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TITLE PAGE

Title:

Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

Running title: Prevalence and risk factors of retinopathy in MS

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ABSTRACT

PURPOSE. To investigate the relationship between metabolic syndrome (MS) and prevalence of retinopathy.

METHODS. A cross-section study was carried out from August 2013 to September 2014 in Fengyutan Sub-District. All participants underwent a standardized interview and extensive examination.

RESULTS. The prevalence for retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. Also higher prevalence of retinopathy with proliferative diabetic retinopathy (PDR) was found in patients with MS. In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% CI, 1.04-1.10, per year increase), higher systolic blood pressure (SBP) (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (DBP) (OR, 1.24; 95% CI, 1.12-1.35, per-10mmHg increase), higher fasting plasma glucose (OR, 1.17; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.07; 95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS.

CONCLUSIONS. The presence of MS and its components are significantly associated with the prevalence of retinopathy.

Keywords: Metabolic syndrome; Prevalence; Retinopathy; Risk factor.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterized by abdominal obesity, hyperglycemia, hyperlipidemia, and hypertension.[1] Insulin resistance has been proposed to be of key pathogenetic importance. The prevalence of MS is increasing East Asian countries including China, leading to increased morbidity and mortality due to type 2 diabetic mellitus (DM) and cardiovascular disease (CVD).[2] The MS is increasingly recognized as being a distinct entity affecting a large proportion of the Chinese population.[3,4] Patients with the MS are at known risk of development of large-vessel diseases and retinal microvascular abnormalities.[5,6] Some combinations of traits of MS may significantly contribute to identify subjects with insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8,9] It is unclear whether the MS is associated with retinopathy in North Chinese population. We examined the cross-sectional association of the MS and retinopathy in this population-based study.

METHODS

Study population

There were more than 80,000 residents and five communities (including Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District, Shenyang, North China. Firstly, four communities were randomly selected from five communities in Fengyutan Sub-District. Secondly, 400 households in each of four selected communities were randomly chosen. The participants had lived in Fengyutan for at least two years at the time the research was conducted. Then the selected

households were informed by community officers using message or telephone call. Finally, a total of 1400 subjects, aged over 40 years were randomly recruited from August 2013 to September 2014. After excluding the patients with cancer, hepatic failure, renal failure, severe psychiatric disturbance, any other systemic medical condition e.g. severe cardiac impairment or severe respiratory impairment, and subjects who did not want to attend this study voluntarily, a total of 1163 (response rate 83.07%) eligible participants attended this research.

Data collection

Information on age, smoking, drinking, and health status was obtained using a standardized questionnaire. In addition, participants were asked whether they suffer from DM and if the diagnosis was made by a physician. All subjects were also asked to provide information on their current medication. Thus, known diabetes was defined according to self-reported physician diagnosis or the use of anti-diabetic agents. Following a community office worker interview, all participants were asked to fast overnight (>8 hours) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without wearing hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second) at a 5-min interval using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP measurement with the fifth phase diastolic pressure was used for analysis. All the participants were took the stereo fundus photography to detect retinopathy by 45°

Non-Mydriatic Fundus Camera (CR6-45NM, Canon, Tokyo, Japan) through undilated pupils. For each subject, two images for each eye centered on the fovea and optic disk were taken in the physiologically within a darkened room. Each image was graded in a masked manner by two well-trained ophthalmologists separately for the presence of retinopathy lesions. If the grades were inconsistent, the other ophthalmologist would give the final diagnosis. The grade of retinopathy for each eye was determined and the individual classification was based upon the worse eye. There were 41 subjects that could not get a clear retinal image because anterior segment opacity. They accepted mydriasis with tropicamide 1% (Santen Pharmaceutical Co.,Ltd. Shiga, Japan) before 20 minutes of dark adaptation and binocular indirect ophthalmoscope by two ophthalmologists who reviewed retinal images.

The mayor and the welfare section of Fengyutan Sub-District approved this study. The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by Institutional Ethics Committee of The First Affiliated Hospital of China Medical University.

Laboratory methods

Blood was drawn from the antecubital vein for determinations of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose levels, and hemoglobin A_1c in the morning after 8 hours fast. Then 75-g oral glucose tolerance test (OGTT) would be done, 2 hours later blood was drawn again. All chemistries (enzymatic assay method) were measured at a commercially available laboratory (The

Endocrinology Laboratory, China Medical University, Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and Diabetes

The International Diabetes Federation 2005 (IDF) standards describe a waist circumstance for Chinese female of ≥80 cm and male of ≥90 cm plus 2 or more of the following 4 risk factors: 1) TG ≥1.70 mmol/L or specific treatment for this lipid abnormality; 2) HDL cholesterol <1.29 mmol/L or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes diagnosed according to 1999 WHO criteria.[11] Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12,13] The retinopathy was concerning about diabetic retinopathy except other microvascular changes namely vascular dilatation, focal narrowing and other changes. For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels. Drinking was defined as alcohol intake more than once per month during the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes

Statistical analyses

Mean±SD was used for measurement data. In univariate analysis, a *t*-test was applied for continuous variables and chi-square test (X^2) for nominal-scale data. Independent

risk factors for retinopathy were analyzed using multiple logistic regressions with step-wise approach. Data management and statistical analyses were performed using SPSS statistical software (Version 16.0, SPSS Inc., Chicago, IL). $P<0.05$ was considered statistically significant.

RESULTS

We recruited 1163 subjects mean age 67.09±5.18 (40-82 years) in this study, which contained 508 (43.68%) males. There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 showed that demographic data, selected clinical and laboratory findings in patients with and without MS.

The prevalence for retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, respectively. Prevalence of retinopathy was significantly higher in patients with MS ($p<0.05$). Table 2 showed that the prevalence of proliferative diabetic retinopathy (PDR) was significantly higher in patients with MS ($p<0.05$). In addition, 6.36% of all persons, 11.79% of diabetes, 18.18% of known diabetes, 7.72% of newly detected diabetes and 3.25% of nondiabetic persons had retinopathy (Fig. 1).

Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR were shown in Table 3. Patients with NPDR were significantly higher prevalence with newly detected diabetes mellitus (DM).

In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% confidence

interval (CI), 1.04-1.10, per year increase), higher systolic blood pressure (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (OR, 1.24; 95% CI, 1.12-1.35, per -10mmHg increase), higher plasma glucose (OR, 1.07; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.17; 95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A_1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (Table 4).

DISCUSSION

The data reported population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; it was a little higher than the study in Beijing.[14] Previous studies reported that the prevalence of the MS was 13.7% in Chinese adult populations. However, the prevalence of the MS was 50.0% in Chinese elder populations.[15,16] It was clear that the prevalence of MS was high and might be due to the number of Chinese elder increasing and would be representing a problem of public health in social.

Previous population-based studies in nondiabetic persons have suggested a prevalence of retinopathy, ranging from 3.5% to 9%.[17-24] It was similar to our outcomes (3.25%). However, another study in China had reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in urban, which may explain partially the lower prevalence found in our study. The overall prevalence of retinopathy was 6.36% in total subjects. It was a little higher than the results of previous meta-analysis in China.[26] Study by Keenan *et al.* showed that the

prevalence of retinopathy was 8.6% in patients with MS, and it was little lower than our results. Similarly, the prevalence of retinopathy (3.6%) in patients without MS was a slightly lower than that of this study.[24]

To the best of our knowledge, it was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population, and MS is an independent risk factor of retinopathy after adjusting age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy were highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in the MS group.[28] Two cross-section studies have reported the association between the retinopathy and MS in subjects without diabetes. The Atherosclerosis Risk in Communities (ARIC) Study revealed a relationship between MS and retinopathy in non-diabetic subjects,[6] whereas in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal the relationship between MS and retinopathy in the non-diabetic population, it might be due to this cross-sectional study could not prevent itself from being with methodological problems. The study design is incapable of estimating causal relation directly. In addition, the results of our study proved higher prevalence of retinopathy including PDR in patients with MS. Therefore, we could hypotheses that MS as a risk factor for retinopathy in the subjects, and more prospective studies are warranted to determine the significance of the MS for predicting risk of retinopathy.

In this study, we found associations of some individual components of MS with a range of retinopathy. After adjusting for age, gender, smoking, drinking and other variables, we also found that no matter the presence of MS or not, as defined by the IDF guideline, longer diabetes duration, higher systolic blood pressure, higher fasting plasma glucose, 2h-postprandial plasma glucose, and higher hemoglobinA_1c were the independent risk factors for retinopathy. Higher diastolic blood pressure was the independent risk factor for retinopathy in patients with MS. HDL levels was not associated with the presence of retinopathy lesions, and some early studies also have revealed this conclusion.[24] According to our results, we also had not found significant association between smoking and drinking in patients with or without MS.

The short coming for this study included it was a population based study in community, so there were no fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) for assistant diagnosis. The study was conducted only in four communities of Shenyang, so there is a selection bias. In addition, we did not investigate the type of diabetes for all subjects.

In summary, our data demonstrate the presence of MS and its components are significantly associated with the prevalence of retinopathy. Rather, in order to prevent retinopathy development, risk factors should be controlled in patients with or without MS. More comprehensive studies are needed to clarify the roles of MS and also its relationship with retinal vascular disorders.

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Contributors

L. L. and J.G. and Z.Y. and J.Y.W and J.L. and W.P.T. researched data. D.S.H. and L.L wrote the manuscript and researched data. L.C. and W.P.T. edited the manuscript. L.L. and L.C. and W.P.T. contributed to the discussion. L.L. and D.D.H. wrote the manuscript.

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Figure legend:

Fig. 1: Prevalence of retinopathy in different groups of this study. MS: metabolic syndrome.

Table 1. Demographic data, selected clinical and laboratory findings in patients with and without MS.

Parameter	With MS(n = 498)	Without MS (n = 665)	p-value
Age (years)	67.1 ±4.2	68.7 ±4.4	0.12
Male (%)	40.2	42.3	0.26
Weight (kg)	74.3 ±12.7	83.4 ±13.6	< 0.001
Height (cm)	168.5 ±10.1	169.3 ±9.7	< 0.001
BMI (kg/m^2)	27.8 ±4.4	30.9 ±4.7	< 0.001
Waist (cm)	94.5 ±9.2	101.4 ±10.3	< 0.001
SBP (mmHg)	124.3 ±12.7	138.4 ±14.2	< 0.001
DBP (mmHg)	78.6 ±9.2	85.0 ±8.6	< 0.001
Triglyceride (mg/dL)	146.4±10.7	176.4±10.3	< 0.001
HDL (mg/dL)	65.2 ±17.4	54.2 ±16.1	< 0.001
FPG (mg/dL)	109.8 ±13.4	97.4 ±11.3	< 0.001
2hPPG (mg/dL)	209.7±11.9	167.1±12.5	< 0.001
HbA_1c (% (mmol/mol))	5.4±0.8	7.1 ±1.1	< 0.001
Duration of DM (years)	5.1 ±1.2	8.2 ±1.6	0.01
Smoking (%)	35.6	40.3	0.11
Drinking (%)	39.8	43.3	0.07
Newly detected DM (%)	19.3	24.5	< 0.001

MS: metabolic syndrome; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1C; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 2. Retinopathy grade in patients with and without MS.

Retinopathy	With MS (n=48)	Without MS (n=26)
Mild-NPDR	10	9
Moderate-NPDR	11	6
Severe-NPDR	12	6
PDR	15	5

MS: metabolic syndrome; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy

Table 3. Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR.

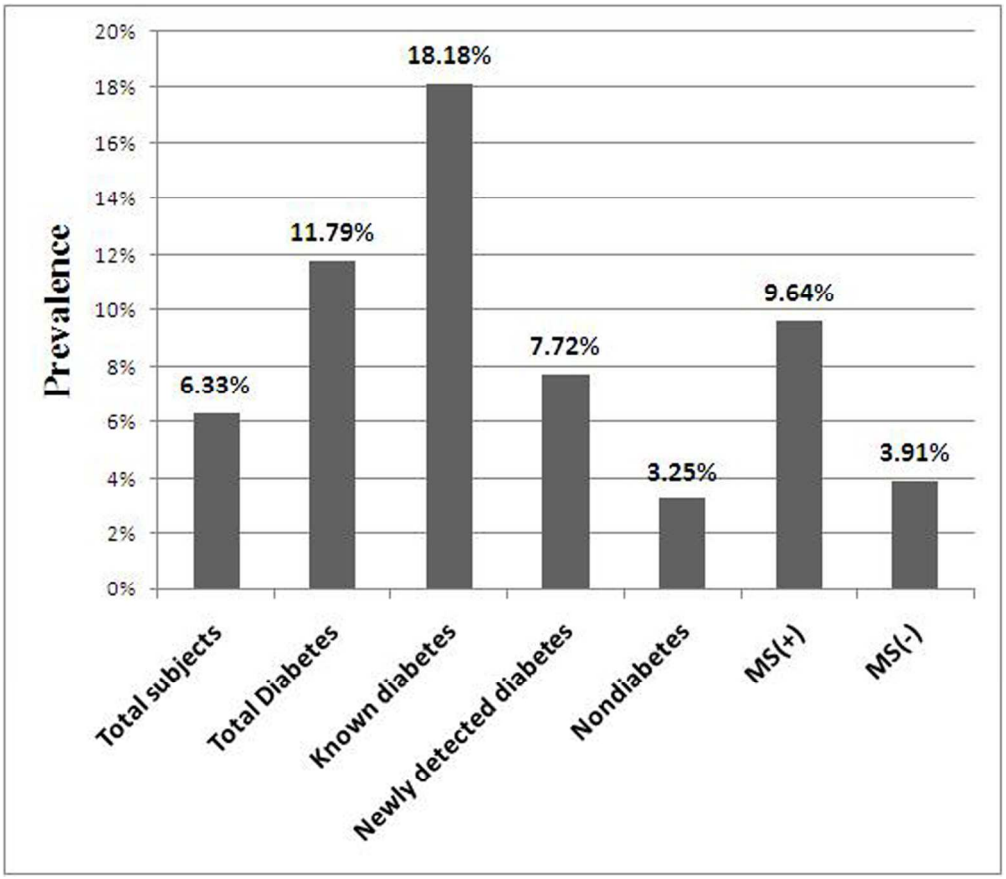
Parameter	NPDR (n=54)	PDR (n=20)	*p*-value
Age (years)	68.1 ±4.1	70.7 ±3.4	0.04
Male (%)	45.2	44.6	0.86
Weight (kg)	84.3 ±10.6	85.6 ±11.2	0.54
Height (cm)	166.8 ±11.2	167.7 ±10.7	0.66
BMI (kg/m^2)	26.9 ±4.3	31.1 ±4.2	< 0.001
Waist (cm)	100.6 ±10.2	102.4 ±11.1	0.22
SBP (mmHg)	123.3 ±11.7	132.5 ±12.2	< 0.001
DBP (mmHg)	77.8 ±8.6	84.9 ±7.9	< 0.001
Triglyceride (mg/dL)	145.8±9.7	175.8±11.3	< 0.001
HDL (mg/dL)	64.2 ±16.2	58.6 ±15.1	0.01
FPG (mg/dL)	96.8 ±10.5	108.9 ±12.5	< 0.001
2hPPG (mg/dL)	199.2±11.4	214.8±12.9	< 0.001
HbA_1c (% (mmol/mol))	6.7	8.8	< 0.001
Duration of DM (years)	6.1 ±1.3	9.4 ±1.5	0.02
Smoking (%)	40.6	42.4	0.14
Drinking (%)	29.9	31.3	0.11
Newly detected DM (%)	30.2	20.5	< 0.001

PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 4. Logistic regression analyses for retinopathy in the population with and without MS.

	With MS				Without MS			
	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value
Age (per 10-year)	0.94 (0.78–1.07)	0.39	0.86 (0.58–1.19)	0.11	0.96 (0.74–1.24)	0.70	0.79 (0.41–1.35)	0.22
Gender (female vs male)	0.81 (0.62–1.04)	0.13	0.72 (0.54–1.02)	0.06	1.20 (0.89–1.68)	0.45	1.02 (0.59–1.72)	0.98
BMI (per kg/m^2)	0.97 (0.94–0.99)	0.01	0.98 (0.92–1.06)	0.41	0.96 (0.91–1.00)	0.06	0.99 (0.93–1.04)	0.60
Diabetes duration (per 10-year)	1.06 (1.03–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.10)	<0.001
Weight (per 10-kg)	1.05 (0.71–1.63)	0.79	1.04 (0.62–1.73)	0.88	1.14 (0.52–2.43)	0.74	1.19 (0.44–3.10)	0.74
Height (per 10-cm)	1.43 (0.97–2.06)	0.06	1.31 (0.82–2.09)	0.26	1.69 (0.88–3.26)	0.13	1.31 (0.54–3.18)	0.56
Waist (per 10-cm)	1.34 (0.78–2.32)	0.26	1.32 (0.68–2.57)	0.38	0.98 (0.36–2.52)	0.94	0.67 (0.21–2.28)	0.55
SBP (per 10-mmHg)	1.14 (1.04–1.22)	<0.001	1.16 (1.09–1.29)	<0.001	1.27 (1.14–1.46)	<0.001	1.35 (1.18–1.55)	<0.001
DBP (per 10-mmHg)	1.12 (1.05–1.22)	<0.001	1.24 (1.12–1.35)	0.02	1.15 (1.04–1.28)	<0.001	1.18 (0.97–1.38)	0.66
Triglycerides (per 10-mg/dL)	1.04 (0.88–1.19)	0.66	0.95 (0.78–1.12)	0.49	1.19 (0.94–1.48)	0.14	1.13 (0.86–1.47)	0.39
HDL cholesterol (per 10-mg/dL)	0.87 (0.64–1.18)	0.49	0.77 (0.53–1.12)	0.20	1.03 (0.88–1.22)	0.51	1.13 (0.85–1.44)	0.37
FPG (per 10-mg/dL)	1.06 (1.01–1.11)	<0.001	1.07 (1.02–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.11 (1.05–1.17)	<0.001
2hPPG (per 10-mg/dL)	1.16 (1.02–1.32)	<0.001	1.17 (1.12–1.21)	<0.001	1.12 (1.01–1.21)	<0.001	1.13 (1.04–1.22)	<0.001
HbA_1c (per % (mmol/mol))	1.25 (1.15–1.35)	<0.001	1.23 (1.13–1.34)	<0.001	1.29 (1.15–1.44)	<0.001	1.26 (1.10–1.44)	<0.001
Current smoker	1.22 (0.87–1.68)	0.39	1.37 (0.79–2.09)	0.47	1.21 (0.68–1.86)	0.59	1.42 (0.68–2.46)	0.44
Current drinker	1.12 (0.57–1.78)	0.33	1.27 (0.68–2.28)	0.65	1.19 (0.58–2.46)	0.59	1.20 (0.55–3.16)	0.55
Newly detected DM	0.89 (0.55–1.26)	0.46	0.78 (0.55–1.23)	0.21	1.00 (0.84–1.32)	0.56	0.96 (0.75–1.33)	0.35

MS: metabolic syndrome; BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose. *Adjusted for age and gender. # Adjusted for age, gender, body mass index, HbA1c, duration of diabetes, SBP and DBP), drinking and smoking.



149x130mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

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TITLE PAGE

Title:

Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

Running title: Prevalence and risk factors of retinopathy in MS

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ABSTRACT

Objectives: To investigate the relationship between metabolic syndrome (MS) and prevalence of retinopathy.

Design: A cross-section study was carried out from August 2013 to September 2014 in Fengyutan Sub-District.

Primary and secondary outcome measures: A total of 1163 eligible participants attended this research. All the participants were took the stereo fundus photography to detect retinopathy. The discrepancy of prevalence for retinopathy in different participants was described.

Results: The prevalence for retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. Also higher prevalence of retinopathy with proliferative diabetic retinopathy (PDR) was found in patients with MS. In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% CI, 1.04-1.10, per year increase), higher systolic blood pressure (SBP) (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (DBP) (OR, 1.24; 95% CI, 1.12-1.35, per-10mmHg increase), higher fasting plasma glucose (OR, 1.17; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.07; 95% CI,1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS.

Conclusions: The presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.

Keywords: Metabolic syndrome; Prevalence; Retinopathy; Risk factor.

Strengths and limitations of this study

- It was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population.
- We found that the presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.
- We did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterized by abdominal obesity, hyperglycemia, hyperlipidemia, and hypertension.[1] Insulin resistance has been proposed to be of key pathogenetic importance. The prevalence of MS is increasing East Asian countries including China, leading to increased morbidity and mortality due to type 2 diabetic mellitus (DM) and cardiovascular disease (CVD).[2] The MS is increasingly recognized as being a distinct entity affecting a large proportion of the Chinese population.[3,4] Patients with the MS are at known risk of development of large-vessel diseases and retinal microvascular abnormalities.[5,6] Some combinations of traits of MS may significantly contribute to identify subjects with

insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8,9] It is unclear whether the MS is associated with retinopathy in North Chinese population. The retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated in this study. We examined the cross-sectional association of the MS and retinopathy in this population-based study.

METHODS

Study population

There were more than 80,000 residents and five communities (including Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District, Shenyang, and North China. Firstly, four communities were randomly selected from five communities in Fengyutan Sub-District. Secondly, 400 households in each of four selected communities were randomly chosen. The participants had lived in Fengyutan for at least two years at the time the research was conducted. Then the selected households were informed by community officers using message or telephone call. Finally, a total of 1400 subjects, aged over 40 years were randomly recruited from August 2013 to September 2014. After excluding the patients with cancer, hepatic failure, renal failure, severe psychiatric disturbance, any other systemic medical condition e.g. severe cardiac impairment or severe respiratory impairment, and subjects who did not want to attend this study voluntarily, a total of 1163 (response rate 83.07%) eligible participants attended this research. Subjects were not attended this study voluntarily or with serious illness such as cancer, liver and kidney function failure were excluded.

Data collection

Information on name, gender, age, smoking, drinking, and health status such as duration of diabetes, hypertension duration, past medical history and treatment methods were obtained using a standardized questionnaire. In addition, participants were asked whether they suffer from DM and if the diagnosis was made by a physician. All subjects were also asked to provide information on their current medication. Thus, known diabetes was defined according to self-reported physician diagnosis or the use of anti-diabetic agents. Following a community office worker interview, all participants were asked to fast overnight (>8 hours) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without wearing hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second) at a 5-min interval using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP measurement with the fifth phase diastolic pressure was used for analysis. All the participants were took the stereo fundus photography to detect retinopathy by 45° Non-Mydriatic Fundus Camera (CR6-45NM, Canon, Tokyo, Japan) through undilated pupils. For each subject, two images for each eye centered on the fovea and optic disk were taken in the physiologically within a darkened room. Each image was graded in a masked manner by two well-trained ophthalmologists separately for the presence of retinopathy lesions. If the grades were inconsistent, the other ophthalmologist would give the final diagnosis. The grade of

retinopathy for each eye was determined and the individual classification was based upon the worse eye. There were 41 subjects that could not get a clear retinal image because anterior segment opacity. They accepted mydriasis with tropicamide 1% (Santen Pharmaceutical Co.,Ltd. Shiga, Japan) before 20 minutes of dark adaptation and binocular indirect ophthalmoscope by two ophthalmologists who reviewed retinal images.

The mayor and the welfare section of Fengyutan Sub-District approved this study. The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by Institutional Ethics Committee of The First Affiliated Hospital of China Medical University.

Laboratory methods

Blood was drawn from the antecubital vein for determinations of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose levels, and hemoglobin A_1c in the morning after 8 hours fast. Then 75-g oral glucose tolerance test (OGTT) would be done, 2 hours later blood was drawn again. All chemistries (enzymatic assay method) were measured at a commercially available laboratory (The Endocrinology Laboratory, China Medical University, and Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and Diabetes

The International Diabetes Federation 2005 (IDF) standards describe a waist circumstance for Chinese female of ≥80 cm and male of ≥90 cm plus 2 or more of the following 4 risk factors: 1) TG ≥1.70 mmol/L or specific treatment for this lipid

abnormality; 2) HDL cholesterol <1.29 mmol/L or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes diagnosed according to 1999 WHO criteria.[11] Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12,13] The retinopathy was concerning about diabetic retinopathy except other microvascular changes namely vascular dilatation, focal narrowing and other changes. For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels. Drinking was defined as alcohol intake more than once per month during the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes.

Statistical analyses

Mean±SD was used for measurement data. In univariate analysis, a *t*-test was applied for continuous variables and chi-square test (X^2) for nominal-scale data. Independent risk factors for retinopathy were analyzed using multiple logistic regressions with step-wise approach. Data management and statistical analyses were performed using SPSS statistical software (Version 16.0, SPSS Inc., and Chicago, IL). $P<0.05$ was considered statistically significant.

RESULTS

~~We recruited 1163 subjects mean age 67.09±5.18 (40-82 years) in this study, which contained 508 (43.68%) males.~~ There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 showed that demographic data, selected clinical and laboratory findings in patients with and without MS.

The prevalence for retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, respectively. Prevalence of retinopathy was significantly higher in patients with MS ($p<0.05$). Table 2 showed that the prevalence of proliferative diabetic retinopathy (PDR) was significantly higher in patients with MS ($p<0.05$). In addition, 6.36% of all persons, 11.79% of diabetes, 18.18% of known diabetes, 7.72% of newly detected diabetes and 3.25% of nondiabetic persons had retinopathy in Table 3. The characteristics of patients with retinopathy in nondiabetic persons were shown in Table 4.

Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR were shown in Table 5. Patients with NPDR were significantly higher prevalence with newly detected diabetes mellitus (DM).

In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% confidence interval (CI), 1.04-1.10, per year increase), higher systolic blood pressure (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (OR, 1.24; 95% CI, 1.12-1.35, per -10mmHg increase), higher plasma glucose (OR, 1.07; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.17;

95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A_1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (Table 6).

DISCUSSION

The data reported population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; it was a little higher than the study in Beijing.[14] Previous studies reported that the prevalence of the MS was 13.7% in Chinese adult populations. However, the prevalence of the MS was 50.0% in Chinese elder populations.[15,16] It was clear that the prevalence of MS was high and might be due to the number of Chinese elder increasing and would be representing a problem of public health in social.

Previous population-based studies in nondiabetic persons have suggested a prevalence of retinopathy, ranging from 3.5% to 9%.[17-24] It was similar to our outcomes (3.25%). However, another study in China had reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in urban, which may explain partially the lower prevalence found in our study. The overall prevalence of retinopathy was 6.36% in total subjects. It was a little higher than the results of previous meta-analysis in China.[26] In our study, the retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated. Study by Keenan *et al.* showed that the prevalence of retinopathy was 8.6% in patients with MS, and it was little lower than our results. Similarly, the prevalence of retinopathy (3.6%) in patients without MS was a slightly lower than that of this study.[24]

To the best of our knowledge, it was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population, and MS is an independent risk factor of retinopathy after adjusting age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy were highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in the MS group.[28] Two cross-section studies have reported the association between the retinopathy and MS in subjects without diabetes. The Atherosclerosis Risk in Communities (ARIC) Study revealed a relationship between MS and retinopathy in non-diabetic subjects,[6] whereas in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal the relationship between MS and retinopathy in the non-diabetic population, it might be due to this cross-sectional study could not prevent itself from being with methodological problems. The study design is incapable of estimating causal relation directly. In addition, the results of our study proved higher prevalence of retinopathy including PDR in patients with MS. Therefore, we could hypotheses that MS as a risk factor for retinopathy in the subjects, and more prospective studies are warranted to determine the significance of the MS for predicting risk of retinopathy.

In this study, we found associations of some individual components of MS with a range of retinopathy. After adjusting for age, gender, smoking, drinking and other variables, we also found that no matter the presence of MS or not, as defined by the

IDF guideline, longer diabetes duration, higher systolic blood pressure, higher fasting plasma glucose, 2h-postprandial plasma glucose, and higher hemoglobinA_1c were the independent risk factors for retinopathy. Higher diastolic blood pressure was the independent risk factor for retinopathy in patients with MS. HDL levels was not associated with the presence of retinopathy lesions, and some early studies also have revealed this conclusion.[24] According to our results, we also had not found significant association between smoking and drinking in patients with or without MS.

The short coming for this study included it was a population based study in community, so there were no fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) for assistant diagnosis. The study was conducted only in four communities of Shenyang, so there is a selection bias. In addition, we did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

CONCLUSION

In summary, our data demonstrate the presence of MS components is significantly associated with the prevalence of retinopathy. Rather, in order to prevent retinopathy development, risk factors should be controlled in patients with or without MS. More comprehensive studies are needed to clarify the roles of MS and also its relationship with retinal vascular disorders.

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Competing interests: None declared.

Ethics approval: The study was approved by the Ethics Committee of The First Affiliated Hospital Of China Medical University.

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Data sharing statement: No additional data are available.

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Table 1. Demographic data, selected clinical and laboratory findings in patients with and without MS.

Parameter	With MS(n = 498)	Without MS (n = 665)	p-value
Age (years)	67.1 ±4.2	68.7 ±4.4	0.12
Male (%)	40.2	42.3	0.26
Weight (kg)	74.3 ±12.7	83.4 ±13.6	< 0.001
Height (cm)	168.5 ±10.1	169.3 ±9.7	< 0.001
BMI (kg/m^2)	27.8 ±4.4	30.9 ±4.7	< 0.001
Waist (cm)	94.5 ±9.2	101.4 ±10.3	< 0.001
SBP (mmHg)	124.3 ±12.7	138.4 ±14.2	< 0.001
DBP (mmHg)	78.6 ±9.2	85.0 ±8.6	< 0.001
Triglyceride (mg/dL)	146.4±10.7	176.4±10.3	< 0.001
HDL (mg/dL)	65.2 ±17.4	54.2 ±16.1	< 0.001
FPG (mg/dL)	109.8 ±13.4	97.4 ±11.3	< 0.001
2hPPG (mg/dL)	209.7±11.9	167.1±12.5	< 0.001
HbA_1c (% (mmol/mol))	5.4±0.8	7.1 ±1.1	< 0.001
Duration of DM (years)	5.1 ±1.2	8.2 ±1.6	0.01
Smoking (%)	35.6	40.3	0.11
Drinking (%)	39.8	43.3	0.07
Newly detected DM (%)	19.3	24.5	< 0.001

MS: metabolic syndrome; BMI: body mass index; HbA_1c: hemoglobin A_1C; HDL: high-density lipoprotein; OR:

odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 2. Retinopathy grade in patients with and without MS.

Retinopathy	With MS (n=48)	Without MS (n=26)
Mild-NPDR	10	9
Moderate-NPDR	11	6
Severe-NPDR	12	6
PDR	15	5

MS: metabolic syndrome; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy

Table 3. Prevalence of retinopathy in different groups of this study.

Item	Retinopathy (n)	Prevalence (%)
Total diabetes	55	11.79
Known diabetes	34	18.18

Newly detected diabetes	21	7.72
Non-diabetes	19	3.25
With MS	48	9.64
Without MS	26	3.91
Total subjects	74	6.36

MS: metabolic syndrome.

Table 4. Demographic data, selected clinical and laboratory findings in retinopathy patients with nondiabetes.

Parameter	Retinopathy patients with nondiabetes
Age (years)	59.1 ±3.2
Male (%)	44.3
Weight (kg)	75.3 ±11.6
Height (cm)	169.8 ±11.1
BMI (kg/m^2)	28.9 ±5.1
Waist (cm)	95.5 ±8.9
SBP (mmHg)	126.3 ±11.6
DBP (mmHg)	79.5 ±9.1
Triglyceride (mg/dL)	148.5±10.6
HDL (mg/dL)	66.3 ±18.1
FPG (mg/dL)	98.7 ±10.5
2hPPG (mg/dL)	189.8±10.5
HbA_1c (% (mmol/mol))	5.2±0.6
Smoking (%)	32.1
Drinking (%)	41.8

BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; SBP: systolic blood pressure; SBP: systolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 5. Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR.

Parameter	NPDR (n=54)	PDR (n=20)	*p*-value
Age (years)	68.1 ±4.1	70.7 ±3.4	0.04
Male (%)	45.2	44.6	0.86
Weight (kg)	84.3 ±10.6	85.6 ±11.2	0.54
Height (cm)	166.8 ±11.2	167.7 ±10.7	0.66
BMI (kg/m^2)	26.9 ±4.3	31.1 ±4.2	< 0.001
Waist (cm)	100.6 ±10.2	102.4 ±11.1	0.22
SBP (mmHg)	123.3 ±11.7	132.5 ±12.2	< 0.001
DBP (mmHg)	77.8 ±8.6	84.9 ±7.9	< 0.001
Triglyceride (mg/dL)	145.8±9.7	175.8±11.3	< 0.001
HDL (mg/dL)	64.2 ±16.2	58.6 ±15.1	0.01
FPG (mg/dL)	96.8 ±10.5	108.9 ±12.5	< 0.001
2hPPG (mg/dL)	199.2±11.4	214.8±12.9	< 0.001
HbA_1c (% (mmol/mol))	6.7	8.8	< 0.001
Duration of DM (years)	6.1 ±1.3	9.4 ±1.5	0.02
Smoking (%)	40.6	42.4	0.14
Drinking (%)	29.9	31.3	0.11
Newly detected DM (%)	30.2	20.5	< 0.001

PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP:

systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 6. Logistic regression analyses for retinopathy in the population with and without MS.

	With MS				Without MS			
	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value
Age (per 10-year)	0.94 (0.78–1.07)	0.39	0.86 (0.58–1.19)	0.11	0.96 (0.74–1.24)	0.70	0.79 (0.41–1.35)	0.22
Gender (female vs male)	0.81 (0.62–1.04)	0.13	0.72 (0.54–1.02)	0.06	1.20 (0.89–1.68)	0.45	1.02 (0.59–1.72)	0.98
BMI (per kg/m^2)	0.97 (0.94–0.99)	0.01	0.98 (0.92–1.06)	0.41	0.96 (0.91–1.00)	0.06	0.99 (0.93–1.04)	0.60
Diabetes duration (per 10-year)	1.06 (1.03–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.10)	<0.001
Weight (per 10-kg)	1.05 (0.71–1.63)	0.79	1.04 (0.62–1.73)	0.88	1.14 (0.52–2.43)	0.74	1.19 (0.44–3.10)	0.74
Height (per 10-cm)	1.43 (0.97–2.06)	0.06	1.31 (0.82–2.09)	0.26	1.69 (0.88–3.26)	0.13	1.31 (0.54–3.18)	0.56
Waist (per 10-cm)	1.34 (0.78–2.32)	0.26	1.32 (0.68–2.57)	0.38	0.98 (0.36–2.52)	0.94	0.67 (0.21–2.28)	0.55
SBP (per 10-mmHg)	1.14 (1.04–1.22)	<0.001	1.16 (1.09–1.29)	<0.001	1.27 (1.14–1.46)	<0.001	1.35 (1.18–1.55)	<0.001
DBP (per 10-mmHg)	1.12 (1.05–1.22)	<0.001	1.24 (1.12–1.35)	0.02	1.15 (1.04–1.28)	<0.001	1.18 (0.97–1.38)	0.66
Triglycerides (per	1.04 (0.88–1.19)	0.66	0.95 (0.78–1.12)	0.49	1.19 (0.94–1.48)	0.14	1.13 (0.86–1.47)	0.39

10-mg/dL)								
HDL cholesterol (per 10-mg/dL)	0.87 (0.64–1.18)	0.49	0.77 (0.53–1.12)	0.20	1.03 (0.88–1.22)	0.51	1.13 (0.85–1.44)	0.37
FPG (per 10-mg/dL)	1.06 (1.01–1.11)	<0.001	1.07 (1.02–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.11 (1.05–1.17)	<0.001
2hPPG (per 10-mg/dL)	1.16 (1.02–1.32)	<0.001	1.17 (1.12–1.21)	<0.001	1.12 (1.01–1.21)	<0.001	1.13 (1.04–1.22)	<0.001
HbA_1c (per % (mmol/mol))	1.25 (1.15–1.35)	<0.001	1.23 (1.13–1.34)	<0.001	1.29 (1.15–1.44)	<0.001	1.26 (1.10–1.44)	<0.001
Current smoker	1.22 (0.87–1.68)	0.39	1.37 (0.79–2.09)	0.47	1.21 (0.68–1.86)	0.59	1.42 (0.68–2.46)	0.44
Current drinker	1.12 (0.57–1.78)	0.33	1.27 (0.68–2.28)	0.65	1.19 (0.58–2.46)	0.59	1.20 (0.55–3.16)	0.55
Newly detected DM	0.89 (0.55–1.26)	0.46	0.78 (0.55–1.23)	0.21	1.00 (0.84–1.32)	0.56	0.96 (0.75–1.33)	0.35

MS: metabolic syndrome; BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

*Adjusted for age and gender. # Adjusted for age, gender, body mass index, HbA1c, duration of diabetes, SBP and DBP), drinking and smoking.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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TITLE PAGE

Title:

Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

Running title: Prevalence and risk factors of retinopathy in MS

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ABSTRACT

Objectives: To investigate the relationship between metabolic syndrome (MS) and prevalence of retinopathy.

Design: A cross-section study was carried out from August 2013 to September 2014 in Fengyutan Sub-District.

Primary and secondary outcome measures: A total of 1163 eligible participants attended this research. All the participants were took the stereo fundus photography to detect retinopathy. The discrepancy of prevalence for retinopathy in different participants was described.

Results: The prevalence for retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. Also higher prevalence of retinopathy with proliferative diabetic retinopathy (PDR) was found in patients with MS. In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% CI, 1.04-1.10, per year increase), higher systolic blood pressure (SBP) (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (DBP) (OR, 1.24; 95% CI, 1.12-1.35, per-10mmHg increase), higher fasting plasma glucose (OR, 1.17; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.07; 95% CI,1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS.

Conclusions: The presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.

Keywords: Metabolic syndrome; Prevalence; Retinopathy; Risk factor.

Strengths and limitations of this study

- It was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population.
- We found that the presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.
- We did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterized by abdominal obesity, hyperglycemia, hyperlipidemia, and hypertension.[1] Insulin resistance has been proposed to be of key pathogenetic importance. The prevalence of MS is increasing East Asian countries including China, leading to increased morbidity and mortality due to type 2 diabetic mellitus (DM) and cardiovascular disease (CVD).[2] The MS is increasingly recognized as being a distinct entity affecting a large proportion of the Chinese population.[3,4] Patients with the MS are at known risk of development of large-vessel diseases and retinal microvascular abnormalities.[5,6] Some combinations of traits of MS may significantly contribute to identify subjects with

insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8,9] It is unclear whether the MS is associated with retinopathy in North Chinese population. The retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated in this study. We examined the cross-sectional association of the MS and retinopathy in this population-based study.

METHODS

Study population

There were more than 80,000 residents and five communities (including Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District, Shenyang, and North China. Firstly, four communities were randomly selected from five communities in Fengyutan Sub-District. Secondly, 400 households in each of four selected communities were randomly chosen. The participants had lived in Fengyutan for at least two years at the time the research was conducted. Then the selected households were informed by community officers using message or telephone call. Finally, a total of 1400 subjects, aged over 40 years were randomly recruited from August 2013 to September 2014. After excluding the patients with cancer, hepatic failure, renal failure, severe psychiatric disturbance, any other systemic medical condition e.g. severe cardiac impairment or severe respiratory impairment, and subjects who did not want to attend this study voluntarily, a total of 1163 (response rate 83.07%) eligible participants attended this research. Subjects were not attended this study voluntarily or with serious illness such as cancer, liver and kidney function failure were excluded.

Data collection

Information on name, gender, age, smoking, drinking, and health status such as duration of diabetes, hypertension duration, past medical history and treatment methods were obtained using a standardized questionnaire. In addition, participants were asked whether they suffer from DM and if the diagnosis was made by a physician. All subjects were also asked to provide information on their current medication. Thus, known diabetes was defined according to self-reported physician diagnosis or the use of anti-diabetic agents. Following a community office worker interview, all participants were asked to fast overnight (>8 hours) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without wearing hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second) at a 5-min interval using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP measurement with the fifth phase diastolic pressure was used for analysis. All the participants were took the stereo fundus photography to detect retinopathy by 45° Non-Mydriatic Fundus Camera (CR6-45NM, Canon, Tokyo, Japan) through undilated pupils. For each subject, two images for each eye centered on the fovea and optic disk were taken in the physiologically within a darkened room. Each image was graded in a masked manner by two well-trained ophthalmologists separately for the presence of retinopathy lesions. If the grades were inconsistent, the other ophthalmologist would give the final diagnosis. The grade of

retinopathy for each eye was determined and the individual classification was based upon the worse eye. There were 41 subjects that could not get a clear retinal image because anterior segment opacity. They accepted mydriasis with tropicamide 1% (Santen Pharmaceutical Co.,Ltd. Shiga, Japan) before 20 minutes of dark adaptation and binocular indirect ophthalmoscope by two ophthalmologists who reviewed retinal images.

The mayor and the welfare section of Fengyutan Sub-District approved this study. The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by Institutional Ethics Committee of The First Affiliated Hospital of China Medical University.

Laboratory methods

Blood was drawn from the antecubital vein for determinations of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose levels, and hemoglobin A_1c in the morning after 8 hours fast. Then 75-g oral glucose tolerance test (OGTT) would be done, 2 hours later blood was drawn again. All chemistries (enzymatic assay method) were measured at a commercially available laboratory (The Endocrinology Laboratory, China Medical University, and Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and Diabetes

The International Diabetes Federation 2005 (IDF) standards describe a waist circumstance for Chinese female of ≥80 cm and male of ≥90 cm plus 2 or more of the following 4 risk factors: 1) TG ≥1.70 mmol/L or specific treatment for this lipid

abnormality; 2) HDL cholesterol <1.29 mmol/L or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes diagnosed according to 1999 WHO criteria.[11] Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12,13] The retinopathy was concerning about diabetic retinopathy except other microvascular changes namely vascular dilatation, focal narrowing and other changes. For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels. Drinking was defined as alcohol intake more than once per month during the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes.

Statistical analyses

Mean±SD was used for measurement data. In univariate analysis, a *t*-test was applied for continuous variables and chi-square test (X^2) for nominal-scale data. Independent risk factors for retinopathy were analyzed using multiple logistic regressions with step-wise approach. Data management and statistical analyses were performed using SPSS statistical software (Version 16.0, SPSS Inc., and Chicago, IL). $P<0.05$ was considered statistically significant.

RESULTS

There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 showed that demographic data, selected clinical and laboratory findings in patients with and without MS.

The prevalence for retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, respectively. Prevalence of retinopathy was significantly higher in patients with MS ($p<0.05$). Table 2 showed that the prevalence of proliferative diabetic retinopathy (PDR) was significantly higher in patients with MS ($p<0.05$). In addition, 6.36% of all persons, 11.79% of diabetes, 18.18% of known diabetes, 7.72% of newly detected diabetes and 3.25% of nondiabetic persons had retinopathy in Table 3. The characteristics of patients with retinopathy in nondiabetic persons were shown in Table 4.

Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR were shown in Table 5. Patients with NPDR were significantly higher prevalence with newly detected diabetes mellitus (DM).

In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% confidence interval (CI), 1.04-1.10, per year increase), higher systolic blood pressure (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (OR, 1.24; 95% CI, 1.12-1.35, per -10mmHg increase), higher plasma glucose (OR, 1.07; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.17; 95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A_1c (OR, 1.23;

95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (Table 6).

DISCUSSION

The data reported population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; it was a little higher than the study in Beijing.[14] Previous studies reported that the prevalence of the MS was 13.7% in Chinese adult populations. However, the prevalence of the MS was 50.0% in Chinese elder populations.[15,16] It was clear that the prevalence of MS was high and might be due to the number of Chinese elder increasing and would be representing a problem of public health in social.

Previous population-based studies in nondiabetic persons have suggested a prevalence of retinopathy, ranging from 3.5% to 9%.[17-24] It was similar to our outcomes (3.25%). However, another study in China had reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in urban, which may explain partially the lower prevalence found in our study. The overall prevalence of retinopathy was 6.36% in total subjects. It was a little higher than the results of previous meta-analysis in China.[26] In our study, the retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated. Study by Keenan *et al.* showed that the prevalence of retinopathy was 8.6% in patients with MS, and it was little lower than our results. Similarly, the prevalence of retinopathy (3.6%) in patients without MS was a slightly lower than that of this study.[24]

To the best of our knowledge, it was the first population-based study provided

evidence that the relationship between MS and retinopathy in North Chinese population, and MS is an independent risk factor of retinopathy after adjusting age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy were highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in the MS group.[28] Two cross-section studies have reported the association between the retinopathy and MS in subjects without diabetes. The Atherosclerosis Risk in Communities (ARIC) Study revealed a relationship between MS and retinopathy in non-diabetic subjects,[6] whereas in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal the relationship between MS and retinopathy in the non-diabetic population, it might be due to this cross-sectional study could not prevent itself from being with methodological problems. The study design is incapable of estimating causal relation directly. In addition, the results of our study proved higher prevalence of retinopathy including PDR in patients with MS. Therefore, we could hypotheses that MS as a risk factor for retinopathy in the subjects, and more prospective studies are warranted to determine the significance of the MS for predicting risk of retinopathy.

In this study, we found associations of some individual components of MS with a range of retinopathy. After adjusting for age, gender, smoking, drinking and other variables, we also found that no matter the presence of MS or not, as defined by the IDF guideline, longer diabetes duration, higher systolic blood pressure, higher fasting

plasma glucose, 2h-postprandial plasma glucose, and higher hemoglobinA_1c were the independent risk factors for retinopathy. Higher diastolic blood pressure was the independent risk factor for retinopathy in patients with MS. HDL levels was not associated with the presence of retinopathy lesions, and some early studies also have revealed this conclusion.[24] According to our results, we also had not found significant association between smoking and drinking in patients with or without MS.

The short coming for this study included it was a population based study in community, so there were no fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) for assistant diagnosis. The study was conducted only in four communities of Shenyang, so there is a selection bias. In addition, we did not investigate the type of diabetes for all subjects. According to study design in community, it was difficult to separate metabolic syndrome and diabetes, further studies are needed to investigate the association between retinopathy and metabolic syndrome patients without diabetes. So the prevalence of retinopathy in diabetes was lower representative. In our study, we used indirect ophthalmoscopy to detect retinopathy for the patients with difficulties in funds examination, this methods could only detect cases with advanced retinopathy nor mild retinopathy cases. In future, we will use non contact or contact lens under biomicroscopy to detect retinopathy.

CONCLUSION

In summary, our data demonstrate the presence of MS components is significantly associated with the prevalence of retinopathy. Rather, in order to prevent retinopathy development, risk factors should be controlled in patients with or without MS. More

comprehensive studies are needed to clarify the roles of MS and also its relationship with retinal vascular disorders.

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Table 1. Demographic data, selected clinical and laboratory findings in patients with and without MS.

Parameter	With MS(n = 498)	Without MS (n = 665)	p-value
Age (years)	67.1 ±4.2	68.7 ±4.4	0.12
Male (%)	40.2	42.3	0.26
Weight (kg)	74.3 ±12.7	83.4 ±13.6	< 0.001
Height (cm)	168.5 ±10.1	169.3 ±9.7	< 0.001
BMI (kg/m^2)	27.8 ±4.4	30.9 ±4.7	< 0.001
Waist (cm)	94.5 ±9.2	101.4 ±10.3	< 0.001
SBP (mmHg)	124.3 ±12.7	138.4 ±14.2	< 0.001

DBP (mmHg)	78.6 ±9.2	85.0 ±8.6	< 0.001
Triglyceride (mg/dL)	146.4±10.7	176.4±10.3	< 0.001
HDL (mg/dL)	65.2 ±17.4	54.2 ±16.1	< 0.001
FPG (mg/dL)	109.8 ±13.4	97.4 ±11.3	< 0.001
2hPPG (mg/dL)	209.7±11.9	167.1±12.5	< 0.001
HbA_1c (% (mmol/mol))	5.4±0.8	7.1 ±1.1	< 0.001
Duration of DM (years)	5.1 ±1.2	8.2 ±1.6	0.01
Smoking (%)	35.6	40.3	0.11
Drinking (%)	39.8	43.3	0.07
Newly detected DM (%)	19.3	24.5	< 0.001

MS: metabolic syndrome; BMI: body mass index; HbA_1c: hemoglobin A_1C; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 2. Retinopathy grade in patients with and without MS.

Retinopathy	With MS (n=48)	Without MS (n=26)
Mild-NPDR	10	9
Moderate-NPDR	11	6
Severe-NPDR	12	6
PDR	15	5

MS: metabolic syndrome; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy

Table 3. Prevalence of retinopathy in different groups of this study.

Item	Retinopathy (n)	Prevalence (%)
Total diabetes	55	11.79
Known diabetes	34	18.18
Newly detected diabetes	21	7.72
Non-diabetes	19	3.25
With MS	48	9.64
Without MS	26	3.91
Total subjects	74	6.36

MS: metabolic syndrome.

Table 4. Demographic data, selected clinical and laboratory findings in retinopathy patients with nondiabetes.

Parameter	Retinopathy patients with nondiabetes
Age (years)	59.1 ±3.2
Male (%)	44.3
Weight (kg)	75.3 ±11.6
Height (cm)	169.8 ±11.1
BMI (kg/m^2)	28.9 ±5.1
Waist (cm)	95.5 ±8.9
SBP (mmHg)	126.3 ±11.6

DBP (mmHg)	79.5 ±9.1
Triglyceride (mg/dL)	148.5±10.6
HDL (mg/dL)	66.3 ±18.1
FPG (mg/dL)	98.7 ±10.5
2hPPG (mg/dL)	189.8±10.5
HbA_1c (% (mmol/mol))	5.2±0.6
Smoking (%)	32.1
Drinking (%)	41.8

BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; SBP: systolic blood pressure; SBP: systolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 5. Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR.

Parameter	NPDR (n=54)	PDR (n=20)	*p*-value
Age (years)	68.1 ±4.1	70.7 ±3.4	0.04
Male (%)	45.2	44.6	0.86
Weight (kg)	84.3 ±10.6	85.6 ±11.2	0.54
Height (cm)	166.8 ±11.2	167.7 ±10.7	0.66
BMI (kg/m^2)	26.9 ±4.3	31.1 ±4.2	< 0.001
Waist (cm)	100.6 ±10.2	102.4 ±11.1	0.22
SBP (mmHg)	123.3 ±11.7	132.5 ±12.2	< 0.001

DBP (mmHg)	77.8 ±8.6	84.9 ±7.9	< 0.001
Triglyceride (mg/dL)	145.8±9.7	175.8±11.3	< 0.001
HDL (mg/dL)	64.2 ±16.2	58.6 ±15.1	0.01
FPG (mg/dL)	96.8 ±10.5	108.9 ±12.5	< 0.001
2hPPG (mg/dL)	199.2±11.4	214.8±12.9	< 0.001
HbA_1c (% (mmol/mol))	6.7	8.8	< 0.001
Duration of DM (years)	6.1 ±1.3	9.4 ±1.5	0.02
Smoking (%)	40.6	42.4	0.14
Drinking (%)	29.9	31.3	0.11
Newly detected DM (%)	30.2	20.5	< 0.001

PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 6. Logistic regression analyses for retinopathy in the population with and without MS.

	With MS				Without MS			
	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value
Age (per 10-year)	0.94 (0.78–1.07)	0.39	0.86 (0.58–1.19)	0.11	0.96 (0.74–1.24)	0.70	0.79 (0.41–1.35)	0.22
Gender (female vs male)	0.81 (0.62–1.04)	0.13	0.72 (0.54–1.02)	0.06	1.20 (0.89–1.68)	0.45	1.02 (0.59–1.72)	0.98
BMI (per kg/m^2)	0.97 (0.94–0.99)	0.01	0.98 (0.92–1.06)	0.41	0.96 (0.91–1.00)	0.06	0.99 (0.93–1.04)	0.60
Diabetes duration	1.06 (1.03–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.10)	<0.001

(per 10-year)								
Weight (per 10-kg)	1.05 (0.71–1.63)	0.79	1.04 (0.62–1.73)	0.88	1.14 (0.52–2.43)	0.74	1.19 (0.44–3.10)	0.74
Height (per 10-cm)	1.43 (0.97–2.06)	0.06	1.31 (0.82–2.09)	0.26	1.69 (0.88–3.26)	0.13	1.31 (0.54–3.18)	0.56
Waist (per 10-cm)	1.34 (0.78–2.32)	0.26	1.32 (0.68–2.57)	0.38	0.98 (0.36–2.52)	0.94	0.67 (0.21–2.28)	0.55
SBP (per 10-mmHg)	1.14 (1.04–1.22)	<0.001	1.16 (1.09–1.29)	<0.001	1.27 (1.14–1.46)	<0.001	1.35 (1.18–1.55)	<0.001
DBP (per 10-mmHg)	1.12 (1.05–1.22)	<0.001	1.24 (1.12–1.35)	0.02	1.15 (1.04–1.28)	<0.001	1.18 (0.97–1.38)	0.66
Triglycerides (per 10-mg/dL)	1.04 (0.88–1.19)	0.66	0.95 (0.78–1.12)	0.49	1.19 (0.94–1.48)	0.14	1.13 (0.86–1.47)	0.39
HDL cholesterol (per 10-mg/dL)	0.87 (0.64–1.18)	0.49	0.77 (0.53–1.12)	0.20	1.03 (0.88–1.22)	0.51	1.13 (0.85–1.44)	0.37
FPG (per 10-mg/dL)	1.06 (1.01–1.11)	<0.001	1.07 (1.02–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.11 (1.05–1.17)	<0.001
2hPPG (per 10-mg/dL)	1.16 (1.02–1.32)	<0.001	1.17 (1.12–1.21)	<0.001	1.12 (1.01–1.21)	<0.001	1.13 (1.04–1.22)	<0.001
HbA_1c (per % (mmol/mol))	1.25 (1.15–1.35)	<0.001	1.23 (1.13–1.34)	<0.001	1.29 (1.15–1.44)	<0.001	1.26 (1.10–1.44)	<0.001
Current smoker	1.22 (0.87–1.68)	0.39	1.37 (0.79–2.09)	0.47	1.21 (0.68–1.86)	0.59	1.42 (0.68–2.46)	0.44
Current drinker	1.12 (0.57–1.78)	0.33	1.27 (0.68–2.28)	0.65	1.19 (0.58–2.46)	0.59	1.20 (0.55–3.16)	0.55
Newly detected DM	0.89 (0.55–1.26)	0.46	0.78 (0.55–1.23)	0.21	1.00 (0.84–1.32)	0.56	0.96 (0.75–1.33)	0.35

MS: metabolic syndrome; BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

*Adjusted for age and gender. # Adjusted for age, gender, body mass index, HbA1c, duration of diabetes, SBP and DBP), drinking and smoking.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

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TITLE PAGE

Title:

Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

Running title: Prevalence and risk factors of retinopathy in MS

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ABSTRACT

Objectives: To investigate the relationship between metabolic syndrome (MS) and prevalence of retinopathy.

Design: A cross-section study was carried out from August 2013 to September 2014 in Fengyutan Sub-District.

Primary and secondary outcome measures: A total of 1163 eligible participants attended this research. All the participants were took the stereo fundus photography to detect retinopathy. The discrepancy of prevalence for retinopathy in different participants was described.

Results: The prevalence for retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. Also higher prevalence of retinopathy with proliferative diabetic retinopathy (PDR) was found in patients with MS. In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% CI, 1.04-1.10, per year increase), higher systolic blood pressure (SBP) (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (DBP) (OR, 1.24; 95% CI, 1.12-1.35, per-10mmHg increase), higher fasting plasma glucose (OR, 1.17; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.07; 95% CI,1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS.

Conclusions: The presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.

Keywords: Metabolic syndrome; Prevalence; Retinopathy; Risk factor.

Strengths and limitations of this study

- It was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population.
- We found that the presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.
- We did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterized by abdominal obesity, hyperglycemia, hyperlipidemia, and hypertension.[1] Insulin resistance has been proposed to be of key pathogenetic importance. The prevalence of MS is increasing East Asian countries including China, leading to increased morbidity and mortality due to type 2 diabetic mellitus (DM) and cardiovascular disease (CVD).[2] The MS is increasingly recognized as being a distinct entity affecting a large proportion of the Chinese population.[3,4] Patients with the MS are at known risk of development of large-vessel diseases and retinal microvascular abnormalities.[5,6] Some combinations of traits of MS may significantly contribute to identify subjects with

insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8,9] It is unclear whether the MS is associated with retinopathy in North Chinese population. The retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated in this study. We examined the cross-sectional association of the MS and retinopathy in this population-based study.

METHODS

Study population

This study was carried in Fengyutan health care center which was one of prevention models for DR of Liaoning Diabetic Eye center. It is located in Fengyutan Sub-District of Shenyang City in North China. There were more than 80,000 residents and five communities (including Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District, Shenyang, and North China. Firstly, four communities were randomly selected from five communities in Fengyutan Sub-District. Secondly, 400 households in each of four selected communities were randomly chosen according to household register or health files in Fengyutan health care center. The participants had lived in Fengyutan for at least two years at the time the research was conducted. Then the selected households were informed by community officers using message or telephone call. Finally, a total of 1400 subjects, aged over 40 years were randomly recruited from August 2013 to September 2014. After excluding the patients with cancer, hepatic failure, renal failure, severe psychiatric disturbance, any other systemic medical condition e.g. severe cardiac impairment or severe respiratory impairment, and subjects who did not want to attend

this study voluntarily, a total of 1163 (response rate 83.07%) eligible participants attended this research. Subjects were not attended this study voluntarily or with serious illness such as cancer, liver and kidney function failure were excluded.

Data collection

Information on name, gender, age, smoking, drinking, and health status such as duration of diabetes, hypertension duration, past medical history and treatment methods were obtained using a standardized questionnaire. In addition, participants were asked whether they suffer from DM and if the diagnosis was made by a physician. All subjects were also asked to provide information on their current medication. Thus, known diabetes was defined according to self-reported physician diagnosis or the use of anti-diabetic agents. Following a community office worker interview, all participants were asked to fast overnight (>8 hours) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without wearing hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second) at a 5-min interval using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP measurement with the fifth phase diastolic pressure was used for analysis. All the participants were took the stereo fundus photography to detect retinopathy by 45° Non-Mydriatic Fundus Camera (CR6-45NM, Canon, Tokyo, Japan) through undilated pupils. For each subject, two images for each eye centered on the fovea and optic disk were taken in the physiologically within a

darkened room. Each image was graded in a masked manner by two well-trained ophthalmologists separately for the presence of retinopathy lesions. If the grades were inconsistent, the other ophthalmologist would give the final diagnosis. The grade of retinopathy for each eye was determined and the individual classification was based upon the worse eye. There were 41 subjects that could not get a clear retinal image because anterior segment opacity. They accepted mydriasis with tropicamide 1% (Santen Pharmaceutical Co.,Ltd. Shiga, Japan) before 20 minutes of dark adaptation and binocular indirect ophthalmoscope by two ophthalmologists who reviewed retinal images.

The mayor and the welfare section of Fengyutan Sub-District approved this study. The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by Institutional Ethics Committee of The First Affiliated Hospital of China Medical University.

Laboratory methods

Blood was drawn from the antecubital vein for determinations of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose levels, and hemoglobin A_1c in the morning after 8 hours fast. Then 75-g oral glucose tolerance test (OGTT) would be done, 2 hours later blood was drawn again. All chemistries (enzymatic assay method) were measured at a commercially available laboratory (The Endocrinology Laboratory, China Medical University, and Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and Diabetes

The International Diabetes Federation 2005 (IDF) standards describe a waist circumstance for Chinese female of ≥80 cm and male of ≥90 cm plus 2 or more of the following 4 risk factors: 1) TG ≥1.70 mmol/L or specific treatment for this lipid abnormality; 2) HDL cholesterol <1.29 mmol/L or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes diagnosed according to 1999 WHO criteria.[11] Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12,13] The retinopathy was concerning about diabetic retinopathy except other microvascular changes namely vascular dilatation, focal narrowing and other changes. For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels. Drinking was defined as alcohol intake more than once per month during the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes.

Statistical analyses

Mean±SD was used for measurement data. In univariate analysis, a *t*-test was applied for continuous variables and chi-square test (X^2) for nominal-scale data. Independent risk factors for retinopathy were analyzed using multiple logistic regressions with step-wise approach. Data management and statistical analyses were performed using

SPSS statistical software (Version 16.0, SPSS Inc., and Chicago, IL). *P*<0.05 was considered statistically significant.

RESULTS

There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 showed that demographic data, selected clinical and laboratory findings in patients with and without MS.

The prevalence for retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, respectively. Prevalence of retinopathy was significantly higher in patients with MS (p<0.05). Table 2 showed that the prevalence of proliferative diabetic retinopathy (PDR) was significantly higher in patients with MS (p<0.05). In addition, 6.36% of all persons, 11.79% of diabetes, 18.18% of known diabetes, 7.72% of newly detected diabetes and 3.25% of nondiabetic persons had retinopathy in Table 3. The characteristics of patients with retinopathy in nondiabetic persons were shown in Table 4.

Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR were shown in Table 5. Patients with NPDR were significantly higher prevalence with newly detected diabetes mellitus (DM).

In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% confidence interval (CI), 1.04-1.10, per year increase), higher systolic blood pressure (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (OR, 1.24;

95% CI, 1.12-1.35, per -10mmHg increase), higher plasma glucose (OR, 1.07; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.17; 95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A_1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (Table 6).

DISCUSSION

The data reported population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; it was a little higher than the study in Beijing.[14] Previous studies reported that the prevalence of the MS was 13.7% in Chinese adult populations. However, the prevalence of the MS was 50.0% in Chinese elder populations.[15,16] It was clear that the prevalence of MS was high and might be due to the number of Chinese elder increasing and would be representing a problem of public health in social.

Previous population-based studies in nondiabetic persons have suggested a prevalence of retinopathy, ranging from 3.5% to 9%.[17-24] It was similar to our outcomes (3.25%). However, another study in China had reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in urban, which may explain partially the lower prevalence found in our study. The overall prevalence of retinopathy was 6.36% in total subjects. It was a little higher than the results of previous meta-analysis in China.[26] In our study, the retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated. Study by Keenan *et al.* showed that the prevalence of retinopathy was 8.6% in patients with MS,

and it was little lower than our results. Similarly, the prevalence of retinopathy (3.6%) in patients without MS was a slightly lower than that of this study.[24]

To the best of our knowledge, it was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population, and MS is an independent risk factor of retinopathy after adjusting age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy were highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in the MS group.[28] Two cross-section studies have reported the association between the retinopathy and MS in subjects without diabetes. The Atherosclerosis Risk in Communities (ARIC) Study revealed a relationship between MS and retinopathy in non-diabetic subjects,[6] whereas in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal the relationship between MS and retinopathy in the non-diabetic population, it might be due to this cross-sectional study could not prevent itself from being with methodological problems. The study design is incapable of estimating causal relation directly. In addition, the results of our study proved higher prevalence of retinopathy including PDR in patients with MS. Therefore, we could hypotheses that MS as a risk factor for retinopathy in the subjects, and more prospective studies are warranted to determine the significance of the MS for predicting risk of retinopathy.

In this study, we found associations of some individual components of MS with a

range of retinopathy. After adjusting for age, gender, smoking, drinking and other variables, we also found that no matter the presence of MS or not, as defined by the IDF guideline, longer diabetes duration, higher systolic blood pressure, higher fasting plasma glucose, 2h-postprandial plasma glucose, and higher hemoglobinA_1c were the independent risk factors for retinopathy. Higher diastolic blood pressure was the independent risk factor for retinopathy in patients with MS. HDL levels was not associated with the presence of retinopathy lesions, and some early studies also have revealed this conclusion.[24] According to our results, we also had not found significant association between smoking and drinking in patients with or without MS.

The short coming for this study included it was a population based study in community, so there were no fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) for assistant diagnosis. The study was conducted only in four communities of Shenyang, so there is a selection bias. In addition, we did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

CONCLUSION

In summary, our data demonstrate the presence of MS components is significantly associated with the prevalence of retinopathy. Rather, in order to prevent retinopathy development, risk factors should be controlled in patients with or without MS. More comprehensive studies are needed to clarify the roles of MS and also its relationship with retinal vascular disorders.

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Table 1. Demographic data, selected clinical and laboratory findings in patients with and without MS.

Parameter	With MS(n = 498)	Without MS (n = 665)	p-value
Age (years)	67.1 ±4.2	68.7 ±4.4	0.12
Male (%)	40.2	42.3	0.26
Weight (kg)	74.3 ±12.7	83.4 ±13.6	< 0.001
Height (cm)	168.5 ±10.1	169.3 ±9.7	< 0.001
BMI (kg/m^2)	27.8 ±4.4	30.9 ±4.7	< 0.001
Waist (cm)	94.5 ±9.2	101.4 ±10.3	< 0.001
SBP (mmHg)	124.3 ±12.7	138.4 ±14.2	< 0.001
DBP (mmHg)	78.6 ±9.2	85.0 ±8.6	< 0.001
Triglyceride (mg/dL)	146.4±10.7	176.4±10.3	< 0.001
HDL (mg/dL)	65.2 ±17.4	54.2 ±16.1	< 0.001
FPG (mg/dL)	109.8 ±13.4	97.4 ±11.3	< 0.001
2hPPG (mg/dL)	209.7±11.9	167.1±12.5	< 0.001
HbA_1c (% (mmol/mol))	5.4±0.8	7.1 ±1.1	< 0.001

Duration of DM (years)	5.1 ±1.2	8.2 ±1.6	0.01
Smoking (%)	35.6	40.3	0.11
Drinking (%)	39.8	43.3	0.07
Newly detected DM (%)	19.3	24.5	< 0.001

MS: metabolic syndrome; BMI: body mass index; HbA_1c: hemoglobin A_1C; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 2. Retinopathy grade in patients with and without MS.

Retinopathy	With MS (*n*=48)	Without MS (*n*=26)
Mild-NPDR	10	9
Moderate-NPDR	11	6
Severe-NPDR	12	6
PDR	15	5

MS: metabolic syndrome; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy

Table 3. Prevalence of retinopathy in different groups of this study.

Item	Retinopathy (n)	Prevalence (%)
Total diabetes	55	11.79
Known diabetes	34	18.18
Newly detected diabetes	21	7.72
Non-diabetes	19	3.25
With MS	48	9.64
Without MS	26	3.91
Total subjects	74	6.36

MS: metabolic syndrome.

Table 4. Demographic data, selected clinical and laboratory findings in retinopathy patients with nondiabetes.

Parameter	Retinopathy patients with nondiabetes
Age (years)	59.1 ±3.2
Male (%)	44.3
Weight (kg)	75.3 ±11.6
Height (cm)	169.8 ±11.1
BMI (kg/m^2)	28.9 ±5.1
Waist (cm)	95.5 ±8.9
SBP (mmHg)	126.3 ±11.6
DBP (mmHg)	79.5 ±9.1
Triglyceride (mg/dL)	148.5±10.6
HDL (mg/dL)	66.3 ±18.1
FPG (mg/dL)	98.7 ±10.5
2hPPG (mg/dL)	189.8±10.5
HbA_1c (% (mmol/mol))	5.2±0.6

Smoking (%)	32.1
Drinking (%)	41.8

BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; SBP: systolic blood pressure; SBP: systolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 5. Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR.

Parameter	NPDR (n=54)	PDR (n=20)	*p*-value
Age (years)	68.1 ±4.1	70.7 ±3.4	0.04
Male (%)	45.2	44.6	0.86
Weight (kg)	84.3 ±10.6	85.6 ±11.2	0.54
Height (cm)	166.8 ±11.2	167.7 ±10.7	0.66
BMI (kg/m^2)	26.9 ±4.3	31.1 ±4.2	< 0.001
Waist (cm)	100.6 ±10.2	102.4 ±11.1	0.22
SBP (mmHg)	123.3 ±11.7	132.5 ±12.2	< 0.001
DBP (mmHg)	77.8 ±8.6	84.9 ±7.9	< 0.001
Triglyceride (mg/dL)	145.8±9.7	175.8±11.3	< 0.001
HDL (mg/dL)	64.2 ±16.2	58.6 ±15.1	0.01
FPG (mg/dL)	96.8 ±10.5	108.9 ±12.5	< 0.001
2hPPG (mg/dL)	199.2±11.4	214.8±12.9	< 0.001
HbA_1c (% (mmol/mol))	6.7	8.8	< 0.001

Duration of DM (years)	6.1 ±1.3	9.4 ±1.5	0.02
Smoking (%)	40.6	42.4	0.14
Drinking (%)	29.9	31.3	0.11
Newly detected DM (%)	30.2	20.5	< 0.001

PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 6. Logistic regression analyses for retinopathy in the population with and without MS.

	With MS				Without MS			
	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value
Age (per 10-year)	0.94 (0.78–1.07)	0.39	0.86 (0.58–1.19)	0.11	0.96 (0.74–1.24)	0.70	0.79 (0.41–1.35)	0.22
Gender (female vs male)	0.81 (0.62–1.04)	0.13	0.72 (0.54–1.02)	0.06	1.20 (0.89–1.68)	0.45	1.02 (0.59–1.72)	0.98
BMI (per kg/m^2)	0.97 (0.94–0.99)	0.01	0.98 (0.92–1.06)	0.41	0.96 (0.91–1.00)	0.06	0.99 (0.93–1.04)	0.60
Diabetes duration (per 10-year)	1.06 (1.03–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.10)	<0.001
Weight (per 10-kg)	1.05 (0.71–1.63)	0.79	1.04 (0.62–1.73)	0.88	1.14 (0.52–2.43)	0.74	1.19 (0.44–3.10)	0.74
Height (per 10-cm)	1.43 (0.97–2.06)	0.06	1.31 (0.82–2.09)	0.26	1.69 (0.88–3.26)	0.13	1.31 (0.54–3.18)	0.56
Waist (per	1.34 (0.78–2.32)	0.26	1.32 (0.68–2.57)	0.38	0.98 (0.36–2.52)	0.94	0.67 (0.21–2.28)	0.55

10-cm)								
SBP (per 10-mmHg)	1.14 (1.04–1.22)	<0.001	1.16 (1.09–1.29)	<0.001	1.27 (1.14–1.46)	<0.001	1.35 (1.18–1.55)	<0.001
DBP (per 10-mmHg)	1.12 (1.05–1.22)	<0.001	1.24 (1.12–1.35)	0.02	1.15 (1.04–1.28)	<0.001	1.18 (0.97–1.38)	0.66
Triglycerides (per 10-mg/dL)	1.04 (0.88–1.19)	0.66	0.95 (0.78–1.12)	0.49	1.19 (0.94–1.48)	0.14	1.13 (0.86–1.47)	0.39
HDL cholesterol (per 10-mg/dL)	0.87 (0.64–1.18)	0.49	0.77 (0.53–1.12)	0.20	1.03 (0.88–1.22)	0.51	1.13 (0.85–1.44)	0.37
FPG (per 10-mg/dL)	1.06 (1.01–1.11)	<0.001	1.07 (1.02–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.11 (1.05–1.17)	<0.001
2hPPG (per 10-mg/dL)	1.16 (1.02–1.32)	<0.001	1.17 (1.12–1.21)	<0.001	1.12 (1.01–1.21)	<0.001	1.13 (1.04–1.22)	<0.001
HbA_1c (per % (mmol/mol))	1.25 (1.15–1.35)	<0.001	1.23 (1.13–1.34)	<0.001	1.29 (1.15–1.44)	<0.001	1.26 (1.10–1.44)	<0.001
Current smoker	1.22 (0.87–1.68)	0.39	1.37 (0.79–2.09)	0.47	1.21 (0.68–1.86)	0.59	1.42 (0.68–2.46)	0.44
Current drinker	1.12 (0.57–1.78)	0.33	1.27 (0.68–2.28)	0.65	1.19 (0.58–2.46)	0.59	1.20 (0.55–3.16)	0.55
Newly detected DM	0.89 (0.55–1.26)	0.46	0.78 (0.55–1.23)	0.21	1.00 (0.84–1.32)	0.56	0.96 (0.75–1.33)	0.35

MS: metabolic syndrome; BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

*Adjusted for age and gender. # Adjusted for age, gender, body mass index, HbA1c, duration of diabetes, SBP and DBP), drinking and smoking.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

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TITLE PAGE

Title:

Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

Running title: Prevalence and risk factors of retinopathy in MS

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ABSTRACT

Objectives: To investigate the relationship between metabolic syndrome (MS) and prevalence of retinopathy.

Design: A cross-section study was carried out from August 2013 to September 2014 in Fengyutan Sub-District.

Primary and secondary outcome measures: A total of 1163 eligible participants attended this research. All the participants were took the stereo fundus photography to detect retinopathy. The discrepancy of prevalence for retinopathy in different participants was described.

Results: The prevalence for retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. Also higher prevalence of retinopathy with proliferative diabetic retinopathy (PDR) was found in patients with MS. In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% CI, 1.04-1.10, per year increase), higher systolic blood pressure (SBP) (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (DBP) (OR, 1.24; 95% CI, 1.12-1.35, per-10mmHg increase), higher fasting plasma glucose (OR, 1.17; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.07; 95% CI,1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS.

Conclusions: The presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.

Keywords: Metabolic syndrome; Prevalence; Retinopathy; Risk factor.

Strengths and limitations of this study

- It was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population.
- We found that the presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.
- We did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterized by abdominal obesity, hyperglycemia, hyperlipidemia, and hypertension.[1] Insulin resistance has been proposed to be of key pathogenetic importance. The prevalence of MS is increasing East Asian countries including China, leading to increased morbidity and mortality due to type 2 diabetic mellitus (DM) and cardiovascular disease (CVD).[2] The MS is increasingly recognized as being a distinct entity affecting a large proportion of the Chinese population.[3,4] Patients with the MS are at known risk of development of large-vessel diseases and retinal microvascular abnormalities.[5,6] Some combinations of traits of MS may significantly contribute to identify subjects with

insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8,9] It is unclear whether the MS is associated with retinopathy in North Chinese population. The retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated in this study. We examined the cross-sectional association of the MS and retinopathy in this population-based study.

METHODS

Study population

This study was carried in Fengyutan health care center which was one of prevention models for DR of Liaoning Diabetic Eye center. It is located in Fengyutan Sub-District of Shenyang City in North China. There were more than 80,000 residents and five communities (including Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District, Shenyang, and North China. A multistage, stratified random sampling was carried for selection of residents. Firstly, four communities were randomly selected from five communities in Fengyutan Sub-District. Secondly, 400 households in each of four selected communities were randomly chosen according to household register or health files in Fengyutan health care center. So there would be 1600 households in our study totally. The participants had lived in Fengyutan for at least two years at the time the research was conducted. Then the selected households were informed by community officers using message or telephone call. Except the subjects who could not be contacted, a total of 1400 subjects, aged over 40 years were randomly recruited from August 2013 to September 2014. After excluding the patients with cancer, hepatic failure, renal failure, severe

psychiatric disturbance, any other systemic medical condition e.g. severe cardiac impairment or severe respiratory impairment, and subjects who did not want to attend this study voluntarily, a total of 1163 eligible participants attended this research. Subjects were not attended this study voluntarily or with serious illness such as cancer, liver and kidney function failure were excluded.

Data collection

Information on name, gender, age, smoking, drinking, and health status such as duration of diabetes, hypertension duration, past medical history and treatment methods were obtained using a standardized questionnaire. In addition, participants were asked whether they suffer from DM and if the diagnosis was made by a physician. All subjects were also asked to provide information on their current medication. Thus, known diabetes was defined according to self-reported physician diagnosis or the use of anti-diabetic agents. Following a community office worker interview, all participants were asked to fast overnight (>8 hours) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without wearing hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second) at a 5-min interval using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP measurement with the fifth phase diastolic pressure was used for analysis. All the participants were took the stereo fundus photography to detect retinopathy by 45° Non-Mydriatic Fundus Camera (CR6-45NM, Canon,

Tokyo, Japan) through undilated pupils. For each subject, two images for each eye centered on the fovea and optic disk were taken in the physiologically within a darkened room. Each image was graded in a masked manner by two well-trained ophthalmologists separately for the presence of retinopathy lesions. If the grades were inconsistent, the other ophthalmologist would give the final diagnosis. The grade of retinopathy for each eye was determined and the individual classification was based upon the worse eye. There were 41 subjects that could not get a clear retinal image because anterior segment opacity. They accepted mydriasis with tropicamide 1% (Santen Pharmaceutical Co.,Ltd. Shiga, Japan) before 20 minutes of dark adaptation and binocular indirect ophthalmoscope by two ophthalmologists who reviewed retinal images.

The mayor and the welfare section of Fengyutan Sub-District approved this study. The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by Institutional Ethics Committee of The First Affiliated Hospital of China Medical University. All subjects provided their written informed consent.

Laboratory methods

Blood was drawn from the antecubital vein for determinations of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose levels, and hemoglobin A_1c in the morning after 8 hours fast. Then 75-g oral glucose tolerance test (OGTT) would be done, 2 hours later blood was drawn again. All chemistries

(enzymatic assay method) were measured at a commercially available laboratory (The Endocrinology Laboratory, China Medical University, and Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and Diabetes

The International Diabetes Federation 2005 (IDF) standards describe a waist circumstance for Chinese female of ≥80 cm and male of ≥90 cm plus 2 or more of the following 4 risk factors: 1) TG ≥1.70 mmol/L or specific treatment for this lipid abnormality; 2) HDL cholesterol <1.29 mmol/L or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes diagnosed according to 1999 WHO criteria.[11] Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12,13] The retinopathy was concerning about diabetic retinopathy except other microvascular changes namely vascular dilatation, focal narrowing and other changes. For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels. Drinking was defined as alcohol intake more than once per month during the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes.

Statistical analyses

Mean±SD was used for measurement data. In univariate analysis, a *t*-test was applied

for continuous variables and chi-square test (X^2) for nominal-scale data. Independent risk factors for retinopathy were analyzed using multiple logistic regressions with step-wise approach. Data management and statistical analyses were performed using SPSS statistical software (Version 16.0, SPSS Inc., and Chicago, IL). $P<0.05$ was considered statistically significant.

RESULTS

The response rate was 83.07% (1163/1400) in this survey. There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 showed that demographic data, selected clinical and laboratory findings in patients with and without MS.

The prevalence for retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, respectively. Prevalence of retinopathy was significantly higher in patients with MS (p<0.05). Table 2 showed that the prevalence of proliferative diabetic retinopathy (PDR) was significantly higher in patients with MS (p<0.05). In addition, 6.36% of all persons, 11.79% of diabetes, 18.18% of known diabetes, 7.72% of newly detected diabetes and 3.25% of nondiabetic persons had retinopathy in Table 3. The characteristics of patients with retinopathy in nondiabetic persons were shown in Table 4.

Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR were shown in Table 5. Patients with NPDR were significantly higher prevalence with newly detected diabetes mellitus (DM).

In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% confidence interval (CI), 1.04-1.10, per year increase), higher systolic blood pressure (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (OR, 1.24; 95% CI, 1.12-1.35, per -10mmHg increase), higher plasma glucose (OR, 1.07; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.17; 95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A_1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (Table 6).

DISCUSSION

The data reported population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; it was a little higher than the study in Beijing.[14] Previous studies reported that the prevalence of the MS was 13.7% in Chinese adult populations. However, the prevalence of the MS was 50.0% in Chinese elder populations.[15,16] It was clear that the prevalence of MS was high and might be due to the number of Chinese elder increasing and would be representing a problem of public health in social.

Previous population-based studies in nondiabetic persons have suggested a prevalence of retinopathy, ranging from 3.5% to 9%.[17-24] It was similar to our outcomes (3.25%). However, another study in China had reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in urban, which may explain partially the lower prevalence found in our study. The overall

prevalence of retinopathy was 6.36% in total subjects. It was a little higher than the results of previous meta-analysis in China.[26] In our study, the retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated. Study by Keenan *et al.* showed that the prevalence of retinopathy was 8.6% in patients with MS, and it was little lower than our results. Similarly, the prevalence of retinopathy (3.6%) in patients without MS was a slightly lower than that of this study.[24]

To the best of our knowledge, it was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population, and MS is an independent risk factor of retinopathy after adjusting age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy were highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in the MS group.[28] Two cross-section studies have reported the association between the retinopathy and MS in subjects without diabetes. The Atherosclerosis Risk in Communities (ARIC) Study revealed a relationship between MS and retinopathy in non-diabetic subjects,[6] whereas in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal the relationship between MS and retinopathy in the non-diabetic population, it might be due to this cross-sectional study could not prevent itself from being with methodological problems. The study design is incapable of estimating causal relation directly. In addition, the results of our study proved higher prevalence of retinopathy including PDR in patients with MS.

Therefore, we could hypotheses that MS as a risk factor for retinopathy in the subjects, and more prospective studies are warranted to determine the significance of the MS for predicting risk of retinopathy.

In this study, we found associations of some individual components of MS with a range of retinopathy. After adjusting for age, gender, smoking, drinking and other variables, we also found that no matter the presence of MS or not, as defined by the IDF guideline, longer diabetes duration, higher systolic blood pressure, higher fasting plasma glucose, 2h-postprandial plasma glucose, and higher hemoglobinA_1c were the independent risk factors for retinopathy. Higher diastolic blood pressure was the independent risk factor for retinopathy in patients with MS. HDL levels was not associated with the presence of retinopathy lesions, and some early studies also have revealed this conclusion.[24] According to our results, we also had not found significant association between smoking and drinking in patients with or without MS.

The short coming for this study included it was a population based study in community, so there were no fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) for assistant diagnosis. The study was conducted only in four communities of Shenyang, so there is a selection bias. In addition, we did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

CONCLUSION

In summary, our data demonstrate the presence of MS components is significantly associated with the prevalence of retinopathy. Rather, in order to prevent retinopathy

development, risk factors should be controlled in patients with or without MS. More comprehensive studies are needed to clarify the roles of MS and also its relationship with retinal vascular disorders.

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Table 1. Demographic data, selected clinical and laboratory findings in patients with and without MS.

Parameter	With MS(n = 498)	Without MS (n = 665)	p-value
Age (years)	67.1 ±4.2	68.7 ±4.4	0.12
Male (%)	40.2	42.3	0.26
Weight (kg)	74.3 ±12.7	83.4 ±13.6	< 0.001
Height (cm)	168.5 ±10.1	169.3 ±9.7	< 0.001
BMI (kg/m^2)	27.8 ±4.4	30.9 ±4.7	< 0.001

Waist (cm)	94.5 ±9.2	101.4 ±10.3	< 0.001
SBP (mmHg)	124.3 ±12.7	138.4 ±14.2	< 0.001
DBP (mmHg)	78.6 ±9.2	85.0 ±8.6	< 0.001
Triglyceride (mg/dL)	146.4±10.7	176.4±10.3	< 0.001
HDL (mg/dL)	65.2 ±17.4	54.2 ±16.1	< 0.001
FPG (mg/dL)	109.8 ±13.4	97.4 ±11.3	< 0.001
2hPPG (mg/dL)	209.7±11.9	167.1±12.5	< 0.001
HbA_1c (% (mmol/mol))	5.4±0.8	7.1 ±1.1	< 0.001
Duration of DM (years)	5.1 ±1.2	8.2 ±1.6	0.01
Smoking (%)	35.6	40.3	0.11
Drinking (%)	39.8	43.3	0.07
Newly detected DM (%)	19.3	24.5	< 0.001

MS: metabolic syndrome; BMI: body mass index; HbA_1c: hemoglobin A_1C; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 2. Retinopathy grade in patients with and without MS.

Retinopathy	With MS (*n*=48)	Without MS (*n*=26)
Mild-NPDR	10	9
Moderate-NPDR	11	6
Severe-NPDR	12	6
PDR	15	5

MS: metabolic syndrome; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy

Table 3. Prevalence of retinopathy in different groups of this study.

Item	Retinopathy (n)	Prevalence (%)
Total diabetes	55	11.79
Known diabetes	34	18.18
Newly detected diabetes	21	7.72
Non-diabetes	19	3.25
With MS	48	9.64
Without MS	26	3.91
Total subjects	74	6.36

MS: metabolic syndrome.

Table 4. Demographic data, selected clinical and laboratory findings in retinopathy patients with nondiabetes.

Parameter	Retinopathy patients with nondiabetes
Age (years)	59.1 ±3.2
Male (%)	44.3
Weight (kg)	75.3 ±11.6
Height (cm)	169.8 ±11.1
BMI (kg/m^2)	28.9 ±5.1

Waist (cm)	95.5 ±8.9
SBP (mmHg)	126.3 ±11.6
DBP (mmHg)	79.5 ±9.1
Triglyceride (mg/dL)	148.5±10.6
HDL (mg/dL)	66.3 ±18.1
FPG (mg/dL)	98.7 ±10.5
2hPPG (mg/dL)	189.8±10.5
HbA_1c (% (mmol/mol))	5.2±0.6
Smoking (%)	32.1
Drinking (%)	41.8

BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; SBP: systolic blood pressure; SBP: systolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 5. Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR.

Parameter	NPDR (n=54)	PDR (n=20)	*p*-value
Age (years)	68.1 ±4.1	70.7 ±3.4	0.04
Male (%)	45.2	44.6	0.86
Weight (kg)	84.3 ±10.6	85.6 ±11.2	0.54
Height (cm)	166.8 ±11.2	167.7 ±10.7	0.66
BMI (kg/m^2)	26.9 ±4.3	31.1 ±4.2	< 0.001

Waist (cm)	100.6 ±10.2	102.4 ±11.1	0.22
SBP (mmHg)	123.3 ±11.7	132.5 ±12.2	< 0.001
DBP (mmHg)	77.8 ±8.6	84.9 ±7.9	< 0.001
Triglyceride (mg/dL)	145.8±9.7	175.8±11.3	< 0.001
HDL (mg/dL)	64.2 ±16.2	58.6 ±15.1	0.01
FPG (mg/dL)	96.8 ±10.5	108.9 ±12.5	< 0.001
2hPPG (mg/dL)	199.2±11.4	214.8±12.9	< 0.001
HbA_1c (% (mmol/mol))	6.7	8.8	< 0.001
Duration of DM (years)	6.1 ±1.3	9.4 ±1.5	0.02
Smoking (%)	40.6	42.4	0.14
Drinking (%)	29.9	31.3	0.11
Newly detected DM (%)	30.2	20.5	< 0.001

PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 6. Logistic regression analyses for retinopathy in the population with and without MS.

	With MS				Without MS			
	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value
Age (per 10-year)	0.94 (0.78–1.07)	0.39	0.86 (0.58–1.19)	0.11	0.96 (0.74–1.24)	0.70	0.79 (0.41–1.35)	0.22
Gender (female vs male)	0.81 (0.62–1.04)	0.13	0.72 (0.54–1.02)	0.06	1.20 (0.89–1.68)	0.45	1.02 (0.59–1.72)	0.98
BMI (per kg/m^2	0.97 (0.94–0.99)	0.01	0.98 (0.92–1.06)	0.41	0.96 (0.91–1.00)	0.06	0.99 (0.93–1.04)	0.60

)								
Diabetes duration (per 10-year)	1.06 (1.03–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.10)	<0.001
Weight (per 10-kg)	1.05 (0.71–1.63)	0.79	1.04 (0.62–1.73)	0.88	1.14 (0.52–2.43)	0.74	1.19 (0.44–3.10)	0.74
Height (per 10-cm)	1.43 (0.97–2.06)	0.06	1.31 (0.82–2.09)	0.26	1.69 (0.88–3.26)	0.13	1.31 (0.54–3.18)	0.56
Waist (per 10-cm)	1.34 (0.78–2.32)	0.26	1.32 (0.68–2.57)	0.38	0.98 (0.36–2.52)	0.94	0.67 (0.21–2.28)	0.55
SBP (per 10-mmHg)	1.14 (1.04–1.22)	<0.001	1.16 (1.09–1.29)	<0.001	1.27 (1.14–1.46)	<0.001	1.35 (1.18–1.55)	<0.001
DBP (per 10-mmHg)	1.12 (1.05–1.22)	<0.001	1.24 (1.12–1.35)	0.02	1.15 (1.04–1.28)	<0.001	1.18 (0.97–1.38)	0.66
Triglycerides (per 10-mg/dL)	1.04 (0.88–1.19)	0.66	0.95 (0.78–1.12)	0.49	1.19 (0.94–1.48)	0.14	1.13 (0.86–1.47)	0.39
HDL cholesterol (per 10-mg/dL)	0.87 (0.64–1.18)	0.49	0.77 (0.53–1.12)	0.20	1.03 (0.88–1.22)	0.51	1.13 (0.85–1.44)	0.37
FPG (per 10-mg/dL)	1.06 (1.01–1.11)	<0.001	1.07 (1.02–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.11 (1.05–1.17)	<0.001
2hPPG (per 10-mg/dL)	1.16 (1.02–1.32)	<0.001	1.17 (1.12–1.21)	<0.001	1.12 (1.01–1.21)	<0.001	1.13 (1.04–1.22)	<0.001
HbA_1c (per % (mmol/mol))	1.25 (1.15–1.35)	<0.001	1.23 (1.13–1.34)	<0.001	1.29 (1.15–1.44)	<0.001	1.26 (1.10–1.44)	<0.001
Current smoker	1.22 (0.87–1.68)	0.39	1.37 (0.79–2.09)	0.47	1.21 (0.68–1.86)	0.59	1.42 (0.68–2.46)	0.44
Current drinker	1.12 (0.57–1.78)	0.33	1.27 (0.68–2.28)	0.65	1.19 (0.58–2.46)	0.59	1.20 (0.55–3.16)	0.55
Newly detected DM	0.89 (0.55–1.26)	0.46	0.78 (0.55–1.23)	0.21	1.00 (0.84–1.32)	0.56	0.96 (0.75–1.33)	0.35

MS: metabolic syndrome; BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

*Adjusted for age and gender. # Adjusted for age, gender, body mass index, HbA1c, duration of diabetes, SBP and DBP), drinking and smoking.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

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TITLE PAGE

Title:

Prevalence and risk factors of retinopathy in patients with or without Metabolic Syndrome– A population-based study in Shenyang.

Running title: Prevalence and risk factors of retinopathy in MS

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ABSTRACT

Objectives: To investigate the relationship between metabolic syndrome (MS) and prevalence of retinopathy.

Design: A cross-section study was carried out from August 2013 to September 2014 in Fengyutan Sub-District.

Primary and secondary outcome measures: A total of 1163 eligible participants attended this research. All the participants were took the stereo fundus photography to detect retinopathy. The discrepancy of prevalence for retinopathy in different participants was described.

Results: The prevalence for retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. Also higher prevalence of retinopathy with proliferative diabetic retinopathy (PDR) was found in patients with MS. In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% CI, 1.04-1.10, per year increase), higher systolic blood pressure (SBP) (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (DBP) (OR, 1.24; 95% CI, 1.12-1.35, per-10mmHg increase), higher fasting plasma glucose (OR, 1.17; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.07; 95% CI,1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS.

Conclusions: The presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.

Keywords: Metabolic syndrome; Prevalence; Retinopathy; Risk factor.

Strengths and limitations of this study

- It was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population.
- We found that the presence of MS components hyperglycemia (fasting glucose and HbA1c) and hypertension (SBP and DBP) are significantly associated with the prevalence of retinopathy.
- We did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterized by abdominal obesity, hyperglycemia, hyperlipidemia, and hypertension.[1] Insulin resistance has been proposed to be of key pathogenetic importance. The prevalence of MS is increasing East Asian countries including China, leading to increased morbidity and mortality due to type 2 diabetic mellitus (DM) and cardiovascular disease (CVD).[2] The MS is increasingly recognized as being a distinct entity affecting a large proportion of the Chinese population.[3,4] Patients with the MS are at known risk of development of large-vessel diseases and retinal microvascular abnormalities.[5,6] Some combinations of traits of MS may significantly contribute to identify subjects with insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8,9] It is unclear whether the MS is associated with retinopathy in North Chinese population. The retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated in this study. We examined the cross-sectional association of the MS and retinopathy in this population-based study.

METHODS

Study population

This study was carried in Fengyutan health care center which was one of prevention models for DR of Liaoning Diabetic Eye center. It is located in Fengyutan Sub-District of Shenyang City in North China. There were more than 80,000 residents and five communities (including Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District, Shenyang, and North China. A multistage,

stratified random sampling was carried for selection of residents. Firstly, those five communities were numbered. Then four communities were randomly selected from five numbers. Secondly, the household register or health files in Fengyutan health care center were numbered, and 400 households in each of four selected communities were randomly chosen using "True Random Number Generator" (https://www.random.org/). The participants had lived in Fengyutan for at least two years at the time the research was conducted. Then the selected households were informed by community officers using message or telephone call. Finally, a total of 1400 subjects, aged over 40 years attended this study from August 2013 to September 2014. After excluding the patients with cancer, hepatic failure, renal failure, severe psychiatric disturbance, any other systemic medical condition e.g. severe cardiac impairment or severe respiratory impairment, and subjects who did not want to attend this study voluntarily, a total of 1163 (response rate 83.07%) eligible participants attended this research. Subjects were not attended this study voluntarily or with serious illness such as cancer, liver and kidney function failure were excluded.

Data collection

Information on name, gender, age, smoking, drinking, and health status such as duration of diabetes, hypertension duration, past medical history and treatment methods were obtained using a standardized questionnaire. In addition, participants were asked whether they suffer from DM and if the diagnosis was made by a physician. All subjects were also asked to provide information on their current medication. Thus, known diabetes was defined according to self-reported physician

diagnosis or the use of anti-diabetic agents. Following a community office worker interview, all participants were asked to fast overnight (>8 hours) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without wearing hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second) at a 5-min interval using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP measurement with the fifth phase diastolic pressure was used for analysis. All the participants were took the stereo fundus photography to detect retinopathy by 45° Non-Mydriatic Fundus Camera (CR6-45NM, Canon, Tokyo, Japan) through undilated pupils. For each subject, two images for each eye centered on the fovea and optic disk were taken in the physiologically within a darkened room. Each image was graded in a masked manner by two well-trained ophthalmologists separately for the presence of retinopathy lesions. If the grades were inconsistent, the other ophthalmologist would give the final diagnosis. The grade of retinopathy for each eye was determined and the individual classification was based upon the worse eye. There were 41 subjects that could not get a clear retinal image because anterior segment opacity. They accepted mydriasis with tropicamide 1% (Santen Pharmaceutical Co.,Ltd. Shiga, Japan) before 20 minutes of dark adaptation and binocular indirect ophthalmoscope by two ophthalmologists who reviewed retinal images.

The mayor and the welfare section of Fengyutan Sub-District approved this study. The

research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by Institutional Ethics Committee of The First Affiliated Hospital of China Medical University.

Laboratory methods

Blood was drawn from the antecubital vein for determinations of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose levels, and hemoglobin A_1c in the morning after 8 hours fast. Then 75-g oral glucose tolerance test (OGTT) would be done, 2 hours later blood was drawn again. All chemistries (enzymatic assay method) were measured at a commercially available laboratory (The Endocrinology Laboratory, China Medical University, and Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and Diabetes

The International Diabetes Federation 2005 (IDF) standards describe a waist circumstance for Chinese female of ≥80 cm and male of ≥90 cm plus 2 or more of the following 4 risk factors: 1) TG ≥1.70 mmol/L or specific treatment for this lipid abnormality; 2) HDL cholesterol <1.29 mmol/L or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes diagnosed according to 1999 WHO criteria.[11] Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12,13]

The retinopathy was concerning about diabetic retinopathy except other microvascular changes namely vascular dilatation, focal narrowing and other changes. For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels. Drinking was defined as alcohol intake more than once per month during the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes.

Statistical analyses

Mean±SD was used for measurement data. In univariate analysis, a *t*-test was applied for continuous variables and chi-square test (X^2) for nominal-scale data. Independent risk factors for retinopathy were analyzed using multiple logistic regressions with step-wise approach. Data management and statistical analyses were performed using SPSS statistical software (Version 16.0, SPSS Inc., and Chicago, IL). $P<0.05$ was considered statistically significant.

RESULTS

There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 showed that demographic data, selected clinical and laboratory findings in patients with and without MS.

The prevalence for retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, respectively. Prevalence of retinopathy was significantly higher in patients with MS ($p<0.05$). Table 2 showed that the prevalence

of proliferative diabetic retinopathy (PDR) was significantly higher in patients with MS ($p<0.05$). In addition, 6.36% of all persons, 11.79% of diabetes, 18.18% of known diabetes, 7.72% of newly detected diabetes and 3.25% of nondiabetic persons had retinopathy in Table 3. The characteristics of patients with retinopathy in nondiabetic persons were shown in Table 4.

Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR were shown in Table 5. Patients with NPDR were significantly higher prevalence with newly detected diabetes mellitus (DM).

In multiple logistic regression, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (odds ratio (OR), 1.07; 95% confidence interval (CI), 1.04-1.10, per year increase), higher systolic blood pressure (OR, 1.16; 95% CI, 1.09-1.29, per -10mmHg increase), higher diastolic blood pressure (OR, 1.24; 95% CI, 1.12-1.35, per -10mmHg increase), higher plasma glucose (OR, 1.07; 95% CI, 1.02-1.11, per-10 mg/dL increase), 2h-postprandial plasma glucose (OR, 1.17; 95% CI, 1.12-1.21, per -10 mg/dL increase), and higher hemoglobin A_1c (OR, 1.23; 95% CI, 1.13-1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (Table 6).

DISCUSSION

The data reported population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; it was a little higher than the study in Beijing.[14] Previous studies reported that

the prevalence of the MS was 13.7% in Chinese adult populations. However, the prevalence of the MS was 50.0% in Chinese elder populations.[15,16] It was clear that the prevalence of MS was high and might be due to the number of Chinese elder increasing and would be representing a problem of public health in social.

Previous population-based studies in nondiabetic persons have suggested a prevalence of retinopathy, ranging from 3.5% to 9%.[17-24] It was similar to our outcomes (3.25%). However, another study in China had reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in urban, which may explain partially the lower prevalence found in our study. The overall prevalence of retinopathy was 6.36% in total subjects. It was a little higher than the results of previous meta-analysis in China.[26] In our study, the retinopathy secondary to MS and retinopathy secondary to diabetes mellitus were differentiated. Study by Keenan *et al.* showed that the prevalence of retinopathy was 8.6% in patients with MS, and it was little lower than our results. Similarly, the prevalence of retinopathy (3.6%) in patients without MS was a slightly lower than that of this study.[24]

To the best of our knowledge, it was the first population-based study provided evidence that the relationship between MS and retinopathy in North Chinese population, and MS is an independent risk factor of retinopathy after adjusting age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy were highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in the MS group.[28] Two cross-section studies

have reported the association between the retinopathy and MS in subjects without diabetes. The Atherosclerosis Risk in Communities (ARIC) Study revealed a relationship between MS and retinopathy in non-diabetic subjects,[6] whereas in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal the relationship between MS and retinopathy in the non-diabetic population, it might be due to this cross-sectional study could not prevent itself from being with methodological problems. The study design is incapable of estimating causal relation directly. In addition, the results of our study proved higher prevalence of retinopathy including PDR in patients with MS. Therefore, we could hypotheses that MS as a risk factor for retinopathy in the subjects, and more prospective studies are warranted to determine the significance of the MS for predicting risk of retinopathy.

In this study, we found associations of some individual components of MS with a range of retinopathy. After adjusting for age, gender, smoking, drinking and other variables, we also found that no matter the presence of MS or not, as defined by the IDF guideline, longer diabetes duration, higher systolic blood pressure, higher fasting plasma glucose, 2h-postprandial plasma glucose, and higher hemoglobinA_1c were the independent risk factors for retinopathy. Higher diastolic blood pressure was the independent risk factor for retinopathy in patients with MS. HDL levels was not associated with the presence of retinopathy lesions, and some early studies also have revealed this conclusion.[24] According to our results, we also had not found significant association between smoking and drinking in patients with or without MS.

The short coming for this study included it was a population based study in community, so there were no fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) for assistant diagnosis. The study was conducted only in four communities of Shenyang, so there is a selection bias. In addition, we did not investigate the type of diabetes for all subjects. So the prevalence of retinopathy in diabetes was lower representative.

CONCLUSION

In summary, our data demonstrate the presence of MS components is significantly associated with the prevalence of retinopathy. Rather, in order to prevent retinopathy development, risk factors should be controlled in patients with or without MS. More comprehensive studies are needed to clarify the roles of MS and also its relationship with retinal vascular disorders.

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Table 1. Demographic data, selected clinical and laboratory findings in patients with and without MS.

Parameter	With MS(n = 498)	Without MS (n = 665)	p-value
Age (years)	67.1 ±4.2	68.7 ±4.4	0.12
Male (%)	40.2	42.3	0.26
Weight (kg)	74.3 ±12.7	83.4 ±13.6	< 0.001
Height (cm)	168.5 ±10.1	169.3 ±9.7	< 0.001
BMI (kg/m^2)	27.8 ±4.4	30.9 ±4.7	< 0.001
Waist (cm)	94.5 ±9.2	101.4 ±10.3	< 0.001
SBP (mmHg)	124.3 ±12.7	138.4 ±14.2	< 0.001
DBP (mmHg)	78.6 ±9.2	85.0 ±8.6	< 0.001
Triglyceride (mg/dL)	146.4±10.7	176.4±10.3	< 0.001
HDL (mg/dL)	65.2 ±17.4	54.2 ±16.1	< 0.001
FPG (mg/dL)	109.8 ±13.4	97.4 ±11.3	< 0.001
2hPPG (mg/dL)	209.7±11.9	167.1±12.5	< 0.001
HbA_1c (% (mmol/mol))	5.4±0.8	7.1 ±1.1	< 0.001
Duration of DM (years)	5.1 ±1.2	8.2 ±1.6	0.01
Smoking (%)	35.6	40.3	0.11
Drinking (%)	39.8	43.3	0.07
Newly detected DM (%)	19.3	24.5	< 0.001

MS: metabolic syndrome; BMI: body mass index; HbA_1c: hemoglobin A_1C; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 2. Retinopathy grade in patients with and without MS.

Retinopathy	With MS (n=48)	Without MS (n=26)
Mild-NPDR	10	9
Moderate-NPDR	11	6
Severe-NPDR	12	6
PDR	15	5

MS: metabolic syndrome; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy

Table 3. Prevalence of retinopathy in different groups of this study.

Item	Retinopathy (n)	Prevalence (%)
Total diabetes	55	11.79
Known diabetes	34	18.18
Newly detected diabetes	21	7.72
Non-diabetes	19	3.25
With MS	48	9.64
Without MS	26	3.91
Total subjects	74	6.36

MS: metabolic syndrome.

Table 4. Demographic data, selected clinical and laboratory findings in retinopathy patients with nondiabetes.

Parameter	Retinopathy patients with nondiabetes
Age (years)	59.1 ±3.2
Male (%)	44.3
Weight (kg)	75.3 ±11.6
Height (cm)	169.8 ±11.1
BMI (kg/m^2)	28.9 ±5.1
Waist (cm)	95.5 ±8.9
SBP (mmHg)	126.3 ±11.6
DBP (mmHg)	79.5 ±9.1
Triglyceride (mg/dL)	148.5±10.6
HDL (mg/dL)	66.3 ±18.1
FPG (mg/dL)	98.7 ±10.5
2hPPG (mg/dL)	189.8±10.5
HbA_1c (% (mmol/mol))	5.2±0.6
Smoking (%)	32.1
Drinking (%)	41.8

BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; SBP: systolic blood pressure; SBP: systolic blood pressure; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 5. Demographic data, selected clinical and laboratory findings in patients with NPDR and PDR.

Parameter	NPDR (n=54)	PDR (n=20)	*p*-value
Age (years)	68.1 ±4.1	70.7 ±3.4	0.04
Male (%)	45.2	44.6	0.86
Weight (kg)	84.3 ±10.6	85.6 ±11.2	0.54
Height (cm)	166.8 ±11.2	167.7 ±10.7	0.66
BMI (kg/m^2)	26.9 ±4.3	31.1 ±4.2	< 0.001
Waist (cm)	100.6 ±10.2	102.4 ±11.1	0.22
SBP (mmHg)	123.3 ±11.7	132.5 ±12.2	< 0.001
DBP (mmHg)	77.8 ±8.6	84.9 ±7.9	< 0.001
Triglyceride (mg/dL)	145.8±9.7	175.8±11.3	< 0.001
HDL (mg/dL)	64.2 ±16.2	58.6 ±15.1	0.01
FPG (mg/dL)	96.8 ±10.5	108.9 ±12.5	< 0.001
2hPPG (mg/dL)	199.2±11.4	214.8±12.9	< 0.001
HbA_1c (% (mmol/mol))	6.7	8.8	< 0.001
Duration of DM (years)	6.1 ±1.3	9.4 ±1.5	0.02
Smoking (%)	40.6	42.4	0.14
Drinking (%)	29.9	31.3	0.11
Newly detected DM (%)	30.2	20.5	< 0.001

PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; BMI: body mass index; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

Table 6. Logistic regression analyses for retinopathy in the population with and without MS.

	With MS				Without MS			
	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value	OR* (95% CI)	*p*-value	OR# (95% CI)	*p*-value
Age (per 10-year)	0.94 (0.78–1.07)	0.39	0.86 (0.58–1.19)	0.11	0.96 (0.74–1.24)	0.70	0.79 (0.41–1.35)	0.22
Gender (female vs male)	0.81 (0.62–1.04)	0.13	0.72 (0.54–1.02)	0.06	1.20 (0.89–1.68)	0.45	1.02 (0.59–1.72)	0.98
BMI (per kg/m^2)	0.97 (0.94–0.99)	0.01	0.98 (0.92–1.06)	0.41	0.96 (0.91–1.00)	0.06	0.99 (0.93–1.04)	0.60
Diabetes duration (per 10-year)	1.06 (1.03–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.10)	<0.001
Weight (per 10-kg)	1.05 (0.71–1.63)	0.79	1.04 (0.62–1.73)	0.88	1.14 (0.52–2.43)	0.74	1.19 (0.44–3.10)	0.74
Height (per 10-cm)	1.43 (0.97–2.06)	0.06	1.31 (0.82–2.09)	0.26	1.69 (0.88–3.26)	0.13	1.31 (0.54–3.18)	0.56
Waist (per 10-cm)	1.34 (0.78–2.32)	0.26	1.32 (0.68–2.57)	0.38	0.98 (0.36–2.52)	0.94	0.67 (0.21–2.28)	0.55
SBP (per 10-mmHg)	1.14 (1.04–1.22)	<0.001	1.16 (1.09–1.29)	<0.001	1.27 (1.14–1.46)	<0.001	1.35 (1.18–1.55)	<0.001
DBP (per 10-mmHg)	1.12 (1.05–1.22)	<0.001	1.24 (1.12–1.35)	0.02	1.15 (1.04–1.28)	<0.001	1.18 (0.97–1.38)	0.66
Triglycerides (per 10-mg/dL)	1.04 (0.88–1.19)	0.66	0.95 (0.78–1.12)	0.49	1.19 (0.94–1.48)	0.14	1.13 (0.86–1.47)	0.39
HDL cholesterol (per 10-mg/dL)	0.87 (0.64–1.18)	0.49	0.77 (0.53–1.12)	0.20	1.03 (0.88–1.22)	0.51	1.13 (0.85–1.44)	0.37
FPG (per 10-mg/dL)	1.06 (1.01–1.11)	<0.001	1.07 (1.02–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.11 (1.05–1.17)	<0.001
2hPPG (per 10-mg/dL)	1.16 (1.02–1.32)	<0.001	1.17 (1.12–1.21)	<0.001	1.12 (1.01–1.21)	<0.001	1.13 (1.04–1.22)	<0.001
HbA_1c (per % (mmol/mol))	1.25 (1.15–1.35)	<0.001	1.23 (1.13–1.34)	<0.001	1.29 (1.15–1.44)	<0.001	1.26 (1.10–1.44)	<0.001
Current smoker	1.22 (0.87–1.68)	0.39	1.37 (0.79–2.09)	0.47	1.21 (0.68–1.86)	0.59	1.42 (0.68–2.46)	0.44
Current drinker	1.12 (0.57–1.78)	0.33	1.27 (0.68–2.28)	0.65	1.19 (0.58–2.46)	0.59	1.20 (0.55–3.16)	0.55
Newly detected DM	0.89 (0.55–1.26)	0.46	0.78 (0.55–1.23)	0.21	1.00 (0.84–1.32)	0.56	0.96 (0.75–1.33)	0.35

MS: metabolic syndrome; BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA_1c: hemoglobin A_1c; HDL: high-density lipoprotein; OR: odds ratio; SBP: systolic blood pressure; DM: diabetes mellitus; 2hPPG: 2h-postprandial plasma glucose; FPG: fasting plasma glucose.

*Adjusted for age and gender. # Adjusted for age, gender, body mass index, HbA1c, duration of diabetes, SBP and DBP), drinking and smoking.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.