

## 26492 Answering reviewers

### Reviewer 1

This paper highlights the important topic of post liver transplant metabolic complications. Overall it is written nicely and is understandable for the reader. It is clearly structured. I have some remarks that should be addressed by the authors:

1. the description of the single aspects of the metabolic syndrom should clearly differnciate between pre and post transplant Situations. Furthermore associations of pre and post transplant conditions should be discussed and literature cited as far as available or a statement given that such data is not available.

These points have now been clarified in the manuscript.

Pre-transplant diabetes and the BMI were found in one study to be predictive factors for the development of post-transplant diabetes. Likewise, patients who are overweight or obese before transplantation are more likely to continue to be overweight or obese after transplantation. On the other hand, hypertension and dyslipidaemia are less common before transplantation as compared with after transplantation. When a patient does have hypertension or dyslipidaemia before liver transplantation these conditions may worsen afterwards, though no studies have yet specifically examined this aspect.

2. Overall the utilization of modern steroid free and minimized immunosuppression protocols should be kept in mind. In my understanding maintenance immunosuppression is rarely using steroids in Liver Transplantation and is based on tacrolimus in Most centers.

Indeed, immunosuppression protocols now favour steroid-free regimens as well as minimal immunosuppression. Nevertheless, steroids are still necessary during the immediate post-transplant period, even for just a short time. In some patients though, for example those who require transplantation due to autoimmune liver disease, it is sometimes necessary to prolong steroid treatment.

A relevant sentence has been added in the Abstract and the Introduction concerning this observation.

3. i do n?tig understand the statement on page 6 of the manuscript that deceased donors have more favourable characteristics regarding age, bmi, or Liver function compared to dcds, which usually have less comorbidity.....?

This sentence has been reworded to make it clearer. The idea is that patients who receive a liver transplant from a living donor (LDLT) have a lower incidence

of insulin resistance due to the more favourable characteristics of the liver regarding various factors.

4. the authors should suggest an explanation why incidences of cva are lower than in heart or kidney recipients (page9). Levels of immunosuppression ?

Yes, this is due to the lower immunosuppression given to liver transplant recipients and the lower pre-transplant prevalence of cardiovascular risk factors in liver transplant patients as compared with kidney or heart transplant recipients.

This has now been explained in more detail in the text.

5. the authors should be careful to discuss any positive effect of hepatitis c on lipid metabolism (Page 10) with all the known problems of a hepatitis c (re-) infection. Instead the new treatment options of hepatitis c might be of interest in these contexts.

A relevant paragraph has been added at the end of section 4.3. It is true; the high efficacy of these new antiviral drugs against HCV means that the impact of the HCV itself will be minimal or even none.

6. a treatment Algorithm and target values for the different aspects of ms would be of high interest for the reader.

Recommendations concerning prevention and treatment of the metabolic syndrome are now given in Table 2. These treatment aims, though, do not really differ from those recommended for the general population.

7. do the authors know of any Data that suggests any reduction of morbidity and mortality after treatment of the ms after liver transplantation?

We have found no specific study analysing the reduction in morbidity and mortality after treatment of post-transplant metabolic syndrome.

## Reviewer 2

The authors present a manuscript highlighting prevalence and potential complications of metabolic syndrome in liver transplant recipients. I would make the following suggestions:

1. In the introduction section the rate of post-transplant metabolic syndrome should be properly referenced to the 4-5 articles evaluating it.

This information has now been added in the Introduction, together with various references (9-13).

2. In the second section the regarding the components, the section on Obesity should be revised. The section starts with weight gain after surgery, then progresses in the same paragraph to discuss pretransplant complications of obesity. It should be organized better so the reader can easily figure out if the authors are discussing pre or post transplant obesity.

This section (2.1) has now been carefully reorganised and amended to address the concern mentioned and clarify the situation.

3. In addition to above, in the obesity section the authors should clarify the sentence showing data from reference 21- it should be clear the authors are discussing pretransplant BMI, otherwise it makes no sense why they are discussing ascites in post transplant patients.

As mentioned above, to avoid the confusion that arose we have added a few comments to clarify this point.

4. In the section on hypertension the authors should not state calcium channel blockers are the treatment of choice and then later exclude all but one. They should just recommend amlodipine/nifedipine and then describe the limitations of the other agents

This has been corrected.

5. In the section on post transplant diabetes, the authors should be careful as many observations are the prevalence of DM increases after liver transplant. The statement that liver transplant resolves up to 70% of pretransplant DM based on a single small series examining hepatic insulin resistance leaves the impression that this is mostly a pretransplant problem.

Various studies have shown that liver transplantation can improve insulin resistance and resolve up to 70% of pre-transplant DM, but only those cases in which the pre-transplant DM was due to insulin resistance. The persistence of DM after transplantation indicates that other factors present before transplantation, such as poor beta cell function, are involved in the perpetuation of the DM. In addition, in these patients as in others, the risk persists of developing DM due to other factors, such as immunosuppression or obesity. This has now been clarified in the manuscript.

6. Under section 4 discussing repercussions of PTMS, section 4.4 discussing NAFLD could be expanded

This section has been expanded to include the relevant considerations.

7. Finally, the conclusion paragraph should be labeled separately

This has now been done.

### Reviewer 3

The authors have reviewed the evidence surrounding metabolic syndrome post liver transplant. This is a worthwhile and interesting review that clearly demonstrates the prevalence and consequence of the problem. The manuscript is well structured and easy to read but would benefit from a figure &/or table to break up the text.

Two tables have been added (Table 1, 2).