Reversing Advanced Hepatic Fibrosis in NASH: Clearly Possible, but Widely at Hand?

Stephen H. Caldwell · Curtis K. Argo

Received: 8 January 2015 / Accepted: 13 January 2015 / Published online: 25 January 2015
© Springer Science+Business Media New York 2015

Nonalcoholic fatty liver disease (NAFLD) has become one of the most commonly diagnosed liver conditions, detectable in almost a third of adults in developed countries, with substantially higher prevalence figures if the study population is narrowed to adults with type 2 diabetes mellitus and/or obesity [1]. Depending on the population under study, 10–20 % of NAFLD patients have the potentially progressive form of NAFLD known as NASH or nonalcoholic steatohepatitis. It is the latter group that has been the target of numerous ongoing therapeutic studies in an effort to slow disease progression to cirrhosis, liver failure, and hepatocellular cancer.

Therapeutic studies of NASH have been hindered by a number of factors, including a strong placebo effect, in part attributable to voluntary lifestyle changes, and limitations of noninvasive endpoints which rely on surrogate markers of cell injury instead of liver biopsy [2]. In contrast, liver biopsy itself has had inherent limitations as an endpoint. Most problematic has been the assessment of a key histological finding in NASH—cellular ballooning. Although ballooning is likely an important marker related to disease pathogenesis [3], agreement among observers regarding this histological hallmark can be surprisingly infrequent, especially absent special staining techniques [4, 5]. Thus, a diagnosis of NAFLD solely based on isolated histological parameters or even composite scores such as the NAFLD Activity Score (NAS) is questionable. Alternatively, although perhaps still debatable, the

absence of NAFLD or the presence of advanced fibrosis stages is arguably more easily agreed upon histological parameters [6]. Moreover, the fibrosis stage itself carries prognostic significance [7].

In this issue of *Digestive Diseases and Sciences*, Glass et al. [8] present their experience with the effects of weight loss on fibrosis stage in a well-defined cohort of NASH patients followed with serial biopsy over a mean of approximately 5 years. Of 45 patients studied with a mean initial fibrosis stage of 1.96, 12 underwent bariatric surgery with Roux-en-Y gastric bypass with the majority experiencing significant weight loss. The most salient findings are nicely encapsulated in Fig. 1 where regression of fibrosis stage based on blinded biopsy review is most evident with the loss of ≥ 10 % total body weight (TBW), variable with 0–10 % TBW loss, with progressive increases more apparent among those experiencing weight gain. Most striking is regression from stage 4 to stage 3 and from stage 3 to stage 2 or even to stage 1. On the basis of multivariate analysis, fibrosis regression was predicted only by weight loss and not influenced by age, gender, glucose tolerance, ferritin level, or heterozygosity for α -1-antitrypsin type.

Although sampling error is a well-known problem with biopsy interpretation, taken in aggregate these results are convincing and support the emerging concept of the reversibility of even advanced stages of liver fibrosis [9]. Moreover, the results support the often challenging but fundamental tenets of NASH management to advise aggressive lifestyle changes with the encouragement of weight loss through dietary changes and exercise [10]. The broad application of bariatric surgery is more problematic due to concerns for costs, surgical eligibility, and perioperative risk with advanced fibrosis stages where postoperative complications can be substantial [11]. A recent study comparing the effects in NAFLD of Roux-en-Y gastric

S. H. Caldwell (✉) · C. K. Argo (✉)
The Division of GI/Hepatology, University of Virginia Health
System, JPA and Lee St., PO Box 800708, Charlottesville,
VA 22908-0708, USA
e-mail: shc5c@virginia.edu

C. K. Argo
e-mail: cka3d@virginia.edu

Fig. 1 A number of variables which modulate disease progression or regression in NASH will likely influence the response to therapeutic interventions, including pharmacological therapy. A common thread linking these variables is their effect on fat metabolism, insulin sensitivity and resistance, and energy homeostasis

bypass (RYGB) versus the less-aggressive intervention of adjustable gastric banding (AGB) reported that RYGB was associated with greater sustained weight loss and more improvement in histological parameters of NASH [12]. Interestingly, however, fibrosis regression from stage 3 and 4 disease (bridging and cirrhosis) was about the same between the two interventions.

As an initial intervention, increasing physical activity and regular exercise is generally recommended in addition to dietary changes as a means to improve physical conditioning and calorie disposal. The most effective “dose” of exercise is uncertain, but one recent study using noninvasive surrogate markers of hepatocellular injury reported that moderate-to-vigorous exercise for at least 250 min/week was associated with the improvement that was, interestingly, independent of weight loss [13]. This level of exercise provides a target activity level that may, however, be difficult to achieve in NASH populations, as illustrated by the observation that physical deconditioning measured by bicycle ergometry was universally present in a cohort of NASH patients involved in a pharmacological study [14].

To date, no alternative interventions have been as effective in slowing or reversing fibrosis in NASH as weight loss of the magnitude reported in the current paper by Glass et al. Pioglitazone, a member of the thiazolidinedione (TZD) PPAR- γ agonists (peroxisome-proliferator-activated receptor “gamma”), is more effective in resolving histological NASH than is vitamin E or placebo and is associated with reduced fibrosis in meta-analyses [15, 16]. Peripheral weight gain, a potential and significant side effect of TZD therapy, is avoidable with efforts aimed at exercise and dietary changes [17]. Concerns over a risk of bladder cancer have proven to be unfounded [18].

Consideration of this medication is warranted either in selected patients in concert with endocrinological consultation or as part of further clinical trials. Other agents under current clinical study as potentially blunting or possibly reversing fibrosis related to NASH include simtuzumab (anti-LOXL2, [lysyl oxidase-like-2]), which is in advanced clinical trials (clinicaltrials.gov NCT01672866 and NCT01672879), and “GR-MD-02”, a galectin-3 inhibitor, which is another promising agent in early clinical studies (clinicaltrials.gov NCT01899859).

Other potential interventions that are commonly advised include changes in dietary composition to especially avoid beverages sweetened with rapidly absorbed high-fructose corn syrup which are particularly steatogenic in the liver [19]. Most but not all studies of ω -3 polyunsaturated fatty acid (PUFA) supplements including our own treatment trial have reported that these agents reduce liver fat without substantial changes in inflammatory activity or fibrosis [14, 20]. The variability in results, yet to be explained, could depend on whether steatosis is detected by global measures of liver fat content or solely by biopsy, or whether the level of steatosis varies among individuals. When we re-analyzed our data taking into account genetic variables, we found that the underlying genotype of fat metabolic pathways appears to influence the response to omega-3 supplements (manuscript submitted).

Given the variables that may modulate disease progression or regression (Fig. 1), it is likely that there will be individual variation in response to even the best treatment due to behavioral changes resulting from encounters with care providers and, likely, the genetic background of the individual. Factors include modifiable levels of physical activity (none to moderate or vigorous exercise), changes in total calorie intake and dietary composition interacting with lipoprotein metabolism, and key governors of hepatic steatosis such as PNPLA3 and possibly TM6SF2 [21]. Other environmental variables that have emerged as potentially significant include the gut microbiome and even cold exposure, which affect adipose tissue metabolism [22].

The study reported by Glass et al. confirms that advanced hepatic fibrosis in the setting of NASH is indeed reversible with significant loss of $\geq 10\%$ of body weight. Although most patients in the current report who achieved this endpoint had Roux-en-Y gastric bypass, the limitations of this intervention in terms of costs, eligibility, and potential complications mandate alternative approaches to affect a similar outcome. Ongoing work with weight loss agents appears promising, and even re-introduction of newer gastric balloons may offer alternatives [23, 24]. Future studies will likely require a measure of patience and discerning individualization to determine optimal therapy.

References

- Argo CK, Caldwell SH. Epidemiology and natural history of non-alcoholic steatohepatitis. *Clin Liver Dis*. 2009;13:511–531.
- Clark JM, Brancati FL. Negative trials in nonalcoholic steatohepatitis: why they happen and what they teach us. *Hepatology*. 2004;39:602–603.
- Kakisaka K, Cazanave SC, Werneburg NW, et al. A hedgehog survival pathway in ‘undead’ lipotoxic hepatocytes. *J Hepatol*. 2012;57:844–851.
- Gawrieh S, Knoedler DM, Saeian K, Wallace JR, Komorowski RA. Effects of interventions on intra- and interobserver agreement on interpretation of nonalcoholic fatty liver disease histology. *Ann Diagn Pathol*. 2011;15:19–24.
- Guy CD, Suzuki A, Burchette JL, et al. Costaining for keratins 8/18 plus ubiquitin improves detection of hepatocyte injury in nonalcoholic fatty liver disease; NASH Clinical Research Network (CRN). *Hum Pathol*. 2012;43:790–800.
- Brunt EM, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA, NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology*. 2011;53:810–820.
- Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology*. 2011;53:1874–1882.
- Glass LM, Dickson RC, Anderson JC, et al. Total body weight loss of $\geq 10\%$ is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-014-3380-3
- Serpaggi J, Carnot F, Nalpas B, et al. Direct and indirect evidence for the reversibility of cirrhosis. *Hum Pathol*. 2006;37:1519–1526.
- Zelber-Sagi S, Ratzin V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. *World J Gastroenterol*. 2011;17:3377–3389.
- Dixon JB. Surgical management of obesity in patients with morbid obesity and nonalcoholic fatty liver disease. *Clin Liver Dis*. 2014;18:129–146.
- Caiazzo R, Lassailly G, Leteurtre E. Gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. *Ann Surg*. 2014;260:893–899.
- Oh S, Shida T, Yamagishi K, et al. Moderate to vigorous physical activity volume is an important factor for managing non-alcoholic fatty liver disease: a retrospective study. *Hepatology*. (Epub ahead of print). doi:10.1002/hep.27544.
- Argo CK, Patrie JT, Lackner C, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. *J Hepatol*. (Epub ahead of print). doi:10.1016/j.jhep.2014.08.036.
- Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362:1675–1685.
- Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2012;35:66–75.
- Argo CK, Iezzoni JC, Al-Osaimi AM, Caldwell SH. Thiazolidinediones for the treatment in NASH: sustained benefit after drug discontinuation? *J Clin Gastroenterol*. 2009;43:565–568.
- Levin D, Bell S, Sund R, et al. Pioglitazone and bladder cancer risk: a multipopulation pooled, cumulative exposure analysis. *Diabetologia*. Epub. 12/7/2014.
- Abdelmalek MF, Suzuki A, Guy C, et al. Increased fructose consumption is associated with fibrosis severity in patients with non-alcoholic fatty liver disease. *Hepatology*. 2010;51:1961–1971.
- Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol*. 2012;56:944–951.
- Kozlitina J, Smagris E, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to non-alcoholic fatty liver disease. *Nat Genet*. (Epub ahead of print). doi:10.1038/ng.2901.
- van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. *N Engl J Med*. 2009;360:1500–1508.
- Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUENCE): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95:297–308.
- Lee YM, Low HC, Lim LG, et al. Intra-gastric balloon significantly improves nonalcoholic fatty liver disease activity score in obese patients with nonalcoholic steatohepatitis: a pilot study. *Gastrointest Endosc*. 2012;76:756–760.