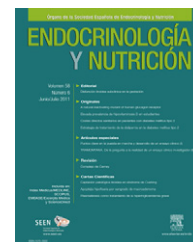




ENDOCRINOLOGÍA Y NUTRICIÓN

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EDITORIAL

Adolescence, obesity, and the role of lipoprotein lipases in the non-alcoholic fatty liver disease[☆]

Adolescencia, obesidad y papel de las lipoprotein lipasas en el hígado graso no alcohólico

Eva Pardina, Julia Peinado-Onsurbe^{*}

Departamento de Bioquímica y Biología Molecular, Facultad de Biología, Universidad de Barcelona, Barcelona, Spain

Non-alcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of diseases ranging from benign steatosis, through non-alcoholic steatohepatitis (NASH), to cirrhosis and hepatocellular cancer in the most severe cases.

While NAFLD has similarities with liver damage caused by excess alcohol consumption, this disease occurs in patients who drink no or small amounts of alcohol. Histologically, NAFLD is characterized by the accumulation in the liver of an amount of fat greater than 5–10% of organ weight, inflammatory foci, Mallory bodies, fibrosis, and even changes typical of cirrhosis.¹

NAFLD is associated with obesity, type 2 diabetes mellitus, hyperlipidemia, hyperuricemia, and polycystic ovary disease, and also with sleep apnea and lipodystrophy.^{1,2} It is also found associated with an increased risk of cardiovascular disease, dyslipidemia, and high blood pressure (although no significant association has been shown).³ In the specific case of obesity, people with NAFLD have greater waist circumference and body mass index (BMI) as compared to people with no NAFLD. However, the distribution of fat, specifically visceral fat, appears to be more significant for the pathogenesis of the disease both because it is

associated with insulin resistance (IR) and because it is a potential source of non-esterified fatty acids (NEFAs), causing fat accumulation in this area to positively correlate with hepatic fat and IR.⁴ The severity of steatosis better correlates with the amount of visceral fat as compared to BMI or total fat, and slightly correlates with subcutaneous adipose tissue.⁵ However, no relationship was found between this fat deposit and NAFLD in some studies.⁶

The prevalence of NAFLD has increased in parallel with the increase in the number of cases of obesity and diabetes, and this condition is becoming the most common cause of liver disease in the Western world.⁷ The prevalence of NAFLD in the overall population ranges from 15% to 30%,^{3,8} while the prevalence of NASH is approximately 3–5%. In the obese population, the prevalence rates of steatosis and NASH are 75–95% and 25–70%, respectively.^{3,4} NAFLD is particularly important in children and adolescents.

In the Santomauro et al.⁹ paper published in this issue, conducted on an obese Venezuelan population aged 7–18 years, a 66.7% prevalence of fatty liver (with various degrees of severity) was found. The condition was shown to be associated with subjects with higher BMI, waist, fat area, basal insulin, and HOMA-IR values as compared to subjects with no fatty liver.

Changes in liver enzymes (AST and ALT, aspartate transaminase and alanine transaminase respectively) have sometimes been used as a tool to diagnose NAFLD. Many studies have reported high AST and ALT levels in patients with morbid obesity with NAFLD and NASH, but have found

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^{*} Corresponding author.

E-mail address: jpeinado@ub.edu (J. Peinado-Onsurbe).

no relationship between NASH and the AST/ALT ratio.³ By contrast, other authors found no transaminase levels outside the normal range in non-obese people with NAFLD.⁸

In the above-discussed Venezuelan study, the author found that neither the presence nor the grade or elevation of transaminases was specific, and that up to 70% of subjects with NAFLD had no enzyme abnormalities.⁹

Several studies have examined the origin of liver lipids and the effect of bariatric surgery in inducing weight loss, but the exact pathophysiology is not yet clear. However, the pathogenesis of fatty liver is clearly multifactorial, and IR has been suggested as an essential requirement for hepatocellular fat accumulation.³

Our group has shown that the presence of lipoprotein lipase (LPL, EC 3.1.1.34), an enzyme that limits the rate at which circulating tissues take up triacylglycerides (TAGs), in the liver of obese patients may be the cause of hepatic steatosis.¹⁰

Free fatty acids resulting from the hydrolysis of TAGs contained in VLDL or CMs are taken up by underlying tissues where these fatty acids are re-esterified, stored, used for obtaining energy, or re-exported as lipoproteins.¹¹ LPL activity occurs in a wide variety of tissues (cardiac and skeletal muscle, white and brown adipose tissue, lung, lactating breast, etc.). LPL is not expressed in adult liver under normal conditions, and when detected, it is assumed to come from peripheral tissues (mainly adipose tissue and muscle). The functional dimer of LPL in peripheral tissue is located in the capillary lumen where, after a short half-life, it monomerizes, becomes inactive, and is transported bound to lipoproteins to the liver, where it is endocytosed and broken down. However, a small fraction of LPL may be transported in dimeric (and thus active) form, be taken up by hepatic receptors, and maintain some short-lasting activity that confers on the liver a minimum capacity to take up circulating TAGs.¹²

Similarly, the normal human liver also has detectable levels of LPL activity, but this should be considered as extra-hepatic in origin, because its mRNA cannot be detected in the liver. In the liver of patients with morbid obesity, however, LPL may have a hepatic origin, because both the activity and mRNA levels of the enzyme in the liver are high.¹⁰

Patients with morbid obesity have high levels of TAGs and NEFAs in both plasma and liver, leading to the characteristic condition of NAFLD.^{13,14} Recent studies have shown that morbid obese subjects not only have an increased adipocyte mass, but also an increased TAG hydrolysis resulting from an increased activity of hormone-sensitive lipase (HSL), which contributes to high plasma NEFA levels.¹⁵

Thus, excess uptake of NEFAs due to their high plasma levels could result in an increase in the hepatic re-esterification rate as compared to the export rate, which would in turn increase TAG accumulation in the liver and lead to hepatic steatosis.¹⁶ On the other hand, the presence of LPL activity in the liver of obese people would allow the liver to hydrolyze TAGs from chylomicrons and VLDL, which would help to remove lipids from plasma. However, this would lead to an even greater increase in hepatic uptake of NEFAs and, thus, to increased steatosis.¹⁰

Our group has also reported higher levels of hepatic lipase (HL, EC 3.1.1.3) activity and mRNA in livers from morbid

obese subjects as compared to people with normal weight. This activity allows for increased amounts of phospholipids (PLs) and total cholesterol (TC) in the liver.¹⁷

After bariatric surgery, however, a dramatic decrease occurs in TAG levels in the liver and plasma, and also in total cholesterol levels. This reduction in TAG content is associated with decreases in other lipids (TC, PLs, etc.), and the amount of lipids by DNA decreases by 62% in the year after bariatric surgery.¹⁷

However, TAG reduction occurs with no concomitant decrease in plasma NEFA levels; in other words, without decreased NEFA absorption by the liver (which depends on the concentration gradient between plasma and cytosol). By contrast, LPL activity levels in the liver show a clear reduction after bariatric surgery, in line with the decrease seen for hepatic TAGs. A good correlation has also been noted between LPL activity levels in the liver and the extent of liver damage both before and after bariatric surgery. All previous observations support the hypothesis that an increase in LPL activity in the liver of obese patients contributes to TAG accumulation in the liver and, thus, to its associated steatosis.¹⁰

The effect of bariatric surgery and weight loss on fatty liver is controversial.^{5,6} However, in children and adolescents, such as those reported by Santomauro et al.⁹, dietary changes and the practice of physical exercise were sufficient to induce the disappearance of fatty liver in 37.5% of cases, although no changes were seen in the remaining 62.5%.⁹ While these results may appear disappointing, it should be noted that total family involvement is required in children and adolescents, not only to change lifestyle, but also to control adherence to physical activity. Diet prescription should be part of a well-organized treatment program to achieve and maintain weight control which may possibly be more successful than simple generic guidance or some recommendations on lifestyle changes made by pediatricians or at a general gastroenterology unit.

References

1. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD single topic conference. *Hepatology*. 2003;37:1202–19.
2. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010;363:1341–50.
3. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol*. 2006;45:600–6.
4. Utzschneider KM, Kahn SE. The role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2006;91:4753–61.
5. Angulo P. NAFLD, obesity, and bariatric surgery. *Gastroenterology*. 2006;130:1848–52.
6. Seppälä-Lindroos A, Vehkavaara S, Häkkinen AM, Goto T, Westerbacka J, Sovijärvi A, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab*. 2002;87:3023–8.
7. Dowma JK, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. *QJM*. 2009;103:71–83.
8. Targher G, Bertolini L, Rodella S, Zoppini G, Lippi G, Day C, et al. Non-alcoholic fatty liver disease is independently

- associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. *Diabetologia*. 2008;51:444–50.
9. Santomauro M, Paoli-Valeri M, Fernández M, Camacho N, Molina Z, Cicchetti R, et al. Hígado graso no alcohólico y su asociación con variable clínicas y bioquímicas en niños y adolescentes obesos: efecto de un año de intervención en el estilo de vida. *Endocrinol Nutr*. 2012, <http://dx.doi.org/10.1016/j.endonu.2012.03.009>.
 10. Pardina E, Baena-Fustegueras JA, Llamas R, Catalán R, Galard R, Lecube A, et al. Lipoprotein lipase expression in livers of morbidly obese patients could be responsible for liver steatosis. *Obes Surg*. 2009;19:608–16.
 11. Enerback S, Gimble JM. Lipoprotein lipase gene expression physiological regulators at the transcriptional and post-transcriptional level. *Biochim Biophys Acta*. 1993;1169:107–25.
 12. Vilaró S, Llobera M, Bengtsson-Olivecrona G, Olivecrona T. Lipoprotein lipase uptake by the liver: localization turnover and metabolic role. *Am J Physiol*. 1988;254:711–22.
 13. Gibbons GF, Islam K, Pease RJ. Mobilisation of triacylglycerol stores. *Biochim Biophys Acta*. 2000;1483:37–57.
 14. Ishii M, Yoshioka Y, Ishida W, Kaneko Y, Fujiwara F, Taneichi H, et al. Liver fat content measured by magnetic resonance spectroscopy at 3.0 tesla independently correlates with plasminogen activator inhibitor-1 and body mass index in type 2 diabetic subjects. *Tohoku J Exp Med*. 2005;206:23–30.
 15. Pardina E, Lecube A, Llamas R, Catalán R, Galard R, Fort JM, et al. Lipoprotein lipase but not hormone-sensitive lipase activities achieve normality after surgically induced weight loss in morbidly obese patients. *Obes Surg*. 2009;19:1150–8.
 16. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114:147–52.
 17. Pardina E, Baena-Fustegueras JA, Catalán R, Galard R, Lecube A, Fort JM, et al. Increased expression and activity of hepatic lipase in the liver of morbidly obese adult patients in relation to lipid content. *Obes Surg*. 2009;19:894–904.