MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3847-3852
DOI: 10.12659/MSM.895373

Received: 2015.07.18
Accepted: 2015.08.04
Published: 2015.12.09

Elevated Whole-Blood Viscosity is Associated with Gallstones

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Source of support: Departmental sources

Background: Gallstones are associated with dyslipidemia, metabolic syndrome, hyperinsulinemia, and carotid intima-media thickness, which all are related to hyperviscosity. Therefore, this study aimed to examine the associations between blood viscosity and gallstones.

Material/Methods: We investigated the associations between blood viscosity and gallstones in a study conducted in middle-aged subjects.

Results: Among 849 enrolled patients, 421 (49.6%) had gallstone disease. Compared with control subjects, whole-blood viscosity (WBV) levels were increased in patients with gallstones. The prevalence of gallstones increased as WBV (3 s^{-1}) quartiles increased. Furthermore, logistic regression analysis showed that WBV (3 s^{-1}) was associated with gallstone disease.

Conclusions: We found that whole-blood viscosity at low shear rate was independently associated with gallstones. Whether control of hyperviscosity would reduce the risk of developing gallstones deserves further investigation.

MeSH Keywords: Blood Viscosity • Gallstones • Risk Factors

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895373

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Background

Gallstone disease is one of the most common gastroenterological disorders in Western counties. Gallstones are associated with the potential risks of the development of cholecystitis, pancreatitis, biliary tract obstruction, and gall bladder cancer [1]. Recent studies documented that dyslipidemia, metabolic syndrome, hyperinsulinemia, and carotid intima-media thickness are related to the development of gallstones [2–6].

Altered hemorheological parameters play an important role in atherogenesis. Elevated viscosity is associated with aging, obesity, metabolic syndrome, insulin resistance, carotid intima-media thickness, and diabetes mellitus [7–11]. A report found that whole-blood viscosity (WBV) is an independent predictor of cardiovascular diseases [12].

However, the association between blood viscosity and gallstones is uncertain. Therefore, the aim of this study was to test the hypothesis that WBV is associated with gallstone disease.

Material and Methods

Study population

Our study included 1774 participants who attended International Physical Examination and Healthy Center in Harbin between January 2013 and December 2013. Control subjects were matched for age, sex, smoking, and drinking. In China, the Health Law requires that employees participate in annual health examination. We excluded 382 subjects with anaemia, chronic hepatic or renal disease, cancer, cystic fibrosis, Crohn's disease, gastrectomy, prophylactic cholecystectomy, medical treatment with hormone replacement therapy and lipid-lowering agents. We also ruled out hypertension, diabetes, and cardiovascular diseases (n=426). We excluded 117 participants with missing data were excluded, leaving 849 subjects in the final analysis. Study participants gave written informed consent and ethics approval was obtained from the Ethics Committee of the Second Hospital of Harbin Medical University.

Clinical examination

All participants underwent a thorough examination, including comprehensive medical history, lifestyle behaviors, physical examination, medication use, and fasting blood samples. Participants were asked about lifestyle behaviors, including cigarette smoking, alcohol consumption, and physical activity. Arterial blood pressure was measured by a mercury sphygmomanometer in a sitting position after the patient had been resting for 15 minutes. Two blood pressure determinations were made and the average was used for analyses. Height and weight were measured, and body mass index (kg/m^2) was calculated.

Biochemical analyses

Blood samples were drawn after the participants had fasted overnight. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglyceride (TG), and fasting plasma glucose (FPG) were determined by standard automated bioassays (Modular Analytics, Roche, Mannheim, Germany). Whole-blood viscosity was assayed at shear rates between 3 s^{-1} and 200 s^{-1} corrected hematocrit of 45% at 37°C using a Cone/Plate viscometer (Succeeder SA-9000, Beijing, China). Blood viscosity was corrected to a standard hematocrit of 45% by a regression equation [13]. The resistance to rotation caused by the fluid produces a value that is proportional to the viscosity of the sample. For high shear rate, the intra- and inter-assay coefficient variations were 2.7 and 5.6%, respectively. For low shear rate, the intra- and inter-assay coefficient variations were 4.6 and 9.8%, respectively. Plasma viscosity was evaluated by Harkness method. Hematocrit was determined by microcentrifugation and hemoglobin was measured with an autoanalyzer (Sysmex XE-2100, Kobe, Japan). Plasma fibrinogen was determined using the Beckman Coulter ACL-TOP analyzer (Lexington, MA, USA). All measurements were conducted within 2 h of sampling.

Diagnostic criteria

Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation. MDRD equation was:

$$eGFR=186.3\times(SCr)^{-1.154}\times(age)^{-0.203}(\times 0.742 \text{ if female}).$$

The abdominal ultrasonography was performed by an experienced ultrasonographer using a sonography machine (Voluson E8, GE, America) with a 3.5-MHz probe. The ultrasonographer was unaware of the objectives of the study and blinded to laboratory values. Gallstones were defined by the presence of strong intraluminal echoes that were gravity-dependent or that attenuated ultrasound transmission (acoustic shadow).

Statistical analysis

Data were expressed as median/inter-quartile range (IQR), mean (SD), and percentages. Normally distributed continuous variables were compared with the *t* test and skewed-distributed with the Mann-Whitney U test. Categorical variables were compared with chi-square test. Factors with significant associations (P<0.20) were eligible for multivariable models using logistic regression analysis. The P value to enter was set at 0.05 and P value to remove was set at 0.10. The variables

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Table 1. Characteristics of patients with gallstones and control subjects.

Variables	Patients with gallstones		Control subjects		*P* value
N	421		428		
Age (years)	50.2	(7.4)	50.3	(10.2)	0.901
Sex (male,%)	179	(42.5)	174	(40.7)	0.582
BMI (kg/m^2)	24.9	(3.0)	24.2	(2.9)	<0.001
Smoker (n,%)	104	(24.7)	91	(21.3)	0.233
Drinking (n,%)	98	(23.3)	86	(20.1)	0.260
Physical activity (n,%)	66	(15.7)	96	(22.4)	0.012
SBP (mmHg)	125.7	(10.6)	124.4	(10.9)	0.069
DBP (mmHg)	76.3	(7.3)	76.0	(7.3)	0.475
TC (mmol/L)	4.77	(1.13)	4.68	(0.90)	0.190
TG (mmol/L)	2.50	(1.78–3.18)	2.14	(1.47–2.68)	<0.001
HDL (mmol/L)	1.37	(1.14–1.59)	1.49	(1.28–1.68)	<0.001
LDL (mmol/L)	2.76	(0.82)	2.74	(0.78)	0.612
FPG (mmol/L)	4.81	(4.32–5.10)	4.71	(4.24–5.14)	0.219
GGT (U/L)	32.0	(19.0–51.0)	28.0	(17.0–51.0)	0.119
Hemoglobin (g/dl)	133.1	(10.4)	132.4	(10.4)	0.309
Hematocrit (%)	43.6	(2.3)	43.4	(2.3)	0.438
Fibrinogen (mg/dl)	303.3	(63.0)	298.4	(71.5)	0.286
WBV 3 s^{-1} (mPa.s)	9.04	(1.12)	7.82	(1.17)	<0.001
WBV 200 s^{-1} (mPa.s)	4.73	(0.42)	4.33	(0.45)	<0.001
PV (mPa.s)	1.59	(0.12)	1.58	(0.11)	0.196
eGFR (mL/min/1.73 m^2)	81.0	(16.6)	79.2	(17.2)	0.115

Data are expressed as median (inter-quartile range) or means (SD) or percentage. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HDL – high-density lipoprotein cholesterol; TC – total cholesterol; LDL – low-density lipoprotein cholesterol; TG – triglyceride; FPG – fasting plasma glucose; GGT – gamma-glutamyl transpeptidase; WBV – whole-blood viscosity; PV – plasma viscosity; eGFR – estimated glomerular filtration rate. *p* value was calculated by the student's *t*-test or Mann-Whitney *U* test or chi-square test.

sex, physical activity, drinking, smoking, diabetes, and gallstones were categorized as 0 (absent) or 1 (present) and the variables age, BMI, FPG, SBP, DBP, HDL, LDL, TC, TG, eGFR, hemoglobin, fibrinogen, WBV, and GGT were included as continuous variables. P values of less than 0.05 from 2-sided tests were considered to indicate statistical significance. All analyses were performed using SPSS version 17.0.

Results

The characteristics stratified by gallstones are shown in Table 1. Patients with gallstones were less active, and had higher BMI, TG, WBV (3 s^{-1}), WBV (200 s^{-1}) and lower HDL compared with control subjects. However, no significant differences were observed for age, sex, drinking, smoking, SBP, DBP, LDL, TC, FPG, GGT, fibrinogen, plasma viscosity, hemoglobin, hematocrit, or eGFR between the 2 groups.

Table 2 shows the characteristics of the participants according to WBV (3 s^{-1}) quartiles. Mean BMI, SBP, DBP, hematocrit, fibrinogen, plasma viscosity, WBV (200 s^{-1}), and the percentage of male and smoker elevated gradually as WBV (3 s^{-1}) increased. However, HDL was decreased as WBV (3 s^{-1}) quartiles increased. Age, FPG, TC, TG, LDL, GGT, eGFR, hemoglobin, the percentage of drinking, and physical activity did not change as WBV (3 s^{-1}) quartiles increased.

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Table 2. Clinical characteristics of subjects according to WBV (3 s^{-1}) quartiles.

	Quartiles of WBV (3 s^{-1})								*P* value
	Q1		Q2		Q3		Q4		
N	213		213		213		210		
Age (years)	49.3	(9.2)	49.5	(9.8)	50.8	(8.7)	51.2	(7.8)	0.075
Sex (male,%)	87	(40.8)	74	(34.7)	113	(53.1)	79	(37.6)	0.001
BMI (kg/m2)	24.1	(3.1)	24.5	(2.9)	24.8	(2.9)	24.8	(3.0)	0.025
Smoker (%)	51	(23.9)	39	(18.3)	63	(29.6)	41	(19.5)	0.024
Drinking (n,%)	47	(22.1)	37	(17.4)	52	(24.4)	48	(22.9)	0.326
Physical activity (n,%)	44	(20.7)	41	(19.2)	44	(20.7)	33	(15.7)	0.526
SBP (mmHg)	121.2	(11.0)	126.0	(10.1)	127.4	(10.3)	125.7	(10.6)	< 0.001
DBP (mmHg)	74.5	(7.5)	76.2	(7.8)	76.7	(7.0)	77.2	(6.5)	0.001
FPG (mmol/L)	4.78	(4.34–5.09)	4.74	(4.34–5.09)	4.78	(4.27–5.15)	4.79	(4.20–5.16)	0.937
TC (mmol/L)	4.73	(1.01)	4.72	(1.12)	4.72	(1.02)	4.72	(0.96)	0.999
TG (mmol/L)	2.24	(1.66–2.88)	2.27	(1.57–2.96)	2.32	(1.65–3.07)	3.40	(1.72–2.92)	0.423
HDL (mmol/L)	1.53	(1.31–1.74)	1.49	(1.27–1.64)	1.38	(1.19–1.60)	1.34	(1.16–1.53)	<0.001
LDL (mmol/L)	2.83	(0.82)	2.74	(0.86)	2.72	(0.74)	2.71	(0.77)	0.425
GGT (U/L)	27.0	(18.0–51.0)	31.0	(18.5–51.0)	31.0	(17.0–51.5)	30.0	(17.0–47.0)	0.612
eGFR (mL/min/1.73 m^2)	81.3	(15.3)	80.5	(18.4)	80.4	(18.0)	78.2	(15.6)	0.268
Hemoglobin (g/dl)	132.9	(10.3)	132.7	(10.4)	132.7	(10.4)	132.6	(10.5)	0.989
Hematocrit (%)	43.1	(2.3)	43.7	(2.2)	43.5	(2.4)	43.8	(2.2)	0.012
Fibrinogen (mg/dl)	289.4	(75.6)	300.6	(63.5)	304.3	(67.0)	309.1	(61.5)	0.020
WBV 200 s^{-1} (mPa.s)	4.31	(0.45)	4.50	(0.42)	4.56	(0.50)	4.75	(0.45)	<0.001
PV (mPa.s)	1.57	(0.12)	1.57(0.11)		1.59	(0.12)	1.60	(0.11)	0.002

Data are expressed as means (SD) or median (inter-quartile range) or percentage. *P* value was calculated by one-way ANOVA test or Kruskal-Wallis or chi-square test. Abbreviations: see Table 1.

The incidence of gallstones was calculated by the quartiles of WBV (3 s^{-1}) levels. The WBV (3 s^{-1}) quartiles were quartile 1 (Q1) (≤7.56 mPa.s), quartile 2 (Q2) (7.57–8.35 mPa.s), quartile 3 (Q3) (8.36–9.13 mPa.s), and quartile 4 (Q4) (≥9.14 mPa.s). The incidence rates of gallstones in Q1, Q2, Q3, and Q4 were 12.68% (27/213), 41.31% (88/213), 63.85% (136/213), and 80.95% (170/210), respectively. The incidence rate in different quartiles showed a significant difference (*P*<0.001) (Figure 1).

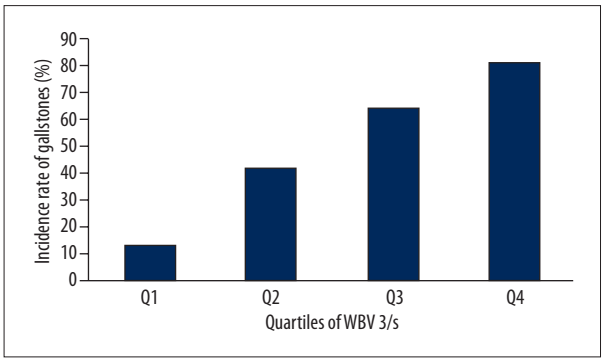

Figure 1. The association between WBV 3 s^{-1} levels and incidence rate of gallstone disease (%). Participants were stratified into quartiles according to their WBV 3 s^{-1} levels. WBV, whole-blood viscosity.

Risk factors for gallstones were evaluated using logistic regression analysis in Table 3. For multiple regression, factors showing a value P<0.20 in Table 1 were selected to enter into the original model. BMI, physical activity, HDL, TG, WBV (3 s^{-1}), and WBV (200 s^{-1}) were significantly associated with gallstones in the model. Notably, WBV (3 s^{-1}) was found to be a "newly observed" independent risk factor for gallstone disease (OR: 2.552, 95% CI: 2.144-3.037; *p*<0.001).

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Table 3. Adjusted ORs and 95% CIs for the presence of gallstones based on logistic regression.

Variables	β	OR (95% CI)	*P* value
BMI (kg/m^2)	0.083	1.087 (1.027–1.151)	0.004
Physical activity	–0.540	0.583 (0.381–0.892)	0.013
TG (mmol/L)	0.218	1.244 (1.094–1.415)	0.001
HDL (mmol/L)	–0.797	0.451 (0.264–0.771)	0.004
WBV 3 s^{-1} (mPa.s)	0.817	2.265 (1.923–2.667)	<0.001
WBV 200 s^{-1} (mPa.s)	1.834	6.257 (4.134–9.470)	<0.001

ORs – odds radios; β – partial regression coefficient; CI – confidence interval. Abbreviations: see Table 1.

Discussion

In this study, we found that WBV levels elevated in patients with gallstones compared with control subjects. The prevalence of gallstones increased as WBV (3 s^{-1}) quartiles increased.

The mechanisms underlying the association between WBV and gallstones remain unclear. Some reports documented that elevated viscosity is associated with obesity, metabolic syndrome, insulin resistance, and diabetes mellitus [7–11]. Blood viscosity is inversely related to flow and contributes to flow-related insulin resistance [14]. Recent studies confirmed the link between increased blood viscosity and insulin resistance [15–17]. Insulin resistance plays key roles both in the pathogenesis of type 2 diabetes and in the development of cholelithiasis [18]. Moreover, hyperinsulinemia increases gallstone formation by increasing the activity of hydroxyl-3-methylglutaryl-coenzyme and directly stimulating the bile acid-independent flow of bile into the perfused liver [19,20]. A recent study confirmed that hepatic insulin resistance directly promotes formation of cholesterol gallstones [21]. In addition, the size of stones inversely correlated with the severity of inflammation [22]. Obesity, dyslipidemia, insulin resistance, and metabolic syndrome all frequently co-occur in gallstone disease and have contributed to the development of gallstones [23,24]. Further studies are needed to investigate the relationship among hyperviscosity syndrome, insulin resistance, and gallstones.

Our study has important clinical implications. We showed that increased blood viscosity is associated with gallstone disease. The implication is that a much broader approach needs to be taken for the prevention of gallstones. Reasonable control of hyperviscosity may be necessary for patients with gallstones.

There are some limitations in the study. First, based on the cross-sectional analysis, the present findings cannot be used to indicate whether WBV is the cause or consequence of gallstones. Second, this study comprised a selected group of Chinese subjects, so the results cannot be generalized directly to other ethnic groups.

Conclusions

We found that whole-blood viscosity at low shear rate was independently associated with gallstones. Whether control of hyperviscosity would reduce the risk of developing gallstones deserves further investigation.

Conflict of interest

None.

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