Author's response to reviews

Title: Lipoprotein lipase in hemodialysis patients. Depletion of tissue stores by a low molecular weight heparin, despite low plasma levels of the enzyme

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Dear Editor

Many thanks to the reviewers for their constructive comments. We have adopted most of the changes they suggested and feel that this has improved our paper considerably. A detailed list of our responses is included. In addition we have made some minor changes of the language but nothing that affects the substance of the manuscript.

We hope that our revised manuscript can now be accepted for publication in BMC Nephrology.

Point by point list of our responses to the reviewer's comments.

Reviewer Marc T Hamilton

1. It was not possible for us to take tissue biopsies from these patients, particularly not while they were heparinized.
   In response to the reviewer's request for an indication of the effect of dalteparin and heparin on LPL efflux/turnover in some animal model we have added the following text to the introduction: "Direct studies of the lipase-heparin interaction have shown that a heparin decasaccharide is enough to fill the heparin-binding groove on the lipase molecule. Decasaccharides fall in the middle or lower size range in preparations of LMW heparins. Several lines of evidence indicate that also in biological systems, decasaccharides are sufficiently long to exert full effect on LPL. Chevreuil et al found that on a weight basis, decasaccharides released more LPL from perfused rat hearts than conventional heparin did. Several groups have reported that LMW heparins or decasaccharides release LPL from tissues in vitro or from cultured cells as efficiently as or even more efficiently than conventional heparin does. It is therefore unlikely that the lower plasma LPL activities after LMW heparin are due to less release of the lipase. More likely, LMW retards clearance of the lipase by the liver less efficiently than conventional heparin does. Two studies have directly demonstrated such a difference in liver perfusion experiments."

2. To soften the title we have deleted the word 'Extensive'.

3. The p value has been added.

4. Yes, information on the effect of LMWH or conventional heparin on LPL clearance has been added to the introduction. See above, 1.

5. 'Prior in vitro studies' has been added as suggested to the conclusions at the end of the manuscript. In the conclusion section of the abstract we have deleted the information from earlier studies. This really did not belong here.

6. Bolded word Ref has been deleted.

7. We have added: "A single injection of a LMW heparin can often replace a primed infusion of conventional heparin."

8. The dose of LMW heparin was that used in clinical practice. This goes back to the manufacturer's recommendations. In the Methods section we say: "A loading dose of 40 IU dalteparin per kg body weight was given, followed by a continuous infusion of 1000 IU/hour, in accordance with the manufacturer's recommendations." In the Discussion we have added to the second paragraph: "The comparisons to our earlier study with conventional heparin are based on clinically relevant doses during HD, as recommended from manufacturer's and clinical guidelines, not on a molecule-for-molecule basis."

9. A new figure 4 is provided showing the change in TG over time including data from all our four studies. The statistical calculations have been inserted into the results.

10. See 9.

11. We have added to the Result section: "The median LDL-cholesterol, calculated by the Friedwald formula, was 2.9 mmol/L (range 2.1-4.9) before the dialysis and increased to 3.75 (2.1-5.6) at 240 min. This corresponds to an increase of 29% (p < 0.05)."
12. A strong aspect of our study is that we addressed the possibility of assay variations as a confounding factor by re-assaying frozen samples from all our four studies at the same time and also analyze LPL mass. The results of these repeated analyses were described in the results section and in Fig 2. They were the basis for the insets in Fig 1 and 3 where results from all four studies were plotted to allow direct comparison. There was no mention of this in the abstract or in the conclusions but we have now added this information

Reviewer Hans Dieplinger.
There were no significant differences in patient characteristics or basal values between the two study occasions. We have added this information to the Table text.
We have included a reference to the study by Kronenberg.