]. In our finding, the univariate logistic regression analysis revealed that AIP was the lipid parameter that was most strongly associated with Mets, with an unadjusted OR of 5.66(95% CI: 1.76, 18.23, P = 0.004). Further, the multivariate logistic analysis models demonstrated that AIP was a significant and independent predictor for Mets and might be better than other lipid ratios.

Some cross-sectional studies have already found the AIP of men was higher than that of women [8,21]. In a prospective study by Onat et al. after a 7.8-year follow-up demonstrated that AIP is an independent index that can be used to predict Mets in both sex [9]. But they haven't found gender differences in the relationship between AIP and Mets. We carried out subgroup analysis by gender and

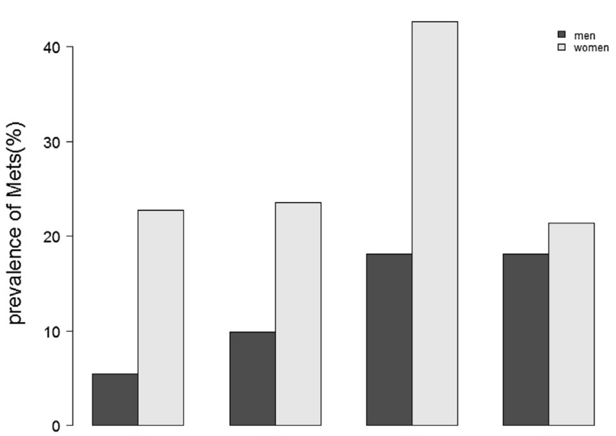

Figure 1 Age-adjusted incident Mets according to the quartiles (Q) of atherogenic index (log of the ratio between the molar values of fasting TGs and HDL-cholesterol) in men and women. Women P for trend = 0.460; men P for trend = 0.007.

found that AIP was the better predictor for Mets in men than in women at 15-year follow-up. Our study also revealed that the incidence of Mets increased with AIP elevated in men while not in women. In the present study, it was found that waist as well as the rate of smoking and alcohol intake of the men were significantly higher compared to the women. In a cross-sectional study conducted in Iran, AIP was significantly correlated with waist circumference [8]. Waist circumference indicate central body fat mass and is associated with abdominal obesity [26]. The AIP is significantly higher in smokers than in non-smokers [27]. Smoking and alcohol are factors that contribute to increased body fat [28]. Therefore, we think that the AIP was a significant and independent predictor for Mets due to abdominal obesity and poor living habits(smoking and drinking) over time in men.

In this study, all participants were representative of a limited geographical region (Chinese) and may not reflect the AIP patterns from the other countries. So that future large population-based multicenter studies are recommended. Furthermore, Mets is just a complex multifactorial health problem, and it has limited practical utility as a diagnostic or management tool, but it is worthwhile to further elucidate the underlying pathways of the clustering of such a lot of risk factors.

The findings indicate that AIP is superior to other lipid parameters for predicting the risk of Mets in an urban Chinese population. The present study also reveals that elevated AIP is an important risk factor for developing Mets in men but not in women.

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Conflicts of interest

The authors declare that they have no competing interests.

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