overload (DIOS) were enrolled in their study, rather than individuals with nonalcoholic steatohepatitis (NASH). The patients with DIOS were selected on the basis of serum ferritin levels >400 μg/L, hepatic iron concentration assessed by magnetic resonance imaging >50 μmol/g, and body mass index >27 kg/m². Accordingly, advanced iron overload is required for a diagnosis of DIOS. In contrast, in our study, only four of the patients with NASH meet these criteria. The remainder of the patients with NASH in our study do not meet their criteria of DIOS. In general, mild or moderate degrees of hepatic iron accumulation are common in patients with NASH. Because we did not observe increased duodenal absorption in our four patients with NASH and DIOS, we agree that iron absorption was lower in patients with DIOS than in lean and overweight controls without iron overload. Overall, we suggest that patients with DIOS exhibit a different pattern of iron absorption from those with NASH.

Koji Miyanishi, M.D., Ph.D.
Masayoshi Kobune, M.D., Ph.D.

Bile Acids and Nonalcoholic Fatty Liver Disease: An Intriguing Relationship

TO THE EDITOR:

Nonalcoholic fatty liver disease stands nowadays as a leading cause of progressive impairment of liver function.

We read with great interest the paper by Nagahashi et al.(1) recently published in Hepatology which highlights the role of conjugated bile acids, sphingosine-1 phosphate receptor 2, and sphingosine kinase 2 in regulating hepatic lipid metabolism and liver lipid content. Such results are exciting and stimulating.

The role of bile acids in the modulation of hepatic lipid metabolism is interesting and controversial; previous evidence by Watanabe et al.(2) showed an inhibitory effect of bile acids on lipogenesis, which was attributed to activation of the farnesoid X receptor (FXR)–small heterodimer partner (SHP) axis and consequent depression of the liver X receptor (LXR)–sterol regulatory element binding protein (SREBP) 1c lipogenic pathway. Evidence from our research group has shown that both exogenous administration of bile acids and endogenous exposure to bile acid overload (as in cholestasis) may reduce hepatic fat accumulation in rat models, although by different mechanisms:(3) (1) by activating the FXR–SHP axis and (2) by inducing cytochrome P450 7A1, which leads to reduced oxysterol hepatic bioavailability and in turn down-regulation of the LXR–SREBP 1c lipogenic pathway.

The findings in the paper by Nagahashi et al.(1) are quite surprising, showing the development of fatty liver disease in SphK2−/− mice in association with decreased expression of SREBP 1c and lipogenic enzymes like FAS. As the authors comment, hepatic fat accumulation might be induced by mechanisms different from increased lipogenesis, such as the reduction of lipid and lipoprotein output from the liver, according to previous evidence in humans.(4) Data from our group are consistent with this hypothesis. Indeed, we detected a beneficial effect of cholic acid feeding in the choline–deficient dietary model (in which hepatic lipid export is reduced) but not in the high-fat model.(2) In other words, the metabolic effects of bile acids on hepatic lipid metabolism seem to be strictly dependent on the experimental model utilized to induce fat liver accumulation as well as on the modality of bile acid exposure (exogenous versus endogenous) and the relative activation of the LXR and FXR pathways.

REFERENCES


Copyright © 2015 by the American Association for the Study of Liver Diseases.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.28290

Potential conflict of interest: Nothing to report.
Experimental evidence like that brought by Nagahashi et al.\(^1\) may bring an enormous contribution to this field, in the perspective of novel pharmacological targets for the treatment of nonalcoholic fatty liver disease.

Lucia Carulli, M.D., Ph.D.\(^1,2\)
Chiara Gabbi, M.D., Ph.D.\(^1,3\)
Marco Bertolotti, M.D.\(^1,2\)
\(^1\)Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze
Università degli Studi di Modena e Reggio Emilia
Modena, Italy
\(^2\)Dipartimento Integrato di Medicina, Endocrinologia, Metabolismo e Geriatria
Azienda USL di Modena
Modena, Italy
\(^3\)Department of Biosciences and Nutrition
Karolinska Institutet,
Novum, Sweden

REFERENCES


Copyright © 2015 by the American Association for the Study of Liver Diseases.
View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.27963
Potential conflict of interest: Nothing to report.

REPLY:

We thank Carulli et al. for their great interest in our recent study and insightful comments on bile acid–mediated regulation of lipid metabolism.\(^1\) Our study clearly shows that sphingosine-1 phosphate receptor 2 (S1PR2), which is activated by conjugated bile acids, regulates nuclear sphingosine kinase 2, allowing for the up-regulation of genes involved in lipid and sterol metabolism by an epigenetic mechanism.\(^1\) Conjugated bile acid–mediated activation of S1PR2 may

---

**FIG. 1.** Role of sphingosine 1-phosphate receptor 2 in the regulation of hepatic metabolism. Abbreviations: CBA, conjugated bile acid; ERK, extracellular signal–regulated kinase; FXR, farnesoid X receptor; PDK, pyruvate dehydrogenase kinase; PKC, protein kinase C; SHP, small heterodimer partner; SphK2, sphingosine kinase 2; S1PR2, sphingosine-1 phosphate receptor 2; VLDL, very low-density lipoprotein.