Thyroid Hormone Status in NASH as Compared to Non-NAFLD Population and Effects of Resmetirom Treatment

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INTRODUCTION

Thyroid hormone (TH) acting via THR (thyroid hormone receptor)-β is vital to maintain normal lipid regulation and mitochondrial function in the liver. Observational studies conflict as to whether there is a significant association between NAFLD and overt or subclinical hypothyroidism. One study reports intrahepatic hypothyroidism in human NASH livers caused by depressed conversion of prohormone T4 to active hormone T3 by deiodinase 1 (DIO1) and elevations in the level of TH degradative enzyme DIO3 made in stellate cells (Fig. 1)[1]. Resmetirom is a highly selective, liver-directed THR-β agonist that reduces NASH, atherogenic lipids and liver enzymes. In more than 400 subjects and patients, resmetirom did not affect levels of thyroid hormone axis hormones, including in NASH patients treated for 36 weeks in a Phase 2 serial liver biopsy study[2].

METHODS

Baseline thyroid hormone levels including TSH, FT4 (free thyroxine), FT3 (free triiodothyronine), RT3 (reverse T3) and ratio of FT3 to RT3 were compared between 125 NASH patients according to fibrosis stage and 116 similar aged non-NAFLD population (heterozygous familial hypercholesterolemia (HeFH), 12-week study), with normal TSH at screening. Numbers of excursions in TSH >ULN during a 12 and 36-week treatment period were assessed in both populations and according to treatment with resmetirom. The effect of 36 weeks of treatment with resmetirom in NASH patients on RT3, and ratio of FT3 to RT3 were assessed.

RESULTS

Non-NASH: average age, 57.3; sex 52.6% (male); BMI, 28.2. NASH: age, 50.2; sex 49.6% (male); BMI, 34.0. There were no differences between the populations in baseline FT4, FT3, or TSH. Baseline RT3 and ratio FT3/RT3 were abnormal in NASH patients, indicating decreased conversion of T4 to active T3, and statistically significantly different from non-NASH patients ($p<0.0001$) with a trend to worsening by fibrosis stage (Fig. 2,3). During the study, asymptomatic, intermittent excursions in TSH > ULN were common in both populations, independent of treatment; non-NASH, 15.7% placebo (pbo) and 11.5% resmetirom, NASH 24.4% pbo and 19% resmetirom (increased % in NASH due to longer study duration). One patient in the NASH study had autoimmune hypothyroidism (Hashimoto's thyroiditis) present at baseline, and as a result of asymptomatic TSH elevations caused by the thyroiditis, the patient remained in the study on thyroxine. In NASH patients, 36 weeks of treatment with resmetirom in Phase 2 Main and Extension studies as compared with pbo statistically significantly reduced RT3 ($p<0.0001$) and increased FT3/RT3 ($p=0.001$) to the normal level in patients with all baseline NASH fibrosis stages and in the F2/F3 population (Figure 4).

Figure 1. Thyroid Hormone Action in NASH

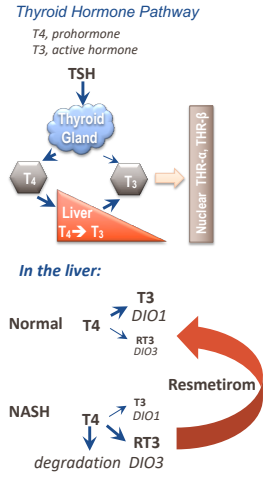


Figure 2. Baseline Thyroid Hormones NASH, non-NASH

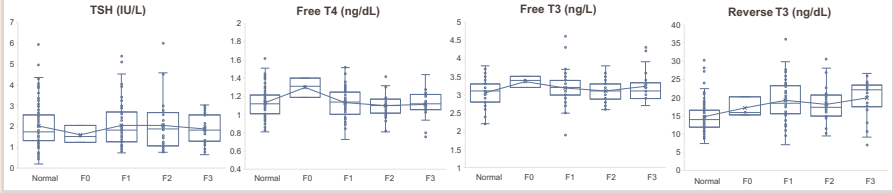


Table 1. Baseline Thyroid Hormones, NASH and non-NASH

Baseline	NASH	non-NASH	Difference
n	125	116	
Mean age, years (SD)	50.3 (11.0)	57.3 (12.1)	
Male, n (%)	62 (49.6)	61 (52.6)	
White	117 (93.6)	115 (99.1)	
Hispanic	59 (47.2)	0	
BMI (SD) (kg/m^2)	35.1 (6.1)	28.2 (4.2)	<0.0001
TSH (IU/L) (SD)	2.01 (1.04)	2.02 (1.01)	0.93
FT4 (ng/dL) (SD)	1.13 (0.16)	1.13 (0.16)	0.86
FT3 (ng/L) (SD)	3.18 (0.38)	3.06 (0.38)	0.015
Reverse T3 (ng/dL) (SD)	19.1 (5.6)	14.8 (4.2)	<0.0001
Free T3/Reverse T3 (SD)	0.181 (0.065)	0.220 (0.57)	<0.0001

Figure 3. Baseline freeT3/reverseT3 NASH and non-NASH

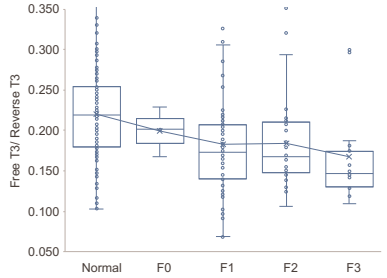
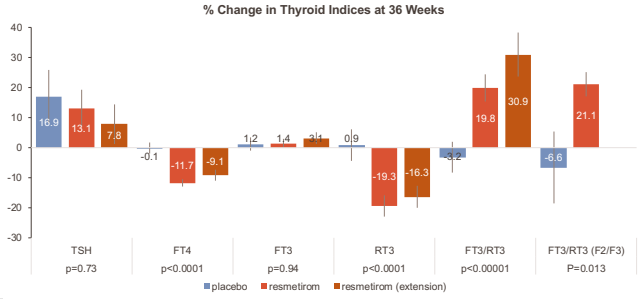


Table 2. Baseline Thyroid Hormones, NASH Study

	Placebo (n=41)	Resmetirom (n=84)	Extension (n=31)
Mean age, years (SD)	47·3 (11·7)	51·8 (10·4)	48.2 (12.3)
Male, n (%)	24 (58·5)	38 (45·2)	16 (51.6)
BMI (SD) (kg/m^2)	33·6 (5·8)	35·8 (6·2)	35.3 (5.2)
FT4 (ng/dL) (SD)	1·1 (0·2)	1·1 (0·15)	1.1 (0.16)
FT3 (ng/L) (SD)	3·2 (0·4)	3·2 (0·4)	3.2 (0.38)
TSH (IU/L) (SD)	2·1 (1·3)	1·9(0·9)	2.1 (0.83)
Reverse T3 (ng/dL) (SD)	18·5 (6·1)	19·3 (5·2)	17.6 (3.83)
Free T3/Reverse T3 (SD)	0.202 (0.105)	0.176 (0.055)	0.191 (0.043)

Figure 4. Resmetirom Significantly Reduces Reverse T3 and Increases Free T3/Reverse T3 in NASH Patients



CONCLUSIONS

- There were no differences in baseline FT4 or TSH in NASH and non-NASH patients of similar age
- RT3 was higher and FT3/RT3 lower in the NASH compared to the non-NASH population suggesting that the NASH liver is hypothyroid with reduced levels of active thyroid hormone, T3
- Treatment with resmetirom resulted in no changes in thyroid axis hormones, but normalized reverse T3 and the T3/ RT3 ratio correcting endogenous thyroid hormone activity and improving hepatic function via increased direct THRbeta activity.

REFERENCES

[1]Bohinc et al., Endocrinology 155(11):4591-601, Nov 2014.
[2]Harrison et al, Lancet 394, 2012-2024, 2019.
[3]Krause C, Grohs M, El Gammal AT, Wolter S, Lehnert H, Mann O, et al. Reduced expression of thyroid hormone receptor beta in human nonalcoholic steatohepatitis. Endocr Connect. 2018;7(12):1448-56.

DISCLOSURES

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