

LIVER DISEASE CONTRIBUTES TO COGNITIVE IMPAIRMENT ASSOCIATED WITH INADEQUATE GLYCEMIC CONTROL IN PATIENTS WITH MULTIPLE ENDOCRINE AND METABOLIC ABNORMALITIES

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Objective: Report cognitive impairment associated with liver disease among endocrine and metabolic patients and its dependence on glycemic control.

Methods: Patients had cognition monitored with the Montreal Cognitive Assessment (MoCA), liver disease determined by liver enzymes, ultrasound, CT, liver spleen scans with modified fractal analysis of liver SPECT (to determine a parameter, Sn from log-log plots of Isocontours and their average activity) and liver biopsy. Fibrosis was monitored with an NAFLD fibrosis calculator. Routine endocrine tests included blood sugars, HbA1c, serum and salivary cortisol, NMR lipid analysis, Free T4, Total T3, reverse T3 and TSH. Statistical analysis of nonparametric t tests and correlation analysis used Excel 2013.

Results or Case Presentation: Among 420 patients with liver-spleen scans, 29 were near normal with Sn 0.81+-0.13, 253 had fatty liver and normal liver enzymes with Sn 2.09+-0.77; 46 had hepatic steatosis, usually with abnormal liver enzymes, with Sn 2.67+-0.94 and 35 had fibrosis, with Sn 3.1+-1.5. MoCA scores were 26.6+-2.1 for near normals, and less, 24.4+-3.56 for 391 patients with any liver disease (p< 0.001); including 24.2+-3.9 for 39 with insulin resistance (p<0.02) and HbA1c > 5.6%, 24.6+-3.2 for 74 with thyroid disease (p<0.03), 24.0+-3.7 for 46 with hepatic steatosis (p < 0.006) and 22.3+-3.4 for 29 with hepatic fibrosis (p < 0.001). Among 20 patients with HbA1c 10+-1.4 who had Sn 3.2+-2.5, MoCA was 21.81+-3.8 (p <0.01). HbA1c correlated with MoCA for 39 liver disease patients with insulin resistance and HbA1c > 5.6% (r=0.56), for 56 with psychiatric depression (r= 0.61) for 46 with hepatic steatosis (R=0.77) and for 25 with hypercortisolism (r=0.67), although hypercortisolism patients had insignificantly decreased MoCA 25.9+-3.3 (p=0.44).

Discussion: Cognitive impairment has multiple causes . A single major factor can cause marked cognitive impairment, such as hepatic encephalopathy. Less often appreciated is that even minor metabolic abnormalities, particularly if coexisting, can result in significant cognitive impairment. Moreover, in a population context, minor metabolic abnormalities, such as obesity and the metabolic syndrome, with nearly invariant fatty liver, reach epidemic proportions; hence, their contribution to cognitive impairment is remarkable. Reversibility of much liver disease and increasingly achievable glycemic control offer potential for significant improvements in cognitive impairment.

Conclusion: Liver disease, particularly mild disease detected by sensitive liver-spleen scans, is at least as epidemic as insulin resistance and contributes significantly, along with inadequate glycemic control, to widespread cognitive impairment.

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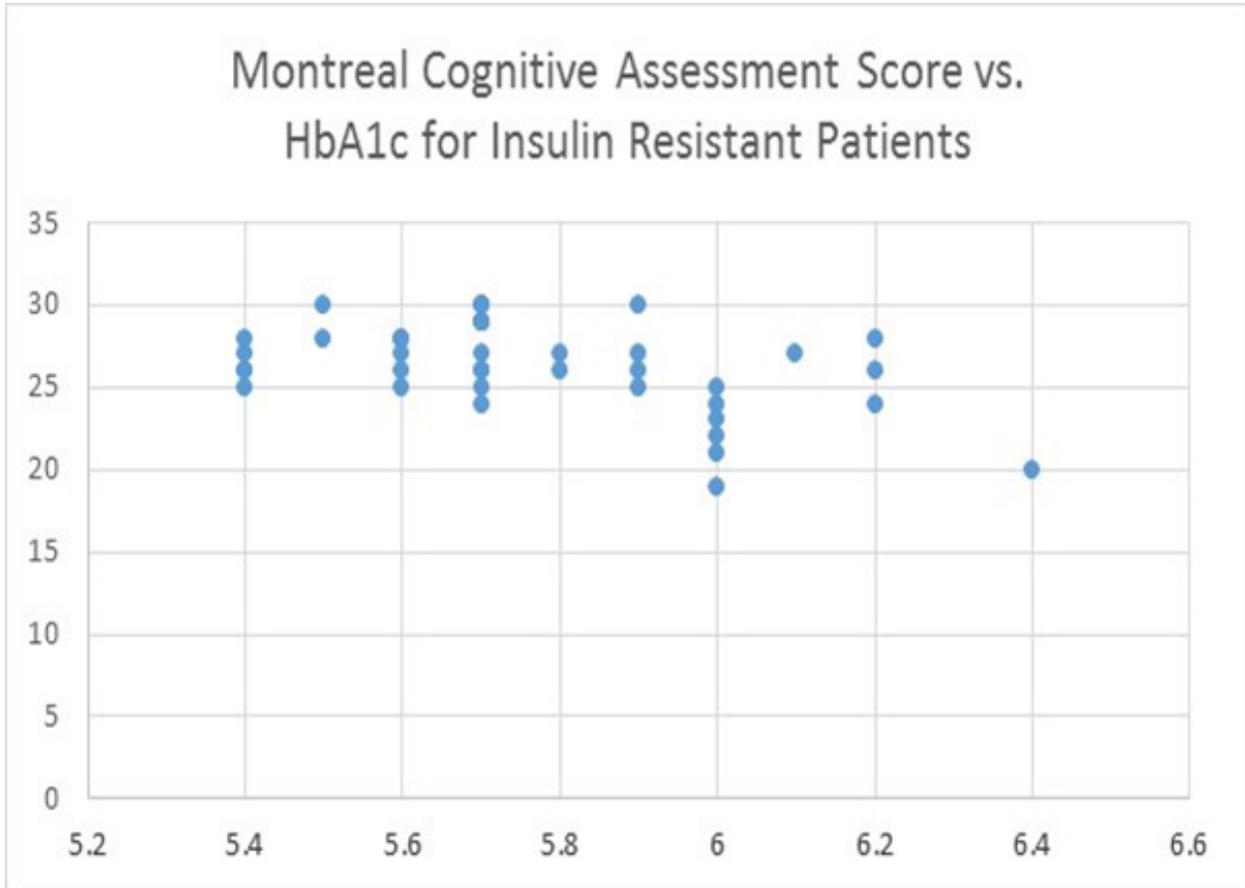


Fig. 2: For insulin resistant patients, HbA1c correlates with the Montreal Cognitive Assessment (MoCA) score, but more significantly visually for abnormal HbA1c > 5.6%, for which $r = 0.56$ with $n = 39$. Using the larger data set above, eliminating patients with hypercortisolism, established dementia or traumatic brain injury, and with 51 patients, $r = 0.67$ for HbA1c 5.4% to 6.4%.

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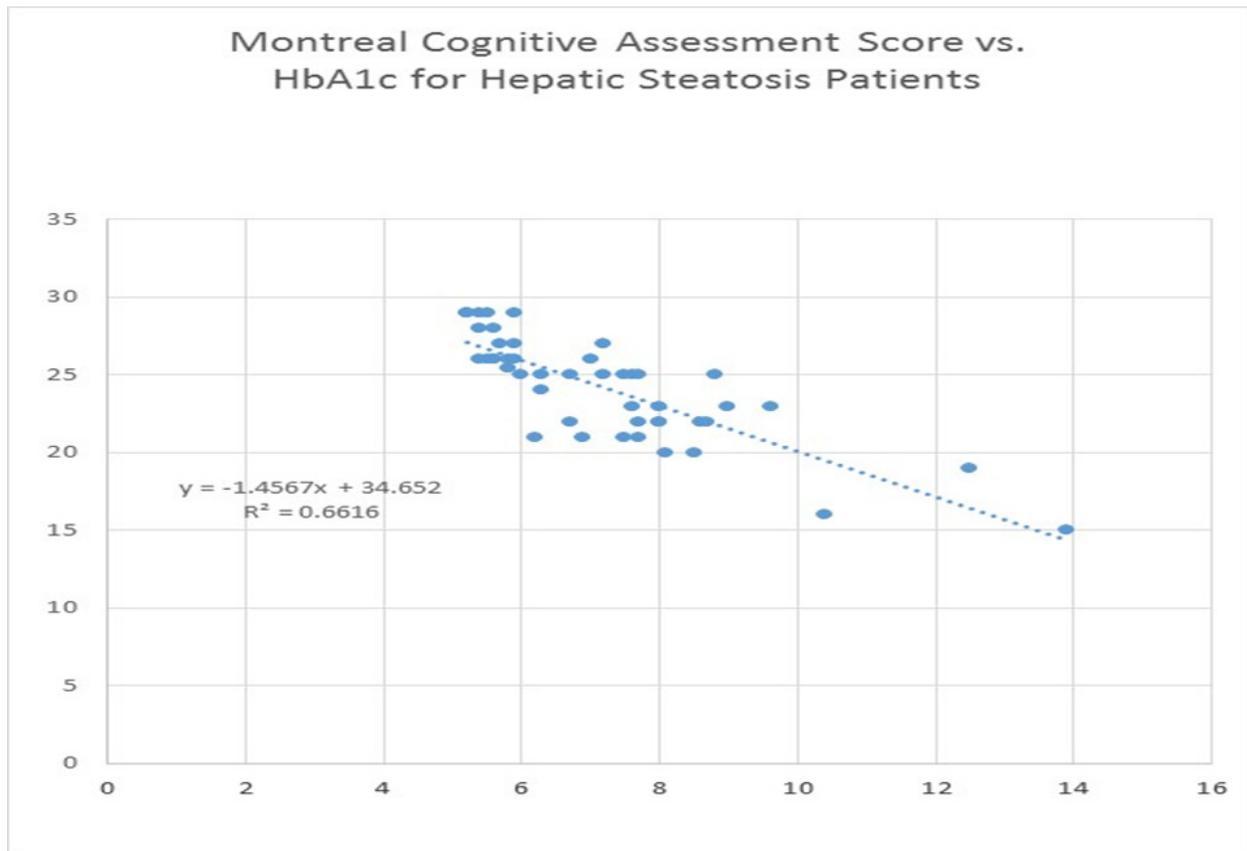


Fig. 3: Montreal Cognitive Assessment (MoCA) score was reviewed and correlated with the closest HbA1c, generally within 3 months before the scan, for 47 patients with hepatic steatosis. Hepatic steatosis was defined by abnormal liver serum enzymes or abnormal abdominal ultrasound, generally with a hepatic fibrosis index < the 95% confidence limit for hepatic steatosis and without evidence of malignancy or advanced portal hypertension. Patients with Cushing's syndrome, traumatic brain injury, established dementia or advanced alcoholism were omitted. The graph above includes several patients with high HbA1c and probable fibrosis increasing Sn to 2.94+-1.27 vs the 2.09+-0.77 noted earlier with 46 hepatic steatosis patients: r above is 0.81 vs. 0.77 for the 46 similar patients described in the text of the abstract.

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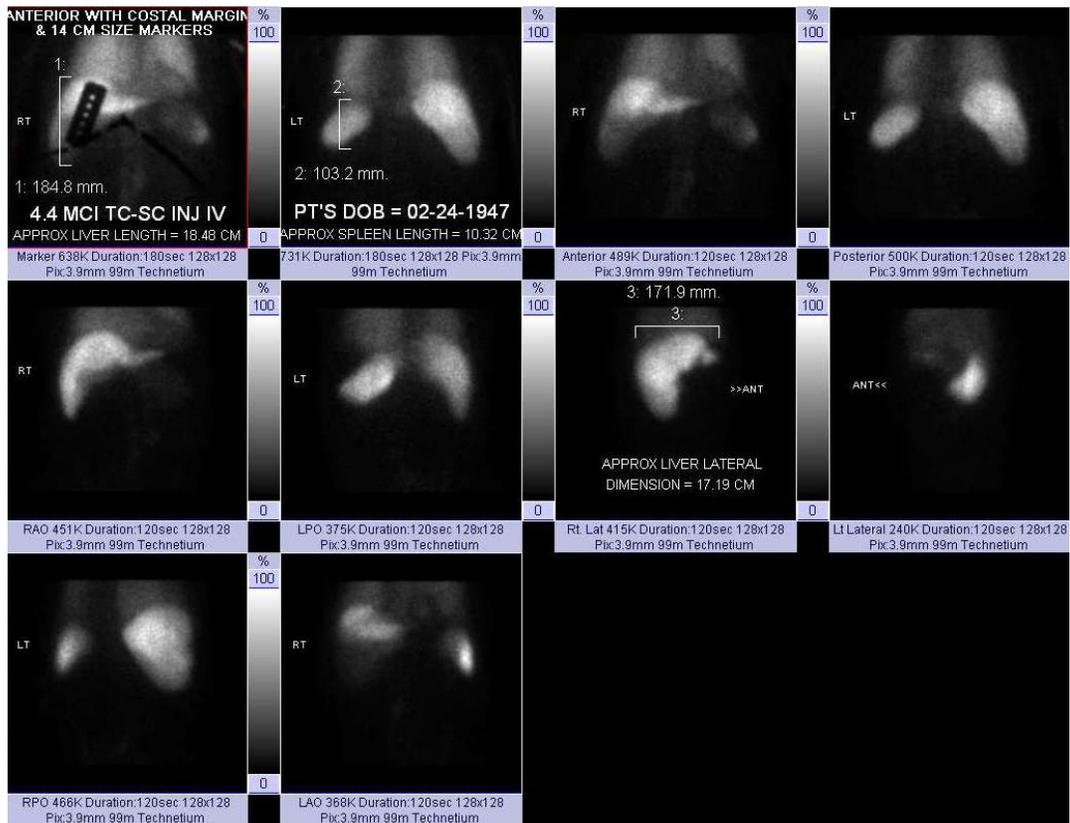


Fig 4: Planar liver-spleen scan for a 68 year-old man whose complex medical history illustrates many aspects of liver disease and other factors impacting cognition. Lung uptake is prominent even without marked spleen uptake but still typical of more advanced portal hypertension. The patient admits drinking alcohol heavily in his youth. His MoCA score 20/30 with HbA1c 5.2 to 5.5% on repeated measures would fall well below the regression line noted above (Fig 3) for hepatic steatosis (or a similar one for patients with depression, from which he also suffers), likely owing to severe traumatic brain injury he experienced over 20 years ago in a motor vehicle accident. He was comatose for over a week and required many months to relearn how to talk, walk and read. About 6 months ago he had another MVA which exacerbated chronic back pain and further increased his chronic pain therapy which includes oxycodone/acetaminophen four daily. He takes multiple other possibly hepatotoxic drugs from several health care providers including 2 grams daily slow release niacin, atorvastatin, cyclobenzaprine and nonprescription analgesics for chronic, left-sided headache. He has mild hypogonadotropic hypogonadism with borderline low T and free T but his PSA of 4.8 is slightly high vs nml < 4.0 pg/ml. His IGF-1 of 52 (nml 47-192) is borderline low in an assay reputed to read relatively high. He is dizzy and hypotensive BP 98/60 on hydrochlorothiazide for hypertension: his PM serum cortisol 13.9 is borderline high (nml < 11.9). Although we reported at least similar improvement in cerebral flow reserve for purified omega-3 fish oil (EPA), his cerebral flow reserve index with EPA was negative and donepezil has not helped his memory.

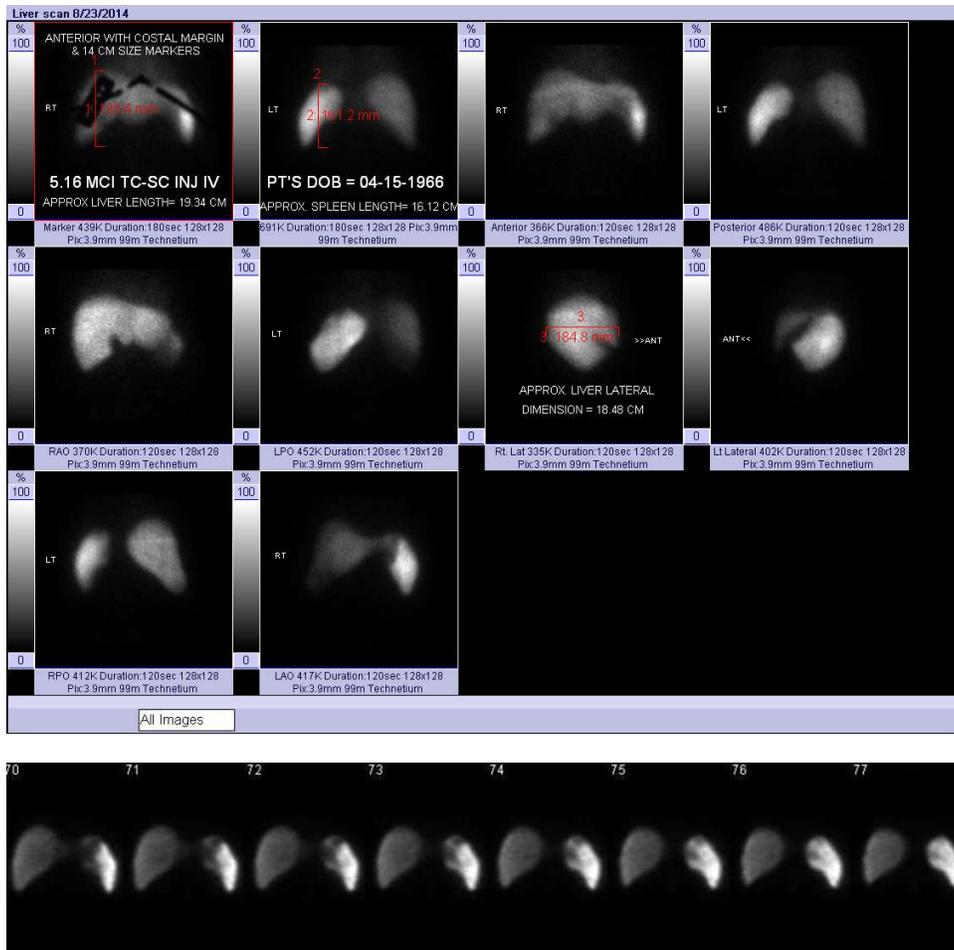


Fig 4 : Liver spleen scan planar images (above, top) and SPECT images, coronal sections , posteriorly to show spleen (above, bottom) for a 49 year-old insulin resistant woman representing the proverbial endocrine patient: post I-131 therapy for toxic nodular goiter associated with supraventricular tachycardia, currently managed with beta blocker and antiplatelet therapy, she progressively gained weight, developed arthritis in her knees requiring arthroscopic surgery, and at BMI 44.9 is pursuing long-term medical therapy for weight loss and considering future bariatric surgery. Her borderline hepatosplenomegaly raised suspicion of possible malignancy with inhomogeneous liver tracer distribution consistent with hepatic steatosis and increased overall spleen (but not bone marrow nor lung) tracer concentration consistent with mild portal hypertension . Patchy decreased tracer concentration in the spleen superiorly led to abdominal CT showing normal adrenal glands but confirming an exophytic 4 cm diameter splenic mass. She had borderline high HbA1c 5.6%, increasing from 5.2% over the last year with progressive weight gain prior to starting bupropion/naloxine (Contrave) and a low carbohydrate 1200 calorie diet. She is prescribed omega -3 fish oil and vitamin E 400 units daily and in light of her Sn 5.83 without hepatic fibrosis per her normal fibrosis index 0.12, will be considered for pioglitazone therapy of hepatic steatosis. With normal HbA1c 5.2 to 5.6% her MoCA score of 29 was also normal. While her splenic mass will likely require surgical biopsy, the traditional use of liver spleen scanning to assess mass lesions applies to less than 1% of our patients, while only 29/510 were considered normal and most of the other 481/510 had NAFLD or hepatic steatosis. Less than 10% had confirmed alcoholism; approximately 3% had gallbladder disease (generally confirmed by hepatobiliary scintigraphy and ultrasound) when scanned. Cases of likely fibrosis by the fibrosis index were near 29, the same as the number of normal cases. Screening to detect early metastases would likely have been impractical in the three cases of mortality due to malignancy in this series, all of whom died within a month or two of discovering liver metastases. Interestingly, Sn in all three cases of fatal metastasis (one melanoma and two adenocarcinoma, likely gastrointestinal origin), was 5+-2, similar to this patient with Sn 5.83. The overall average Sn is 2.34 +- 1.18 in our series of 481 patients with abnormal Sn > 1.05.

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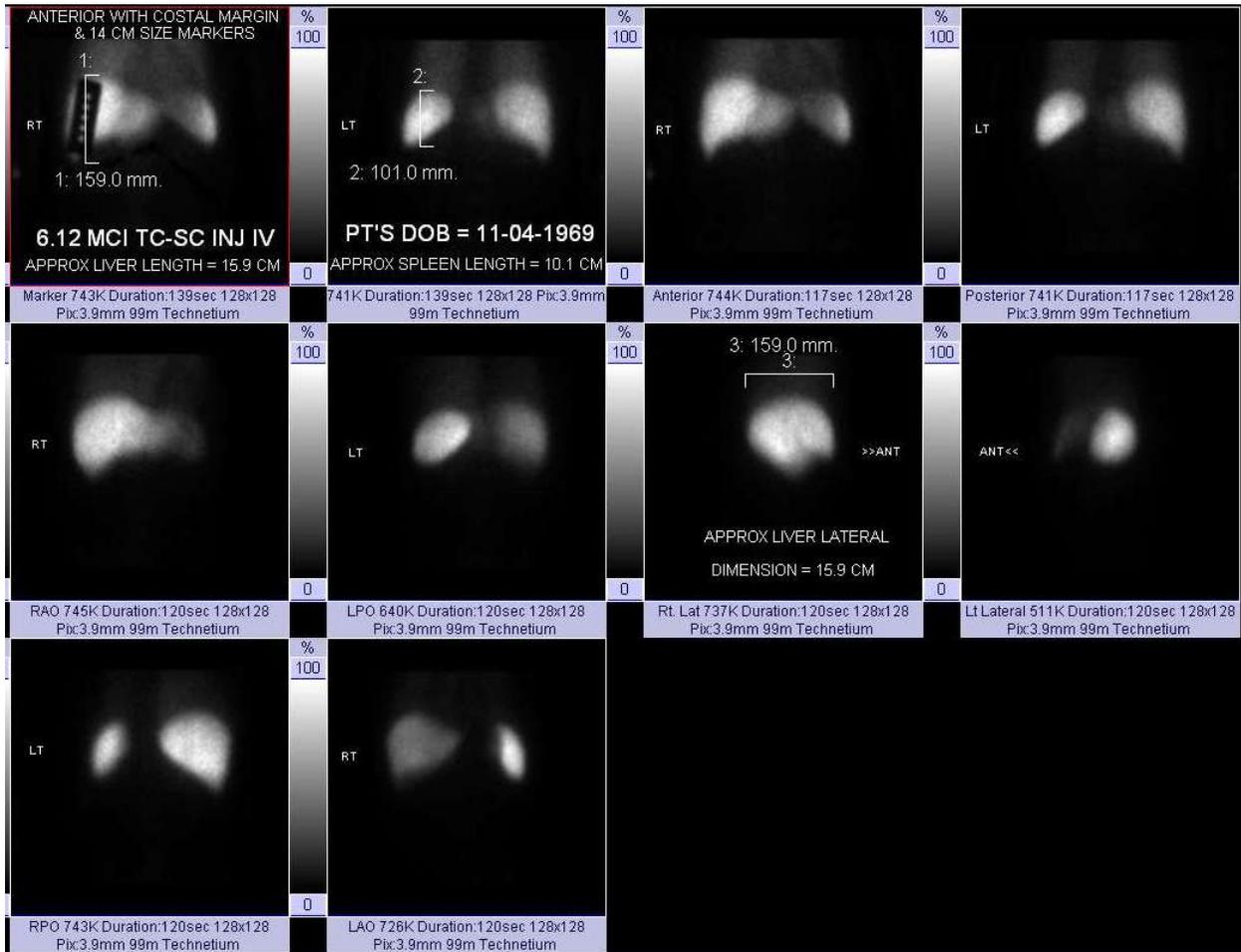


Fig 5: Liver spleen scan planar images in a 45 year-old man with modest increased spleen concentration of Tc-99m-sulfur colloid, consistent with mild portal hypertension. MRI confirmed post cholecystectomy and prominent left periaortic vessels consistent with portosystemic shunt from portal hypertension. His mild imaging abnormality correlated with Sn 1.07, near the upper limit of normal recently reanalyzed as 0.803+0.125 (nml < 1.05) for 29 patients without known liver disease. He has hypogonadism with normal thyroid function and denies excessive use of alcohol: his body mass index 23.9 is normal but he has history of hyperlipidemia.

Summary: What Does This Data Mean?

If overt cognitive impairment causes such as traumatic brain injury, established dementia, neurotoxins, hypoxic brain injury and hypercortisolism are excluded, there is a clear correlation of average recent hyperglycemia extent, reflected by HbA1c, with the extent of mild cognitive impairment, reflected by the Montreal Cognitive Assessment score. While hyperglycemia modulates cognition in multiple neuroendocrine states, including at least:

- A. Nonalcoholic fatty liver disease (NAFLD), generally coincident with insulin resistance,
- B. Hepatic steatosis meaning fatty liver disease with evidence of liver cell injury,
- C. Hepatic fibrosis or cirrhosis with also increased potential to hypoglycemic injury,
- D. Thyroid disease including hyperthyroidism and hypothyroidism,
- E. Probably cerebrovascular disease, only excluded in overt vascular dementia,
- F. Likely alcoholic liver disease, only excluded in advanced encephalopathy,
- F. Psychiatric disease, particularly depression, whether unipolar or bipolar,
- G. Likely in combinations of any of the above conditions, often coexisting.

Cushing's syndrome may be a key exception since:

1. Hypercortisolism results in average MoCA scores higher than predicted from HbA1c;
2. Thus, cognitive impairment in liver disease may be due to steroid responsive inflammation.