



January 29, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14841-review.doc).

Title: Epidemiology, management, and economic evaluation of screening of gallstone disease among Type 2 Diabetes: a systematic review

Author: Lujie Chen, Yu-Ting Peng, Fu-Li Chen, Tao-Hsin Tung

Name of Journal: *World Journal of Clinical Cases*

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

1 Format has been updated

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

Reply to Referee 02903403

(1)The format in several sentences should be modified, 'hard return' should be replaced with 'space' on Page 5 Paragrph 1

Ans. Thanks for the reviewer's useful comments. The descriptions have been corrected. Please see page 6, line 2-13.

(2)Page 7 last sentence: 'Zeeland' should be 'Zealand'

Ans. Thanks for the reviewer's useful comments. The descriptions have been corrected. Please see page 8, line 2 from bottom.

(3)A table listed for the comparison of incidence of GSD in DM population in different ethnicities would be preferred for readers on Page 7 last paragraph to Page 8. And if there are more data from other western/asian population?

Ans. Thanks for the reviewer's useful comments. The table and descriptions have been corrected. Please see table 1, table 2, and page 8, line 7-11 from bottom.

(4)Page 11, in four-state Markov chains model: the authors should be aware that single stone might not always consequentially develop into multiple stone.

Ans. Thanks for the reviewer's useful comments. The descriptions have been corrected. Please see page 12, line 11-13 from bottom.

(5)Any discussion on statin or ezetimibe with gallstone disease?

Ans. Thanks for the reviewer's useful comments. The descriptions have been corrected. Please see page 13, line 4-19 from bottom.

(6)Page 16 'NTD' Should be exchanged to global currency such as dollar.

Ans. Thanks for the reviewer's useful comments. The descriptions have been corrected. Please see page 15 and page 16.

(7) If any mechanisms for DM leading to GSD should also be discussed.

Ans. Thanks for the reviewer's useful comments. The descriptions have been corrected. Please see page 8, line 9-14.

Reply to Referee 02954463

The Authors propose the screening of gallstone disease among patients who have a history of treated diabetes mellitus, in order to decrease the risk of cholecystectomy. This assertion is based on the fact that early treatment of gallstone disease reduces the morbidity and prevent serious outcomes such as acute gallstone pancreatitis and gallbladder cancer, slowing the progression of cholecystectomy. Considering the fact that dissolution therapy with oral bile acids could be only suggested to an extremely limited patient population (symptomatic gallbladder disease patients who are unfit for surgery and have small, uncalcified, and cholesterol-enriched stones), the majority of patients with or without complications will need surgery. Thus, the ultrasound screening is not appropriate in the natural course of gallstone disease. Finally, correction of punctuation is needed.

Ans. Thanks for the reviewer's useful comments. All the descriptions have been corrected.

Reply to Referee 00069630

In this review, the authors try to discuss epidemiology, management, and economic evaluation of screening of GSD among type 2 diabetes. It is interesting and important. However, with the limitation of research field, the authors cannot correctly understand some clinical matters. 1 · "From the viewpoint of preventive medicine, early detection of this disorder by regular screening followed by early treatment could prevent the resulting cholecystectomy." It is the basic assumptions of the authors in this manuscript. However, GSD has a more complicated clinical aspect. It is not the rule for people with gallbladder stone definitely to progress towards more serious complications. In clinic, 60% of the patients with gallbladder stone are asymptomatic throughout their life. In these people, early detection may not help them to avoid possible healthy problem. Furthermore, up to now, there is no effectively early treatment for GSD that could prevent the resulting cholecystectomy. What we could and we should do now for GSD patients is to find the patients more likely to has a serious outcome in the future and perform an early cholecystectomy to avoid the secondary common bile duct stone, gallstone pancreatitis and possible cancerization. That is why some asymptomatic patients are indicated for cholecystectomy. Also, some asymptomatic patients with diabetes and cardio-cerebrovascular complications should be treated with cholecystectomy in a stable condition to avoid unpredictable attack of GSD. That is currently the aim for GSD screening. 2 · If the four-state Markov chains model for the disease natural course of GSD following the pathway of proliferative phase was mapped as follows: ?12 ?23 ?34 No GSD Single stone Multiple stones Cholecystectomy. (State 1) (State 2) (State 3) (State 4) Authors take Markov chain model as the natural course of GSD. It is obviously unsuitable model since the natural history of GSD may be heterogeneous and more complicated. According to current knowledge, there is no relationship between the number of gallstone and cholecystectomy. We still have no clear idea about how the gallstone product and what is the progression factors for GSD.

Ans. Thanks for the reviewer's useful comments. All the descriptions have been corrected.

Reply to Referee 00227683

Authors reviewed epidemiology, management, and economic evaluation of screening of gallstone disease from the viewpoint of preventive medicine. The review may be helpful to the diagnosis and management of screening of gallstone disease. I have comments in details as follows:

(1) Regarding the title, "among type 2 diabetes" can be removed from the title. Because it seems that the content of the paper can't focus on "among type 2 diabetes".

Ans. Thanks for the reviewer's useful comments. All the descriptions have been corrected. However, we still try to keep the type 2 diabetes in the title.

(2) Regarding prevalence, morbidity (incidence) and mortality in epidemiology including design or method, authors should define them clearly on the base of the studies reviewed. It is better that the authors should reviewed Epidemiology, management, and economic evaluation of screening of gallstone disease among patients with or without type 2 diabetes, in hospital-based or population-based study, respectively. Otherwise, it is unclear to readers.

Ans. Thanks for the reviewer's useful comments. The table and descriptions have been corrected. Please see table 1, table 2, and page 8, line 7-11 from bottom.

(3) Regarding screening of gallstone disease, it is not appropriate to discuss it in the natural course of gallstone disease. On the contrary, the influence of different-time screening on cholecystectomy may be listed in a paragraph of the text like "the economic evaluation of screening of gallstone disease".

Ans. Thanks for the reviewer's useful comments. All the limitations have been corrected. Please see page 17.

3 References and typesetting were corrected

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

Sincerely yours,

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