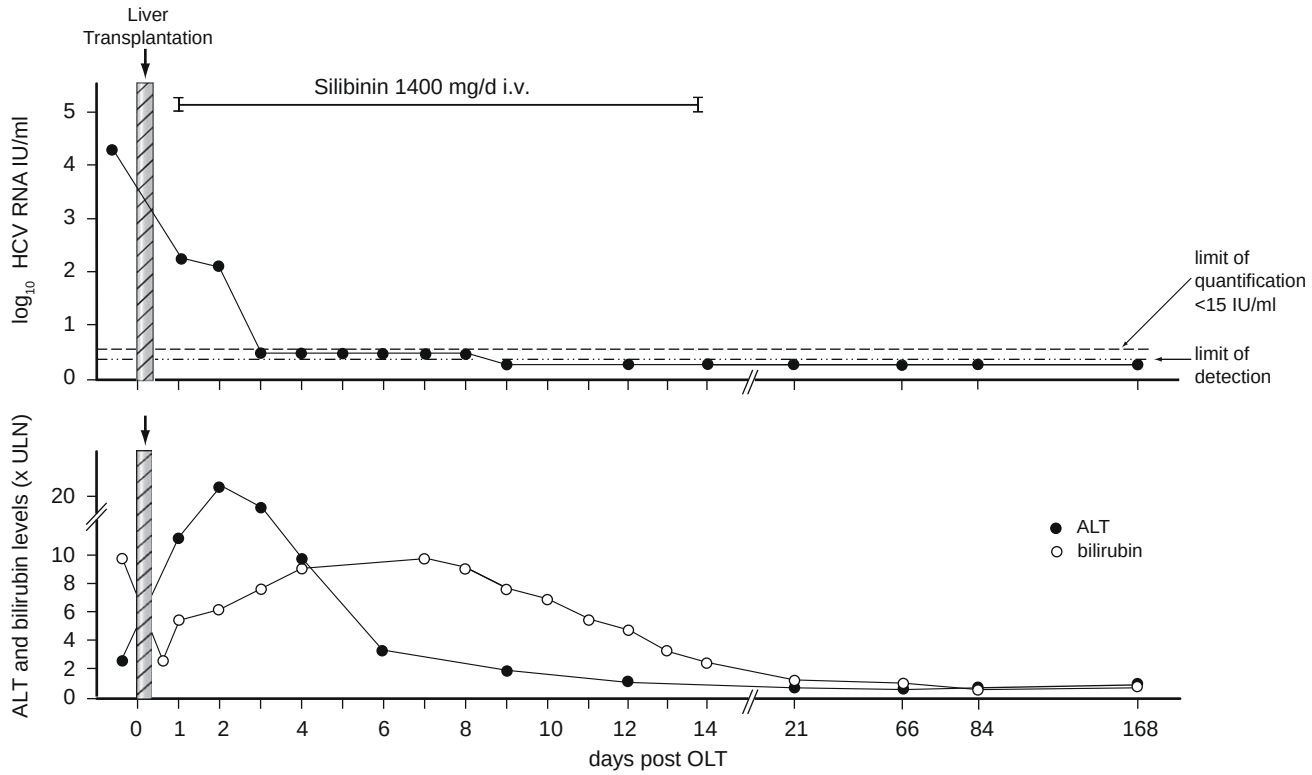

Fig. 1. Effect of intravenous silibinin administration on the course of hepatitis C viremia (upper panel) and aminotransferase (ALT) and bilirubin levels (lower panel) after liver transplantation. HCV RNA levels were measured by real-time PCR assay (Cobas AmpliPrep Taqman®, Roche Diagnostics, Germany); ALT and bilirubin levels are depicted as relative values of the upper limit of normal (ULN).

Combination of acarbose and ezetimibe prevents non-alcoholic fatty liver disease: A break of intestinal insulin resistance?

To the Editor:

We read with great interest the study by Nozaki and colleagues [1] that evaluated the effect of combination therapy of ezetimibe, an intestinal cholesterol adsorption inhibitor, and acarbose, an alpha glucosidase inhibitor, on the prevention of the high-fat diet induced, non-alcoholic fatty liver disease (NAFLD) in mice. In their study, the authors concluded that the combination of both drugs for 24 weeks significantly reduced steatosis, inflammation, and fibrosis in the liver of animals, compared to long-term monotherapy with either drug. Insulin resistance and liver steatosis are interlinked metabolic abnormalities, whose prevalence is rapidly increasing worldwide [2]. We absolutely agree that the effective pharmacological therapy for prevention or treatment of NAFLD does not exist today, and we thus acknowledge that the recent study by Nozaki and colleagues has paved the way towards a new therapeutic approach for the prevention and treatment of NAFLD. However, we have some concerns regarding this study and its conclusions, which are outlined as follows:

The authors use the high-fat diet which contains more than 57% of calories from fat and only 22.8% of carbohydrates to induce the NAFLD in animals. Despite the importance of impairment in the lipid metabolism and quantity of the dietary fat intake for the development of NAFLD [2], the high carbohydrate intake is also involved in the pathogens of NAFLD: first, the "soft drinks" without fat content were associated with hepatic steatosis independent of insulin resistance in humans [3]; second, dietary habits with high glycemic index were associated with liver steatosis [4]. Thus, the additional model using the high glycemic load were of interest for such experimental design. Another point is the action of the acarbose in the studied dietary conditions: the strong reduction of carbohydrate intake led to the diminished action of acarbose and promising effects for ezetimibe. Interestingly and surprisingly, the reduction of fasting glycemia and insulinemia under ezetimibe treatment was as pronounced as the effects of the antidiabetic drug acarbose. Based on the principal postprandial actions of both drugs, the data from oral stimulation tests, such as oral glucose loading or meal test, could be of great interest regarding the mechanisms of NAFLD prevention.

The major and very intriguing observation is the effect of the combination of acarbose and ezetimibe during the progression of NAFLD in the high-fat diet. The authors concluded two hypotheses in order to explain the observed effects: (i) the additive or multiplicative effects of both drugs on cholesterol reduction accompanying the inhibition of gut glucose absorption lead to the improvement of systemic insulin sensitivity and/or (ii) the promotion of lipid discharge from the liver and the β-oxidation of lipids in the liver.

Regarding the first hypothesis, after a 12-week high-dose acarbose treatment (300 mg/d), our data in humans showed no effects on whole body insulin sensitivity, measured in the euglycemic clamp, and no changes in body weight [5]. Moreover, we observed

a strong and significant decrease in the postprandial glucose and insulin concentration as an index for the improvement in the intestinal and hepatic insulin sensitivity. In the sub-group analysis of subjects with an elevated hepatic fat content, we observed 26% of the decrement under acarbose treatment [Rudovich et al., unpublished data], (Fig. 1). However, no definitive conclusion can be drawn from this first human data due to small observation sizes.

No data exists on the effects of ezetimibe on insulin sensitivity in humans. Thus, the reduction in the body weight is primarily responsible for the observed improvement of insulin sensitivity under combination therapy in the study from Nozaki et al. [1].

The strongest effect of the combination therapy on the markers of the lipid metabolism in the liver was the upregulation of the SREBP-2 gene. The authors consider this effect as a secondary and compensative reaction of diminished hepatic cholesterol synthesis. The upregulation of SREBP-2 under ezetimibe application is not only a hepatic effect and was observed on the different types of enteroendocrine cells of the gut [7]. Moreover, the secretion of some gastro-intestinal hormones such as cholecystokinine and glucagons-like peptide-1 are modulated by SREBP-2 via regulation of the sweet taste receptor expression [7]. Thus, the upregulation of SREBP-2 under combination therapy of ezetimibe and acarbose can lead to remarkable changes in the acute postprandial and chronic secretion of different gastro-intestinal hormones. Based on the new mechanisms for the regulation of the rate of production of triglyceride-rich lipoproteins in the gut and the strong involvement of the gastro-intestinal hormones in this process [8], the intestinal effects on the drug combination studied are decisive for the observed prevention of NAFLD. Moreover, the modulation of gastro-intestinal hormone responses may explain a dramatic weight reduction observed under combination of acarbose and ezetimibe in this study.

In conclusion, the combination of ezetimibe and acarbose is a very promising pharmacological strategy to prevent, and possibly to treat, the NAFLD. The dysregulation of intestinal lipid and carbohydrate metabolism, i.e. "intestinal insulin resistance" [8], seems to be an important mechanism in the pathogenesis of NAFLD.

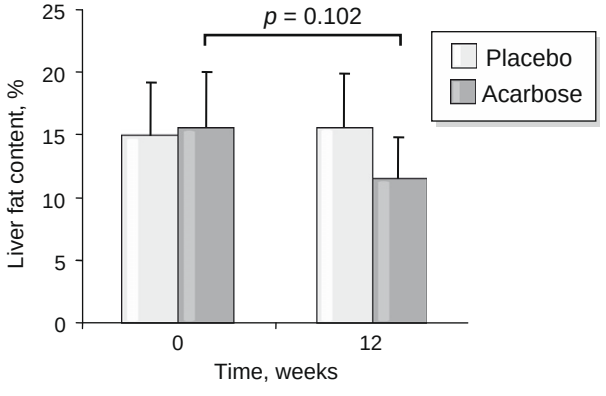

Fig. 1. Effect of 12 weeks double-blind parallel group acarbose ($n = 12$) and placebo treatment ($n = 12$) on hepatic fat content measured by magnetic resonance spectroscopy. Data are presented as the means ± SEM. p in the two-side paired T-test (baseline vs. end of the treatment (12 weeks)). Single voxel MRS was performed on a 1.5 T whole body imager (Magnetom Vision, Siemens Healthcare, Erlangen, Germany) in the morning after overnight fasting twice during the study. All subjects have an elevated hepatic fat content (defined as hepatic fat content $\geqslant$6% [6]). Acarbose 50 mg was taken orally two times daily (100 mg/d) in the first titration week, 50 mg three times daily (150 mg/d) in the second titration week and 100 mg three times daily (300 mg/d) with each meal in the following treatment period (weeks 3–12).

Conflicts of interest

The Authors have declared that they received funding from the drug companies involved in order to carry out their research in this manuscript.

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References

[1] Nozaki Y, Fujita K, Yoneda M, Wada K, Shinohara Y, Takahashi H, et al. Long-term combination therapy of ezetimibe and acarbose for non-alcoholic fatty liver disease. J Hepatol 2009;51:548–556.
[2] Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of non-alcoholic fatty liver disease. World J Gastroenterol 2007;14; 13:3540–3553.
[3] Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. J Hepatol 2009;51:918–924.
[4] Valtuena S, Pellegrini N, Ardigo D, Del Rio D, Numeroso F, Scazzina F, et al. Dietary glycemic index and liver steatosis. Am J Clin Nutr 2006;84:136–142.
[5] Rudovich N, Ernst A, Pivovarova O, Traberth A, Bergmann A, Pfeiffer AFH. Acarbose increases atrial natriuretic peptide levels in subjects with metabolic syndrome: a novel mechanism of cardiovascular protection. J Diab. 2009;1:A42.
[6] Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288:E462–E468.
[7] Jeon TI, Zhu B, Larson JL, Osborne TF. SREBP-2 regulates gut peptide secretion through intestinal bitter taste receptor signaling in mice. J Clin Invest 2008;118:3693–3700.
[8] Hsieh J, Hayashi AA, Webb J, Adeli K. Postprandial dyslipidemia in insulin resistance: mechanisms and role of intestinal insulin sensitivity. Atheroscler Suppl 2008;9:7–13.

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