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PHYTO- AND PELOID PRODUCTS IN A COMPLEX SPA THERAPY OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

Non-alcoholic fatty liver disease has emerged a major challenge because of it prevalence, difficulties in diagnosis, complex pathogenesis, and lack of approved therapies. As the burden of hepatitis C abates over the next decade, non-alcoholic fatty liver disease will become the major form of chronic liver disease in adults and children and could become the leading indication for liver transplantation. This overview briefly summarizes the most recent data on the pathophysiology, diagnosis, and treatment of non-alcoholic fatty liver disease. Ongoing clinical trials are focused on an array of disease mechanisms and reviewed here are how these treatments fit into the current paradigm of substrate overload lipotoxic liver injury. Many of the approaches are directed at downstream events such as inflammation, injury and fibrogenesis. Addressing more proximal processes such as dysfunctional satiety mechanisms and inappropriately parsimonious energy dissipation are potential therapeutic opportunities that if successfully understood and exploited would not only address fatty liver disease but also the other components of the metabolic syndrome such as obesity, diabetes and dyslipidemia.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become increasingly common in parallel with the increasing prevalence of obesity and other components of the metabolic syndrome [1], [2] and it is projected to be the leading indication for liver transplant within a decade [3]. Briefly reviewed here are key studies presented in the past two years that have shed light on the natural history, diagnosis, and pathogenesis of non-alcoholic steatohepatitis (NASH). Data from recent treatment trials are reviewed and placed in the context of our current understanding of the pathogenesis of NASH.

NASH clearly progresses to cirrhosis with further decompensation leading to death or liver transplantation in some individuals. Unfortunately we still do not have a firm handle on how often this occurs based on

longitudinal studies, but the estimates based on cross-sectional data are that 20-30% of adults living in affluent parts of the world consuming a western diet have too much fat in the liver (i.e., NAFLD), 2-5% have the subset of NAFLD in which substantial liver injury is also present (i.e., NASH) and 1-2% of all adults may be at risk for progressing to NASH cirrhosis [4]. The projected annual economic impact of this disease burden has been estimated to be $103 billion in the US and €35 billion in the UK, Germany, France, and Italy combined [5]. An ability to identify which patients are at greatest risk for progressing to cirrhosis is essential for targeting therapeutic interventions. Several studies have demonstrated the importance of any degree of liver fibrosis in the setting of NAFLD in predicting adverse outcomes. The late Paul Angulo and his coauthors collected data on 619 patients who had repeated liver biopsies (median 12.6 years apart) across multiple continents and reassessed their biopsies by one expert pathologist [6]. They demonstrated that fibrosis, hepatocyte ballooning and portal inflammation but not steatosis correlated with reduced survival. Loomba and colleagues also examined outcomes and demonstrated that fibrosis progression does occur in NAFL (NAFLD that is not NASH) but at a slower rate than in NASH [7].

2. Patients and Methods

Whereas NAFLD can be diagnosed by imaging studies such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), the presence of NASH still requires a liver biopsy to identify the presence and location of its features such as inflammation, hepatocyte ballooning, Mallory-Denk bodies, and early fibrosis [13]. Because of the invasive nature and cost of a biopsy, non-invasive means of detecting NASH and various stages of liver fibrosis are sorely needed. A study measuring specific serum metabolites identified by mass spectrometry plus the presence of elevated AST, fasting insulin and the PNPLA3 genotype was found to be good at discerning NASH from NAFL in a northern European cohort [14]. NASH is primarily a disorder of fat metabolism and thus serum lipidomic studies may offer the best opportunity to find specific lipids in the blood that can distinguish NASH from NAFL. Using a purely lipidomic approach, Loomba and colleagues found specific oxidized arachidonic acid species that robustly differentiated NASH from NAFL in a small but extensively characterized cohort in the US [15]. Non-invasively assessing fibrosis is the other major unmet need in NASH diagnostics. A large number of algorithms based on clinical data and imaging to assess fibrosis have been developed, but their major strength tends to be in identifying advanced fibrosis with less utility in earlier stages [16- 19]. A newer technique takes a different approach by looking at collagen turnover using stable isotope labeling of new collagen [20], a technique that may have promise in treatment trials where current histological, serum and instrument based testing lack sensitivity for small changes over short time periods.

3. Results

Lifestyle modification with a focus on healthy eating, weight loss when needed, and regular exercise remain the cornerstone of therapy in adults [28- 31] and children [32]. When recommending healthy food choices, a Mediterranean diet has been shown to be a good alternative to a western diet [13], [33]. Bariatric surgery can be a good option in selected patients and a long term follow up study has been shown to reverse NASH and even substantial fibrosis in some [34], [35]. However, surgery is possible in only a minority of patients and there is clearly a need for pharmacological therapy [36], [37]. Prior clinical trial data suggest that pioglitazone or vitamin E may be beneficial in non-diabetic NASH patients [38] and the benefit of pioglitazone on reversing NASH and improving fibrosis was recently confirmed in diabetic patients [39]. More recent trial results are reviewed below and the substrate overload lipotoxic liver injury (SOLLI) model of NASH pathogenesis provides an organized approach to understanding these multiple potential points of attack (Fig. 2). There are no approved drugs for NASH but recent trial data suggests that different approaches may be beneficial in subgroups of patients with NASH. It probably makes sense that no single therapy will reverse NASH in all patients since different patients likely manifest the phenotype of NASH in

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response to different genetic predispositions and environmental exposures. In addition, a major challenge for taking potential treatments through to approval by government agencies has been identifying meaningful trial endpoints. The field has moved forward due to the combined efforts to address these issues by regulatory agencies, industry, and academics [40].

4. Discussion

The facial nerve canal begins to develop as a narrow groove or sulcus within the cartilage of the otic capsule. Ossification then starts from the apical otic ossification center at 21 gestational weeks and from the canalicular ossification center at 26 gestational weeks near the stapedius muscle. The two centers fuse near the region of the oval window until one year after birth [2], [12]. From an anatomical and radiological standpoint, the facial canal is completely developed by four years of age [13]. However, middle ear inflammations can affect the development of the facial canal in children [12]. Also, facial canal dehiscence may develop due to prior ear surgery, trauma and the pressure effect from tumorous lesions [2]. The incidence of facial canal dehiscence was reported in a relatively wide range from 0.5% [5] to 74% [6] based on histologic and surgical studies. Dehiscence of the facial canal must be at least 1 mm in size to be detected during surgery [12]. However, the incidence of facial canal dehiscence is higher in histological studies, since it can be detected in microdehiscences of less than 1 mm in cadaveric studies [2]. Takashi and Sando found that 40% of all dehiscences were detected on the inferior to inferomedial aspect of the facial canal in the posterior half of the oval window area [6]. Baxter revealed that 85% of all dehiscences occurred through the inferior surface of the tympanic segment toward the oval window niche [14]. In fact, it is not possible to see these dehiscent areas with routine otologic surgery.

5. Conclusions

As we enter an era of increasing genomic, lipidomic and metabolomic information, the future is bright for improving our understanding of the pathogenesis of NASH to the point where we can provide individualized treatment. A challenge in the field now is to correlate the emerging data with treatment responses to attain this goal.

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