Ghrelin: a new treatment for non-alcoholic fatty liver disease?

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Li et al. [1] report in this issue of the journal that administration of ghrelin might improve inflammation, oxidative stress, and apoptosis during and after non-alcoholic fatty liver disease development (NAFLD).

Non-alcoholic fatty liver disease development is becoming an increasingly important disease condition [2], as NAFLD and non-alcoholic steatohepatitis (NASH) are the most common chronic liver disease in the western world, which is associated with end-stage liver disease and hepatocellular carcinoma. Moreover, an increasing number of liver transplantations is performed due to NASH and transplantation in this cohort seems to be associated with high mortality and postoperative complications, most likely due to associated obesity and diabetes [3].

In a recent review by Takamura et al. [4], they nicely addressed the remarkable changes in the liver in NAFLD by addressing NAFLD both as a consequence and as a cause of insulin resistance through lessons learned from the liver of patients with type 2 diabetes. The development of NAFLD is linked to food intake, as diet seems to be an important contributor to the pathogenesis of NAFLD [5]. In a recent review by de Wit et al. [5], they specifically mentioned that saturated fat and fructose seem to stimulate hepatic lipid accumulation and progression into NASH, whereas unsaturated fat, choline, antioxidants, and high-protein diets rich in isoflavones seem to have a more preventive effect. Therefore, it is not surprising that gut hormones that are known to control the uptake of nutrients by organs are now increasingly investigated in the light of NAFLD.

Interestingly, the report by Yan Li in this journal adds up to the rapidly increasing number of publications on the effects of ghrelin (and its analogs) on a multitude of physiological and pathophysiological conditions. Both ghrelin and des-acyl ghrelin (DAG) appear to have many functions and effects that are much wider than the direct control over food intake [6].

In a recent publication by Estep et al. [7], they report on the relation of the three ghrelin gene products (ghrelin, DAG, and obestatin) and their involvement in those metabolic and inflammatory pathways that are linked with the development of NAFLD. They studied 75 morbidly obese patients with biopsy-proven NAFLD (41 with histologic NASH) and found that patients with NASH had twofold higher concentration of DAG than patients with non-NASH. Ghrelin and obestatin concentrations positively correlated with fibrosis stage. Apparently, products of the ghrelin gene may be important for the pathogenesis of NASH and fibrosis [7].

In another report on this topic by Okamatsu et al. [8], again the relation between appetite regulating hormones and NAFLD was studied, but in this case in 49 prepubertal overweight children and 49 age-matched controls of normal weight. The incidence of presumed NAFLD was 28.6 % in overweight children, and in these subjects, serum leptin levels were associated with aspartate aminotransferase/alanine aminotransferase ratios and serum insulin levels. Interestingly, also plasma ghrelin levels significantly correlated with liver function index [8].

In line with the observations by Okamatsu, Gutierrez-Grobo et al. reported that serum ghrelin and obestatin concentrations are correlated with a low risk of developing NAFLD. However, ghrelin/obestatin ratio was not correlated with NAFLD [9] in their cross-sectional study in 98 subjects (51 NAFLD patients and 47 controls), in which

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ghrelin and obestatin were evaluated in multivariate logistic regression analyses. Noteworthy is that the authors used an assay without using protease inhibitors that are essential to protect acylated ghrelin from being de-acylated, which questions what peptides are really involved in their observed correlations [10].

Ghrelin exerts its actions via the ghrelin receptor GHSR-1a while DAG seems to use its own, yet unidentified receptor. Still, DAG can change gene expression in liver tissue, as DAG rapidly modulates lipogenic and insulin signaling pathway gene expression in metabolically active tissues of GHSR deleted mice [11].

Anyway, Yan Li's report nicely links the effects of gut hormones to the status of the first large organ that they meet down stream, being the liver. Apparently, they can modify the way the liver stores nutrients that it takes up from the portal circulation, which for sure makes them likely candidates to be developed into future treatment modalities for the increasing medical problem of NASH and NAFLD.

References

1. J.H. Yan Li, L. Lake, C. Xuehui, P.Hua, C. Meng, Z. Qinggui, Administration of ghrelin improves inflammation, oxidative stress, and apoptosis during and after non-alcoholic fatty liver disease development. *Endocrine*. (2012). doi:[10.1007/s12020-012-9761-5](https://doi.org/10.1007/s12020-012-9761-5)
2. S.E. Mahady, J. George, Management of nonalcoholic steatohepatitis: an evidence-based approach. *Clin. Liver Dis.* **16**, 631–645 (2012)
3. M. Heuer, G.M. Kaiser, A. Kahraman, M. Banysch, F.H. Saner, Z. Mathe, G. Gerken, A. Paul, A. Canbay, J.W. Treckmann, Liver transplantation in nonalcoholic steatohepatitis is associated with high mortality and post-transplant complications: a single-center experience. *Digestion* **86**, 107–113 (2012)
4. T. Takamura, H. Misu, T. Ota, S. Kaneko, Fatty liver as a consequence and cause of insulin resistance: lessons from type 2 diabetic liver [Review]. *Endocr. J.* (2012)
5. N.J. de Wit, L.A. Afman, M. Mensink M. Muller, Phenotyping the effect of diet on non-alcoholic fatty liver disease. *J. Hepatol.* (2012)
6. P.J. Delhanty, S.J. Neggers, A.J. Van der Lely, Ghrelin: the differences between acyl- and des-acyl ghrelin. *Eur. J. Endocrinol.* (2012)
7. M. Estep, M. Abawi, M. Jarrar, L. Wang, M. Stepanova, H. Elariny, A. Moazzez, Z. Goodman, V. Chandhoke, A. Baranova, Z.M. Younossi, Association of obestatin, ghrelin, and inflammatory cytokines in obese patients with non-alcoholic fatty liver disease. *Obes. Surg.* **21**, 1750–1757 (2011)
8. Y. Okamatsu, K. Matsuda, I. Hiramoto, H. Tani, K. Kimura, Y. Yada, T. Kakuma, S. Higuchi, M. Kojima, T. Matsuishi, Ghrelin and leptin modulate immunity and liver function in overweight children. *Pediatr. Int.* **51**, 9–13 (2009)
9. Y. Gutierrez-Grobe, I. Villalobos-Blasquez, K. Sanchez-Lara, A.R. Villa, G. Ponciano-Rodriguez, M.H. Ramos, N.C. Chavez-Tapia, M. Uribe, N. Mendez-Sanchez, High ghrelin and obestatin levels and low risk of developing fatty liver. *Ann. Hepatol.* **9**, 52–57 (2010)
10. S. Aydin, Is it appropriate to study blood ghrelin and obestatin in non-alcoholic fatty liver disease (NAFLD) without using protease inhibitors? *Ann. Hepatol.* **11**, 145–146 (2012)
11. P.J. Delhanty, Y. Sun, J.A. Visser, A. van Kerkwijk, M. Huisman, W.F. van Ijcken, S. Swagemakers, R.G. Smith, A.P. Themmen, A.J. van der Lely, Unacylated ghrelin rapidly modulates lipogenic and insulin signaling pathway gene expression in metabolically active tissues of GHSR deleted mice. *PLoS ONE* **5**, e11749 (2010)