Dear Reviewers and editors,

Thank you for giving us the opportunity to submit a revised draft of our manuscript- "**Management of Metabolic-Associated Fatty Liver Disease: The Diabetology Perspective**". We appreciate the time and effort that reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect the suggestions provided by the reviewers. We have highlighted the changes within the manuscript. Here is a point-by-point response to the reviewers' comments.

Many thanks

Yours sincerely

Authors

Reviewer #1:

1. The global prevalence of obesity leads to various metabolic disorders, particularly metabolic-associated fatty liver disease (MAFLD) and type 2 diabetes mellitus (T2DM). As the diseases of metabolic syndrome, MAFLD and T2DM have similar pathogenesis. It is important for this review to summarize the management of MAFLD from a diabetologist's perspective.
   Answer: We thank the reviewer for their comment

2. This review concisely and coherently organized and presented the comprehensive management of MAFLD from the aspects of lifestyle intervention, drug treatment and surgical treatment. This article also summarized emerging concepts and the management of special populations with MAFLD, such as pregnant women, children and the elderly individuals.
   Answer: Many thanks for the reviewer for their supportive comments

3. At present, the treatment of MAFLD is still a world problem, because there are no drugs approved by the FDA for the management of the disease. Most of drugs for T2DM or others have not been recommended for MAFLD due to their efficacy and side effects. It is necessary to improve the knowledge of the personalized treatment options with targeted drugs on MAFLD. Further research is still urgent needed on novel therapies, including novel therapeutic and surgical approaches for MAFLD.

   Answer: We share the similar concern and raise the similar question in our review

Reviewer #2:

Major:

1. Due to the rapid growth of knowledge in this field. Please add the subheading of search strategies and the date of searching after the introduction part.
   Answer: we have done a PubMed search using MeSH terms and key words appropriate to the individual subheadings we elaborated in the text while writing the initial manuscript. We used the most recent and appropriate citations from high-quality literature including systematic reviews, randomised controlled trials and professional body guidelines. We have now briefly described the search strategy in the introduction section of the revision now as suggested though this paper is not a systematic review.

2. Page 6: Please review more information regarding the role of liver biopsy in those patients because liver biopsy may require intermediate to high-risk fibrosis patients or NASH diagnosis or exclude other coexisting diseases.

   Answer: Although liver biopsy remains the gold standard for diagnosis of MAFLD it cannot be done on everyone due to the invasive nature of the test, limitation in the availability of expertise widely, peri-procedural complication and the histology is subjected to interpretation errors. Sequential testing for MAFLD using blood test and non-invasive testing does reduce the number of liver biopsy required for the confirmation. In the data from the STELLAR studies sequential testing alone had a reasonable specificity and sensitivity with area under the curve between 0.75 to 0.80 to discriminate advanced fibrosis in MAFLD patient. Our recommendations are line with AACE/AASLD 2022 guidelines where liver biopsy is required only for intermediate to high-risk fibrosis patients or NASH diagnosis or exclude other coexisting diseases. Bariatric surgery provides an opportunity to perform liver biopsy and can be potentially utilised if the diagnosis of MAFLD is uncertain via the non-invasive tests while obese patients undergo this treatment modality for other reasons.

   Anstee QM, Lawitz EJ, Alkhouri N, Wong VW-S, Romero-Gomez M, Okanoue T, Trauner M, Kersey K, Li G, Han L, Jia C, Wang L, Chen G, Subramanian GM, Myers RP, Djedjos CS, Kohli A, Bzowej N, Younes Z, Sarin S, Shiffman ML, Harrison SA, Afdhal NH, Goodman Z, Younossi ZM. Noninvasive Tests Accurately Identify

Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials. Hepatology 2019; 70: 1521–1530. [DOI: 10.1002/hep.30842]

3. Currently, there are many dietary regimens to improve obesity and MAFLD. It's essential to review whether the type of diet affects the metabolic parameters, including the ketogenic, low carbohydrate, and the Mediterranean diet. Lastly, what regimen is suitable for this group of patients?

   Answer: Although various dietary regimen is available starting from carbohydrate, very low carbohydrate diet, ketogenic diet and Mediterranean diet, the ultimate aim for all these dietary regimens is to aim for calorie deficiency due to restriction of macronutrient (sugar and saturated fat). Of all the dietary regimen, the evidence base is stronger for low glycaemic index Mediterranean diet which has shown to reduce the NAFLD score (median score -4.14, 95% CI -6.78,-1.49) when compared to the regular diet within six months duration. Mediterranean also has cardiovascular protection property. Due to multiple benefits with the Mediterranean diet several societies recommend preferred first line approach for this for MAFLD patient.

   Misciagna G, Del Pilar Díaz M, Caramia DV, Bonfiglio C, Franco I, Noviello MR, Chiloiro M, Abbrescia DI, Mirizzi A, Tanzi M, Caruso MG, Correale M, Reddavide R, Inguaggiato R, Cisternino AM, Osella AR. Effect of a low glycemic index Mediterranean diet on non-alcoholic fatty liver disease. A randomized controlled clinici trial. The journal of nutrition, health & aging 2017;21:404–12 [DOI: 10.1007/s12603-016-0809-8]

4. Besides exercise intervention, increased physical activity is helpful in those patients. Please review more information regarding the suggestion of increased physical activity, i.e., walking steps.

   Answer: We thank the reviewer for the comment about the walking steps and quantification of physical activity. But it will be difficult to quantify exercise alone without considering amount of calorie intake. Hence the reason we had quantified the duration of exercise as per the evidence cited in the manuscript and the weight loss as the outcome rather than the just a step count measure as this might become wrong target for MAFLD treatment.

5. The exercise comprised two methods, including aerobic and resistance training. Please review more papers about these types of exercises.

   Answer: Many thanks for the reviewer for this valuable comment. We have now added more literature on the benefit of both the aerobic and resistance training exercise in the management of MAFLD.

   Both aerobic exercise and resistance training exercise results in reduction in the intrahepatic triglycerides (IHTG) content. In a randomised control trial from Thailand, a 12-week regimen of moderate intensity aerobic exercise results in similar reduction of intrahepatic fat and improvement of insulin resistance in MAFLD patients when compared with resistance exercise and dietary modification. A metanalysis involving six studies with 94 participants suggest that having a structured exercise regimen results in greater reduction of IHTG and body weight. Hence the combination of aerobic exercise with resistance component in a structured exercise program and dietary regimen would maximise the weight loss and greater reduction in IHTG in MAFLD.

   Charatcharoenwitthaya P, Kuljiratitikal K, Aksornchanya O, Chaiyasoot K, Bandidniyamanon W, Charatcharoenwitthaya N. Moderate-Intensity Aerobic vs Resistance Exercise and Dietary Modification in Patients With Nonalcoholic Fatty Liver Disease: A Randomized Clinical Trial. Clin Transl Gastroenterol 2021; 12: e00316. [PMID: 33939383 DOI: 10.14309/ctg.0000000000000316]

   Sargeant JA, Gray LJ, Bodicoat DH, Willis SA, Stensel DJ, Nimmo MA, Aithal GP, King JA. The effect of exercise training on intrahepatic triglyceride and hepatic insulin sensitivity: a systematic review and meta-analysis. Obes Rev 2018; 19: 1446–1459. [PMID: 30092609 DOI: 10.1111/obr.12719]

6. In summary, lifestyle intervention is hard to achieve, but encouragement is necessary. Please explain more information about the method to improve compliance with lifestyle intervention.
   Answer: We thank the reviewer for the comment. We have added more practical, and evidence-based approach to maintaining the compliance with MAFLD patient.

Maintaining compliance in any chronic disorder is always challenging, different models like health behavioural model and protectional motivation theory have been proposed to improve the compliance, but all the models highlight the importance of explaining the effectiveness of the lifestyle changes to the patient and emphasising the importance for maintaining the target achieved for prevention of progression of MAFLD.

Zelber-Sagi S, Bord S, Dror-Lavi G, Smith ML, Towne Jr SD, Buch A, Webb M, Yeshua H, Nimer A, Shibolet O. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. World Journal of Gastroenterology [Internet] 2017;23:1881 [DOI: 10.3748/wjg.v23.i10.1881]

7. Based on current evidence, pioglitazone is only used in patients with biopsy-proven NASH, especially with T2DM. Therefore, this sentence can misinterpret; “when there is evidence of NASH (raised transaminases and/or non-invasive tests)”. Please modify the sentence.

Answer: We thank the reviewer for this comment on the use of pioglitazone for biopsy proven NASH. But there have been other studies that had pioglitazone in patient with probable NASH without any biopsy. The AACE 2022 guidelines states that pioglitazone can be used in NASH in patient with Type 2 DM. The sentence structure is now altered in accordance with the guidelines.

AACE 2022 guidelines
“Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and non-invasive tests.”

8. Although bladder cancer risk had been reported from pioglitazone, the data is controversial. Please add more data about this risk.

Answer: We now included more data on the risk of bladder cancer issue with Pioglitazone as below in the main manuscript.

The association between Pioglitazone and bladder is controversial. US-FDA has issued safety warning and advise against the use of Pioglitazone in patient with active bladder cancer and to exercise caution when used in patient with previous history of bladder cancer. In a meta-analysis of 26 studies, the hazard ratio for developing bladder cancer in patient with type 2 diabetes with pioglitazone exposure was 1.07 (95% C.I- 0.96–1.18) and was not statistically significant with the number needed to treat for one patient to develop bladder cancer was 899 to 6380 individuals.

Tang H, Shi W, Fu S, Wang T, Zhai S, Song Y, Han J. Pioglitazone and bladder cancer risk: a systematic review and meta-analysis. Cancer Medicine [Internet] 2018;7:1070–80 [DOI: 10.1002/cam4.1354]

Filipova E, Uzunova K, Kalinov K, Vekov T. Pioglitazone and the Risk of Bladder Cancer: A Meta-Analysis. Diabetes Ther 2017; 8: 705–726. [PMID: 28623552 DOI: 10.1007/s13300-017-0273-4]

9. Please add more data regarding the PIVENS study, which determined the efficacy of pioglitazone and vitamin E in patients with biopsy-proven NASH.

Answer: More data added to the section on vitamin E

PIVEN study utilised two by two factorial study design to evaluate the efficacy of α-tocopherol, at a dosage of 800 international units daily and pioglitazone in patient with biopsy proven NASH without diabetes. At the end of 96 weeks patient on Vitamin E therapy showed improvement in NASH as assessed by liver biopsy when compared to placebo (43% vs. 19%, P=0.001). The long-term efficacy of vitamin E to delay the progression of NASH is yet to be determined and there are some reports of increased all-cause mortality with high dose vitamin E but this is not proven and meta-analysis have failed to confirm this association

Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Natta MV, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. New England Journal of Medicine 2010; 362: 1675–1685. [DOI: 10.1056/nejmoa0907929]

Minor:

1. Please correct the term “metabolically-associated fatty live disease (MAFLD)” to “metabolic-associated fatty liver disease (MAFLD)” in the abstract and Core Tip.
   Answer: Many thanks, it is now corrected.

2. Please remove liver failure from the keyword. The additional “obesity” and “NAFLD” keywords are appropriate and relevant to this review.
   Answer: Thank you, it is now changed as per the reviewer’s suggestion

3. MAFLD is a new term that is not the same as NAFLD. Please substitute the “MAFLD” for “NAFLD” in the drugs used to manage MAFLD.
   Answer: We have now added NAFLD where necessary.

4. Please check the English style throughout the manuscript.
   Answer: Many thanks for the reviewer’s comment, we review the manuscript and corrected the style where needed.

Reviewer #3:

1. The Authors said that, because of the interplay between MAFLD and diabetes, all patients with one of these conditions should be evaluated/monitored for the other. This point poses logistic issues. Who should monitor these patients? GP? Hepatologists? Diabetologists? This is an important point, in my opinion, since the number of potentially involved patients is very large. There could be many patients who are monitored/followed-up twice, and others that are not monitored at all. A comment would be valuable.

   Answer: Many thanks for the reviewers comment and we have now created a new figure (Figure 3), which addresses the practical aspect of the management of MAFLD at different health tier (Primary care Vs Specialist) and also the choice of the medication.

2. There are many therapies that have recently revolutionized the treatment of diabetes. Some of these (e.g., semaglutide) seem effective also in reducing fibrosis in patients with MAFLD. Moreover, these patients share often arterial hypertension, obesity, CKD and other metabolic diseases. What type of strategy the Authors suggest? Multidisciplinary consultation for an individualized treatment plan for all patients? for patients who fail first-line therapy?
   Answer: Many thanks for the reviewers comment and we have now created a new figure – Figure 3 for the choice of the first line agent and team involved in the management of these patients.

3. What therapy (between SGLT2-i and GLP1-Ras) the Authors suggest as first line therapy in patients with diabetes and MAFLD?
   Answer: Many thanks for the reviewers comment and we have addressed this issue in new figure – Figure 3.

4. What is the Authors' advice about bariatric surgery? Do they consider it after failure of weight loss or do they consider it earlier, in patients with MAFLD, Type 2 DM and BMI>35?
   Answer: Many thanks for the reviewers comment we have addressed this issue already in the metabolic surgery section of the main manuscript.

5. I congratulate the Authors for the section about pregnancy
   Answer: Many thanks for the reviewer for this encouraging comment

6. HCC shares different characteristics in patients with MAFLD than in patients with different underlying etiologies. This point should be discussed more in depth, in my opinion.

   Answer: When compared with chronic hepatitis C infection the cumulative incidence of MAFLD patient developing HCC is lower (4% Vs 2.5%) at 1 year and (30% Vs 11%) at 5 years.(1) Moreover patients with MAFLD has tendency to develop HCC even without cirrhosis and the risk is five time when compared those with chronic hepatitis C infection.(24) As these patients without cirrhosis are not in the surveillance program they tend to present with bigger tumour burden with reduced median survival (18). Recent data suggest that patient who develop HCC due to MAFLD cirrhosis live longer than hepatitis C related HCC after curative treatment

Oda K, Uto H, Mawatari S, Ido A. Clinical features of hepatocellular carcinoma associated with nonalcoholic fatty liver disease: a review of human studies. Clinical Journal of Gastroenterology [Internet] 2015;8:1–9 [DOI: 10.1007/s12328-014-0548-5]Available from: https://dx.doi.org/10.1007/s12328-014-0548-5

Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, May SB, Kramer JR, Richardson PA, Davila JA. Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans Is Associated With Nonalcoholic Fatty Liver Disease. Clinical Gastroenterology and Hepatology [Internet] 2016;14:124–31.e1 [DOI: 10.1016/j.cgh.2015.07.019]Available from: https://dx.doi.org/10.1016/j.cgh.2015.07.019

Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, Aslam T, Patanwala I, Gaggar S, Cole M, Sumpter K, Stewart S, Rose J, Hudson M, Manas D, Reeves HL. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014; 60: 110–117. [PMID: 23978719 DOI: 10.1016/j.jhep.2013.08.011]

Tan DJH, Ng CH, Lin SY, Pan XH, Tay P, Lim WH, Teng M, Syn N, Lim G, Yong JN, Quek J, Xiao J, Dan YY, Siddiqui MS, Sanyal AJ, Muthiah MD, Loomba R, Huang DQ. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. The Lancet Oncology 2022; 23: 521–530. [DOI: 10.1016/S1470-2045(22)00078-X]

Minor –

1. I suggest to add a brief definition of NASH, NAFLD, MAFLD, for the non-expert reader –
   Answer: We have now amended the introduction of the paper with a new paragraph briefly defining these terms.

2. Why SPB has been reported as the only complication of Portal hypertension (Table)?
   Answer: Many thanks for the reviewers' comments. We did not mean to say SBP as only complication, we meant it in terms of management where prophylaxis would change the outcome

3. Liver transplantation in patients with MAFLD is an established therapeutic option. Nevertheless, high BMI, type-2 DM may deserve special attention in the setting of LT. A comment would be important.

   Answer: Many thanks for the reviewer for this comment Liver transplantation is used either for end stage liver disease or HCC due to MAFLD. The transplant related mortality and morbidity is high compared to the HCC due to other aetiology due to very high BMI in MAFLD patient and also diabetes related cardiovascular complications. But it is interesting to note that post-transplant 5 year survival is not different between MAFLD and non-MALFD aetiology because of the lower risk of graft failure balances the higher risk of sepsis and cardiovascular disease in MAFLD patient when compared to other aetiology.

Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism 2020;111:154170 [DOI: 10.1016/j.metabol.2020.154170]

Cholankeril G, Wong RJ, Hu M, Perumpail RB, Yoo ER, Puri P, Younossi ZM, Harrison SA, Ahmed A. Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. Digestive Diseases and Sciences 2017;62:2915–22 [DOI: 10.1007/s10620-017-4684-x]

Reviewer #4:

This review described the management of the metabolic-associated fatty liver disease. Since MAFLD is a novel concept proposed in 2020, little is known about its management and more time will be needed for its establishment. Still, the review will help us understand he concept of MAFLD and develop future treatments.

Answer: Many thanks for the reviewer for this encouraging comment.

Response to Editor's comments #:

Language quality, tables and figures have been modified to the Journal's specifications.

The corresponding author has already got and RCA account which has recently been updated by the BPG group.