Association of total bilirubin and indirect bilirubin content with metabolic syndrome among Kazakhs in Xinjiang

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Research

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Abstract

Background: Some studies have shown that a high level of bilirubin is a protective factor against the metabolic syndrome (MS), while a high level of transaminase is a risk factor for the MS. However, the results are inconsistent, and there are few cohort studies.

Methods: Using an ambispective cohort study, 565 Kazakhs from Xinjiang, China were selected as the study subjects. The serum bilirubin and transaminase levels of the subjects were divided into quartiles, and their relationships with MS and its components were analyzed. The definition of metabolic syndrome was based on the Joint Interim Statement (JIS) diagnostic criteria.

Results: The average follow-up time for the subjects was 5.72 years. 204 subjects had MS, the cumulative incidence was 36.11%, and the incidence density was 63.10/1000 person-years. Multivariate Cox regression analysis showed that the levels of total bilirubin (TBIL) and indirect bilirubin (IBIL) were negatively correlated with the occurrence of MS. Compared to the lowest quartile level (Q1), the hazard ratios of MS for levels of TBIL at the Q2-Q4 quartile were: 0.408 (0.266-0.626), 0.374 (0.244-0.572), and 0.328 (0.216-0.500) while IBIL at Q2-Q4 level showed an MS hazard ratio of 0.572 (0.374-0.875), 0.432 (0.283-0.659), 0.434 (0.289-0.653), all at a 95% confidence level. In addition, TBIL and IBIL levels were negatively correlated with increased blood pressure, waist circumference, and triglyceride levels, and their highest TBIL quartile risk (Q4) was 0.479, 0.484, and 0.498 times higher than the lowest quartile (Q1).

Conclusion: Serum TBIL and IBIL levels were negatively correlated with MS and its components (blood pressure, waist circumference and triglycerides).

Background

Metabolic syndrome (MS) is a clustering of complex medical conditions, including hypertension, hyperglycemia, central obesity, hypertriglyceridemia, and high-density lipoprotein cholesterol reduction. It can lead to cardiovascular disease, type 2 diabetes, lipid disorder, liver steatosis, and other circulatory system disorders[1]. Although the etiology and pathogenesis of MS have not been clarified, it is generally believed that factors such as insulin resistance, inflammation, and oxidative stress play an important role in its occurrence and development[1–3]. An increasing weight of evidence suggests that serum bilirubin has physiological functions, such as anti-inflammatory, antioxidant, improving vascular endothelial function, and enhancing insulin sensitivity[4, 5]. A high level of bilirubin has a protective effect for MS[6, 7].Transaminase can promote inflammation and induce insulin resistance[8]. High levels of alanine aminotransferase (ALT) is a risk factor for MS[6, 9]. The results of a cohort study showed that male γ-glutamyl transpeptidase levels (HR = 1.511, 95% CI: 1.160–1.968) and female ALT levels (HR = 1.504, 95% CI: 1.129–2.003) are related to MS, but that direct bilirubin (DBIL), total bilirubin (TBIL), ALT, aspartate aminotransferase (AST) in men and DBIL, TBIL, and AST levels in women are not[10]. The results of the above mentioned studies are inconsistent.

Kazakhs in Xinjiang, China are nomadic minorities in the mountainous areas, living remotely. They are relatively poor, economically, and their culture and customs are significantly different from other ethnic groups[11, 12]. A previous study by our research group found the prevalence of MS in Kazakhs to be higher than other ethnic groups in Xinjiang and the national average[13].Therefore, this study takes Xinjiang Kazakh residents as the research group and explores the relationship between both serum bilirubin and transaminase with MS and its components. This provides theoretical support for early diagnosis and prevention of metabolic syndrome in the Xinjiang Kazakh population and may provide evidence for people living in Kazakhstan and Uzbekistan.

Methods

Research subjects

Based on the geographical distribution of Xinjiang's ethnic minorities in northwestern China, a representative county (six villages in Nalati Township, Xinyuan County) was selected and an ambispective cohort study was conducted on the local Kazakh population. The study baseline was conducted in 2009 and 2012. The subjects were followed up in 2013, 2016, and 2017. A total of 785 subjects were included in the study, excluding 10 subjects with chronic liver disease, 2 subjects with cancer, and 208 subjects with MS at baseline. A total of 565 subjects were included in the study.

Epidemiological investigation and biochemical test

A questionnaire was used and face-to-face interview was conducted by uniformly trained investigators to collect personal information, disease history, family history, and lifestyle behavior. During the survey, height, weight, waist circumference (WC), systolic (SBP), and diastolic blood pressure (DBP) were measured and recorded, according to standardized methods. The total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol(LDL-C) were measured using automatic biochemical analyzer (Olympus Au 2700; Olympus diagnostics, Hamburg, Germany). Each subject signed an informed consent form. The investigation was approved by the ethics review committee of the First Affiliated Hospital of Shihezi University Medical College (IERB No. SHZ2010LL01), and its operations and methods were carried out in accordance with the relevant guidelines.

Definition of MS

Our identification of metabolic syndrome is based on the Joint Interim Statement (JIS) diagnostic criteria[14]. For MS to be diagnosed, three or more of these five indicators must be observed: (1) Men WC ≥ 85cm, Women WC ≥ 80cm; (2) SBP ≥ 130mm Hg or DBP ≥ 85mm Hg, or have received treatment,

or have previously diagnosed hypertension; (3) FPG ≥ 5.6mmol/L , or have received treatment, or have previously diagnosed type 2 diabetes. (4) TG ≥ 1.70 mmol/L or received treatment; (5) Men HDL-C < 1.0 mmol/L, Women HDL-C < 1.30 mmol/L, or received treatment.

Statistical analysis

Data analysis was performed using SPSS version 20.0 (Chicago, Illinois, USA). Mean ± standard deviation was used to describe continuous variables, and percentages were used to describe categorical variables. Rank sum tests were used to compare baseline characteristics between men and women, and chi-square tests to compare categorical variables. Serum bilirubin and transaminase levels in this population differed between men and women. Therefore, this study was classified according to the quartiles of serum bilirubin and transaminase levels (Q1, Q2, Q3, and Q4), separately for each gender. The multivariate COX proportional-hazards model was used to analyze the relationship between serum bilirubin or transaminase levels and MS and its components. We adjusted for smoking, drinking, age, gender, waist circumference, blood pressure, fasting plasma glucose, triglyceride and high-density lipoprotein cholesterol. Subsequently, the hazard ratio (HR) and 95% confidence interval (95% CI) of serum bilirubin and transaminase levels to MS and its components were calculated. All statistical tests were bilateral, and P < 0.05 indicated statistical significance.

Results

Baseline characteristics

565 subjects were included in this survey, including 221 males (39.1%). The average age of the total population was 40.33 ± 11.86 years, of which the average age of men was 42.10 ± 12.93 years, and women 39.20 ± 10.99 years. The average age of men was, statistically, significantly higher than that of women., and the difference was statistically significant (P = 0.011). In a comparison of baseline characteristics between the two sexes, the levels of WC, SBP, DBP, TG, TBIL, IBIL, ALT, and AST were higher in men than women, and HDL-C levels were higher in women than men. The differences were statistically significant (P < 0.05). As shown in Table 1.

Table 1 Baseline characteristics based on different genders

	Total	Men	Women	*P*
Number (%)	565	221(39.1)	344(60.9)	
Age (years)	40.33±11.86	42.10±12.93	39.20±10.99	**0.011**
Smoking, N (%)	187(33.1)	117(52.9)	70(20.3)	**<0.001**
Drinking, N (%)	55(9.7)	52(23.5)	3(0.9)	**<0.001**
WC (cm)	81.58±9.97	83.64±9.77	80.26±9.88	**<0.001**
SBP (mmHg)	127.84±21.72	132.10±21.64	125.11±21.36	**<0.001**
DBP (mmHg)	81.92±13.79	84.06±13.52	80.54±13.81	**<0.001**
FPG (mmol/L)	4.37±0.97	4.48±1.12	4.29±0.86	0.214
TG (mmol/L)	1.05±0.84	1.05±0.52	1.05±0.99	**0.018**
TC (mmol/L)	4.13±0.94	4.17±0.86	4.11±0.99	0.212
HDL-C (mmol/L)	1.42±0.37	1.36±0.36	1.46±0.38	**<0.001**
LDL-C (mmol/L)	2.08±0.67	2.13±0.64	2.04±0.69	0.054
BMI (kg/m^2)	23.26±3.44	23.43±3.32	23.15±3.51	0.359
TBIL (μmol/L)	10.84±4.70	11.84±4.71	10.19±4.59	**<0.001**
IBIL (μmol/L)	8.08±3.82	8.76±3.88	7.65±3.73	**<0.001**
DBIL (μmol/L)	2.58±1.48	2.72±1.56	2.48±1.42	0.054
ALT (IU/L)	15.34±10.36	16.43±8.28	14.64±11.45	**<0.001**
AST (IU/L)	27.37±12.48	28.70±11.84	26.52±12.82	**0.002**

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, Triglycerides; TC, total cholesterol, HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; TBIL, total bilirubin ; IBIL, indirect bilirubin; DBIL, direct bilirubin, ALT, alanine aminotransferase; AST, aspartate aminotransferase

The incidence of metabolic syndrome

The subjects were followed up for 3233.04 person-years, with an average follow-up time of 5.72 ± 1.49 years per subject. During this period, a total of 204 subjects developed MS, with a cumulative incidence of 36.11% and the incidence density was 63.10/1000 person-years. Among them, 70 men had MS, the cumulative incidence was 31.67%, and the incidence density was 55.71 / 1000 person-years. The cumulative incidence increased with age (χ^2 trend = 43.166, P < 0.001) and 134 women had MS, the cumulative incidence was 38.95% and the incidence density was 67.80 / 1000 person-years. The cumulative incidence increased with age (χ^2 trend = 76.391, P < 0.001). There was no statistically significant difference in cumulative incidence and incidence density between men and women. As shown in Table 2.

Table 2 Comparison of the incidence of metabolic syndrome in different age groups

Group	Number	Number of MS	Cumulative incidence (%)	Incidence density (10^{-3}person-years)	χ^2_{trend}	P
total	565	204	36.11	63.10		
men	221	70	31.67	55.71		
<35	69	14	20.29	36.75	43.166	**<0.001**
35-45	70	23	32.86	54.96		
>45	82	33	40.24	72.19		
women	344	134	38.95	67.80		
<35	128	38	29.69	51.49	76.391	**<0.001**
35-45	121	51	42.15	72.24		
>45	95	45	47.37	84.52		

Analysis of influencing factors for metabolic syndrome

We divided the indicators into four groups from low to high, according to the quartile, and explored the relationship between the different quartile levels and the risk of MS. After adjusting for age, sex, smoking, drinking, waist circumference, blood pressure, fasting plasma glucose, triglyceride, and high-density lipoprotein cholesterol, we found that TBIL and IBIL levels were negatively correlated with MS. Compared to the lowest quartile level (Q1), the HR (95% CI) of TBIL Q2-Q4 levels were 0.408 (0.266-0.626), 0.374 (0.244-0.572), and 0.328 (0.216-0.500), and that of IBIL Q2-Q4 were 0.572 (0.374-0.875), 0.432 (0.283-0.659), and 0.434 (0.289-0.653). With the increase of TBIL and IBIL levels, its negative correlation with MS also increased. However, there was no correlation between DBIL, ALT, or AST and MS. As shown in Table 3.

Table 3 Analysis of influencing factors for incident metabolic syndrome

Parameter		*HR*	*95%CI*	*P*
TBIL				
	Q1	ref	ref	ref
	Q2	**0.408**	**0.266-0.626**	**<0.001**
	Q3	**0.374**	**0.244-0.572**	**<0.001**
	Q4	**0.328**	**0.216-0.500**	**<0.001**
IBIL				
	Q1	ref	ref	ref
	Q2	**0.572**	**0.374-0.875**	**0.010**
	Q3	**0.432**	**0.283-0.659**	**<0.001**
	Q4	**0.434**	**0.289-0.653**	**<0.001**
DBIL				
	Q1	ref	ref	ref
	Q2	1.191	0.792-1.793	0.401
	Q3	1.185	0.786-1.785	0.418
	Q4	0.969	0.633-1.481	0.883
	ALT			
	Q1	ref	ref	ref
	Q2	1.057	0.690-1.620	0.799
	Q3	1.165	0.746-1.820	0.502
	Q4	0.978	0.607-1.576	0.929
	AST			
	Q1	ref	ref	ref
	Q2	0.711	0.477-1.060	0.094
	Q3	0.747	0.488-1.142	0.178
	Q4	1.003	0.643-1.565	0.988

Analysis adjusted for age, sex, smoking, drinking, waist circumference, blood pressure, fasting plasma glucose, triglycerides, and high-density lipoprotein cholesterol

Correlation analysis of serum bilirubin, transaminase and MS components

From multivariate Cox regression model analysis, TBIL and IBIL levels were found to be negatively correlated with increased blood pressure, increased waist circumference, and increased triglycerides. The risk of elevated blood pressure, increased waist circumference, and elevated triglycerides at the highest quartile level of TBIL (Q4) was 0.479, 0.484, and 0.498 respectively, at the lowest quartile (Q1). AST levels were positively correlated with elevated fasting glucose and triglycerides. The highest quartile levels of fasting glucose and triglycerides were 2.33 times and 2.20 times that of the lowest quartile. No correlation was found between DBIL, ALT and the occurrence of MS components. As shown in Table 4.

Correlation analysis of serum bilirubin, transaminase and MS at baseline with different components

Multivariate Cox regression analysis showed that, in the populations with no MS component or one MS component, at baseline, each index was not related to the risk of MS. In a population with two MS components at baseline, TBIL and IBIL levels are negatively correlated with the risk of MS. Compared to the lowest quartile level (Q1), the risk HRs (95% CI) of TBIL Q2-Q4 group were 0.410 (0.232, 0.725), 0.413 (0.232, 0.737), and 0.351 (0.198, 0.624), and those of the IBIL Q2-Q4 group were 0.380 (0.212, 0.682), 0.335 (0.190, 0.593), and 0.302 (0.165, 0.553). With an increase in TBIL and IBIL levels, the risk of MS is gradually reduced. However, DBIL, ALT, and AST are not related to the risk of MS. As shown in Table 5.

Table 4 Correlation analysis of serum bilirubin, transaminase and MS components

	Elevated blood pressure [a] (n=351)		Increased waist circumference [b] (n=366)		Raised fasting glucose [c] (n=676)		Raised triglycerides [d] (n=602)		Reduced HDL-C [e] (n=515)	
	HR (95%CI)	*P*	*HR (95%CI)*	*P*	*HR(95%CI)*	*P*	*HR(95%CI)*	*P*	*HR(95%CI)*	*P*
TBIL										
Q1	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Q2	**0.427(0.265,0.689)**	**<0.001**	**0.587(0.387,0.891)**	**0.012**	1.080(0.557,2.091)	0.820	**0.536(0.329,0.873)**	**0.012**	0.706(0.465,1.072)	0.102
Q3	**0.371(0.213,0.645)**	**<0.001**	**0.537(0.333,0.866)**	**0.011**	0.987(0.488,1.998)	0.972	**0.688(0.423,1.119)**	**0.132**	0.760(0.497,1.164)	0.207
Q4	**0.479(0.299,0.765)**	**0.002**	**0.484(0.306,0.765)**	**0.002**	0.623(0.300,1.294)	0.205	**0.498(0.300,0.826)**	**0.007**	0.702 (0.461,1.068)	0.099
IBIL										
Q1	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Q2	**0.596(0.361,0.981)**	**0.042**	**0.528(0.348,0.800)**	**0.003**	1.161(0.592,2.277)	0.664	**0.573(0.351,0.937)**	**0.026**	0.818(0.527,1.269)	0.370
Q3	**0.439(0.266,0.726)**	**0.001**	**0.460(0.295,0.716)**	**0.001**	1.335(0.667,2.673)	0.414	0.669(0.414,1.078)	0.099	0.954(0.615,1.478)	0.832
Q4	0.641(0.405,1.015)	0.058	**0.447(0.281,0.709)**	**0.001**	0.865(0.422,1.773)	0.692	**0.606(0.368,0.997)**	**0.049**	0.776(0.501,1.203)	0.257
DBIL										
Q1	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Q2	0.865(0.516,1.451)	0.583	1.134(0.737,1.746)	0.568	0.808(0.459,1.422)	0.459	1.214(0.780,1.889)	0.389	1.066(0.752,1.513)	0.718
Q3	1.505(0.933,2.428)	0.093	1.329(0.860,2.054)	0.200	0.805(0.431,1.504)	0.496	1.165(0.724,1.876)	0.529	0.856(0.567,1.294)	0.461
Q4	0.860(0.529,1.398)	0.543	0.828(0.528,1.297)	0.410	0.570(0.318,1.023)	0.060	0.631(0.382,1.041)	0.071	0.792(0.545,1.153)	0.224
ALT										
Q1	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Q2	1.054(0.630,1.762)	0.842	1.238(0.795,1.927)	0.345	1.531(0.818,2.865)	0.183	1.230(0.757,1.999)	0.403	1.117(0.741,1.682)	0.597
Q3	1.000(0.627,1.597)	0.998	1.141(0.756,1.723)	0.530	1.069(0.588,1.942)	0.827	1.159(0.728,1.846)	0.534	0.862(0.594,1.250)	0.433
Q4	0.854(0.500,1.458)	0.563	1.381(0.857,2.225)	0.185	0.995(0.509,1.944)	0.988	0.708(0.406,1.234)	0.223	0.758(0.504,1.141)	0.185
AST										
Q1	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Q2	0.652(0.400,1.063)	0.087	1.087(0.706,1.674)	0.704	1.431(0.686,2.986)	0.339	1.323(0.645,2.716)	0.445	1.113(0.721,1.171)	0.629
Q3	0.644(0.381,1.068)	0.100	1.028(0.655,1.614)	0.904	1.816(0.891,3.703)	0.101	1.736(0.856,3.522)	0.126	1.073(0.706,1.630)	0.742
Q4	1.231(0.752,2.017)	0.409	1.505(0.941,2.406)	0.088	**2.335(1.128,4.836)**	**0.022**	**2.200(1.075,4.502)**	**0.031**	1.075(0.689,1.677)	0.751

a. The model with adjustment for age, sex, waist circumference, fasting blood glucose, triglycerides and high-density lipoprotein cholesterol;

b. The model with adjustment for age, sex, blood pressure, fasting blood glucose, triglycerides and high-density lipoprotein cholesterol;

c. The model with adjustment for age, sex, blood pressure, waist circumference, triglycerides and high-density lipoprotein cholesterol;

d. The model with adjustment for age, sex, blood pressure, waist circumference, fasting blood glucose and high-density lipoprotein cholesterol;

e. The model with adjustment for age, sex, blood pressure, waist circumference, fasting blood glucose and triglycerides.

Table 5 Analysis of serum bilirubin, transaminase and MS at baseline with different components

	MS component number = 0 (n=104)		MS component number = 1 (n=237)		MS component number = 2 (n=224)	
	HR(95%CI)	*P*	*HR(95%CI)*	*P*	*HR(95%CI)*	*P*
TBIL						
Q1	ref	ref	ref	ref	ref	ref
Q2	5.476(0.561,53.467)	0.144	0.524(0.226,1.213)	0.131	**0.410(0.232,0.725)**	**0.002**
Q3	3.556(0.406,31.146)	0.252	0.671(0.297,1.515)	0.337	**0.413(0.232,0.737)**	**0.003**
Q4	2.695(0.281,25.886)	0.390	0.698(0.307,1.587)	0.391	**0.351(0.198,0.624)**	**<0.001**
IBIL						
Q1	ref	ref	ref	ref	ref	ref
Q2	2.776(0.283,27.212)	0.381	0.551(0.265,1.145)	0.110	**0.380(0.212,0.682)**	**0.001**
Q3	5.992(0.679,52.894)	0.107	0.388(0.174,0.865)	0.021	**0.335(0.190,0.593)**	**<0.001**
Q4	2.809(0.302,26.120)	0.364	0.734(0.371,1.455)	0.376	**0.302(0.165,0.553)**	**<0.001**
DBIL						
Q1	ref	ref	ref	ref	ref	ref
Q2	0.799(0.182,3.509)	0.766	1.539(0.729,3.250)	0.259	1.269(0.738,2.183)	0.388
Q3	1.494(0.375,5.943)	0.569	1.879(0.829,4.258)	0.131	1.280(0.743,2.204)	0.374
Q4	0.222(0.041,1.215)	0.083	1.460(0.715,2.982)	0.299	0.954(0.521,1.746)	0.878
ALT						
Q1	ref	ref	ref	ref	ref	ref
Q2	0.699(0.168,2.908)	0.623	0.923(0.454,1.880)	0.826	1.225(0.656,2.289)	0.524
Q3	1.419(0.386,5.215)	0.599	0.926(0.439,1.954)	0.840	1.184(0.614,2.280)	0.614
Q4	0.406(0.085,1.942)	0.259	0.602(0.247,1.464)	0.263	1.287(0.661,2.509)	0.458
AST						
Q1	ref	ref	ref	ref	ref	ref
Q2	1.049(0.297,3.703)	0.941	0.743(0.356,1.553)	0.430	0.602(0.348,1.041)	0.070
Q3	1.941(0.463,8.134)	0.364	0.575(0.272,1.218)	0.148	0.694(0.385,1.251)	0.224
Q4	0.948(0.183,4.919)	0.950	0.786(0.349,1.773)	0.562	0.976(0.534,1.782)	0.937

The model with adjustment for smoking, drinking, age, sex, waist circumference, blood pressure, fasting blood glucose, triglycerides, and high-density lipoprotein cholesterol.

Discussion

In the Xinjiang Kazakh population, we determined the incidence of MS according to JIS diagnostic criteria, and analyzed the association of serum bilirubin and transaminase to the MS and its components. The cumulative incidence of MS was 36.11% and the incidence density was 63.1/1000 person-years. Recent studies in China have shown that the cumulative incidence of the MS in 7 years was 18.55%[15]. The incidence density of MS in the rural areas of South Korea was 30 / 1000 person-years for men and 46.4 / 1000 person-years for women[16]. In the Kazakh population in this study, the cumulative incidence and incidence density of the MS are significantly higher than those previously cited. These figures suggest that the incidence of MS in Xinjiang Kazakhs is of concern and should merit an enhanced programme for prevention and treatment in this area.

This study found that as the levels of TBIL and IBIL increase, the risk of MS is gradually reduced, suggesting that high levels of bilirubin have a protective effect against the MS. Bilirubin is the main metabolite of heme and has long been considered a marker of liver dysfunction. Studies have found that bilirubin is related to cardiovascular diseases, diabetes, metabolic syndrome, obesity, and other diseases. Low levels of serum bilirubin increase its risk, while mildly increased serum bilirubin confers protection against these diseases[17]. Bilirubin is recognized as the most effective endogenous antioxidant due to its continuous production in the redox cycle of bilirubin / biliverdin which can effectively scavenge hydrogen peroxide free radicals and inhibit lipid

peroxidation of serum LDL[18,19]. In terms of preventing LDL oxidation, bilirubin is 20 times more effective than the vitamin E analogue Trolox[20]. Other studies have found that bilirubin has an anti-inflammatory effect. C-reactive protein (CRP) is a marker of chronic inflammation. A number of studies have shown that serum bilirubin levels are negatively correlated with CRP levels[21, 22]. Bilirubin can also inhibit the over-expression of vascular adhesion molecules induced by the inflammatory cytokine TNF a, thereby playing an anti-inflammatory role[23]. In addition, mildly elevated bilirubin levels may increase insulin sensitivity. In experimental studies, bilirubin can improve the insulin sensitivity in leptin receptor deficiency and in diet-induced obese mice[24, 25].

In view of the effects of bilirubin, some other studies have found a negative correlation between serum total bilirubin level and MS which is consistent with the results of this study[7, 26, 27]. However, no correlation between baseline total bilirubin and MS was observed in Japanese men and women[28]. The relationship between bilirubin subtype and MS was also inconsistent. A five-year cohort study showed that DBIL levels in Chinese men were negatively correlated with MS, but not with TBIL and IBIL[29]. The results of this study showed that serum TBIL and IBIL levels, but not DBIL, were negatively correlated with the MS. However, many studies have found that indirect bilirubin (also known as unconjugated bilirubin, UCB) has anti-inflammatory and anti-oxidation effects. In patients with Gilbert syndrome (increased serum UCB levels), serum bilirubin concentration was inversely related to oxidative stress marker levels[30]. Clinical research shows that elevated UCB levels can reduce the expression of pro-inflammatory cytokines and increase the body's antioxidant capacity[31]. In addition, evidence from experimental studies *in vitro* and *in vivo* strongly supports human data. A study on the treatment of experimental colitis by UCB, in a rat model, showed that UCB treatment can reduce the inflammatory response induced by trinitrobenzene sulfonic acid and had a strong anti-inflammatory effect[32]. Hypochlorous acid (HOCl), an oxidant produced by myeloperoxidase (MPO), can induce protein and lipid oxidation. An *in vitro* experimental study showed that the addition of exogenous UCB to the serum and plasma of humans and rats can protect proteins and lipids from MPO-induced oxidation and reduce the production of chloramine and its decomposition products induced by HOCl and MPO[33].

Our study on the Kazakh population of Xinjiang has not found a relationship between transaminase and the risk of MS. This is inconsistent with the results of other studies[6, 9]. There are two possible explanations. One is that the sample size of the study population is small and/or the test efficiency is low; the other is down to genetic differences, diets, and living habits.

We found that TBIL and IBIL levels were inversely related to increased blood pressure, increased waist circumference, and increased triglycerides. A recent study found that TBIL levels were negatively correlated with blood pressure (OR 0.69, 95% CI, 0.50-0.96) and central obesity (OR, 95% CI = 0.80, 0.66-0.97) in women[27]. Studies have reported that bilirubin can significantly reduce the weight of obese model mice, and can inhibit macrophage infiltration and pro-inflammatory cytokine expression in adipose tissue[25]. In addition, bilirubin can regulate lipid metabolism, with higher bilirubin concentrations and lower serum lipid concentrations[34]. A retrospective cohort study in South Korea also demonstrated a significant negative correlation between bilirubin and hypertriglyceridemia in the male population[35].

Our study found a negative correlation between TBIL or IBIL levels and the risk of MS in a study population with two MS components at baseline. In the study population with no MS component and one MS component at baseline, the levels of TBIL, IBIL, DBIL, ALT, AST and risk of MS were not significantly different. This may be due to the fact that, when the research subject has two components of MS, the metabolic disorder is further aggravated. The serum bilirubin can clear superoxide and peroxidative free radicals produced due to MS, inhibit lipid peroxidation, and fight oxidative stress. Protective effects, such as reduced inflammatory response, are enhanced.

Our study reports that serum TBIL and IBIL levels are negative indicators for MS and are negatively related to its components (blood pressure, waist circumference, and triglycerides). These data indicate that the occurrence and development of MS in this population might be prevented by increasing bilirubin levels.

There are some limitations to our research. First, the small sample size of this study may limit the validity of our findings. Second, we did not measure parameters of oxidative stress, inflammatory mediators, and bilirubin metabolism-related enzymes in the study subjects. Third, each subject's bilirubin and transaminase levels were measured only once at each physical examination, but there may be short-term fluctuations.

Conclusions

This study found that serum TBIL and IBIL levels were negatively correlated with MS and its components (blood pressure, waist circumference, and triglycerides) in the Kazakh population in Xinjiang, China. Further, large prospective studies are needed to determine the impact of other liver function parameters on the occurrence and development of MS.

Declarations

Ethics Approval and Consent to Participate:

All subjects gave their informed consent for inclusion before they participated in the study. The study was approved by the Institutional Ethics Review Board (IERB) of the First Affiliated Hospital of Shihezi University School of Medicine (IERB No. SHZ2010LL01).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due the papers written using this dataset have not been published but are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Author contributions:

Shu-xia Guo conceived and designed the study, oversaw the data analysis, and edited the manuscript. Hao Hao played a role in data analyses and wrote the manuscript. Hao Hao and Heng Guo, and played a large role in data collection and data analysis. Ru-lin Ma, Yi-zhong Yan, Yun-hua Hu, Jiao-long Ma, Xiang-hui Zhang, Xin-ping Wang, Kui Wang, La-ti Mu, Yan-peng Song, Jing-yu Zhang, Jia He, Heng Guo, and helped collect the data. Hao Hao and Heng Guo contributed equally to this work.

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