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NASH Therapy: omega 3 supplementation, vitamin E, insulin sensitizers and statin drugs

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Non-alcoholic steatohepatitis (NASH) is the more aggressive form of non-alcoholic fatty liver disease (NAFLD). NASH can progress to hepatic fibrosis, cirrhosis, portal hypertension and primary liver cancer. Therapy is evolving with a substantial number of trials of promising new agents now in progress. In this article however, we will examine data for several older forms of therapy which have been fairly extensively studied over the years: Polyunsaturated Fatty Acid (PUFA) supplements, vitamin E, insulin sensitizing agents with a focus on pioglitazone and statin agents. Early interest in PUFA derived from their potential benefit in cardio-metabolic disease and the close association of NAFLD/NASH with Metabolic Syndrome. Results have been variable although most studies show reduction of liver fat without other major effects and their effects are influenced by concomitant weight loss and underlying genetic factors. Vitamin E has had some efficacy in pediatric NASH but questionable efficacy in even mild NASH among adults. Pioglitazone has shown significant histological benefit in a number of trials but concern over side-effects (especially weight gain) have dampened enthusiasm. A newer insulin sensitizer, liraglutide, has also shown promise in a small randomized, controlled trial. Very limited data exists regarding the histological effects of the statins in NASH and these agents appear to be fairly neutral with neither clear cut benefit nor detriment. Their use is best guided by cardiovascular risks rather than liver histology. **(Clin Mol Hepatol 2017;23:103-108)**

Keywords: Fatty liver; Steatohepatitis; Non-alcoholic steatohepatitis (NASH); Non-alcoholic fatty liver disease (NAFLD); Polyunsaturated Fatty Acid (PUFA)

INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is a type of non-alcoholic fatty liver disease (NAFLD) that can silently lead to progressive liver damage, hepatic fibrosis, portal hypertension and cirrhosis sometimes further complicated by primary liver cancer.[1] The condition can be clinically silent for years until it presents suddenly with variceal bleeding or new onset fluid retention such as ascites or hydrothorax. Based on the fundamental pathophysiological mechanisms involved in disease progression which centers on poorly controlled lipid peroxidation or fat rancidification and its relationship to diabetes mellitus and dyslipidemia, several treatment options have undergone clinical study including PUFA supplementation (Poly-Unsaturated Fatty Acids or Omega 3 fatty ac-

Abbreviations:

AMP, activated protein kinase-adenosine monophosphate-activated protein kinase; CREBP, Carbohydrate responsive element binding protein; DHA, docosahexanoic acid; EPA, eicosapentanoic acid; FXR, farnesoid X receptor; GLA, gamma lenolenic acid; HMG Co, A reductase inhibitor - 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor; HNF-4α, hepatocyte nuclear factor 4 alpha; IU/D, international units per day; LXRα, Liver X receptor alpha; N3, omega 3; N6, omega 6; NAS, NAFLD Activity Score; NASH, Non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; PNPLA3, Patatin-like phospholipase domain-containing protein 3; PPAR, peroxisome proliferator activated receptor; PPAR-γ, peroxisome-proliferator-activated gamma receptor; PUFA, polyunsaturated fatty acids; RXR, retinoid X receptor; SREBP, Sterol regulatory element-binding proteins; TZDs, thiazolidinediones

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ids) anti-oxidant therapy with vitamin E (tocopherols), insulin sensitization with anti-diabetic agents such as the 'TZDs' (thiazolidinediones) and, based on the association of NAFLD with dyslipidemia, there has been attention given to anti-cholesterol medications such as the statins. In this discussion, I will highlight some of the work in this area.

OMEGA 3 FATTY ACID (PUFA, OMEGA-3, 'FISH OIL' SUPPLEMENTS)

PUFA (polyunsaturated fatty acids) are important lipid nutrients which constitute key fatty acid components of the triglyceride/diglyceride and phospholipid membranes of cells and sub-cellular organelle membranes such as the endoplasmic reticulum and the mitochondria.[2] The fatty acid composition of these phospholipid membranes influences susceptibility to free-radical induced oxidative injury and to activation of inflammatory and anti-inflammatory pathways through their metabolism to structurally related prostaglandins and leukotrienes. These agents also act as ligands for nuclear receptors to stimulate transcription of genes involved in lipid and energy metabolism.[3]

In the most straight forward perspective, PUFA can be seen as consisting of two nutritionally essential 18 carbon fatty acids which are usually ingested as components of ester links of three fatty acids linked to a three carbon glycerol backbone (i.e. triacylglycerides or 'triglycerides'): 1. Linoleic Acid 18:2 (9,12) also known as Omega 6 (N6) fatty acids and 2. Linolenic Acid 18:3 (9,12,15) also known as Omega 3 (N3) fatty acids. The nomenclature and biochemistry of these agents and their downstream metabolites is remarkably complex. 'Unsaturated' refers to the presence of carbo-carbon double bonds (minus a hydrogen bond) with the number of double bonds indicated as 2 or 3 in the formal name and the indication of the position of the 'first' double bond from one terminal of the molecule: hence the terms 'N3 or N6'. Note that N6 fatty acids have two double bonds and that N3 have three double bonds. They are considered 'essential' because the body cannot synthesize these fatty acids from other precursors. End products of their metabolism include short acting eicosanoids which consist of families of prostaglandins and thromboxanes formed through the activity of cyclooxygenase and lipoxygenase acting on fatty acids cleaved from the membrane bound phospholipids attached to the 3 carbon glycerol backbone.

Through the activities of elongation and desaturation enzymes in the endoplasmic reticulum and the mitochondria, N6 linoleic acid is converted to gamma lenolenic acid (GLA) which is further metabolized (elongated) to arachidonic acid 20:4 (5,8,11,14). N6 PUFA are generally considered pro-inflammatory. Common dietary sources include corn products, safflower seed oil, soy bean oil, and sunflower seeds. In contrast to the N6 fatty acids, N3 Linolenic Acid is, by the same enzymes pathways, further elongated and desaturated to eicosapentanoic acid (EPA) which is further metabolized to Docosahexanoic Acid (DHA). N3 PUFA are generally considered anti-inflammatory because of the properties of their downstream metabolic derivative eicosanoids. Common sources of the N3 fatty acids include fish oil, flax seed, canola, walnuts, and brasil nuts.

Early interest in 'Omega 3' (N3) supplements as possible therapy of NASH can be traced to the close association between the metabolic syndrome (insulin resistance), cardiovascular disease, fatty liver and reports of the cardiovascular benefits of diets rich in omega 3 fatty acids.[4-6] Interest was further stimulated by the possible role of skeletal muscle phospholipid membrane composition and insulin sensitivity where lower insulin sensitivity was associated with lower skeletal muscle PUFA content thought to represent myocyte phospholipid membrane composition.[7] Subsequently, lipidomic studies of human fatty liver indicated an association between fatty acid related cellular injury and relatively diminished N3 fatty acids.[8] In addition, data has accrued which reveals the importance of fatty acids as key nuclear transcription factors which influence the expression of hepatic fat and energy metabolic pathways.[9,10] These include PPAR receptors (peroxisome proliferator activated receptor), SREBP, CREBP, LXRα, FXR, RXR, HNF-4α all of which influence hepatic fat metabolism.

A number of trials of Omega 3 supplements have been conducted in the treatment of human NASH. Some variation in results is likely explained by nuances of the trials including formulation of omega 3, duration and dose of the supplement, measured target endpoints, control for concomitant exercise and dietary changes, genetic and epigenetic background of the study subjects and factors as subtle as the pattern of supplement ingestion.[11,12] None of the studies have shown improvement in key prognostic histological features such as fibrosis. However, most but not all trials have shown reduction in hepatic fat content. Using biopsy as the measure of fat content, one study reported no change in steatosis after 12 months of a synthetic EPA supplement up to 2,700 mg/day compared to placebo treated subjects.[13] In contrast, using MRS to provide a more global measure of liver fat content, the WELCOME trial reported significant hepatic fat reduction after 15-18 months of 4,000 mg/day of a synthetic mixture of EPA and DHA compared

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to placebo (derived from olive oil).[14] The reduction in liver fat was predictable by changes in erythrocyte N6-N3 phospholipid composition. Similarly, our own study of 12 months of 3,000 mg/day of a fish oil derived mixture of EPA and DHA versus soy bean oil placebo, showed reduced liver fat by the Dixon modified MRI but the effect was significantly less evident in patients who lost even a modest amount of weight during the study period.[15] As reported by others,[16] the effect was also influenced by the PNPLA3 genotype being greater among individuals with steatosis prone GG allele. Because PUFA are more prone to oxidative injury than saturated fatty acids, it is also notable that none of the trials have observed evidence of increased injury.

Taken together, the effects of omega 3 supplements appear to reduce liver fat overall within a 1-2 year time frame but neither reduce nor exacerbate steatohepatitis. The effect is influenced by both the ability to lose even a modest amount of weight through diet and aerobic activity and by the underlying individual genetic background governing hepatic fat metabolism. Whether or not higher dietary ingestion of N3 fatty acids over a longer term (ie a lifetime) influences the course of fatty liver and NASH remains uncertain but seems plausible. The effect may be mediated by skeletal muscle phospholipid metabolism although we could not detect a beneficial effect on exercise capacity.

VITAMIN E

Vitamin E constitutes a family of tocopherols and tocotrienols which have been studied over the years in the treatment of NASH based on their well-known anti-oxidant properties and the key role of lipid peroxidation in NASH pathogenesis.[17] Most studies have used α tocopherol with somewhat variable results. In an early histology based trial, vitamin E (800 IU/d) combined with ursodeoxycholic acid (12-15 mg/kg) with for two years versus single or double placebo controls showed histological improvement in the combination group.[18] Favorable results were also noted when vitamin E was combined with vitamin C in an early clinical trial.[19]

The most significant effects have been seen in pediatric NASH patients. The TONIC trial randomized 173 pediatric patients to one of three groups for two years of therapy: vitamin E (800 IU/day) n=58, metformin (1,000 mg/day) n=57 and placebo n=58.[20] Biopsy was the primary endpoint. Most were obese with evidence of insulin resistance. The mean age was 13 years and 80% were male and 70% were Caucasian. The fibrosis stage was mild in all. Using one of the more reliable histological endpoints, the study demonstrated resolution of NASH in follow up biopsy in 28% in the placebo group, 41% in the metformin group and, significantly, in 58% of the vitamin E group.

The results were less impressive in the companion adult trial of vitamin E among adults known as the PIVENS trial which randomized non-diabetic NASH patients to one of three groups: vitamin E (800 IU/day) n=84, pioglitazone (30 mg/day) n=80, and placebo n=83 for two years of therapy.[21] The fibrosis was stage was mild. While it was one of the largest NASH trials at that time, the study has been criticized for its target population (very mild NASH in the absence of diabetes) and for problems with histological inclusion criteria (variable cellular ballooning) and its primary endpoint of reduction of the histological NAS (NAFLD Activity Score).[22] A close look at the study results in terms of the more reliable endpoint of NASH resolution showed significantly greater efficacy of pioglitazone (see below) compared to vitamin E which was only marginally better than placebo: pioglitazone: 47% (P=0.001), vitamin E: 36% (P=0.05) and placebo: 21%.

Taken together, the data suggest that high dose vitamin E (800 IU/day) appears to have some benefit in mild NASH among pediatric patients but only a limited effect in adults. Concerns regarding safety with the long term use of the agent[23,24] and its limited efficacy have dampened enthusiasm although it is notable that no evidence vitamin E related adverse events were reported during two years of therapy in these trials.

INSULIN SENSITIZING AGENTS

Because of the close association of fatty liver with insulin resistance and type 2 diabetes, there has been long term interest in the potential benefits of anti-diabetic, insulin sensitizing agents in NASH. Early studies of metformin, a biguanide which alters cellular bioenergetics through AMP-activated protein kinase,[25] showed favorable effects in experimental rodent models of NASH but subsequent human trials didn't realize a substantial benefit although the lack of weight gain and usually good tolerance (aside from occasional GI side-effects) have sustained interest in the agent among some practitioners.[26,27] Much greater interest has been focused on the thiazolidinediones or TZD's since the initial report of their use in NASH.[28] These agents are ligands of the 'gamma' peroxisome-proliferator-activated gamma receptor (PPAR-γ) which is a nuclear transcription receptor activated by fatty acids and expressed in adipocytes, enterocytes and myocytes and influences expression of metabolic pathway components involved in lipid

and glucose metabolism.

Randomized and controlled trials, including the more recent PIVENS trial noted above, have consistently shown histological benefit with these agents in a sizable minority of treated patients (40-50% with histological response).[21,29,30] Similar results have been seen with rosiglitazone although subsequent concerns regarding adverse effects on lipoprotein profiles which raised safety concerns were never resolved.[31-33] In a more recent study from of 45 mg/day pioglitazone for 18 months of placebo controlled therapy followed by 18 months of open label therapy (101 adults of approximate age 50 years about 1/2 being diabetic and 3/4 of Hispanic descent), consistent results were also seen with resolution of NASH on follow-up biopsy in 51% of treated patients versus 19% of placebo treated controls (P<0.001).[34]

Despite the track record in terms of efficacy with biopsy based evaluation,[35,36] safety concerns have dampened enthusiasm for use of the TZDs in NASH.[37] While the purported risk of bladder cancer appears to be a spurious legal miscarriage,[38] other risks appear to be more genuine.[39,40] In addition, the effect of increased peripheral fat stores evident as a several kilogram weight gain in many treated patients, while avoidable, has also led to decreased patient acceptance.[41] Moreover, the lack of studies in more advanced fibrosis stages of NASH where the risk-benefit may be more acceptable significantly limits this group of agents.

The close links between fatty liver (NAFLD), fatty liver with fibrosing steatohepatitis (NASH) and diabetes has led to the study of other, newer anti-diabetic agents recently reported in randomized and controlled trials of NASH. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is an orally administered insulin sensitizer which did not show benefit in a controlled trial[42] while liraglutide, a parenterally administered analogue of glucagon-like peptid-1 (an incretin) did show histological improvement compared to a placebo treated group after approximately one year of therapy in the 'LEAN' trial.[43] Nine of 23 (39%) treated patients versus 2 of 22 (9%) had histological resolution of NASH. Gastrointestinal side-effects were common in both groups but more so in the treated group. Further study seems warranted with longer follow-up and larger study groups.

STATINS

The use of the HMG Co-A reductase inhibitors or statins remains something of an enigma in terms of their effects in fibrosing steatohepatitis.[44] Based on one very small prospective trial,[45] these agents don't overtly benefit or exacerbate NASH although for those with significant vascular risks, the net benefit favors their use when indicated for co-existing vascular risks.[46,47] In one long term cohort study of serial biopsy in NASH patients with (n=17) and without (n=51) statin therapy, mean fibrosis scores improved in the statin treated group but the percentage of patients with advanced stage fibrosis was higher in the treated group (29% versus 12%) at the end 10-15 years of follow-up.[48] As with other agents noted above, the patient's PNPLA3 genotype may significantly influence the effect of these medications.[49] Much more work is needed to clarify their role but presently the best advice is that their use should be governed by conventional risks of vascular disease rather than presence or absence of NASH.

Conflicts of Interest

The author has no conflicts to disclose.

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