

Format for ANSWERING REVIEWERS

February 9, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15689-edited_revision.doc).

Title: Cholecystectomy is Independently Associated with Nonalcoholic Fatty Liver Disease in Asian Population

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The manuscript has been improved according to the suggestions of reviewers:

1. [Format has been updated.](#)

[Author contributions, ethics approval, informed consent, biostatistics, conflict-of-interest, data sharing, and comments section were added.](#)

[Abstract was edited according to the revision guideline.](#)

ABSTRACT

AIM: To investigate the relationship between gallstone disease and nonalcoholic fatty liver disease (NAFLD) in a large Asian population.

MATERIALS AND METHODS: A cross-sectional study including 17,612 subjects recruited from general health check-ups at the Seoul National University Hospital, Healthcare System Gangnam Center between January 2010 and December 2010 was

conducted. NAFLD and gallstone disease were diagnosed based on typical ultrasonographic findings. Subjects who were positive for hepatitis B or C, or who had a history of heavy alcohol consumption (> 30 g/day for men and > 20 g/day for women) or another type of hepatitis were excluded. Gallstone disease was defined as either the presence of gallstones or previous cholecystectomy, and these two entities (gallstones and cholecystectomy) were analyzed separately. Clinical parameters including body mass index, waist circumference, hypertension, diabetes, smoking status, and regular physical activity were reviewed. Laboratory parameters, including serum levels of gamma-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, fasting glucose, fasting insulin, total cholesterol, triglycerides, and high-density lipoprotein, were also reviewed.

RESULTS: The mean age of the subjects was 48.5 ± 11.3 years, and 49.3% were male. Approximately 30.3% and 6.1% of the subjects had NAFLD and gallstone disease, respectively. The prevalence of gallstone disease (8.3% vs. 5.1%, $P < 0.001$), including both the presence of gallstones (5.5% vs. 3.4%, $P < 0.001$) and a history of cholecystectomy (2.8% vs. 1.7%, $P < 0.001$), was significantly increased in the NAFLD group. In the same manner, the prevalence of NAFLD increased with the presence of gallstone disease (41.3% vs. 29.6%, $P < 0.001$). Multivariate regression analysis showed that cholecystectomy was associated with NAFLD (odds ratio [OR] 1.35, 95% confidence interval [CI] 1.03-1.77, $P = 0.028$). However, gallstones were not associated with NAFLD (OR 1.15, 95% CI 0.95-1.39, $P = 0.153$). The independent association between cholecystectomy and NAFLD was still significant after additional adjustment for insulin resistance (OR 1.45, 95% CI 1.01-2.08, $P = 0.045$).

CONCLUSION: This study shows that cholecystectomy, but not gallstones, is independently associated with NAFLD after adjustment for metabolic risk factors. These data suggest that cholecystectomy may be an independent risk factor for NAFLD.

2. Revision has been made according to the suggestions of the reviewer

1) Reviewer 1

This is an interesting paper on the association of gallstone disease with nonalcoholic

fatty liver disease (NAFLD), two frequent conditions sharing similar risk factors. The authors examined a wide sample of Asian population (17,612 people), showing that over 30% of the subjects had NAFLD and over 6% presented gallstone disease, with the prevalence of gallstone disease significantly increasing in the presence of NAFLD and vice-versa. Multivariate regression analysis showed that cholecystectomy, but not gallstones, was associated with NAFLD, even after adjustment for insulin resistance. The authors conclude that cholecystectomy, but not gallstones, is independently associated with NAFLD after adjustment for metabolic risk factors, data suggesting that cholecystectomy may be an independent risk factor for NAFLD. The methodology is sound. The paper is clearly written and the results and their interpretation are convincing. I only have minor suggestions for manuscript improvement, as follows:

-An important aspect of cholelithiasis is the frequent occurrence of biliary colics/associated cholecystitis and referred tenderness in the upper right abdominal quadrant. Pain/acute inflammation is normally the main reason for deciding to proceed with cholecystectomy. Although the authors explain the association between cholecystectomy and NAFLD mainly in terms of alterations of bile acid metabolism subsequent to cholecystectomy and/or gallbladder-related hormonal effects, it cannot be excluded a relationship between pain/inflammatory symptoms preceding/motivating cholecystectomy and the occurrence of NAFLD. Was there any attempt in the examined patients to assess previous occurrence of biliary pain/number of colics? This aspect should be discussed by the authors and a relevant paper quoted in this regard, i.e., Giamberardino et al, Relationship between pain symptoms and referred sensory and trophic changes in patients with gallbladder pathology. *Pain*. 2005 Mar;114(1-2):239-49.

Thank you for the reviewer's comment. According to the reviewer's comment, we discussed the effect of pain on the relationship of cholecystectomy and NAFLD in the discussion section as follows (page 11, line 6);

"There may be an association between pain or inflammatory symptoms, which are associated with gallbladder pathology, before cholecystectomy and the occurrence of NAFLD^[35]. Recent population based study^[13] demonstrated that cholecystectomy in subjects with pain had a lower OR for NAFLD than cholecystectomy in subjects without

pain. As we did not have any data concerning abdominal pain or biliary colic due to our study design, we could not evaluate the effect of pain on the association between cholecystectomy and NAFLD. Further prospective studies should be conducted to investigate the exact mechanism of the association between cholecystectomy and NAFLD.”

-Which type of cholecystectomy was performed in the patients? Open or laparoscopic? In such a large sample, I suppose that both interventions were represented. Was there any difference in the prevalence of NAFLD among patients undergoing open cholecystectomy and those undergoing laparoscopy? These two procedures differ greatly regarding invasiveness and postoperative outcome in the patients, also with respect to postoperative pain. It would be interesting to know if there is any correlation of NAFLD with the type of intervention and also with the percentage of conversion (if any), especially as conversion shares some of the risk factors of NAFLD (e.g., diabetes) [see Costantini et al, Risk factors for conversion of laparoscopic cholecystectomy, *Ann Ital Chir.* 2012 May-Jun;83(3):245-52; and Controlling pain in the post-operative setting, *Int J Clin Pharmacol Ther.* 2011 Feb;49(2):116-27].

Thank you for the reviewer’s comment. Unfortunately, we do not have data about the type of cholecystectomy because we performed ultrasonographic evaluation of gallbladder and acquired the questionnaire regarding the previous history of cholecystectomy, not type of the cholecystectomy due to retrospective study design. Although some of them answered as “laparoscopic cholecystectomy”, most of them did not divide “open cholecystectomy” and “laparoscopic cholecystectomy”, separately. Therefore, we have added this in the limitation as follows (page 11, line 1);

“Fourth, the type of cholecystectomy (open or laparoscopic) and the conversion rate of cholecystectomy (laparoscopic to open), which may have affected its association with NAFLD, were not reviewed in this study, because the previous history of cholecystectomy, not the type of cholecystectomy were only available due to our study design.”

2) Reviewer 2

The introduction section was written in detail. There are 17 references cited in this section and the total number of references is 38. Some sentences may be moved/added to the discussion section and shortened.

Thank you for the reviewer's comment. According to the reviewer's comment, we have moved last paragraph of introduction section to the discussion section as follows (page 10, line 13);

"However, it is hard to apply this result directly to Asian populations because the prevalence of and risk factors for gallstone disease vary across ethnicities^[9, 18, 19]. In general, BMI, one of the risk factors for gallstones, is lower in Asians compared with Western populations; however, Asians have a higher risk of visceral obesity than Caucasian populations with the same BMI^[20, 21]. Thus, differences in general obesity, as assessed by BMI and visceral obesity, may have some effect on the association between gallstone disease and NAFLD. Until now, studies evaluating the association between gallstone disease and NAFLD in Asian populations are scarce. And, this is the largest study confirming the independent association between cholecystectomy, but not gallstones, and NAFLD in an Asian population."

I think more clear information about the health system must be given in the material and method section. What is the way to give the chance of collecting this large number of subjects in one year period? For example how is obtaining ultrasonography for each subject available? Is this a routine examination for periodic check-up?

Thank you for the reviewer's kind comment. About 25,000 subjects perform a routine health check-up voluntarily in Seoul National University Gangnam Center yearly. Some of subjects are supported by their company. Blood sampling and abdominal ultrasonography (hepatic ultrasonography) are two baseline tests, therefore, most of subjects perform abdominal ultrasonography. According to the reviewer's comment, we have added the information in the method section as follows (page 6, line 3);

"Subjects who voluntarily visited the Seoul National University Hospital, Healthcare System Gangnam Center, for a health check-up between January 2010 and December 2010

were initially enrolled. Most of all screenees routinely underwent hepatic ultrasonography and blood sampling as part of their health care program.”

2) Reviewer 3

No comment

3. Comments were added as follows;

COMMENTS

Background

Nonalcoholic fatty liver disease (NAFLD) and gallstone disease are both prevalent diseases that share the same risk factors, including insulin resistance and obesity. However, the association between gallstone disease and NAFLD has not been definitively established.

Research frontiers

This study investigated the relationship between gallstone disease (presence of gallstones or previous cholecystectomy) and NAFLD in a large Asian population.

Innovations and breakthroughs

This study showed that cholecystectomy, but not gallstones, is independently associated with NAFLD after adjustment for other established metabolic risk factors in a large Asian population.

Applications

Clinicians may be more alert to the risk of NAFLD in patients with a history of cholecystectomy.

Terminology

Cholecystectomy is the surgical removal of the gallbladder for symptomatic gallstones or other gallbladder conditions.

Peer review

This study is original and interesting and includes a large population. This study showed an independent association between cholecystectomy and NAFLD in the Asian population. Further prospective studies are warranted to confirm these associations.

4. References and typesetting were corrected.

5. English edition was done at American Journal Experts (English Certificate is attached.)

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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