Thyroid Hormones and Thyromimetics: A New Approach to Nonalcoholic Steatohepatitis?

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of hepatic disorders that ranges from excess lipid storage in the liver (hepatosteatosis) to progressive nonalcoholic steatohepatitis (NASH), which can lead to cirrhosis and hepatocellular cancer. First described in the clinical literature 40 years ago, NAFLD now has become a pandemic that affects approximately 25% of adults worldwide, with its prevalence estimated to be 60%-80% in patients with type 2 diabetes mellitus (DM) and obesity.[1] Currently, there are no U.S. Food and Drug Administration–approved pharmacological therapies for NASH, and liver transplantation is the only treatment for end-stage NAFLD. Thus, new strategies that can reduce or reverse the severity of NASH are urgently needed.

Thyroid hormones (THs), T_4, and the more biologically active form, T_3, stimulate fatty acid β-oxidation and oxidative phosphorylation in the liver.[2] Numerous studies have shown an inverse relationship between serum TH levels and NAFLD given that patients with hypothyroidism and subclinical hypothyroidism have increased risk for NAFLD and *vice versa*.[3] Transcriptomes of liver samples obtained from bariatric surgery patients also showed that the most prominent altered gene set was associated with TH action.[4] Additionally, T_3 and several thyromimetics decreased intrahepatic triglycerides in rodent models of hepatosteatosis.[2] Although TH increases the transcription of carnitine palmitoyl-transferase 1alpha (a carrier protein that promotes fatty acid uptake into mitochondria) and adipose triglyceride lipase (a lipase that converts triglycerides to fatty acids), hepatic autophagy of fat droplets and their conversion to free fatty acids within fused autolysosomes (lipophagy) appears to be crucial for TH-mediated β-oxidation of fatty acids.[5] Additionally, TH maintains mitochondria quality during this process by autophagy of mitochondria (mitophagy) and mitochondrial biogenesis.[2] Studies from patients with late-stage NASH and a rodent model of NASH showed decreased hepatic deiodinase 1 (*Dio1*), increased deiodinase 3 expression, and decreased intrahepatic T_3 concentration.[2] A clinical study in diabetic Asian male patients with hepatosteatosis found that low-dose levothyroxine (T_4) supplementation for 4 months significantly decreased hepatic fat content, as measured by magnetic resonance spectroscopy.[6] Recently, thyromimetics that target the liver and/or the main TH receptor (THR) isoform in the liver, THRβ, have been developed to prevent and/or treat hepatosteatosis and NASH[2] and have less thyrotoxic effects, such as atrial arrhythmias or osteoporosis, attributable to their selectivity for the THRβ versus THRα isoform.[2]

Two promising thyromimetic compounds, VK2879 and MGL-3196, are being studied for their effects on hepatosteatosis, inflammation, and fibrosis in NASH (VOYAGE/NCT04173065[7]). Harrison et al. recently published a report on "Resmetirom (MGL-3196) for the treatment of NASH: a multicentre, randomised, double-blind, placebo-controlled (RDBPCT), phase 2 trial" in the *Lancet*.[7] They enrolled adults with biopsy-confirmed NASH (fibrosis stages 1-3) and hepatic fat content >10% assessed by magnetic resonance imaging/proton density fat fraction (MRI-PDFF).[7] The study's primary endpoint was the percentage relative change from baseline in hepatic fat content as measured by MRI-PDFF at 12 weeks. Secondary endpoints included similar measurements at 36 weeks, determination of responders that had ≥30% reduction after treatment (an amount that correlates with a ≥2-point reduction in histological NAFLD activity score [NAS] score[8]), absolute percentage fat content loss after treatment, and ≥2-point reductions in NAS score associated with various parameters such as weight loss, fibrosis, and histological changes. After screening patients, 84 were randomly assigned to the resmetirom treatment (40-80 mg/d) and 41 to the placebo groups. Patients underwent MRI-PDFF at baseline and at 12 and 36 weeks treatment as well as liver biopsies at baseline and 36 weeks treatment. Resmetirom-treated patients had decreased percentage of relative hepatic fat content than placebo-treated patients at 12 weeks (–36% resmetirom vs. –10% placebo; $P < 0.0001$) and 36 weeks. They also had decreased absolute amount of percentage of hepatic

fat content at 12 weeks (–7.1% vs. –2.5%; $P < 0.0001$) and 36 weeks. Sixty percent of resmetirom-treated patients had >30% fat reduction compared to 18% of placebo-treated patients ($P < 0.0001$), with similar results at 36 weeks. Interestingly, 56% of patients treated with resmetirom had a >2-point NASH score reduction in liver biopsies compared to 32% of patients treated with placebo ($P < 0.024$). Although several serum markers for fibrosis were reduced at 12 and 36 weeks, no significant differences in amount of fibrosis were observed by histology between resmetirom- versus placebo-treated patients. These promising results suggest that resmetirom or other liver/THRβ-selective thyromimetics may be able to decrease hepatosteatosis and NASH severity, and a large, multicenter RDBPCT of resmetirom in NASH patients currently is underway (MAESTRO-NASH/ NCT03900429).

Several issues arise from these studies. First, although resmetirom causes only small changes in serum fT_4 levels and has relatively few side effects, it still will be important to screen patients at risk for atrial arrhythmias and osteoporosis before considering treatment. The long-term health effects of resmetirom or other thyromimetics also need to be monitored for both TH- or drug-specific effects. Second, there was a lack of significant improvement in hepatic fibrosis by histology in the resmetirom- versus placebo-treatment groups; however, the study was not adequately powered to evaluate changes in fibrosis, and the time period of the study may not have been long enough to detect changes in fibrosis. Alternatively, it is possible that this drug may be more effective in earlier-stage NASH when there is less fibrosis or when the fibrosis potentially is still reversible. Stratifying patients according to NASH stage and examining their response, particularly with respect to fibrosis, will be useful. Third, the issue of cost also needs to be considered, particularly for patients in third-world countries, where NASH also is highly prevalent. We have observed that hepatic *DIO1* mRNA and activity decrease in late-stage NASH, leading to decreased intrahepatic T_3 concentration.[6] Thus, it is possible that low-dose levothyroxine (T_4) may be effective to treat hepatosteatosis and early NASH,[6] whereas low-dose T_3 or thyromimetics that do not undergo *DIO1* deiodination may be more useful for later stages of NASH. Finally, given that NASH is a complex disease involving the liver, macrophages, and stellate cells, it is possible that THs or thyromimetics could be combined with other drugs that impact other mechanisms of NASH, such as fatty acid synthesis or inflammation, to achieve even better clinical results.

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