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Prevalence and risk factors of retinopathy in patients with or without metabolic syndrome: a population-based study in Shenyang

Lei Liu,[1] Song Yue,[1] Jingyang Wu,[1] Jiahua Zhang,[1] Jie Lian,[2] Weiping Teng,[3] Desheng Huang,[4] Lei Chen[1,3]

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LL and SY contributed to the work equally and should be regarded as co-first authors

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For numbered affiliations see end of article.

Correspondence to
Professor Lei Chen; carol1422@163.com; and Professor Desheng Huang; huangdsll@163.com

ABSTRACT

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

Design: A cross-sectional 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. All the participants were subjected to stereo fundus photography to detect retinopathy. The discrepancy of prevalence of retinopathy in different participants was described.

Results: The prevalence of retinopathy was 9.64% in patients with MS and 3.91% in patients without MS. A higher prevalence of retinopathy with proliferative diabetic retinopathy was found in patients with MS. In multiple logistic regression analysis, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (OR 1.07; 95% CI 1.04 to 1.10, per year increase), higher systolic blood pressure (SBP) (OR 1.16; 95% CI 1.09 to 1.29, per 10 mm Hg increase), higher diastolic blood pressure (DBP) (OR 1.24; 95% CI 1.12 to 1.35, per 10 mm Hg increase), higher fasting plasma glucose (OR 1.07; 95% CI 1.02 to 1.11, per 10 mg/dL increase), higher 2 h postprandial plasma glucose (OR 1.17; 95% CI 1.12 to 1.21, per 10 mg/dL increase), and higher haemoglobin A1c (HbA1c) (OR 1.23; 95% CI 1.13 to 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, hyperglycaemia (fasting glucose and HbA1c) and hypertension (SBP and DBP), are significantly associated with the prevalence of retinopathy.

Strengths and limitations of this study

- It is the first population-based study to provide evidence of a relationship between metabolic syndrome (MS) and retinopathy in a North Chinese population.
- We found that the presence of MS components, hyperglycaemia (fasting glucose and HbA1c) and hypertension (systolic blood pressure and diastolic blood pressure), 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 less representative.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of metabolic disorders characterised by abdominal obesity, hyperglycaemia, hyperlipidaemia 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 diabetes mellitus (DM) and cardiovascular disease.[2] MS is increasingly recognised as being a distinct entity affecting a large proportion of the Chinese population.[3 4] Patients with MS are at known risk of developing large-vessel diseases and retinal microvascular abnormalities.[5 6] Some combinations of traits of MS may be of significant help in identifying subjects with insulin resistance.[7] Insulin resistance is a risk factor for diabetic retinopathy (DR).[8 9] It is unclear whether MS is associated with retinopathy in North Chinese populations. Retinopathy secondary to MS and retinopathy secondary to DM were differentiated in this study. We examined the cross-sectional association of MS and retinopathy in this population-based study.

METHODS

Study population

This study was carried out in Fengyutan Healthcare Centre which was part of a model

for prevention of DR in Liaoning Diabetic Eye Centre. It is located in the Fengyutan Sub-District of Shenyang City in North China. There are more than 80 000 residents and five communities (Yutan, Yonghuan, Taoyuan, Qingnian and Zhongxin community) in Fengyutan Sub-District. Multistage, stratified random sampling was carried out on a selection of residents. First, the five communities were numbered, and then four were randomly selected from the five numbers. Second, the household health files registered in Fengyutan Healthcare Centre were numbered, and 400 households in each of the four selected communities were randomly chosen using a 'true random number generator' (https://www.random.org/). The participants had lived in Fengyutan for at least 2 years at the time the research was conducted. The selected households were informed by community officers using web page message or a telephone call. Finally, a total of 1400 subjects aged over 40 years attended from August 2013 to September 2014. After exclusion of patients with cancer, hepatic failure, renal failure, severe psychiatric disturbance or any other systemic medical condition (for example, severe cardiac or respiratory impairment) and subjects who would not attend voluntarily, 1163 (response rate 83.07%) eligible participants were enrolled.

Data collection

Information on name, gender, age, smoking and drinking habits, and health status (eg, duration of diabetes, hypertension duration, medical history and treatment methods) were obtained using a standardised questionnaire. In addition, participants were asked whether they had 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 antidiabetic agents. Following an interview with a community office worker, all participants were asked to fast overnight (>8 h) before a physical examination. Waist circumference was measured at the level of the umbilicus in the standing position. Height and weight were measured without hats or heavy coats. Blood pressure (BP) was measured in the sitting position (first) and supine position (second), with a 5 min interval, using an upright standard sphygmomanometer. Subjects were asked to avoid vigorous physical activity and smoking for at least 30 min before BP measurement. The second BP measurement with fifth-phase diastolic pressure was used for analysis. All participants were subjected to stereo fundus photography to detect retinopathy by 45° through undilated pupils (non-mydriatic fundus camera; CR6-45NM; Canon, Tokyo, Japan). For each subject, two images for each eye centred on the fovea and optic disc were taken in a darkened room. Each image was graded in a blinded 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; the individual classification was based on the worse eye. A clear retinal image could not be obtained for 41 subjects because of anterior segment opacity. Mydriasis with tropicamide 1% (Santen Pharmaceutical Co, Shiga, Japan) before 20 min of dark adaptation and binocular indirect ophthalmoscopy by two ophthalmologists who reviewed the retinal images was accepted.

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. The research was approved by the institutional ethics committee of The First Affiliated Hospital of China Medical University.

Laboratory methods

Blood was drawn from the antecubital vein for determination of high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose, and haemoglobin A1c in the morning after an 8 h fast. The 75 g oral glucose tolerance test was then carried out; 2 h later blood was drawn again. All biochemical analyses (enzymatic assay method) were performed at a commercial laboratory (The Endocrinology Laboratory, China Medical University, Shenyang, China).

Definition of MS, retinopathy, smoking, drinking and diabetes

The International Diabetes Federation 2005 (IDF) definition of MS describes a waist circumstance for a Chinese woman of ≥80 cm and a man of ≥90 cm plus two or more of the following four risk factors: (1) triglyceride concentration ≥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 BP (systolic BP (SBP) ≥130 mm Hg or diastolic BP (DBP) ≥85 mm Hg) or treatment of previously diagnosed hypertension; and (4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[10] Diabetes was diagnosed according to the 1999 WHO criteria.[11] Stereoscopic colour fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.[12 13] 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 retinopathy levels. Drinking was defined as alcohol intake more than once a month over the past 12 months. Smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes.

Statistical analysis

Mean±SD was used to express measurement data. In univariate analysis, a t test was applied for continuous variables and χ^2 test for nominal-scale data. Independent

Table 1 Demographic data and selected clinical and laboratory findings for patients with and without MS

Variable	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 (mm Hg)	124.3±12.7	138.4±14.2	<0.001
DBP (mm Hg)	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
HbA1c (%)	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

Unless otherwise indicated, values are mean±SD.
2hPPG, 2 h postprandial plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, haemoglobin A1C; HDL, high-density lipoprotein; MS, metabolic syndrome; SBP, systolic blood pressure.
To convert values for HbA1c in % into mmol/mol, subtract 2.15 and multiply by 10.929 or use the conversion calculator at www.hba1c.nu/eng/.

risk factors for retinopathy were analysed using multiple logistic regression with a stepwise approach. Data management and statistical analyses were performed using SPSS statistical software (V.16.0). p<0.05 was considered significant.

RESULTS

There were 498 subjects with MS. The overall prevalence of MS was 42.82%. Table 1 shows the demographic data and selected clinical and laboratory findings for patients with and without MS.

The prevalence of retinopathy was 9.64% (n=48) in patients with MS and 3.91% (n=26) in patients without MS, so it was significantly higher in patients with MS (p<0.05). Table 2 shows that the prevalence of proliferative DR (PDR) was also significantly higher in patients with MS (p<0.05). In addition, 6.36% of all participants, 11.79% of patients with diabetes, 18.18% of patients with known diabetes, 7.72% of patients with newly detected diabetes, and 3.25% of non-diabetic participants had retinopathy (table 3). The characteristics of non-diabetic patients with retinopathy are shown in table 4.

Demographic data and selected clinical and laboratory findings in patients with non-PDR (NPDR) and PDR are shown in table 5. Patients with NPDR had a significantly higher prevalence of newly detected DM.

In multiple logistic regression analysis, independent risk factors for any retinopathy in patients with MS were longer diabetes duration (OR 1.07; 95% CI 1.04 to 1.10, per year increase), higher SBP (OR 1.16; 95% CI 1.09 to 1.29, per 10 mm Hg increase), higher DBP (OR 1.24; 95% CI 1.12 to 1.35, per 10 mm Hg increase), higher fasting plasma glucose (OR 1.07; 95% CI 1.02 to 1.11, per 10 mg/dL increase), higher 2 h postprandial plasma glucose (OR 1.17; 95% CI 1.12 to 1.21, per 10 mg/dL increase), and higher haemoglobin A1c (OR 1.23; 95% CI 1.13 to 1.34, per % increase). Similar independent risk factors, except for DBP, were found for any retinopathy in patients without MS (table 6).

Table 2 Retinopathy grade in patients with and without MS

Retinopathy grade	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; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 3 Prevalence of retinopathy in different groups of participants

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

MS, metabolic syndrome.

Table 4 Demographic data and selected clinical and laboratory findings in patients with non-diabetic retinopathy

Variable	Value
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 (mm Hg)	126.3±11.6
DBP (mm Hg)	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
HbA1c (%)	5.2±0.6
Smoking (%)	32.1
Drinking (%)	41.8

Unless otherwise indicated, values are mean±SD.
2hPPG, 2 h postprandial plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; SBP, systolic blood pressure.
To convert values for HbA1c in % into mmol/mol, subtract 2.15 and multiply by 10.929 or use the conversion calculator at www.hba1c.nu/eng/.

DISCUSSION

The data provide population-based information regarding the prevalence of MS and its relationship to retinopathy. The overall prevalence of MS was 42.82% using IDF criteria; this is a little higher than in the study in Beijing.[14] Previous studies have reported a prevalence of 13.7% in adult Chinese populations. However, a prevalence of 50.0% has been found in older Chinese populations.[15 16] It is clear that the prevalence of MS is high and this might be due to the number of older Chinese increasing, which will present a social and public health problem in future.

Previous population-based studies on non-diabetic subjects have suggested a prevalence of retinopathy ranging from 3.5% to 9%.[17–24]—similar to our finding (3.25%). However, another study in China reported that the prevalence of retinopathy among participants without diabetes was 13.6%.[25] Our study was carried out in an urban region, which may partially explain the lower prevalence found. The overall prevalence of retinopathy was 6.36% in all subjects, which is a little higher than the results of a previous meta-analysis in China.[26] In our study, retinopathy secondary to MS and retinopathy secondary to DM were differentiated. The study by Keenan *et al*[24] showed that the prevalence of retinopathy was 8.6% in patients with MS, which is a little lower than our results. Similarly, the prevalence of retinopathy in patients without MS (3.6%) was slightly lower than in our study.

To the best of our knowledge, this is the first population-based study to provide evidence of a relationship between MS and retinopathy in a North Chinese population and that MS is an independent risk factor for retinopathy after adjustment for age, gender and other factors. Previously, a community-based study in South China (Shanghai) reported that retinopathy was highly associated with accumulated metabolic abnormalities.[27] In addition, another hospital-based study in China found that the prevalence of DR was higher in a group with MS than in a group without.[28] Two cross-

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

Variable	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 (mm Hg)	123.3±11.7	132.5±12.2	<0.001
DBP (mm Hg)	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
HbA1c (%)	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

Unless otherwise indicated, values are mean±SD.
2hPPG, 2 h postprandial plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure.
To convert values for HbA1c in % into mmol/mol, subtract 2.15 and multiply by 10.929 or use the conversion calculator at www.hba1c.nu/eng/.

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

	With MS				Without MS			
Risk factor	**OR* (95% CI)**	**p Value**	**OR† (95% CI)**	**p Value**	**OR* (95% CI)**	**p Value**	**OR† (95% CI)**	**p Value**
Age (per 10 years)	0.94 (0.78 to 1.07)	0.39	0.86 (0.58 to 1.19)	0.11	0.96 (0.74 to 1.24)	0.70	0.79 (0.41 to 1.35)	0.22
Gender (female vs male)	0.81 (0.62 to 1.04)	0.13	0.72 (0.54 to 1.02)	0.06	1.20 (0.89 to 1.68)	0.45	1.02 (0.59 to 1.72)	0.98
BMI (per kg/m^2)	0.97 (0.94 to 0.99)	0.01	0.98 (0.92 to 1.06)	0.41	0.96 (0.91 to 1.00)	0.06	0.99 (0.93 to 1.04)	0.60
Diabetes duration (per 10 years)	1.06 (1.03 to 1.10)	<0.001	1.07 (1.04 to 1.10)	<0.001	1.08 (1.04 to 1.12)	<0.001	1.07 (1.04 to 1.10)	<0.001
Weight (per 10 kg)	1.05 (0.71 to 1.63)	0.79	1.04 (0.62 to 1.73)	0.88	1.14 (0.52 to 2.43)	0.74	1.19 (0.44 to 3.10)	0.74
Height (per 10 cm)	1.43 (0.97 to 2.06)	0.06	1.31 (0.82 to 2.09)	0.26	1.69 (0.88 to 3.26)	0.13	1.31 (0.54 to 3.18)	0.56
Waist (per 10 cm)	1.34 (0.78 to 2.32)	0.26	1.32 (0.68 to 2.57)	0.38	0.98 (0.36 to 2.52)	0.94	0.67 (0.21 to 2.28)	0.55
SBP (per 10 mm Hg)	1.14 (1.04 to 1.22)	<0.001	1.16 (1.09 to 1.29)	<0.001	1.27 (1.14 to 1.46)	<0.001	1.35 (1.18 to 1.55)	<0.001
DBP (per 10 mm Hg)	1.12 (1.05 to 1.22)	<0.001	1.24 (1.12 to 1.35)	0.02	1.15 (1.04 to 1.28)	<0.001	1.18 (0.97 to 1.38)	0.66
Triglycerides (per 10 mg/dL)	1.04 (0.88 to 1.19)	0.66	0.95 (0.78 to 1.12)	0.49	1.19 (0.94 to 1.48)	0.14	1.13 (0.86 to 1.47)	0.39
HDL cholesterol (per 10 mg/dL)	0.87 (0.64 to 1.18)	0.49	0.77 (0.53 to 1.12)	0.20	1.03 (0.88 to 1.22)	0.51	1.13 (0.85 to 1.44)	0.37
FPG (per 10 mg/dL)	1.06 (1.01 to 1.11)	<0.001	1.07 (1.02 to 1.11)	<0.001	1.09 (1.05 to 1.13)	<0.001	1.11 (1.05 to 1.17)	<0.001
2hPPG (per 10 mg/dL)	1.16 (1.02 to 1.32)	<0.001	1.17 (1.12 to 1.21)	<0.001	1.12 (1.01 to 1.21)	<0.001	1.13 (1.04 to 1.22)	<0.001
HbA1c (per %)	1.25 (1.15 to 1.35)	<0.001	1.23 (1.13 to 1.34)	<0.001	1.29 (1.15 to 1.44)	<0.001	1.26 (1.10 to 1.44)	<0.001
Current smoker	1.22 (0.87 to 1.68)	0.39	1.37 (0.79 to 2.09)	0.47	1.21 (0.68 to 1.86)	0.59	1.42 (0.68 to 2.46)	0.44
Current drinker	1.12 (0.57 to 1.78)	0.33	1.27 (0.68 to 2.28)	0.65	1.19 (0.58 to 2.46)	0.59	1.20 (0.55 to 3.16)	0.55
Newly detected DM	0.89 (0.55 to 1.26)	0.46	0.78 (0.55 to 1.23)	0.21	1.00 (0.84 to 1.32)	0.56	0.96 (0.75 to 1.33)	0.35

*Adjusted for age and gender.
†Adjusted for age, gender, BMI, HbA1c, duration of diabetes, SBP, DBP, drinking and smoking.
2hPPG, 2 h postprandial plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; MS, metabolic syndrome; SBP, systolic blood pressure.
To convert values for HbA1c in % into mmol/mol, subtract 2.15 and multiply by 10.929 or use the conversion calculator at www.hba1c.nu/eng/.

sectional studies have reported an association between 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] and, in another study in Japan, a similar association was found.[29] Although the researchers in these studies did not reveal any relationship between MS and retinopathy in the non-diabetic population, this might be due to methodological problems in this cross-sectional study. The study design means that a causal relation cannot be directly determined. In addition, the results of our study showed a higher prevalence of retinopathy, including PDR, in patients with MS. Therefore, we can hypothesise that MS is a risk factor for retinopathy, and more prospective studies are warranted to determine the significance of 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 whether MS was present or not (as defined by the IDF guidelines), longer diabetes duration, higher SBP, higher fasting plasma glucose, higher 2 h postprandial plasma glucose, and higher haemoglobinA1c were independent risk factors for retinopathy. Higher DBP was an independent risk factor for retinopathy in patients with MS. HDL cholesterol level was not associated with the presence of retinopathy lesions, as found in some earlier studies.[24] We also found no significant association between smoking and drinking in patients with or without MS.

Shortcomings of this study include the following: it was a population-based study in a community, so there was no fundus fluorescein angiography and optical coherence tomography to assist diagnosis; the study was conducted in only four communities of Shenyang, so there was selection bias; we did not investigate the type of diabetes for all subjects, so the prevalence of retinopathy in diabetes was less representative.

CONCLUSIONS

Our data demonstrate that the presence of MS components is significantly associated with the prevalence of retinopathy. 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 its relationship with retinal vascular disorders.

Author affiliations
[1]Department of Ophthalmology, The First Affiliated Hospital of China Medical University, Shenyang, China
[2]Health Center, Fengyutan Sub-District, Shenyang, China
[3]Key Laboratory of Endocrine Diseases in Liaoning Province, The First Affiliated Hospital of China Medical University, Shenyang, China
[4]Department of Epidemiology, School of Public Health, China Medical University, Shenyang, China

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