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Clinical Study of Serum Homocysteine and Non-Alcoholic Fatty Liver Disease in Euglycemic Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Yanjin Hu*
ABCDEF 1 Jia Liu*
BCD 1 Xuejie Dong
BCD 1 Yuan Xu
ABCDEF 2 Song Leng
ABCDEFG 1 Guang Wang

1 Department of Endocrinology, Beijing Chao-yang Hospital, Capital Medical University, Beijing, P.R. China
2 Health Management Center, The Second Hospital of Dalian Medical University, Dalian, Liaoning, P.R. China

* These authors contributed equally to this work

Corresponding Authors: Guang Wang, e-mail: wangguang@bjcyh.com, Song Leng, e-mail: dllengsong@126.com

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Background: Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease. NAFLD includes a spectrum of hepatic pathologies: simple fatty liver, steatohepatitis and cirrhosis. Insulin resistance may contribute to NAFLD. The liver plays an important role in the production and metabolism of homocysteine (HCY), which is known to be an independent risk factor for cardiovascular disease. High HCY level can aggravate NAFLD by increasing the reactive oxygen species and activating oxidative stress. In this study, we investigated the relationship between HCY and NAFLD in euglycemic patients.

Material/Methods: A total of 1143 euglycemic patients were recruited: 519 patients with non-alcoholic fatty liver disease (NAFLD) and 624 sex and age-matched controls without NAFLD.

Results: The NAFLD group had significantly higher HCY level (13.78±5.84 *vs.* 11.96±3.58 mmol/L, $p<0.001$), as well as higher body mass index (BMI), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), glutamic-pyruvic transaminase (ALT), glutamic-oxalacetic transaminase (AST), fasting plasma glucose (FPG), fasting insulin (FINS), homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for beta cell function (HOMA-B), and lower high density lipoprotein cholesterol (HDL-C). HCY level was positively correlated with HOMA-IR (r=0.239, $p<0.001$), TG (r=0.356, $p<0.001$) and negatively correlated with HDL-C (r=–0.161, $p<0.001$). In the logistic regression analysis, BMI (beta=0.345, $p<0.001$), HOMA-IR (beta=0.654, $p<0.01$), TG (beta=0.881, $p<0.001$), and HCY (beta=0.04, $p=0.044$) were the predictors of NAFLD.

Conclusions: Higher HCY level existed in NAFLD patients and was correlated with the severity of insulin resistance. HCY is an independent risk factor for NAFLD.

MeSH Keywords: Fatty Liver • Homocysteine • Insulin Resistance

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Background

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, it presents a cluster of hepatic damage ranging from simple non-alcoholic fatty liver to non-alcoholic steatohepatitis [1]. In recent years, changes in lifestyle and dietary intake excess have contributed to a high prevalence of NAFLD. Insulin resistance causes the imbalance of fatty acid metabolism of hepatocytes and contributes to further steatosis of the liver [2,3]. In an insulin resistance state, such as with type 2 diabetes mellitus (T2DM) and obesity, the actions mediated by insulin, such as suppression of lipolysis of white adipose tissue and hepatic gluconeogenesis, are impaired [4]. Plasma-free fatty acids increase and more triglycerides are synthesized in the liver with insulin resistance of adipose tissue. Therefore, researchers have suggested that NAFLD may be closely related to insulin resistance and T2DM.

Homocysteine (HCY) is a non-protein sulfur containing amino acid. It is an intermediate in the metabolism of methionine and an independent risk factor for cardiovascular disease [5]. HCY is formed from the metabolism of methionine and decomposed by remethylation and transsulfuration, which is mainly carried out in the liver. Moreover, the liver also expresses genes coding for methionine adenosyltransferase [6]. The liver plays an important role in HCY metabolism. In the pathological state of NAFLD, the change of HCY level has been studied with inconsistent findings. However, hyperhomocysteinemia (HHCY) has been found to inhibit insulin sensitivity by inducing endoplasmic reticulum stress in adipose tissue [7]. HHCY also aggravates insulin resistance followed by the increase production of resistin in adipocytes [8,9]. Studies have shown HHCY is a risk factor for NAFLD [10,11]. However, the data available on the relationship between HCY and NAFLD is conflicting and large-scale studies are lacking.

In our study, we investigated the relationship of plasma HCY, NAFLD, and insulin resistance. In order to exclude the interference of hyperglycemia, we chose euglycemic patients for inclusion in our study.

Material and Methods

Patients

A total of 1143 patients were recruited from the endocrinology department of Beijing Chao-yang Hospital during January 2014 and January 2015. The patients were divided into two groups: 519 patients with NAFLD and 624 patients without NAFLD. Diagnosis of NAFLD was determined using ultrasound imaging (bright liver); exclusions included any cause of chronic liver disease, such as viral hepatitis, and history of alcohol ingestion (alcohol ingestion >20 g/d). Patients were also excluded if they had a history of diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma, nephropathy, acute or chronic renal diseases, severe anemia, pancreatitis, acute myocardial infarction, or stoke. Patients were excluded if they were treated with anti-diabetic drugs, anti-hypertension drugs, anti-dyslipidemia drugs, or folic acid and vitamin B. All patients provided written informed consent. This study was approved by the ethics committee of the Beijing Chao-yang Hospital.

Laboratory and iconography measurements

All patients underwent a screening assessment at baseline that included measurements of weight, height, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST), fasting plasma glucose (FPG), fasting serum insulin (FINS), and HCY level. HCY, FPG, TC, HDL-C, LDL-C, ALT and AST were measured on a Dade-Behring Dimension RXL Autoanalyzer (Dade Behring Diagnostics, Marburg, Germany). Fasting insulin was measured on a Beckman Access 2 (Fullerton, CA, USA). Body mass index (BMI) was calculated by height/weight (kg/m^2). Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR) and beta cell function (HOMA-B). HOMA-IR index was calculated by the following equation: HOMA-IR=FPG (mmol/L) x FINS (mU/L)/22.5, HOMA-B=20× FINS (mU/L)/[FPG (mmol/L)–3.5] [12]. All patients underwent abdominal Doppler ultrasound imaging to assess hepatic disease; Ultrasound test was performed by an experienced operator who was blinded to the clinical and laboratory data. Abdominal ultrasound was performed using Philips Healthcare iU22 xMATRIX with 5-2MHz curved transducer.

Statistical analysis

The continuous data variables (age, BMI, TC, LDL-C, HDL-C, GLU, HCY, and FINS) were expressed as mean ± standard deviation (Mean ±SD). Non-normal distributed variables (ALT, AST, TG, HOMA-IR, and HOMA-B) were expressed as median (IQR). Independent t-test or Mann-Whitney test was used for analysis between groups. Partial correlation was used to estimate the relationship between HCY and HOMA-IR, AST, ALT. BMI, TC, HDL-C, LDL-C and TG.

Logistic regression analysis was used to confirm whether the parameters were independent risk factors of NAFLD. Data analysis was performed using the SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). All tests were two tailed and p value <0.05 was considered statistically significant.

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Table 1. General information and characteristics of all subjects.

	Control n=624	NAFLD n=519
Age, years	41.8±12.1	42.9±10.0
BMI, kg/m^2	22.71±3.92#	26.77±4.15
TC, mmol/L	4.83±0.91#	5.16±0.87
LDL-C, mmol/L	2.75±0.73#	3.03±0.71
HDL-C, mmol/L	1.36±0.31#	1.11±0.21
TG, mmol/L	0.92 (0.70, 1.32)#	1.73 (1.24, 2.43)
AST, U/L	21.0 (18.0, 26.0)#	22.0 (19.0, 27.0)
ALT, U/L	27.0 (20.0, 41.0)#	31.0 (22.0, 43.0)
FPG, mmol/L	5.37±0.48#	5.69±0.82
HCY, mmol/L	11.96±3.58#	13.78±5.84
FINS, mU/l	9.81±4.60#	15.40±6.20
HOMA-IR	2.19 (1.47, 3.07)#	3.71 (2.70, 4.74)
HOMA-B	100.55 (68.65, 136.47)#	140.08 (98.32, 189.50)

Summary of the general information and characteristics of the research in 519 NAFLD subjects and 624 sex- and age-matched healthy control. Age, BMI, TC, LDL-C, HDL-C, FPG, FINS and HCY were expressed as the mean ±sd. AST, ALT, TG, HOMA-IR and HOMA-B were expressed as median (IQR). # P<0.001 compared with NAFLD. NAFLD – non-alcoholic fatty liver disease; BMI – body mass index; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglyceride; ALT – glutamic-pyruvic transaminase; AST – glutamic-oxalacetic transaminase; FPG – fasting plasma glucose; FINS – fasting serum insulin; HCY – homocysteine; HOMA-IR – homeostasis model assessment-insulin resistance; HOMA-B – homeostasis model assessment-β cell function.

Results

Baseline characteristics of all patients.

Baseline measurements of patients' characteristics and HCY levels are summarized in Table 1. The age and sex were similar between groups. The NAFLD group had a significantly higher BMI (26.77±4.15 *vs.* 22.71 3.92 kg/m^2, p<0.001), TC (5.16±0.87 *vs.* 4.83±0.91 mmol/L, p<0.001), LDL-C (3.03±0.71 *vs.* 2.75±0.73 mmol/L, p<0.001), TG [1.73 (1.24, 2.43) *vs.* 0.92 (0.70, 1.32) mmol/L, p<0.001], ALT [31.0 (22.0, 43.0) *vs.* 27.0 (20.0, 41.0), p<0.001], AST [22.0 (19.0, 27.0) *vs.* 21.0 (18.0, 26.0), p<0.001], FPG (5.69±0.82 *vs.* 5.37±0.48 mmol/L, p<0.001), FINS (15.40±6.20 *vs.* 9.81±4.60 mU/L, p<0.001), HOMA-IR [3.71 (2.70, 4.74) *vs.* 2.19 (1.47, 3.07), p<0.001], HOMA-B [140.08 (98.32, 189.50) *vs.* 100.55 (68.65, 136.47), p<0.001], and lower HDL-C (1.11±0.21 *vs.* 1.36±0.31 mmol/L, p<0.001). The plasma HCY was also significantly higher in the NAFLD group (13.78±5.84 *vs.* 11.96±3.58 mmol/L, p<0.001).

Table 2. Partial correlation analysis between HCY and BMI, HOMA-IR, TC, LDL-C, HDL-C, TG, AST and ALT.

	All subjects (n=1143)	
	r	p-value
BMI, kg/m^2	0.045	0.133
HOMA-IR	0.239	0.000
TC, mmol/L	0.013	0.665
HDL-C, mmol/L	–0.161	0.000
LDL-C, mmol/L	0.039	0.198
TG, mmol/L	0.356	0.000
AST, U/L	0.021	0.495
ALT, U/L	0.033	0.274

Partial correlation was used to estimate the correlation between HCY and BMI, HOMA-IR, TC, HDL-C, LDL-C, TG, AST and ALT after correction of age and sex. BMI – body mass index; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglyceride; ALT – glutamic-pyruvic transaminase; AST – glutamic-oxalacetic transaminase; HCY – homocysteine; HOMA-IR – homeostasis model assessment-insulin resistance.

Table 3. Logistic regression analysis for the relationship between BMI, TC, TG, HCY HOMA-IR and NAFLD.

	All subjects (n=1143)		
	B	OR	p-value
BMI (kg/m^2)	0.345	1.412	0.000
TC (mmol/L)	0.100	1.105	0.298
TG (mmol/L)	0.881	2.414	0.000
HCY (mmol/L)	0.040	1.041	0.044
HOMA-IR	0.654	1.923	0.000

Logistic regression analysis was used to estimate the relationship between BMI, HOMA-IR, TC, TG, HCY and NAFLD. NAFLD – non-alcoholic fatty liver disease. BMI – body mass index; TC – total cholesterol; TG – triglyceride; HCY – homocysteine; HOMA-IR – homeostasis model assessment-insulin resistance.

Partial correlation analysis between HCY and other parameters

Partial correlation analysis after the correction for age and sex are shown in Table 2. HCY was positively correlated with

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HOMA-IR (r=0.239, $p<0.001$) and TG (r=0.356, $p<0.001$) and negatively correlated with HDL-C (r=–0.161, $p<0.001$).

Logistic regression analysis between plasma HCY and other parameters

Logistic regression analysis between NAFLD and BMI, TC, TG, HCY, and HOMA-IR are shown in Table 3. BMI (beta=0.345, $p<0.001$), HOMA-IR (beta=0.654, $p<0.001$), TG (beta=0.881, $p<0.001$) and HCY (beta=0.040, $p<0.05$) were the independent risk factors of NAFLD in euglycemic patients.

Discussion

Our study showed that the NAFLD group had significantly higher HCY levels and HOMA-IR. HCY level was positively correlated with HOMA-IR and TG, and negatively correlated with HDL-C. In the logistic regression analysis, BMI, HOMA-IR, TG, and HCY levels were the risk predictors for NAFLD in all patients.

We observed that NAFLD patients had significantly higher TC, LDL-C, and TG, and lower HDL-C than controls. We also found that the FINS, HOMA-IR, and HOMA-B were higher in NAFLD patients. These results suggest that patients in the NAFLD group already had developed insulin resistance, hyperinsulinemia and related dyslipidemia. We also found fasting glucose was higher in the NAFLD group than the control group. This may indicate that the increased pancreatic beta-cells could not compensate for the severity of insulin resistance. Previous research reports [13,14] are consistent with this finding. In our logistic regression analysis, HOMA-IR was found to be an independent risk factor for NAFLD. In another study, HCV infection followed by cirrhosis of liver was found to impair insulin sensitivity [15]. However, in NAFLD patients, insulin resistance appears to be an initiating factor for disease. Besides its ability of promoting hepatic lipogenesis, insulin resistance is also involved in the development of oxidative stress and contributes to high reactive oxygen species (ROS) level. Oxidative stress can promote necroinflammation in NAFLD. For patients with NAFLD, the risk of insulin resistance and T2DM should be evaluated. Early intervention considered for of insulin resistance to prevent NAFLD patients from developing T2DM and other metabolic disease.

HCY is regulated by environmental and genetic factors. The major genetic factors are the variants of genes encoding HCY metabolism such as methylenetertrahydrofolate reductase (MTHFR) C677T and A1298C. Environmental factors may include low folic acid. Our study population was drawn from Beijing, an area known for low supplementation with folic acid and a high MTHFR mutation rate. Populations of Asian (including China) have higher plasma HCY than populations in other continents [16–18]. In our study, there was a significant higher HCY level in the NAFLD group than control group. This observation was consistent with other study results [6,13]. There are a number of possible explanations for the elevated HCY levels. HCY is an intermediate in methionine metabolism. HCY metabolism has two metabolic pathways including remethylating back to methionine and degrading to cysteine by a transsulfuration pathway [19]. The liver plays an important role in expression of genes involved in the synthesis and metabolism of HCY and conversion of HCY into cysteine via the transsulfuration pathway mediated by the enzymes cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CGL). Elena Bravo et al. found high-fat diet-induced NAFLD rats had higher HCY through downregulation of hepatic CBS and CGL [11]. Other studies have reported different results [20–22]. Study variations in study population and study emphasis may contribute to the differences in study results. In addition, in other studies sample sizes were small (between 10–30 cases) compared to our study. Other studies provided hepatic biopsies to prove the diagnosis of NAFLD, whereas our study used ultrasound imaging read by experienced doctors of iconography to diagnose NAFLD. The differences in diagnostic method and study size make comparisons between studies difficult.

Our correlation analysis suggests that there was no relationship between HCY level and transaminase (ALT and AST). However, HCY was positively correlated with HOMA-IR and TG. These two indexes reflect the severity of insulin resistance. And our results suggest that HCY level was closely correlated with the severity of insulin resistance. Li Yang et al. found that HHCY could inhibit insulin sensitivity by inducing endoplasmic reticulum stress in adipose tissue [8]. Najib et al. found HCY inhibited insulin receptor tyrosine kinase activity and impaired insulin signaling by a mechanism involving oxidative stress [23,24]. In other clinical studies, conclusions were not consistent [25,26]. The main cause of the inconsistencies was different methods for estimating insulin resistance: HOMA-IR is not suitable for patients with diabetes and sometimes unstable while the gold standard method, euglycemic clamp, often limits the sample size [27,28].

In our logistic regression, we found that HCY level was an independent risk factor for NAFLD. More quality studies about the relationship of HCY and NAFLD patients are needed. Werstuck et al. found HCY could induce endoplasmic reticulum stress activates of unfolded protein response and the sterol regulatory element-binding protein in human hepatocytes. They also found cholesterol and triglycerides were elevated in HHCY mice [7]. Matte et al. found HCY induced oxidative stress and inflammatory infiltration [29]. Woo et al. reported that HCY could lead to the injury of the liver by increasing superoxide anion production [30]. Other studies found that non-alcoholic steatohepatitis (NASH) was significantly associated with

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higher level of HCY. Studies by Leach et al. and Pastore et al. found HCY to be negatively correlation with reduced glutathione (GSH) [13,31]. Wijekoon et al. found that cysteine (formed from HCY via the transsulfuration pathway) could limit GSH production [32]. The pathogenesis of NAFLD is believed to be "multiple hit". The first hit is known as hepatic lipid accumulation, caused by insulin resistance and an imbalance of lipid metabolism. The following hits are the further damage of hepatocytes caused by the increase of reactive oxygen species, activates of oxidative stress and lipid peroxidation, and the decrease of reduced anti-inflammatory factors in the state of fatty acid overload. HHCY is a risk factor of oxidative stress in the liver as mentioned previously. HCY is responsible for the further progression of steatosis and fibrosis of the liver. Our study showed that BMI, HOMA-IR, TG, and HCY levels were the predictors of NAFLD. This is consistent with previous studies and generally consensus.

Our research had many limitations. First, we used the HOMA-IR to estimate insulin resistance. HOMA-IR is not a precise index compared with the euglycemic clamp. However, in research with large study populations, it is acceptable and HOMA-IR is strongly correlated with euglycemic clamp in euglymic patients. Second, we did not measure folate and vitamin B12 in our study. Finally, we diagnosed NAFLD only by ultrasound imaging, which could vary based on physician experience and expertise.

Conclusions

Higher HCY level existed in NAFLD patients and was correlated with the severity of insulin resistance. HCY is an independent risk factor for NAFLD in euglycemic patients.

Conflict of interest

None.

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