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Association between Hematocrit Level and the Development of Non-Alcoholic Fatty Liver Disease in Chinese Adults: A 5-Year Study

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is recognized as a major cause of liver-related morbidity and mortality. The aim of this study was to examine the longitudinal association between baseline hematocrit (HCT) level and the development of NAFLD in Chinese adults. We performed a prospective cohort study of 2798 healthy Chinese adults without NAFLD at baseline. A Cox proportional hazards model was used to determine hazard ratios for NAFLD incidence in two groups determined by baseline hematocrit levels (group A, HCT <49%; group B, HCT \geq 49%). During 10346.5 person-years of follow-up, 474 (16.9%) NAFLD cases developed between 2008 and 2012. After adjusting for multiple covariates and change in the covariates during the follow-up period, the hazard ratios (95% confidence interval) for NAFLD incidence when comparing group B with group A were 1.17 (1.03-1.31) and 1.70 (1.26-2.31), respectively (p<0.001).

Conclusions: HCT level may be a predictor of the development of NAFLD in Chinese adults.

Keywords: Hematocrit; Non-alcoholic fatty liver disease; Prospective cohort study

Introduction

Non-alcoholic fatty liver disease (NAFLD) ranges in manifestations from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis and results from hepatic fat accumulation in patients without a history of excessive alcohol consumption [1]. NAFLD affects approximately 20-30% of the general population, and its prevalence is rising worldwide. In addition, NAFLD is recognized as a major cause of liver-related morbidity and mortality [2]. In the absence of treatment, NAFLD, especially the more severe forms, can progress to cirrhosis, liver failure, and hepatocellular carcinoma [3-4].

There is a strong association between NAFLD and insulin resistance, type 2 diabetes, hyperlipidemia, obesity, and other metabolic disorders [5-6]. Hematological parameters including red blood cell (RBC) count, hematocrit (HCT), and hemoglobin (HGB) are also known to be independently associated with insulin resistance [7-9] and NAFLD [10] in diverse populations. Li et al. [11] reported that the prevalence of NAFLD is positively associated with HCT levels in Hunan, China. However, to our knowledge, no prospective studies, using a Cox proportional hazards model, of the association between HCT levels and the development of NAFLD have been reported. Thus, we conducted a prospective cohort study to investigate the association between baseline HCT level and of NAFLD incidence in Chinese adults.

Materials and Methods

Study design and participants

Participants in the medical health check-up program at the Central Hospital of Xuzhou, an affiliated hospital of Southeast University Medical School in Nanjing, China, were included in the prospective cohort study. The medical health check-up program is used to promote employee health and to enhance early detection of existing diseases. Employees of industrial companies around Xuzhou, China, including retired employees, undergo either an annual or biennial health check-up.

All study participants signed written informed consent forms

before inclusion in the project. A total of 4792 workers who had HCT determined at a health check-up in 2008 were included in the study (Figure 1). Of the 4792 participants, 1316 subjects were excluded based on the following criteria that could affect NAFLD incidence or HCT levels: history of alcohol consumption or weekly alcohol intake ≥ 140 g in males or \geq 70 g in females (907 subjects); fatty liver disease (51 subjects); drug-induced liver disease (26 subjects); autoimmune liver disease (5 subjects); iron-deficiency anemia (7); use of medications that can influence the hematologic system, including lipid-lowering medications (121 subjects); past history of a malignancy (38 subjects); past history of cardiovascular disease (63 subjects); and type 2 diabetes at baseline (98 subjects). An additional 678 subjects were excluded for not attending any follow-up visits between 2008 and 2012. Without follow-up visit(s), the development of NAFLD could not be identified and individual person-years could not be calculated. A total of 2798 participants were included in the final analysis and were followed for the development of NAFLD. In patients with NAFLD, the time of NAFLD occurrence was assumed to be the midpoint between the visit at which NAFLD was first detected and the baseline visit in 2008. Person-years were calculated as the sum of follow-up times from the baseline until the assumed time of NAFLD development or until the final examination of each participant. The total follow-up period was 10346.5 person-years, and the average follow-up period was 3.74 ± 1.52

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Received January 11, 2017; Accepted January 23, 2017; Published January 30, 2017

Citation: Liu X, Liang J, Qiu Q, Teng F, Wang Y, et al. (2017) Association between Hematocrit Level and the Development of Non-Alcoholic Fatty Liver Disease in Chinese Adults: A 5-Year Study. J Metabolic Synd 6: 220. doi: 10.4172/2167-0943.1000220

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person-years. Participants were divided into two groups based on HCT levels at baseline: group A, HCT <49%; and group B, HCT \ge 49%.

The study was reviewed and approved by the ethics committee of the Central Hospital of Xuzhou, Affiliated Hospital of Medical School of Southeast University, China.

Blood sampling and laboratory measurements

Blood samples were obtained from the antecubital vein into tubes containing EDTA following an overnight fasting period of 10 h immediately following clotting of the sample, serum was obtained by centrifugation of the clotted blood sample for 15 minutes at 3000 rpm. Fasting blood glucose (FBG), HCT, glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST), serum uric acid (SUA), total protein (TP), serum albumin (ALB), serum γ -glutamyltransferase (γ -GGT), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were determined enzymatically using an auto-analyzer (Type 7600; Hitachi Ltd., Tokyo, Japan). Type 2 diabetes was defined as fasting blood glucose of at least 7.0 mmol/l or current use of blood glucose-lowering agents [12].

Physical examination

Height and weight were measured without shoes, and body mass index (BMI) calculated by dividing weight in kilograms by height in meters squared. NAFLD was diagnosed according to the guidelines of the Chinese Society of Hepatology [13] and was based on ultrasonic examination using a LOGIQ 9 Plus Digital B/W Ultrasound System (General Electric Company, USA).

A trained nurse measured blood pressure on the right arm of seated subjects, who rested for at least 5 minutes before measurement. Three measurements, at one-minute intervals, were obtained. Systolic BP and diastolic BP were defined as the mean of the three Systolic BP and diastolic BP readings, respectively. Hypertension was defined as blood pressure greater than 140/90 mmHg at initial examination [14].

Page 2 of 5

Administration of a lifestyle questionnaire

All subjects completed a questionnaire about health-related behavior. In addition, subjects were asked questions about weekly frequency of physical activity, which was defined as activity, such as cycling, swimming, or jogging, that lasted long enough to produce perspiration. Questions regarding alcohol intake included questions about the frequency of alcohol consumption on a weekly basis and the average amount of alcohol consumed on a daily basis [13]. Participants who reported that they smoked at the time of interview were considered to be current smokers. In addition, examining physicians obtained medical history and drug prescription history from participants.

Statistical Analysis

Data are expressed as mean \pm standard deviation. Geometric mean values of quantitative traits were compared using T-tests. Categorical variables were compared using chi-squared tests. Cox proportional hazards models were used to estimate adjusted hazard ratios and 95% confidence intervals for the incidence of NAFLD, comparing group B (HCT \geq 49%) to group A (HCT <49%). The multivariate models were adjusted for variables that might confound the relationship between HCT and the incidence of NAFLD, including sex, age, BMI, ALT, AST, LDL, TG, TC, BP, FBG, smoking status, and regular exercise.

Data were analyzed using an SAS software package (SAS, Version 9.1.3; SAS Institute Inc., Cary, North Carolina, USA). A p value of less than 0.05 was considered to be significant.

Results

The baseline characteristics of the study participants divided by group based on HCT levels are shown in Table 1. At baseline, the mean age and BMI of study participants were 41.4 ± 12.5 years (range, 22-89 years) and 23.9 ± 2.8 kg/m², respectively. Over 60% of the participants were male. There were significant differences between the two groups for all clinical variables other than FBG, TC, LDL-C, ALB, and regular exercise (Table 1). Between 2008 and 2012, during the 10346.5 personyears of follow-up, there were 474 (16.9%) cases of NAFLD that developed.

The change in clinical and laboratory measurements during the follow-up period is shown in Table 2. In group B (HCT \geq 49%), the mean change in HCT was 0.12%, whereas the mean change in HCT for group A was -0.80% (P<0.001). In addition, SBP, DBP, TG, LDL-C, FBG, weight, BMI, and serum γ -GGT levels were significantly higher in group B than in group A (P<0.001).

The hazard ratios and 95% confidence intervals for the incidence of NAFLD are shown in Table 3. In the unadjusted model, the hazard ratio and 95% confidence interval for the incidence of NAFLD when group B was compared with group A was 1.89 (1.41-2.54). In models 1 and 2, the adjusted hazard ratios and 95% confidence intervals for the incidence of NAFLD were 1.17 (1.03-1.31) and 1.70 (1.26-2.31), respectively (P<0.001 for trend).

Discussion

In our large prospective cohort study of Chinese adults, we showed that baseline elevation of HCT level was positively and significantly associated with the development of NAFLD, using Cox proportional hazards models. This association was independent of age, BMI, blood

Characteristic	Group A (HCT <49%) (N=2538)	Group B (HCT ≥ 49%) (N=260)	p-value
Person-years (total)	9542.88	803.62	
Person-years (average)	3.78 ± 1.21	3.06 ± 1.46	<0.001
Male (%)	64.9	68.8	0.571
Age (years)	41.3 ± 12.45	41.6 ± 12.17	<0.001
Weight (kg)	65.4 ± 10.79	72 ± 8.96	<0.001
Body mass index (kg/m²)	23.6 ± 2.98	25.0 ± 2.97	<0.001
Systolic Blood pressure (mmHg)	112.3 ± 13.57	117.6 ± 10.42	<0.001
Diastolic blood pressure (mmHg)	74.7 ± 10.4	78.9 ± 10.44	<0.001
Fasting blood-glucose (mmol/L)	5.3 ± 0.95	5.3 ± 1.13	0.552
Total cholesterol (mmol/L)	4.7 ± 0.92	4.6 ± 0.83	0.831
Triglycerides (mmol/L)	1.2 ± 0.87	1.6 ± 0.95	<0.001
High density lipoprotein (mmol/L)	1.4 ± 0.34	1.2 ± 0.28	<0.001
Low density lipoprotein (mmol/L)	2.8 ± 0.70	2.8 ± 0.62	0.762
Glutamate pyruvate transaminase (U/L)	15.9 ± 14.86	19.4 ± 14.74	<0.001
Glutamic oxaloacetic transaminase (U/L)	24.5 ± 10.69	27.0 ± 10.43	<0.001
Total protein (g/L)	75.0 ± 4.65	73.8 ± 4.76	<0.001
Serum albumin (g/L)	47.0 ± 2.28	47.3 ± 2.47	0.067
Serum γ-glutamyltransferase (U/L)	18.1 ± 13.86	24.6 ± 20.53	<0.001
Current smoker (%)#	40.3	52.1	
Regular exercise (%)•	17.4	13.9	0.219
Development of NAFLD	405	69	<0.001

Data are presented as mean ± standard deviation or as percentages.

*The reference groups for smoking status were ex-smokers and non-smokers.

•The reference group for regular exercise were those individuals who took part in physical activity less than once a week.

HCT: Hematocrit; NAFLD: Non-Alcoholic Fatty Liver Disease.

Table 1: Baseline characteristics of participants classified into groups dependent on hematocrit level at baseline.

Characteristic	Group A (HCT <49%)	Group B (HCT ≥ 49%)	p-value				
Weight (kg)	0.00 (-3.00-4.00)	3.00 (0.00-7.25)	<0.001				
Body mass index (kg/m ²)	0.0 (-1.16-1.14)	0.72 (-0.30-2.32)	<0.001				
Systolic blood pressure (mmHg)	6.00 (0.00-18.00)	9.00 (1.00-20.25)	<0.001				
Diastolic blood pressure (mmHg)	4.00 (-3.00-12.00)	7.00 (0.00-15.25)	<0.001				
Fasting blood-glucose (mmol/L)	-0.06 (-0.47-0.37)	0.18 (-0.26-0.65)	<0.001				
Total cholesterol (mmol/L)	-0.02 (-3.14-0.58)	0.04 (-1.77-0.74)	0.061				
Triglycerides (mmol/L)	-0.09 (-0.68-0.34)	0.05 (-0.81-0.87)	<0.001				
High density lipoprotein (mmol/L)	0.00 (-3.0022)	0.00 (-0.42-0.15)	0.901				
Low density lipoprotein (mmol/L)	0.06 (-0.37-0.79)	0.08 (-0.36-0.89)	<0.001				
Glutamate pyruvate transaminase (U/L)	2.00 (-7.00-8.00)	5.00 (-8.00-15.00)	<0.001				
Glutamic oxaloacetic transaminase (U/L)	-7.00 (-16.00-2.00)	-6.50 (-18.00-0.00)	0.133				
Total protein (g/L)	-1.00 (-7.40-2.50)	-0.20 (-6.38-3.30)	0.051				
Serum albumin (g/L)	0.30 (-3.00-2.10)	0.40 (-2.98-2.10)	0.612				
Serum γ-glutamyltransferase (U/L)	3.00 (-6.00-13.00)	11.00 (-5.00-26.25)	<0.001				
Hematocrit (%)	-0.80 (-2.60-1.20)	0.12 (-1.83-1.20)	<0.001				
Data are expressed as mean (range). HCT: Hematocrit.							

Table 2: Changes in clinical and laboratory measurements between 2008 and 2012 of participants classified into groups by hematocrit level at baseline.

pressure, ALT and blood lipid levels, blood pressure, smoking status, and regular exercise. In addition, the association remained statistically significant following adjustments for metabolic factors. These findings suggest that high HCT levels may be a good predictor for the development of NAFLD.

It has been reported previously that elevated HCT levels are a predictor of insulin resistance and metabolic syndrome, which are closely related to NAFLD [7-9]. Our data are consistent with what has been reported previously [7-11]. However, the mechanism by which elevated HCT level is associated with NAFLD is not well understood; there are several possible explanations.

HCT is the most important factor in blood viscosity. When HCT increases, blood viscosity increases. Blood flow rate and blood glucose supply to the muscles are reduced, resulting in insulin resistance [10]. In addition, higher blood viscosity is related to peripheral arterial resistance and blood pressure [15]. It has been shown recently that hematological parameters, including HCT level, are positively associated with insulin resistance and the prevalence of metabolic syndrome in a Japanese population [16]. As it is known that metabolic syndrome is strongly associated with an increased risk of NAFLD incidence [17-19], it can be suggested that elevated HCT levels are related to the risk of NAFLD incidence.

The liver has a major contribution to total circulatory

Page 4 of 5

	Person-years	NAFLD cases	Incidence density (per 100 person-years)	Unadjusted	Model 1	Model 2		
Group A (HCT <49%)	9542.88	405	4.24	1 (reference)	1 (reference)	1 (reference)		
Group B (HCT ≥ 49%)	803.62	69	8.59	1.89 (1.41-2.54)	1.17 (1.03-1.31)	1.70 (1.26-2.31)		
Age (years) [*]					1.05 (1.02-1.08)	1.03 (0.86-1.23)		
Body mass index (kg/m ²)					1.36 (1.28-1.45)	1.01 (1.00-1.02)		
Systolic blood pressure (mmHg)					1.00 (1.00-1.01)	1.00 (0.98-1.01)		
Diastolic blood pressure (mmHg)					1.02 (1.00-1.05)	1.00 (1.00-1.01)		
Fasting blood-glucose (mmol/L)					1.20 (1.06-1.36)	1.14 (1.06-1.23)		
Triglycerides (mmol/L)					1.29 (1.03-1.62)	1.08 (1.00-1.17)		
Low density lipoprotein (mmol/L)					1.32 (0.69-2.54)	0.89 (0.84-1.02)		
Glutamate pyruvate transaminase (U/L)					1.01 (1.00-1.02)	1.01 (1.00-1.01)		
Serum γ-glutamyltransferase (U/L)					1.01 (1.00-1.01)	1.01 (1.00-1.01)		
Current smoker (%)#					1.04 (1.01-1.07)			
Regular exercise (%)•					0.91 (0.84-0.99)			

Data are presented as hazard ratio (95% confidence interval). Model 1 was adjusted for age, body mass index, glutamate pyruvate transaminase, low-density lipoprotein, systolic blood pressure, diastolic blood pressure, triglycerides, serum γ-glutamyltransferase, smoking status, and regular exercise. Model 2 was adjusted for change in the variables age, body mass index, glutamate pyruvate transaminase, low-density lipoprotein, systolic blood pressure, diastolic blood pressure, triglycerides, and serum γ-glutamyltransferase.

The hazard ratio was calculated for a 5-year increase in age.

*The reference groups for smoking status were ex-smokers and non-smokers.

•The reference group for regular exercise were those individuals who took part in physical activity less than once a week.

Table 3: Hazard ratios and 95% confidence intervals for the incidence of non-alcoholic fatty liver disease adjusted for covariates and changes in covariates during the study period.

reticuloendothelial system phagocytosis capacity. It is known that the liver plays a critical role in the removal of old and/or dysfunctional blood cells [20,21]. Thus, it is not surprising that increased HCT levels are associated with declining hepatic function in NAFLD patients. If old and/or defective erythrocytes cannot undergo phagocytosis in the reticuloendothelial system, the total circulating red blood cell count increases in order to deliver an adequate amount of oxygen to cells. This finding may also explain the paradox of HCT in exercise physiology [22] that moderate exercise may improve the capacity of the reticuloendothelial system and lead to decreases in HCT level.

Elevated HCT levels may reflect increasing oxidative stress [23]. It has been reported previously that systemic oxidative stress is related to NAFLD [24]. In Japan, an association between the localization of oxidized phosphatidylcholine and NAFLD has been observed [25-27]. In a rat model, it has been shown that there is a dose-response relationship between levels of nitrotyrosine, a marker of oxidative stress, and increasing HCT tertiles [28]. Furthermore, iron overload is considered to be one of the key factors that cause NAFLD [29].

There are a number of limitations to this study. First, bias from loss to follow-up may have affected the results. Participants not included in the analysis (N=1994) were older and had less favorable metabolic profiles at baseline than those included in the analysis. Loss to follow-up of the higher-risk individuals likely resulted in a conservative bias and subsequent underestimation of risk. Second, our study only evaluated Chinese Han adults. Thus, the study findings cannot necessarily be extrapolated to other countries or ethnic groups. Lifestyle, eating habits, alcohol intake, and disease susceptibility may differ according to race and country of origin. Thus, there may be differences in covariates in individuals from other countries or in individual of different ethnicities.

Despite the limitations of the study, the present study is the first to identify a longitudinal relationship between baseline HCT and the development of NAFLD using Cox proportional hazards model. Our findings, obtained from a large cohort, indicate that baseline HCT may be an early predictor of the development of NAFLD. In addition, this association was significant after adjusting for multiple baseline covariates

Acknowledgements

This research was sponsored by the Jiangsu Provincial Bureau of Health foundation (H201356), the International Exchange Program, and Jiangsu Six Talent Peaks Program (2013-WSN-013). This study was also supported by the Xuzhou Outstanding Medical Academic Leader project and Xuzhou Science and Technology grants (XM13B066 and XZZD1242). The authors thank all subjects for participating in the study.

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Page 5 of 5

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