Reviewer #1

This is a comprehensive review about the mechanism and management of DM in patients with chronic liver disease (CLD), including HCV, NAFLD/NASH, and cirrhosis. This review is well written and of great value because clinicians are sometimes worried about glucose control for CLD patients.

Major comments

1. HCV and insulin resistance: The authors should cite the following manuscript and mention the role of HCV core protein for hepatic insulin resistance: Shintani et al., Gastroenterology. 2004 Mar;126(3):840-8. doi:10.1053/j.gastro. 2003. 11.056. PMID: 14988838.

- Thank you very much for this recommendation. This is an excellent article and I have included it into the appropriate section.

2. Section 8 3: The authors titled “Acarbose”. There are some alpha-glucosidase inhibitors other than acarbose. The authors should seek the manuscripts more broadly.

- I appreciate this insightful feedback. I have extended this section to include discussions regarding other a-glucosidase inhibitors, including voglibose and miglitol.

3. Section 8 3: The authors should cite the following manuscript and mention the efficiency and safety of alpha-glucosidase inhibitor for treating NASH: Komatsu et al., Hepatol Res. 2018 Dec;48(13):1092-1098. doi: 10.1111/ hepr. 13223. Epub 2018 Jul 27. PMID: 29935004

- I have now included this reference as part of the revision as described above.

4. The authors should discuss the association between sulfonylurea intake and HCC in CLD patients.

- Excellent point. I have now included several references to studies on the association between sulfonylurea and HCC.

Reviewer #2

In this manuscript titled „Clinical Implications, Diagnosis, and Management of Diabetes in Patients with Chronic Liver Diseases” authored by Waihong Chung, Kittichai Promrat and Jack Wands a complex task is reviewed. General opinion: The MS is generally well written, clear and reviews this complex, difficult topic using 226 references. Structure is organized in a logical manner, the task is of high interest to the clinicians due to that both patient populations (T2DM and NAFLD) are huge World wide and the overlap is substantial. Therefore the general opinion is supportive. Nevertheless there are a few points where the MS could be potentially improved as follows:

a-) Page 1 – point 2. (“Diabetes and chronic liver disease”), 1st paragraph: Authors do refer to the ADA guideline as one that “now make specific recommendations regarding screening patient s with prediabetes and T2DM for NAFLD”. While this statement is true there are other major recognized organizations who even jointly published guidelines to help treatment such as the “Clinical Practice

Guidelines for the management of non-alcoholic fatty liver disease" by the EASL-EASD-EASO1 and "The diagnosis and management of non-alcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases"2. These guidelines should also be incorporated and cited appropriately.

- Excellent point. I have now included those two guidelines in the manuscripts.

b-) Page 1 – point 2., 3rd paragraph: Authors characterized the relationship between DM and HCV as "particularly noteworthy". Accordingly a number of experimental and clinical observations are lined up to support this relationship. However one major path that may contribute to the risk of (type 2) DM development in patients with chronic HCV infection is still missing: The increased serum DPP-4 activity3,4 and CD26 expression in human hepatoma cell line transfected by HCV non-structural (NS) genome region cDNA5 may potentially also have a DM inducing effect via the increased degradation of the incretin hormones.

- The HCV-DDP-4/GLP-1 was only briefly eluded to in the Hepatogenic Diabetes section in the original draft. I have now edited this section to make explicit comment on this important pathway. Thank you very much for the feedback.

c-) Page 2 – point 3 ("Diabetes and End-Stage Liver Diseases) - 2nd and 3rd paragraph Authors outline that the incidence of HCC and HCC-specific mortality are nearly double in patients with pre-existing DM and give a good overview of the topic including even the treatment modalities such as TACE. However, the genetic susceptibility is not discussed. It is somehow missing from the whole review, despite it would be particularly relevant in this chapter. Hassan et al reported a higher risk of HCC for subjects with a homozygous GG genotype of the rs738409 variant of PNPLA3 (aOR: 3.21), however among individuals with diabetes mellitus the adjusted OR nearly reached a 20-fold increased (19.1) indicating a significant interplay between PNPLA3 genotype and DM on HCC as an outcome.6 This aspect should also be included here.

- Excellent suggestion. I have now included a brief discussion of the importance of certain PNPLA3 variant into this section.

d-) Page 5. point 6.3 ("Hemoglobin A1c") Correct writing of Hemoglobin A1c is as follows: Hemoglobin A1c In addition based on this paragraph it might be the impression of the reader that the HbA1c is not a good marker in any chronic liver disease. However due to that the NAFLD/MAFLD is the most common CLD in the more advanced countries where – in vast majority of the cases – HbA1c is not only a good, but an essential marker of mean glycemic control back to 2-3 months and monitoring, but also is appropriate for diagnosis in diabetes care I would suggest to temper down the tone of this paragraph. The NGSP lists the conditions that interfere with HbA1c measurement (http://www.ngsp.org/factors.asp). Perhaps the authors are correct on that the more advanced CLD cases, in particular when co-occuring with other diseases/compliactions such as nutritional and vitamin deficiencies (folate, B12), portal hypertension with hypersplenia most likely should be mentioned, however I would suggest to temper down the tone of this paragraph (in particular, where references 89 and 90 cited, e.g.: "The accuracy and validity of A1c in patients with liver disease is suboptimal"), etc.

- Point well taken. I have revised part of this section to stress that A1c remains a useful glycemic marker in most patients and to tone down the criticism on the use of A1c in patients with chronic liver diseases.

e-) Page 9. point 8.5. (“Dipeptidyl peptidase-4 inhibitors”) A few studies with DPP-4 inhibitors or even the drug names are missing. I.e.: the authors left out Vildaglitpin from the list of DPP-4 inhibitors. The studies reporting positive effect of DPP-4 inhibitors of live endpoints, but currently missing from this review are: 1. Alam et al published that Sitagliptin 100 mg once daily for 1 year ameliorates NAS by improving steatosis and ballooning, irrespective of diabetes.7 2. Kosi-Trebotic et al reported that 6 months of DPP-4-therapy led to a significant overall decrease in HCL and body weight such as a reduction of myocardial fat content only in women.8

- I sincerely appreciate the suggestions and have included the sitagliptin study from Alam et al into this section. I have, however, not included the study from Kosi-Trebotic because the study was not specifically designed to study the use of DPP-4 inhibitors in patients with chronic liver diseases.

f-) More recently a panel of international experts reached consensus on the criteria for Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), which is expected to unify the terminology, enhance the legitimacy of clinical practice and clinical trials, improve clinical care and move the clinical and scientific field of liver research forward.9,10 This newer terminology and the more precise definition never occurred in this MS, I would suggest to discuss the evolution of NAFLD to MAFLD and the potential advantages that the use of MAFLD might provide for future studies.

- Thank you very much for this insightful feedback and for teaching me about this exciting new concept of MAFLD. I have thoroughly enjoyed reading the references that you provided and have included a brief discussion on MAFLD toward the end of the manuscript.