Critical Modulation of Liver Function by the Thyroid Contributes Specifically to Pathogenesis in Multiple Endocrine and Metabolic Disorders

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Abstract Body: Introduction: We have analyzed liver-spleen SPECT with fractal slopes, Sb, positive, and Sw, negative, for areas of best and worst liver function. As the absolute value of S increases, liver function is more heterogeneous and more compromised.

Methods: Liver-spleen SPECT used Tc-99+m-sulfer colloid IV and high resolution collimators. Modified fractal analysis used plots of LN (Is) vs. Ln (Av/Pk), for peak, Pk, and average, Av, liver counts in isocontours, Is. Sb > 0 is the limiting slope as both Av/Pk and is approach 1, Is near 100% of Pk. Similarly, Sw < 0 is from plots of Ln(100+B)-(Is)] vs. Ln (Av/Mn), where Mn is the least liver count and B is the Is value for the liver boundary. Sn was Sb normalized for body and liver-spleen size. / Uncertainties noted are standard deviations and abnormal > 2 Std dev from mean.

Results: Among 744 patients, 163 (22%) had thyroid disease and Sn was abnormal in 724 (97%), among whom 163/596 (27%) had abnormal serum ALT or ASt. Limiting slopes were linear for Sb and fit binomial or trinomial for Sw. Euthyroid patients without liver disease due to hepatotoxins, viral hepatitis, cholecystitis or cysts had Sn 0.96+-0.13; Sw -0.94+-0.11 (p 0.6, NS) for 20 near normal; Sn 1.88+-0.31 for 123 NAFL; Sn 2.89+-0.56 for 88 NASH and Sn 3.82+-0.87 for 25 hepatic fibrosis patients. In each group, dysthyroid patients had Sn > and /or Sw < their group average Sn, often near average Sn for the next more abnormal group. The highest Sn in a thyroid patient was 5.01, post thyroid storm, similar to Sn 5.27 with HbA1c > 10% or Sn 6.30 in fatal liver metastases. Mild hypothyroidism led to NAFL in 3 lean, type 1 diabetic (not NAFL prone) with no other liver disease. In insulin resistant patients, thyroid and glycemic status effects were nearly additive. Subclinical thyroid disease in 5 near normal cases had only Sw abnormal in 4 and Sb in 1. In treated thyroid patients with 86 follow-up studies at 3 to 40 months. Sn was worse in 27 (31%), unchanged in 17 (20%) and better in 42 (49%).

Conclusion: Quantitative analysis of high resolution liver SPECT reveals that thyroid status critically affects hepatic function and directly impacts hepatocentric pathogenesis, such as insulin resistance.

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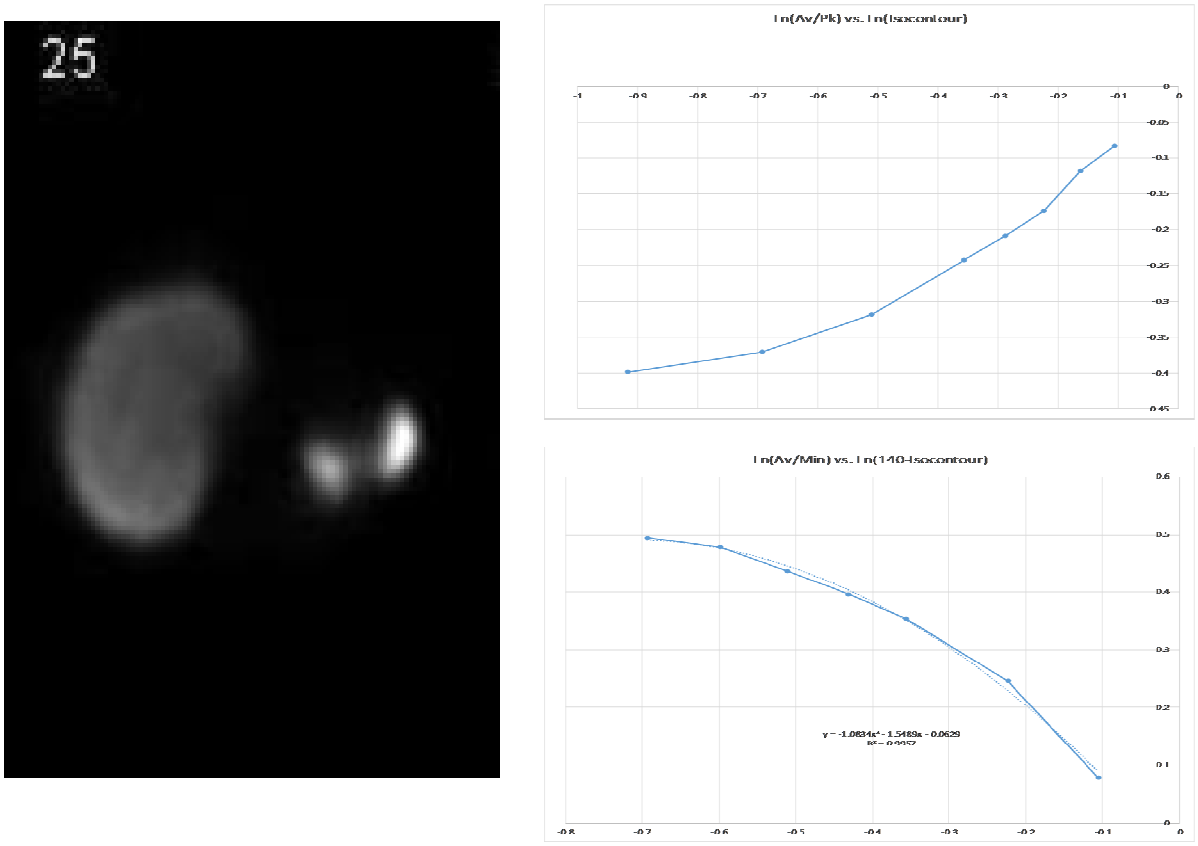

Fig. 1: A 70 year-old thyroid cancer (differentiated papillary follicular) patient with well controlled (HbA1c 5.8%) type 2 diabetes mellitus (BMI 24.3) is post thyroidectomy and I-131 ablation of thyroid remnants with a negative thyroid cancer scan shortly before the SPECT liver spleen scan shown. She has had mildly suppressed TSH, e.g. 0.194 mIU/ml with (normal 0.45-4.50 mIU/ml) and has had osteoporosis. Her Sn value was 1.41, significantly (3.8 standard deviations) > normal Sn 0.956+-0.120. The degree of heterogeneity in her liver (axial SPECT above, left) is difficult to appreciate without quantitative analysis. Log plots for positive (above right) and negative (above left) slopes were used to determine Sn and Sw with a linear fit for Sn and a binomial fit for Sw. The normalization factor to multiply by Sb to get Sn was: (2)(BMi/23)[(Liver span)/15][Liver AP diameter)/(14.58)][(Spleen span)/(7.2)][13.5/ECF][1.6/BSA]. Of interest, the negative slope Sw = -1.549 even more sensitively detects abnormality vs. normal Sw 0.933+-0.099, being 6.22 standard deviations from normal.

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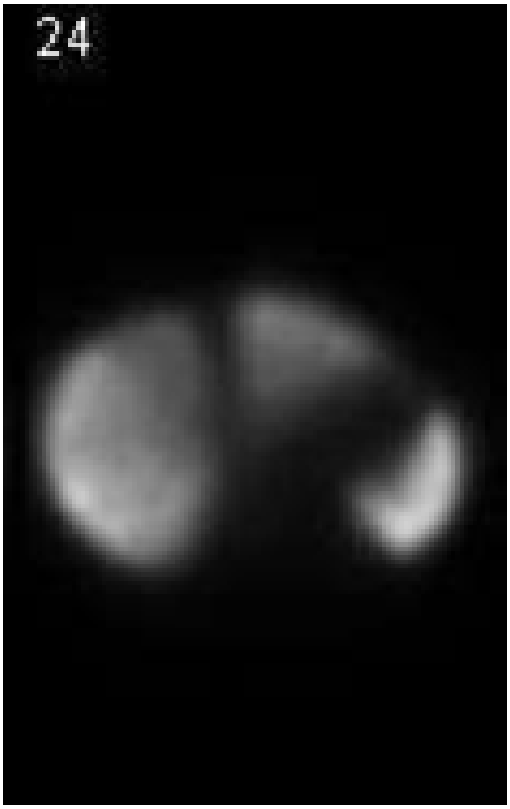

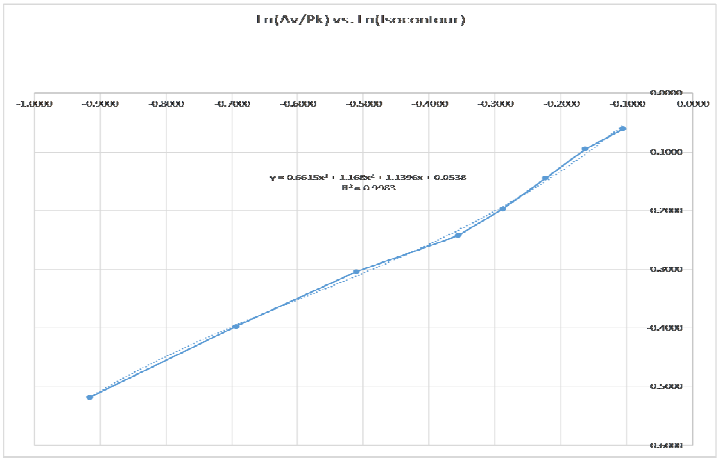

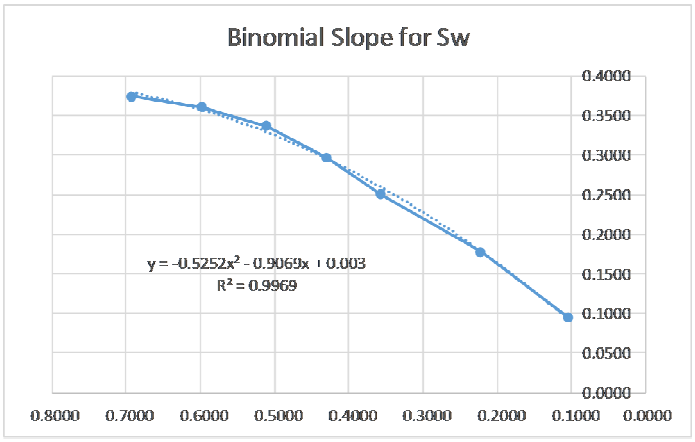

Fig 2. Axial SPECT is visibly more heterogeneous for a 44 year-old woman with polyglandular failure, factitious hyperthyroidism (found taking 225 mcg Synthroid twice daily) and morbid obesity, BMI 42.4. She had abnormal transaminase, more prominent shift of colloid to the spleen, borderline splenomegaly and Sn 3.544, consistent with hepatic steatosis more marked than Sn 2.90+-0.521 in patients with hepatic steatosis and no thyroid disease. In this patient Sw –0.7962 was less negative than usual, suggesting less heterogeneity in the areas of more impaired liver function. Also of interest is the photopenic wedge-shaped division between the right and left lobes of the liver.

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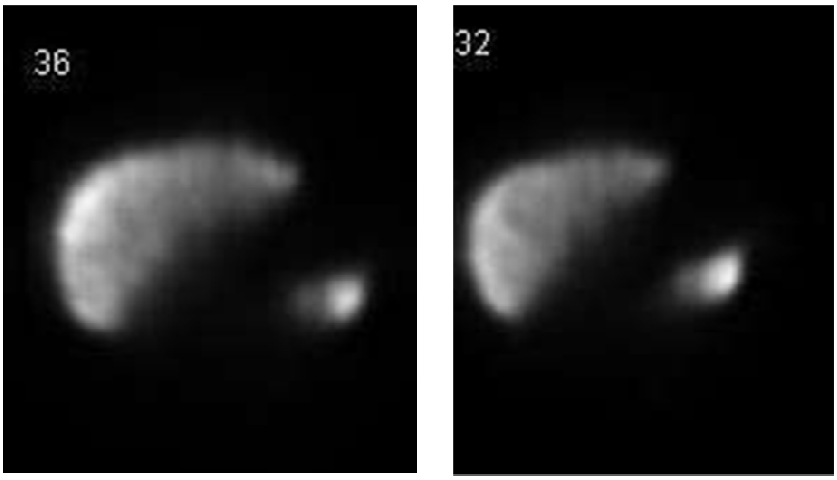

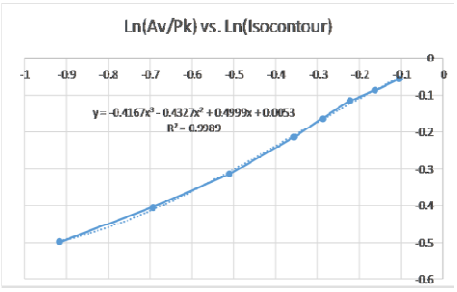

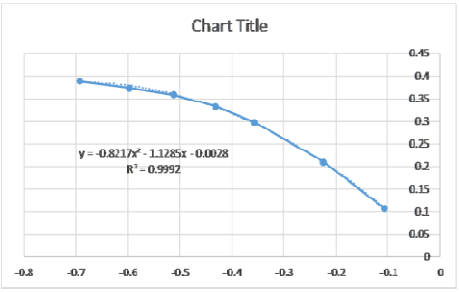

Fig. 3. Axial liver SPECT for a 57 year-old type 2 diabetic woman with HbA1c 6.2% is shown on the right at which time the patient was snoking cigarettes and had Sn 1.43, consistent with NAFL. On the left is her axial SPECT after 1 years when Sn had decreased to 0.945, within normal limits 0.956+-0.120 after the patient stopped smoking and took 4 grams of omega 3 fish oil and 400 units Natural vitamin E for one year. Her weight increased 9 lb from 227.8 to 236.8 lbs. Among patients who took prescription omega 3 fish oil for over a year, 70% had improved Sn; however, normalization of Sn required several years or more in patients with more abnormal initial liver function. This patient had more serial scans than any other in our series and actually moved back and forth between normal and abnormal twice over 4 years. Her positive slope curve for her most recent scan shows greater improvement (lower slope) in the area of best live function. Her Sw – 0.955 was similar to other normal values 0.0933+-0.099.

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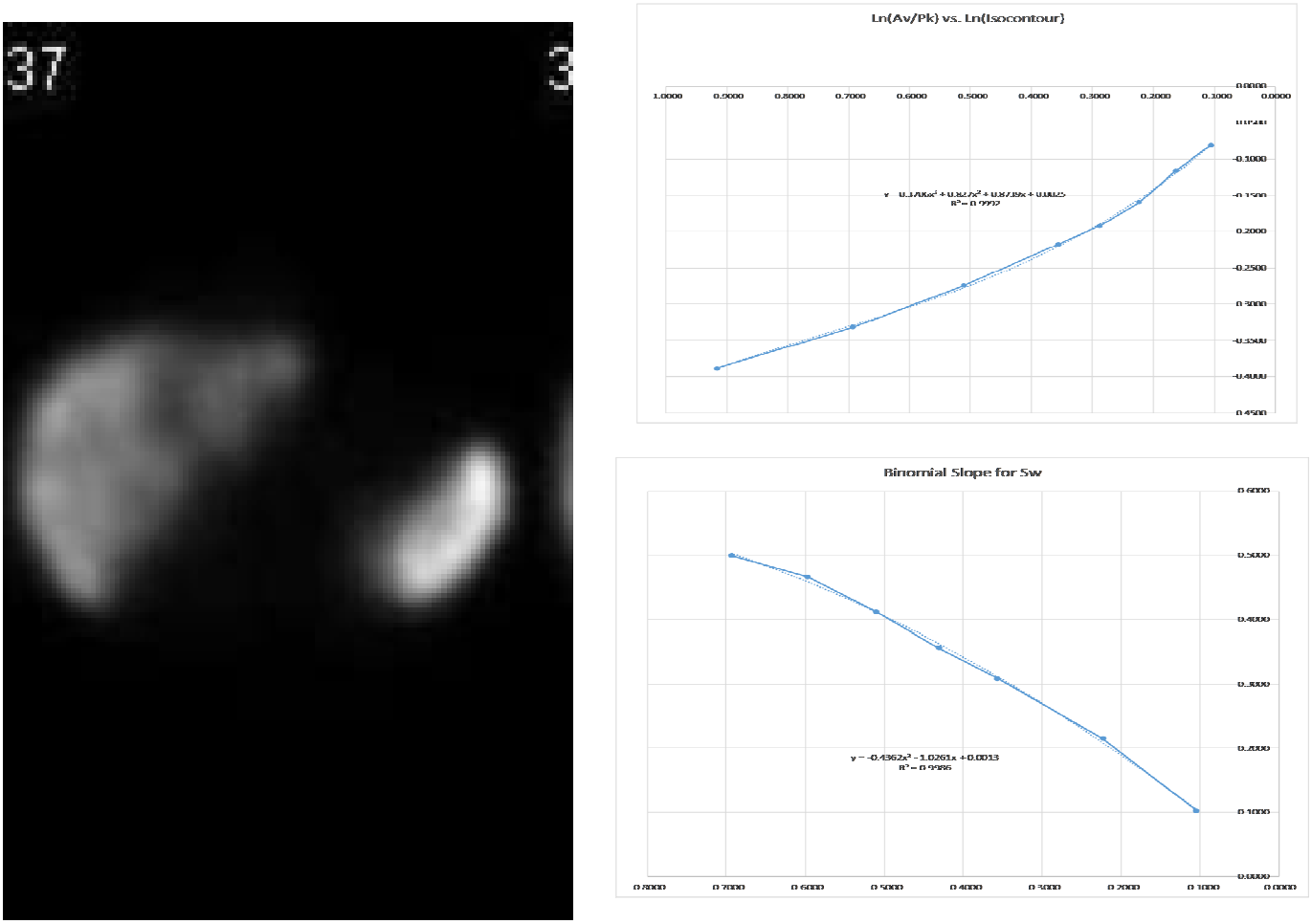

Fig. 4. A 45 year-old woman with Graves' disease post I-131 therapy remained mildly hyperthyroid and had the axial SPECT shown above on the right. Her abdominal ultrasound confirmed diffuse fatty liver although her BMI was normal at 23.8 and she had normal serum transaminases. In fact, less than 28% of all our patients with abnormal Sn had abnormal transaminases. Her Sn value of 1.863 was typical of NAFL although she would otherwise have been considered normal: in fact it generally was observed cf. Fig 5 that patients with thyroid disease had one category more abnormal Sn than would otherwise have been expected if their thyroid was normal.

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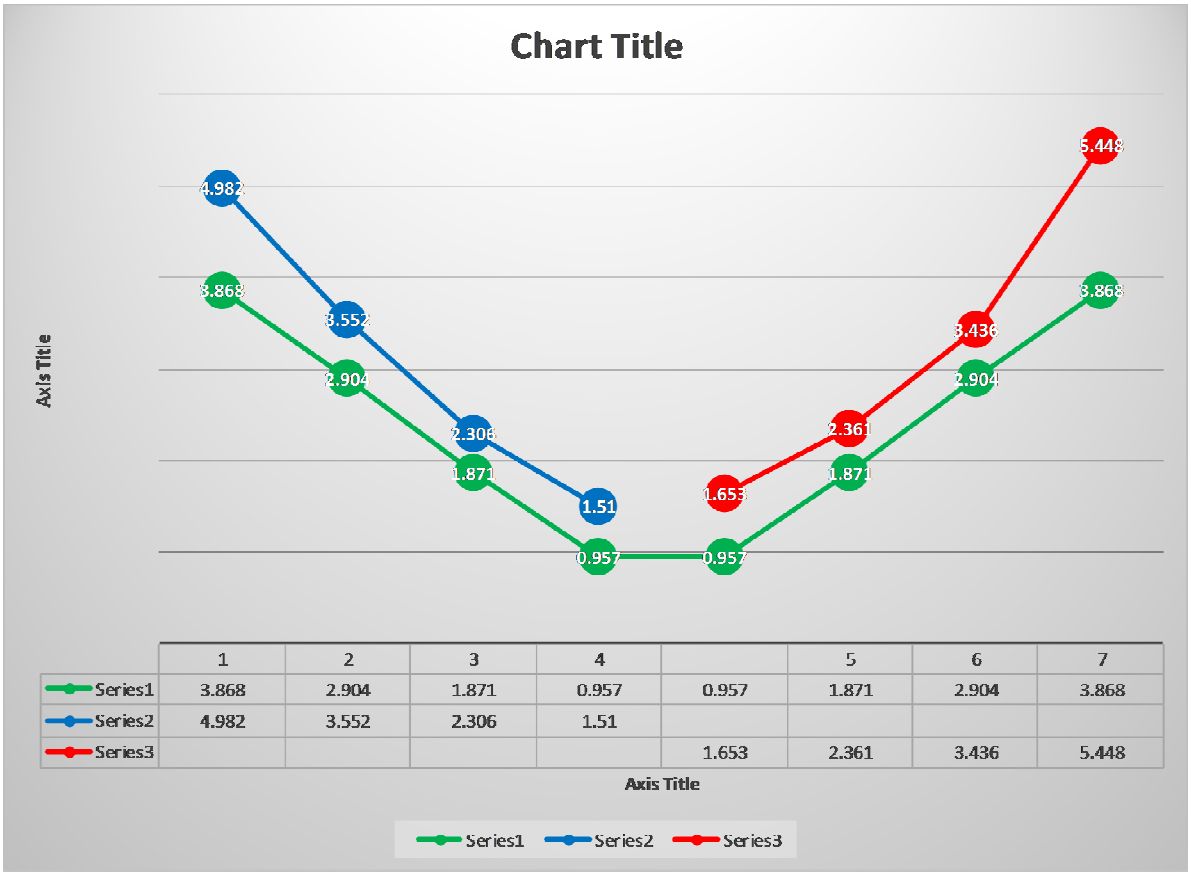

Fig 5. In the graph above, the green line shows Sn values for euthyroid patients who were normal, in the center (n =23), had NAFL (n = 126) for the first point to the right or to the left, had NASH (hepatic steatosis) for the third point to the right or to the left (n =94) ; or had hepatic fibrosis (n = 29) for the fourth point to the right or to the left. In red are plotted data for hyperthyroid patients and in blue for hypothyroid patients in similar categories, showing that thyroid disease exacerbates the degree of liver injury in each category. Although error bars are omitted for clarity, the points in each category were significantly different despite n of only about 7 in each of the thyroid categories.

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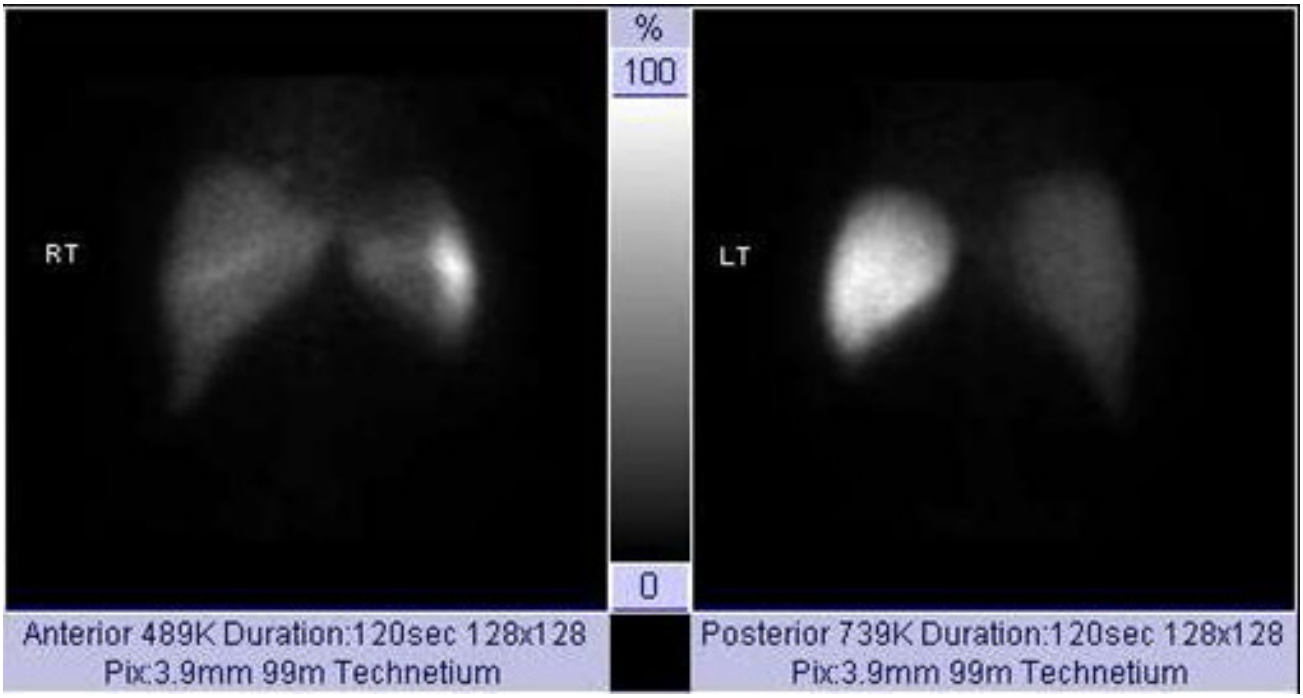

Fig 6: Planar liver-spleen scan anterior and posterior for a 48 year-old woman with hepatic fibrosis who also has significant cognitive impairment with Montreal Cognitive Assessment 17/30, possibly contributing to incomplete adherence to prescribed levothyroxine for chronic thyroiditis. Her TSH was 20.5 with normal < 4.50 mIU/ml. She had evidence of hepatic fibrosis with thrombocytopenia contributing to a positive score on her hepatic fibrosis index. Sn was 4.98 similar to Sn 4.98+-0.69 for a group of 9 hypothyroid patients with hepatic fibrosis, significantly ($p < 0.001$) less than Sn 3.86+-0.87 in a group of 29 hepatic fibrosis patients without thyroid disease who also had no history of viral hepatitis or excessive exposure to alcohol or other hepatotoxins. Note the colloid shift with more prominent uptake by this patient's enlarged spleen. Mild cognitive impairment was typical of patients with liver disease overall, MoCA was 23.9+-3.55 among 751 patients with some degree of NAFL (vs. normal MoCA > 25).

Conclusions:

1. Even subclinical thyroid disease, either hyperthyroid or hypothyroid, exacerbates liver dysfunction, particularly if it is present chronically.

2. Liver function recovery is possible with maintenance of euthyroidism but may take months to years.

3. Hepatic dysfunction in thyroid patients is likely part of the pathogenesis of type 2 diabetes mellitus.

4. Conventional liver-spleen scanning with modified fractal analysis of SPECT provides a sensitive and reproducible method for management of thyroid patients with liver disease.