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Dear Editor,

Title: Major Influence of Renal Function on Hyperlipidemia after Living Donor Liver Transplantation
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Thanks a lot for dealing with our manuscript and giving us the opportunity to submit the revised manuscript to *World Journal of Gastroenterology*. The comments from the reviewers are really helpful for the improvement of our manuscript. We have carefully prepared a revision strictly according to the points made in the reports and most of advices have been adopted. The alterations have been highlighted (red color) in the revised manuscript. We wish the main viewpoint could be clearly clarified and revised manuscript would be considered for publication in *World Journal of Gastroenterology*.

Please let me know if there is any problem.

Once again, thank you very much.

Sincerely yours,

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

Comments to the Author(s):

Reviewer #1 00722219: Major Influence of Renal Function on Hyperlipidemia after Living Donor Liver Transplantation is good retrospective study. There were some limitations in this study. But

the limitations were explained in this manuscript by authors. In my opinion, this study is original and it is acceptable.

Thanks a lot.

Reviewer #2 00053868: The authors have studied a series of 115 adult recipients of living donor liver transplantation, finding that post-transplant hyperlipidemia is related to early renal dysfunction. This is an interesting finding, but the manuscript has some details that should be reviewed.

- Renal function should not be evaluated according to creatinine levels. Formulas of estimating GFR should be used.

Yes, that is a very good question. Whether to use formulas of estimating GFR to assess the renal function in patients with acute kidney injury (AKI) or acute renal dysfunction (ARD) is still under debate.

In our opinion, to evaluate the chronic kidney disease, estimated GFR is a better diagnose marker than serum creatinine, because the MDRD or adjusted MDRD estimated GFR was derived from patients with chronic kidney disease who had renal functional changes over several months and years. However, to assess the AKI or ARD, serum creatinine should be equal to or even better than MDRD or adjusted MDRD estimated GFR. Because serum creatinine will sharply increase within several hours or days in patients with AKI and estimated GFR measurements do not represent the non-steady-state conditions. Serum creatinine and urine output are markers of severity in AKI, and have been found as risk predictors for outcome. As utilized in the Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [1] and Model for End-Stage Liver Disease (MELD) scoring system [2], serum creatinine is the most commonly used clinical indicator of renal function. Most of the studies in liver transplantation defined ARD or AKI according to the serum creatinine levels [3-8]. Furthermore, in our previous study, we found similar specificity, sensitivity and accuracy between serum creatinine and its-based formulas (CG and MDRD) using ^{99}mTc DTPA-GFR as a standard control in a cohort of patients undergoing liver transplantation during the early post-transplant period [9].

- In the analysis of factors related to hyperlipidemia, BMI should be used as a continuous variable.

Actually, except ERD, all other parameters independently related to hyperlipidemia (serum creatinine, GR/WR, GV/SLV and BMI) are quantitative variables. To better elucidate the severity of each risk factor and easier calculate the possible risk score [10], we use ROC curve to select cutoff values with best diagnostic specificity and sensitivity and transfer these quantitative variables to categorical variables.

- Was prednisolone withdrawn in all the patients in the first month?. It is possible that patients with worse renal function received prednisolone for a longer period of time, in an attempt to maintain lower levels of tacrolimus? Was sirolimus/everolimus used in patients with renal dysfunction? The use of high doses of steroids / cumulative doses of steroids of both groups should be compared.

That is a good question.

Reduced-steroid or steroid-free immunosuppression has been greatly advocated in recent years because of the side effects of steroid. In our center, steroid is routinely withdrawn early following liver transplantation. For patients with pre-transplant renal insufficiency, anti-IL2 receptor antibody would be given in the peri-operative period (e.g. during operation, post-transplant day 4, 8, 12 and so on), allowing the delay of low-dose tacrolimus. Prompt renal replacement should be given under the guidance of nephrologists for patients with post-transplant acute kidney failure. Conversion to sirolimus would be performed in liver transplant patients with chronic renal insufficiency months after liver transplantation.

In this study population, an IL-2 receptor blocker was used in patients with pre-transplant renal insufficiency and prednisolone was withdrawn within the first post-transplant month.

- The definition of hyperlipidemia should be based on the measurement of triglycerides / cholesterol at a given time point (?six months?).

Yes, you are quite right. The definition of hyperlipidemia is based on the measurement of triglycerides / cholesterol at the sixth month after liver transplantation.

- The finding of different incidences of cardiovascular events in both groups is very interesting.

Cardiovascular events should be listed (including the moment of their occurrence).

Yes, the detailed information has been added in the revised-manuscript.

Cardiovascular events were defined as nonfatal myocardial infarction, arrhythmia, cardiac arrest, stroke and any causes resulting in heart failure.

Nine recipients (7.8%) developed cardiovascular events, including four nonfatal myocardial infarction, two cardial arrhythemia, one cardiac arrest and two stroke, with a mean onset time of 10.5 months (median: 8 months, range: 3-15 months). The incidence of cardiovascular events in PTHL group (n = 5, 17.9%) was significantly higher than that in non-PTHL group (n = 4, 4.6%).

- Minor comment: in table 1, the second line should be Male/female (%).

Yes. We presented these variables as numbers and percentages.

- Some other factors should be studied as potentially related with the development of hyperlipidemia: post-transplant diabetes mellitus, post-transplant BMI,…

Yes, we have analyzed these factors in the revised manuscript.

Reference

1. Bellomo R, Ronco C, Kellum JA, et al: Acute Dialysis Quality Initiative Workgroup: Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs. The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:204, 2004
2. Kamath PS, Wiesner RH, Malinchoc M, et al: A model to predict survival in patients with end-stage liver disease. Hepatology 33:464, 2001
3. Inoue Y, Soyama A, Takatsuki M, et al. Acute kidney injury following living donor liver transplantation. Clin Transplant. 2012 Sep;26(5):E530-5.
4. Leithead JA, Tariciotti L, Gunson B, et al. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. Am J Transplant. 2012 Apr;12(4):965-75.
5. Lebron Gallardo M, Herrera Gutierrez ME, Seller Perez G, et al: Risk factors for renal dysfunction in the postoperative course of liver transplant. Liver Transpl 10:1379, 2004
6. Cabezuelo JB, Ramirez P, Rios A, et al: Risk factors of acute renal failure after liver transplantation. Kidney Int 69:1073, 2006
7. Gainza FJ, Valdivieso A, Quintanilla N, et al: Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. Transplant Proc 34:250, 2002
8. Chuang FR, Lin CC, Wang PH, et al: Acute renal failure after cadaveric related liver transplantation. Transplant Proc 36:2328, 2004
9. Ling Q, Xu X, Li JJ, et al. Alternative definition of acute kidney injury following liver transplantation: based on serum creatinine and cystatin C levels. Transplant Proc. Dec;39(10):3257-60, 2007
10. Ling Q, Xu X, Wei Q, et al. Downgrading MELD improves the outcomes after liver transplantation in patients with acute-on-chronic hepatitis B liver failure. PLoS One ;7(1):e30322, 2012,