

1. In this study, the authors found that HCV infection was an independent factor contributing to the increase in serum CETP, the increase in CETP resulted in abnormal retention of TG in HDL. These findings suggest that CETP is one of the factors that contribute to abnormal lipoprotein metabolism in patients with active HCV infection. This study has scientific basis and is interesting. I have the following comments in detail: 1) Title: Cholesteryl ester transfer protein increase in chronic hepatitis C virus infection, this title does not suit for your study, you could not say CETP increase HCV infection. 2) How did you select the patients? Randomly or sequentially? 3) Have you performed multicollinearity analysis before multiple regression analysis? What were the correlation patterns among serum lipids? 4) Any impact of HCV genotypes on your result - the serum CETP levels of patients with active HCV infection were significantly higher than those of patients in whom HCV eradication was achieved (mean \pm standard deviation [SD], 2.84 ± 0.69 vs 2.84 ± 1.00 $\mu\text{g/ml}$, $P = 0.008$). You know, in active group, the 1b genotype is 87%, while in eradication group 1b genotype is only 65%.

Thank you for reviewing our paper.

1) According to your suggestion, we have modified the title. The new title is “High level of serum cholesteryl ester transfer protein in active HCV infection.”

2) We apologize for not better describing how we selected the patients. We randomly selected the patients and enrolled them in our study. We have added an explanation regarding this in the manuscript (Materials and Methods/Patient Population).

3) We have already indicated the VIF (Variance Inflation Factor) value. As the value is very low (less than 5) in our regression model, the possibility of multicollinearity in our model is negligible. We believe this to be accurate as VIF is a most popular and reliable indicator for judging the existence of multicollinearity.

4) As you have indicated, the proportion of HCV-G1b patients was different between the eradication group and active HCV group. However, differences in the HCV genotype did not have an effect on serum CETP level. Therefore, the difference of HCV genotype was not selected as a factor potentially contributing to the serum CETP level. To help clarify this, we have now explained this in the Results (HCV infection status (active infection or eradication) as an independent determinant that significantly contributed to the serum CETP level).

2. This manuscript provides a study on the CETP levels in patients of active HCV infection and recoveries. This is an interesting article. But there are some major issues

as below:

1. How did the authors select samples? How to avoid sample bias?

Thank you for your comments.

We apologize for not better describing how we selected the patients. We randomly selected the patients and enrolled them in our study. We have added an explanation regarding this in the manuscript (Materials and Methods/Patient Population).

We think that sample bias is not the major problem of our study, because we performed multiple regression analysis. By multiple regression analysis, we adjusted the differences in the background between the active HCV group and the eradicated group. Therefore, any potential difference between the two groups that may have potentially affected the serum CETP level has been corrected for in the analysis.

2. How many patients with liver function abnormal (ALT, AST, gamma-GT, etc) in these two groups, especially in active HCV infection group?

Thank you for your comments. We indicated below the number of patients with abnormal liver function. However, this data was not added to the manuscript as it was not central to the findings.

The number of patients with abnormal liver function:

	Eradication	Active HCV
AST(>33)	3	36
ALT (>36)	3	29
γ GTP(>28)	15	30

Do the authors analyze the association between the CETP and liver function, HbA1c? Because the R² values were very low in the selected six factors, in which it means not a strong relationship even though P<0.05. And how is the relationship between HCV infection status and liver function?

As you mentioned, the R² value of our regression model was 0.221. This means only 22.1% of the serum CETP level can be explained in this model. However, there is a considerable number of known and unknown factors, including genetic and epigenetic factors, that may affected the CETP level. Therefore, we believe that our regression model fairly well explains the serum CETP concentration. It is possible that CETP level could be negatively associated with a diabetic state or HbA1c levels. However, we did not find any significant correlation between CETP and HbA1c or FBG or other

parameters in our patients. Therefore, we did not select these factors as candidates. To help clarify this, we have more clearly described the reason why HbA1c and FBG were not selected as candidates in the Results (HCV infection status (active infection or eradication) as an independent determinant that significantly contributed to the serum CETP level).

Because the status of HCV infection is elucidated as an independent factor in our multiple regression analysis, the effect of active HCV infection on the serum CETP level is independent of other factors that may be associated with liver function such as albumin levels.

3. How is the impact of HCV genotype? Because most of genotype are 1b in these sample size.

Thank you for your comments. As you mentioned, the ratio of the HCV G1b patients was different between the eradication group and active HCV group. In addition, HCV genotype may possibly influence the lipid metabolism. However, as indicated in the manuscript, there were no differences in serum CETP level between HCV G1b and G2 patients in either the active HCV or eradication groups. Therefore, difference of HCV genotype was not selected as a factor associated with the serum CETP level.

4. Each table should be made a note.

Thank you for your comments. We added a note for each table as you have indicated.

5. There is a wrong typing in abstract. “ 2.84 ± 0.69 vs 2.84 ± 1.00 $\mu\text{g/ml}$, $P = 0.008$ ” should be “ 2.84 ± 0.69 vs 2.40 ± 1.00 $\mu\text{g/ml}$, $P = 0.008$ ”?

Thank you for your comments. We sincerely apologize for the incorrect data in the abstract. We have corrected the precise data in the text.

3. An interesting aspect of HCV infection is that it correlates with aberrant lipid and lipoprotein metabolism. The current manuscript by Satoh and colleagues shows that active HCV infection correlates with increased levels of cholesteryl ester transfer protein (CETP). While the manuscript shares this interesting finding, some of the conclusions are unfounded and there are some errors in the manuscript that should be corrected prior to publishing:

1) The first line of the results section of the abstract makes an error in the primary finding of the paper, that CETP levels are 2.84 compared to 2.40. That this error passed

the attention of the authors warrants a request that the authors go through the manuscript in its entirety to double-check every number.

Thank you for your comments. We sincerely apologize for the incorrect data in the abstract. We have corrected the precise data in the text.

2) The authors state that their "results indicate that active HCV infection may promote CETP activity". To my mind, the reverse is more likely; that lower CETP activity contributed to effective viral clearance. This could be mediated by diminished lipoviral particles (see Bridge SH, et al. Gut 2011 and Felmlee DJ et al. 2010). If CETP activity contributes to vascular lipoviral particle formation, this may be a mechanism for sustaining infection. This should be thoroughly discussed as an alternate possibility.

Thank you for your comments. We have added additional text to the discussion section regarding the possibility that CETP activity may contribute to vascular lipoviral particle formation and thus for sustaining infection. In addition, we have added references to support this.

3) The scale on Fig.2 y-axis should be standardized for both Eradication and Active HCV group. The figure legends could use more detail and correct punctuation.

Thank you for your comments. As you have suggested, we have corrected the scale on the Fig. 2 y-axis so that it is standardized for both the eradication and active HCV groups. Moreover, we have added additional notes to each table and figure.

I'm unsure what the primary finding is of Fig. 2 regarding VLDL and chylomicron vs. CETP. There is a negative correlation between TRL TG and CETP levels, which is more robust in the Eradication group. Since CETP exchanges a cholesteryl-ester molecule for a TAG molecule, it would be very useful to supplement this figure with cholesterol levels of the different fractions.

Thank you for your comments. To help clarify this, we added the association between CETP level and each lipoprotein cholesterol component as Figure 2A.

4) The numbers don't exactly agree between the results section and the tables. The CETP levels of HCV eradicated are 2.40 in the results and 2.39 in Table 1.

Thank you for your comments. We sincerely apologize for the incorrect data in the text. We have corrected the precise data.