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Original Article

Nonalcoholic fatty liver disease and its relevant factors increased the risk of gallstone disease: a systematic review and meta-analysis

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Abstract: Background: The association between nonalcoholic fatty liver disease (NAFLD) and gallstones disease (GD) remains inconsistent and controversial. A systematic review of studies was conducted to explore their relationship and relevant risk factors by meta-analysis. Materials and methods: We carried out a literature search in Pubmed, Embase, Cochrane library, Medline and Web of Scienc to screen for citations before Aug 31st, 2015. A statistical analysis was performed using Review Manager version 5.2. Results: Eight studies involving 43,749 participants from different ethnics and regions were included. Among them, five trials carried out subgroup of GD patients in NAFLD population. The result showed NAFLD was significantly correlated with GD (Odds ratio [OR]=1.75, 95% confidence interval [CI]: 1.51-2.04, P<0.01). The incidence of GD in NAFLD participants increased with age, BMI, fasting glucose, homeostasis model assessment-insulin resistance (HOMA-IR) and the manifestation of metabolic syndrome (MS) as well as female gender. Conclusion: The present systematic review and meta-analysis demonstrated that NAFLD was independently predictor of GD. In the background of NAFLD, the occurrence of GD varied according to the gender, and with positive relationship of NAFLD relevant risks.

Keywords: Nonalcoholic fatty liver disease, gallstones disease, risk factors, meta-analysis

Introduction

The incidence of nonalcoholic fatty liver disease (NAFLD), a common chronic liver disease, is increasing worldwide [1]. Representing a spectrum of diseases related to excessive fat accumulation in the liver without the background of excessive alcohol consumption, NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), varied stages of fibrosis, cirrhosis and ultimately hepatocellular carcinoma [2]. Generally, NAFLD is often associated with obesity, insulin resistance (IR), type 2 diabetes mellitus (DM), hypertension (HTN), as well as dyslipidemia and other metabolic risk factors [3-5]. Although the molecular mechanisms of disease pathogenesis and progression remain poorly understood, most studies support the theory named "multi-hit hypothesis", in which IR and oxidative stress play a pivotal role [6].

Gallstones disease (GD) is a kind of alimentary tract disorders, which is reported to link with overweight, IR and hypertriglyceridemia [7, 8]. Given that common risk factors frequently coexist in GD and NAFLD, there is mounting interest to elucidate their relationship. A survey from the third National Health and Nutrition Examination Survey indicated that GD affected 10% to 15% individuals in the United States [9]. Patients with NAFLD might be prone to a high prevalence of GD, especially with more advanced liver disease and altered glucose regulation [10]. However, the results of their association differ, with some demonstrating a positive relationship [11-13], and some rejecting [14-17]. Therefore, we performed a meta-analysis including current randomized controlled trials (RCTs) to assess the association and risk factors between NAFLD and GD.

Materials and methods

Search strategy

We searched Pubmed, Embase, Cochrane library, Medline and Web of Science with no lan-

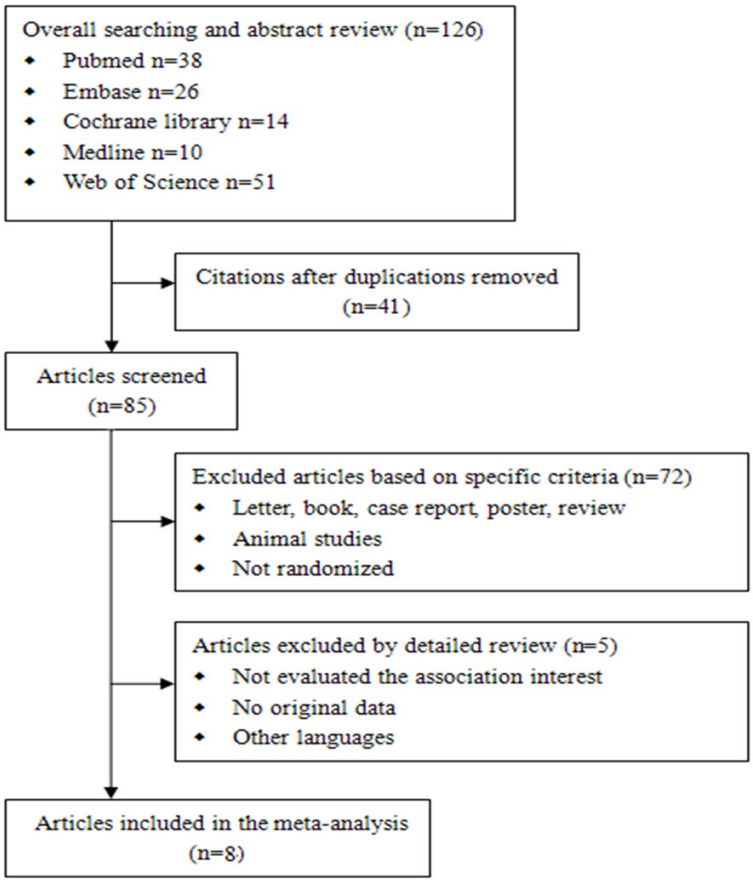

Figure 1. Flow diagram of study identification.

guage restriction from the beginning of indexing for each database to Aug 31st, 2015. The search terms were "NAFLD" or "NASH" or "nonalcoholic steatohepatitis" or "nonalcoholic fatty liver disease" or "fatty liver" and "gallstones" or "cholelith" or "cholelithiasis". The conference proceedings and reference lists of reviews were searched manually for additional relevant studies.

Inclusion and exclusion criteria

The inclusion criterion was determined by two investigators (Q.J.J. and D.W.J). It was as follows: published as an original article, used cohort or cross-sectional design, RCTs with participants of any sex or ethnic origin with NAFLD/NASH diagnosed on the basis of radiological or histological evidence of fatty liver. GD was diagnosed by imaging examination such as abdominal ultrasonography in the presence of one of the following criteria: (i) one or more echogenic, distally shadowing, possibly movable structures in the gallbladder; (ii) echogenic material within the gallbladder with constant shadowing and little or no visualization of the gallbladder; and (iii) absence of gallbladder and coupled with a history of cholecystectomy. Such causes of hepatic steatosis as viral, alcoholic, drug-induced, autoimmune and genetic liver diseases (eg. Wilson's disease) were excluded. Disagreement between two reviewers was resolved by discussion.

The trials should be designed as GD(+)/(-) group among general population or NAFLD patients at least. The objective outcomes like age, gender, BMI, lipid profiles etc. must be measured, otherwise the articles were excluded from this review.

Data extraction and methodological quality

Data were abstracted independently by two reviewers and included: author, publication year, district, study design, outcomes and group. The quality of the studies was assessed by Newcastle-Ottawa scale (NOS) score, of which 1-3 for low-quality, 4-6 for intermediate and 7-9 for high-quality. All included studies scored over 7.

Statistical analysis

We analyzed the data using Review Manager (RevMan Version 5.2). Some outcomes as NAFLD, gender, body mass index (BMI), DM, metabolic syndrome (MS) etc. were assessed as a dichotomous variable (presented as odds ratio [OR] with 95% confidence interval [CI]). Other outcomes like total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), homeostasis model assessment (HOMA)-IR and high-density lipoprotein (HDL) etc. were presented as continuous variables (weighted mean difference [WMD] with 95% CI). Mantel-Haenszel chi-square tests were used to determine significant level of difference. If the chi-

Table 1. Characteristics of studies on GD risks and NAFLD

First author (year)	Region/Country	Participants and group (number of cases)		Study design	Diagnostic method of fatty liver	Outcome measures	NOS score
		GD(+)/(-) group	GD(+)/(-) group of NAFLD population				
Chen [18] (2014)	Taipei/China	1296 (23/1276)	NA	Cohort	Ultrasonagraphy	Age, FPG, HBP, BMI, TC, TG, HDL, BUN, Cr, AST, ALT, UA of GD(+)/(-) group	7
Koller [19] (2012)	Bratislava/Slovakia	482 (166/316)	NA	Cross-sectional	Ultrasonagraphy	Age, gender, BMI, HBP, TC, TG, HDL, GD, ALT of marker (+)/(-) NAFLD group	7
Lee [20] (2014)	Taitan/China	12033 (768/11265)	NA	Cross-sectional	Ultrasonagraphy	Age, gender, BMI, HBP, FPG, ALT, AST, HDL, TC, DM etc. of GD(+)/(-) group	8
Liu [21] (2014)	Shandong/China	11200 (498/10702)	4713 (289/4424)	Cohort	Ultrasonagraphy	Age, BMI, HBP, cholesterol, triglycerides, HDL, LDL of NAFLD (+)/(-) group; Gender of GD(+)/(-) group of NAFLD population	8
Kwak [22] (2015)	Soul/South Korea	17612 (1069/16543)	5337 (292/5045)	Cross-sectional	Ultrasonagraphy	Age, FPG, HBP, BMI, TC, TG, HDL, AST, ALT, DM of GD(+)/(-) group	8
Fracanzani [23] (2012)	Bologna/Italy	NA	524 (107/417)	Cohort	Liver biopsy	Gender, age, cholesterol, triglycerides, FPG, BMI, DM, HOMA-IR, MS, HDL	7
Loria [24] (2005)	Modena/Italy	NA	161 (32/129)	Cross-sectional	Ultrasonagraphy (all) and liver biopsy (partly)	Gender, age, cholesterol, triglycerides	7
Yilmaz [25] (2014)	Diyarbakir/Turkey	NA	441 (54/387)	Cohort	Liver biopsy	Gender, age, cholesterol, triglycerides, FPG, BMI, DM, HOMA-IR, MS, HDL	8

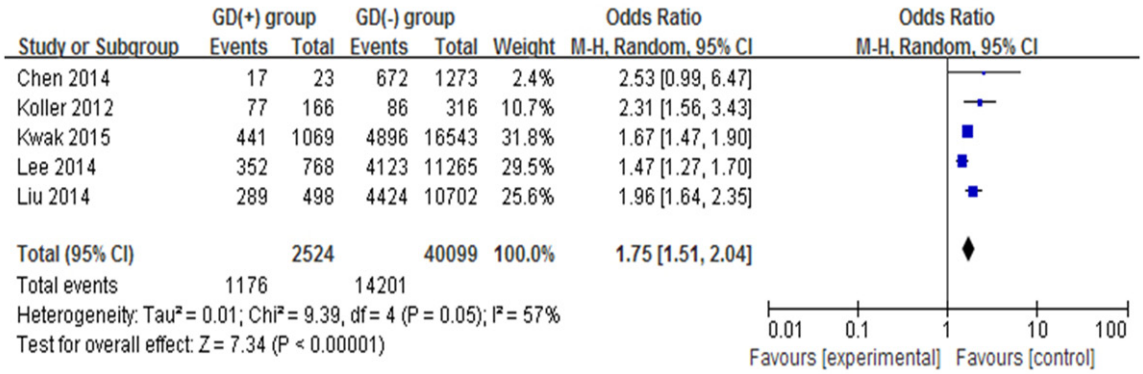

Figure 2. Forrest plot of NAFLD and GD.

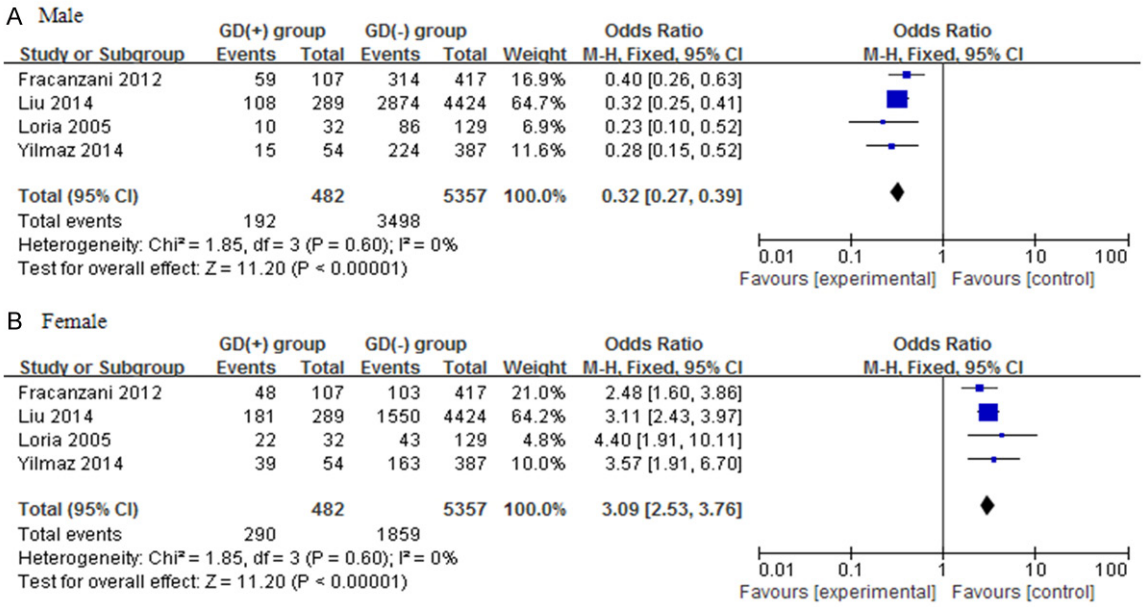

Figure 3. Forrest plot of gender in NAFLD population with GD. A. Male; B. Female.

square test was significant below P=0.05, the amount of heterogeneity using I^2 statistics was quantified. If I^2 was obvious (over 50%), the random effects model was adopted; Otherwise, the fixed effects model was chosen.

Results

Search results

The literature search yielded 126 items from Pubmed, Embase, Cochrane library Medline and Web of Science (**Figure 1**). Publication dates ranged from 2005 to 2015. Full text articles were retrieved only for thirteen publications and assessed for eligibility. Among these thirteen publications, five were excluded because they did not design study as the group which we needed, or not in English, or no original data. Therefore, we identified and included eight publications that met the inclusion criteria in the systematic review [10, 18-24].

Trial characteristics

Table 1 contains characteristics of the studies included in this analysis. All studies were RCT. Among eight articles, three showed basic data between GD(+) and GD(-) in general population only, three among NAFLD patients only, and two in both population. One publication was originated from Turkey, one from Slovakia, one from South Korea, two from Italy (different regions) and three from China (conducted by different

Table 2. Analysis of characteristics in NAFLD patients with or without GD

Variables	n of studies	Involved cases		WMD [95% CI]/OR [95% CI]	I^2 (%)	$P_{difference}$
		GD(+)	GD(-)			
Age (yr)	3 [23-25]	193	955	6.3 [4.23, 8.38]	72	<0.01
Triglycerides (mg/dl)	3 [23-25]	193	955	14.33 [-21.48, 49.93]	100	0.43
Total cholesterol (mg/dl)	3 [23-25]	193	955	7.7 [-12.50, 27.90]	95	0.46
BMI (kg/m^2)	2 [23, 25]	161	804	1.86 [0.67, 3.06]	0	0.002
Fasting glucose (mmol/l)	2 [23, 25]	161	804	0.74 [0.33, 1.15]	30	0.0004
Diabetes (Yes/No)	2 [23, 25]	161	804	6.13 [0.37, 101.03]	97	0.2
HOMA-IR	2 [23, 25]	161	804	0.87 [0.46, 1.28]	91	<0.0001
Metabolic syndrome (Yes/No)	2 [23, 25]	161	804	2.18 [1.52, 3.12]	0	<0.0001
HDL-cholesterol (mg/dl)	2 [23, 25]	161	804	2.09 [-0.04, 4.23]	0	0.06

research groups), with a total of 43,749 participants. The diagnosis of NAFLD was confirmed by unltrsonagraphy in six articles and liver biopsy in three. According to the NOS score, all eight studies were of high quality.

GD and NAFLD

Five articles [18-21] reported the number of NAFLD in GD(+) and GD(-) participants and showed a significant difference in the experimental group compared with the control one (OR=1.75, 95% CI: 1.51-2.04, P<0.01). The random effects model was used due to high heterogeneity (I^2=57%) (**Figure 2**).

Risk factors of GD in NAFLD patients

Four RCTs [10, 21, 23, 24] recorded the gender allocation among NAFLD population with or without GD (**Figure 3**). Significant homogeneity was observed (I^2=0%). Female gender showed high OR (OR=3.09, 95% CI: 2.53-3.76, P<0.01) while male was 0.32 (95% CI: 0.27-0.39, P<0.01).

As shown in **Table 2**, age, TG and TC were analyzed in three studies [10, 23, 24]. Only age had an obviously positive association between these two groups (WMD=6.3, 95% CI: 4.23-8.38, I^2: 72%, P<0.01). BMI, FPG, DM, HOMA-IR, MS and HDL-cholesterol were provided in two publications [10, 24], elevated BMI, high FPG, increased HOMA-IR were related to NAFLD patients accompanied with GD (P<0.01). The OR of MS to GD reached 2.18 (95% CI: 1.52-3.12, P<0.01) with significant homogeneity.

Discussion

Both NAFLD and GD have similar risk factors like indices or surrogate markers of insulin resistance, obesity, DM and physical inactivity. Although only a minority of GD patients suffers symptoms heralding cholecystitis, biliary pain and ever acute pancreatitis, it is a leading cause of hospital admissions in gastroenterology department and the burden has increased more than 20% since the 1980s [25, 26]. Moreover, the very high prevalence of GD and NAFLD makes it very likely a chance co-occurrence in a high number of cases. Taken together, the coexisting of GD and NAFLD constitutes a main issue in public health. The possible association of NAFLD and GD has been explored in some researches in different ethics and geographical areas with conflicting results [11-24]. It is still unclear whether the development of NAFLD increases the prevalence of GD or underlying risk factors in GD subjects with NAFLD.

In that regard, we conducted a meta-analysis recruiting a total of 43,749 participants from four cross-sectional and four cohort studies to provide an objective basis for clinical recommendations. To our knowledge, this is the first meta-analysis on this topic to assess the association between NAFLD and GD. Due to the different way of group division, some clinical studies in this field were excluded [27-29]. Actually, several of them shared similar opinions. In our study, NAFLD was found to be an independent predictor of GD with OR of 1.75 (95% CI: 1.51-2.04, P<0.00001). The GD participants seem to have more chance to get NAFLD. Impaired gallbladder motility and increased bile lithogenicity might affect these two diseases simultaneously. As to those who undergone cholecystectomy, the absence of gallbladder increased the risk of NAFLD development via alterations in bile acid transport causing elevat-

ed hepatic triglyceride content and very-low-density lipoprotein production [30]. Possible pathophysiological explanation was also provided in some experimental and human data, giving an evidence for the NAFLD-GD associtaion [31, 32]. The farnesoid X receptor and its mRNA, which regulated the transcription of ATP-binding cassette transporters on the hepatocyte canalicular membrane, decreased in NAFLD patients. Thus, the activity of bile salt export pump and multidrug resistant glycoprotein became low. The decreased expression of this receptor could cause a decline in the biliary concentration of bile acids and phospholipids reducing thereby the solubility of cholesterol. The liver X receptor protein and mRNA involved in cholesterol bile regulation would increase during NAFLD progression and then lead to higher risk of gallstone formation.

According to the meta-analysis results, the gender of female was related positively to GD coexisting with NAFLD. The gender-specific factor was in accordance with some reported papers [4, 9], which indicated that GD was deemed to be female-predominant disease while NAFLD affecting middle-aged women more often. Furthermore, our meta-analysis also suggested that GD patients with NAFLD had the typical risk factors as follows: old age, increased BMI, elevated FPG level and high HOMA-IR, as well as having manifestations of MS. It was believed that patients with NAFLD did have changes in one or multiple pathogenic mechanism to promote lithogenesis. The most non-conventional one was IR [33]. Insulin enhanced the bile lithogenic process by stimulating cholesterol biosyntheisis and decreasing bile acid synthesis [34]. With increased the cholesterol saturation index of bile and decreased the concentration and proportion of a biliary antinuclearing protein, insulin facilitated the formation of cholesterol gallstones [35]. Therefore, IR was the main pathogenic risk factor both in NAFLD and GD. The common states accompanied by IR were overweighed, high FPG or DM and MS. Some researches confirmed that overweighed or obesity could alter gallbladder motility and induce biliary cholesterol secretion, meanwhile, FPG level played an important role in gallbladder motor function [36, 37]. Besides, the overgrowth of small intestinal bacterial in NAFLD subjects might increase biliary deoxycholic acid and cause bile sovrasaturation and gallstone formation [38].

However, there are several limitations in the present meta-analysis. Firstly, six involved studies diagnosed NAFLD by ultrasonography rather than histology. Actually, ultrasonography is one of the commonest ways in detecting steatosis during clinical practice. It is difficult to carry out liver biopsy, an invasive operation, in large population in every trial. That is also the reason we fail to take NAFLD histological subtypes into account. Secondly, GD in the present study identifies patients with cholecystolithiasis or those who have previously undergone cholecystectomy. Only one study suggested that cholecystectomy itself, instead of gallstones, might be an independent risk factor for NAFLD [22]. It is better to divide GD population into more detail subgroups if we had enough samples or data, otherwise accurate statistical analysis results would not be obtained when only one or two studies were included in the meta-analysis.

Conclusions

Our meta-analysis revealed that NAFLD increased the risk of GD significantly and independently. The common risk factors like female gender, age, BMI, FPG, HOMA-IR and MS manifestations were related positively to GD when coexisting with NAFLD. Awareness of the link between NAFLD and GD may result in an earlier prevention and treatment. Further studies in different subgroups of GD or NAFLD are needed if possible.

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Disclosure of conflict of interest

None.

Abbreviations

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FPG, fasting plasma glu-

cose; GD, gallstones disease; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HTN, hypertension; IR, insulin resistance; TC, total cholesterol; TG, triglycerides; WMD, weighted mean difference; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NOS, Newcastle-Ottawa Scale; OR, odds ratio; RCTs, randomized controlled trials.

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