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EDITORIAL

Betaine and nonalcoholic steatohepatitis: Back to the future?

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Abstract

Nonalcoholic steatohepatitis (NASH) is an important indication for liver transplantation in many Western countries. Obesity and insulin resistance are the two most common risk factors for NASH, which can lead to recurrent NASH after liver transplantation. There is currently no approved therapy for NASH, and treatment is directed at risk factor modification and lifestyle changes. Betaine has been used for NASH, with mixed results, and may show promise in conjunction with other agents in clinical trials.

Key words: Betaine; Nonalcoholic steatohepatitis; Cirrhosis; Obesity; Insulin resistance

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INTRODUCTION

Nonalcoholic steatohepatitis (NASH), a subtype of nonalcoholic fatty liver disease, can lead to cirrhosis and is an increasingly important cause of liver transplantation in the United States[1]. It is thus subject to intense translational research. Despite a number of clinical trials on the treatment of NASH, there is still no approved therapy, and management is often directed at aggressive reduction of the two most common risk factors: obesity and insulin resistance. These limitations in management have led to renewed interest in the pathophysiology of this epidemic, as a prerequisite to embarking upon further clinical trials. However, most data in this area has been derived from animal models.

Betaine, a naturally occurring dietary compound, originally discovered in sugar beet juice, would appear to be an ideal agent for treating NASH. It is synthesized *in vivo* from the oxidation of choline, and has several effects that may impact the natural history of NASH. These include: (1) its role as a methyl donor for the conversion of homocysteine to methionine; (2) direct substitution for S-adenosylmethionine (SAM) for the direct methylation of phosphatidylethanolamine to phosphatidylcholine; (3) its downstream effects on oxidative stress and transsulfuration reactions; (4) activation of AMP-activated protein kinase; and (5) its properties as a lipotrope and osmolyte[2]. As a naturally acting agent, side effects with betaine would be expected to be minimal; however, in reality, this depends on whether it is administered as betaine anhydrous oral solution or as capsules.

Four clinical trials of betaine for the treatment of NASH have been reported. The first study by Miglio *et al*[3] was of limited value because histopathology was not used to diagnose NASH. Abdelmalek *et al*[4] first reported their experience with betaine in a pilot study of 10 patients treated for one year. Biochemical and histological improvement were noted, although three patients did not complete the study. Mukherjee *et al*[5] reported statistically significant improvement in liver function tests and histopathological

scores in their series of 35 patients treated with betaine for one year; however, this study was limited by the absence of a control arm. Abdelmalek *et al*[6] subsequently reported the results of their second study, which remains the largest and most robustly designed trial evaluating betaine for NASH. The primary aim of this study was to determine if 20 grams per day of anhydrous betaine improved liver function tests after one year of therapy. The secondary aim was to assess its impact on histology. Thirty-five patients completed this randomized placebo-controlled trial (17 betaine *vs* 18 placebo), which included pre- and post-measurement of serum anti-oxidant activity, adipokines, cytokines, homocysteine, S-adenosylhomocysteine (SAH), methionine, and liver biopsies scored according to the Brunt criteria[7]. These variables were analyzed according to the paired *t* test. At the conclusion of the study, betaine had no effect on aminotransferases, and of those patients who did show normalized aminotransferases, the proportion was similar with the placebo group. Betaine also had no effect on adiponectin, cytokine, and SAH levels. The impact of betaine on histology was also disappointing, with no change in fibrosis observed during the study. In addition, fewer patients treated with betaine versus placebo (29% *vs* 61%, $P < 0.01$) improved the steatosis grade by > 1 point. However, more betaine-treated patients compared to placebo (71% *vs* 22%, $P < 0.005$) had no change in steatosis over the study duration.

Such negative findings would appear to shut the door on betaine's therapeutic potential for NASH; however, several limitations in the study, rightfully acknowledged by the investigators, merit review. Probably the most important was the high number of patients who dropped out, which simply meant this randomized controlled study lacked power to detect a difference between the two groups. A large number of patients also had advanced fibrosis (stage 3-4), although descriptive statistics are lacking. As NASH is a chronic condition that normally takes several years to progress into cirrhosis, it is not surprising that no effect was noted after only 1 year of treatment[8]. Furthermore, it remains unclear what optimum dose and preparation of betaine are required for NASH, as the investigators extrapolated data used for homocystinuria. For example, study patients had a significantly higher incidence of gastrointestinal side effects (33% *vs* 9%, $P < 0.05$), which contributed to study withdrawal. It is plausible that a lower dose of anhydrous betaine or betaine capsules, which do not require addition with a solution before administration, might have led to improved compliance and fewer side effects. Serum betaine levels were also not measured and, although the ideal range remains to be determined, documentation would have confirmed compliance rather than accepting a subject's qualitative response in a possible attempt to appease an investigator[9].

A study by Kathirvel *et al*[10] aimed at understanding how betaine reverses hepatic insulin resistance in an animal model of nonalcoholic fatty liver disease may also provide support for re-considering betaine in future trials of NASH. It is more than likely that future trials of NASH will need to be of longer duration to fully assess the impact of treatment, and multiple medications may be required, given the multifactorial processes involved in its pathogenesis. However, betaine, by virtue of its multiple effects and low cost, strongly needs to be reconsidered in larger, prospective studies for NASH as monotherapy will enhance compliance during treatment which is likely to be prolonged in the majority of patients. Risk factor medication remains the mainstay of NASH management, but it is being increasingly recognized that NASH may develop in their absence, re-emphasizing the necessity of well- funded trials of appropriate duration (including cost-effectiveness analyses) for this silent epidemic[11].

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