Recognition of Reversible Liver Disease: A Window of Opportunity in the Metabolic Syndrome Epidemic

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Background: Fatty liver (FL) is a fundamental aspect of visceral adiposity and the metabolic syndrome. Potentially reversible liver disease (RELD) includes FL, hepatic steatosis (FL with hepatocellular damage) and alcoholic or viral hepatitis.

Methods: Diagnostic tests included SPECT liver-spleen scans with modified fractal (Sn) analysis and blood tests. FL was confirmed by ultrasound, CT or biopsy. Untreated insulin resistant (IR) patients had HbA1c (5.7-6.1)% and diabetics (DM), HbA1c > 6.1%.

Results: Near normal (27) patients had Sn 0.822+-0.133. RELD patients had Sn>1.09 (95% CL of normals). Sn 3.0+-0.21 was higher ($p < 0.001$) in 16 hepatic steatosis patients than Sn 2.15+-0.12 in 42 with FL. Sn 2.44+-1.33 in DM was higher ($p < 0.04$) than Sn 2.15+-0.98 in IR. Severely hyperglycemic diabetics (HbA1c 10.8+-1.5%; n=21) had Sn 3.22+-1.98, similar ($p=0.65$) to Sn 3.68+-1.43 for 60 patients with splenomegaly and ($p =0.11$) to Sn 2.56+-0.34 in 14 patients with hepatoxin exposure. RELD included cases of cirrhosis, severe diabetes, acute cholecystitis, splenomegaly, Cushing's syndrome and viral hepatitis. Abnormal Sn>1.09 (RELD) detected liver disease in 87.0% (315/362) of all patients, including 90.6% (145/160) with DM and 87.7% (136/155) with IR, more sensitively than abnormal liver enzymes 14.1% (51/362). Sn was stable or improved in 71% (25/35) of cases 2 to 24 months after therapies including mifepristone, Qsymia, omega 3 fish oil, vitamin E, pioglitazone and GLP-1 agonists.

Conclusions: Recognition of FL and RELD facilitates multiple, specific liver disease therapies which have potential to reduce the devastating impact of the metabolic syndrome epidemic.

1. **Formula for Modified Fractal Calculation**:

Sn = (S)(L)(1.6/BSA)(BMI/23)

Where S = Limiting Slope near Intercept of Log I vs. Log (A/P)
Fort I = Isocontour and A = Average and P = Peak Liver Activity

L = Normalized Product of Liver Span, l, Liver AP diameter, a and Spleen Span, s, so that
L = (l)(a)(s)/1050 in cm.

BSA = SQRT [(Ht)(Wt)/3600] for Height, Ht in cm and Weight, Wt in kg.

BMI = Body Mass Index = [Wt in kg]/ [(Ht in m)(Ht in m)]

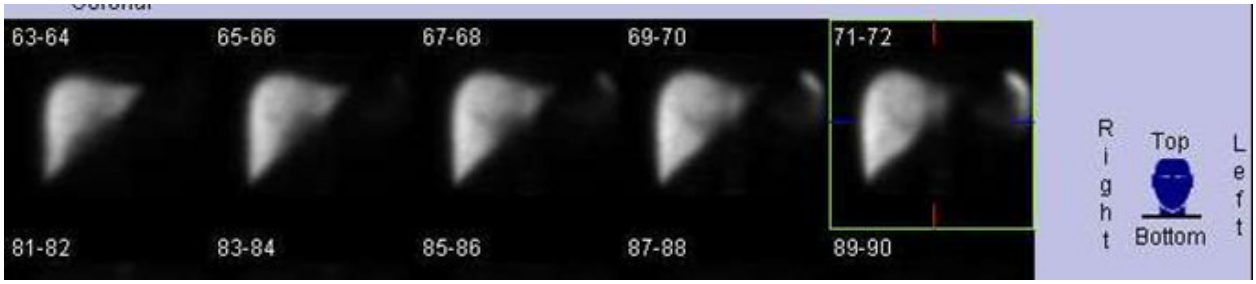

Fig. 1. A 59 year-old woman with BMI 22 exemplifies a normal liver Sn value of 0.859, interestingly without evidence of fatty liver despite type 1 DM and history of HbA1c 8.5% to 9.0%. She has low insulin requirements not suggestive of significant insulin resistance.

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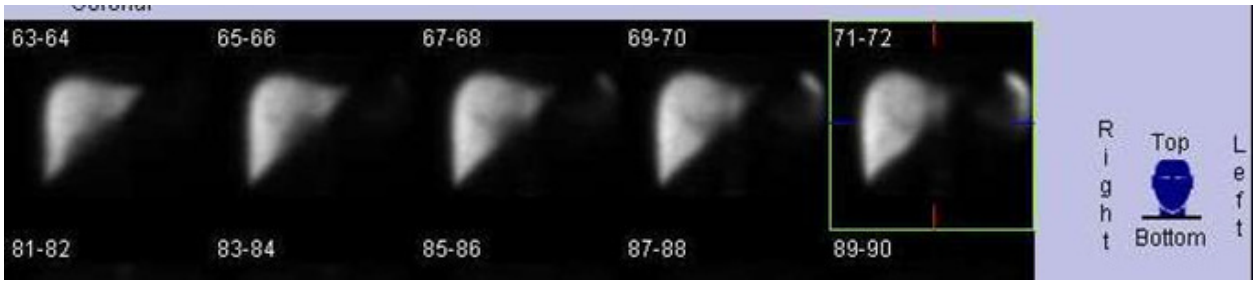
2.



59 year old IR woman with chronic thyroditis and fatty liver confirmed by abdominal ultrasound but with normal AST, ALT and alkaline phosphatase. Patient showed an improved Sn from 1.43 to 0.95 (within normal limits 0.822+-0.133) within one month of a low carbohydrate diet and medical weight loss therapy with Qsymia. Fatty liver recurred with increase in Sn to 1.68 after the patient stopped Qsymia, despite starting vitamin E 400 units daily. Although 71% (25/35) of patients either improved or stabilized Sn and clinical evidence of fatty liver, such as waist circumference and BMI, this patient illustrates that even after successful therapy, RELD can recur without persistent lifestyle modifications or interruption of effective therapy.

3.

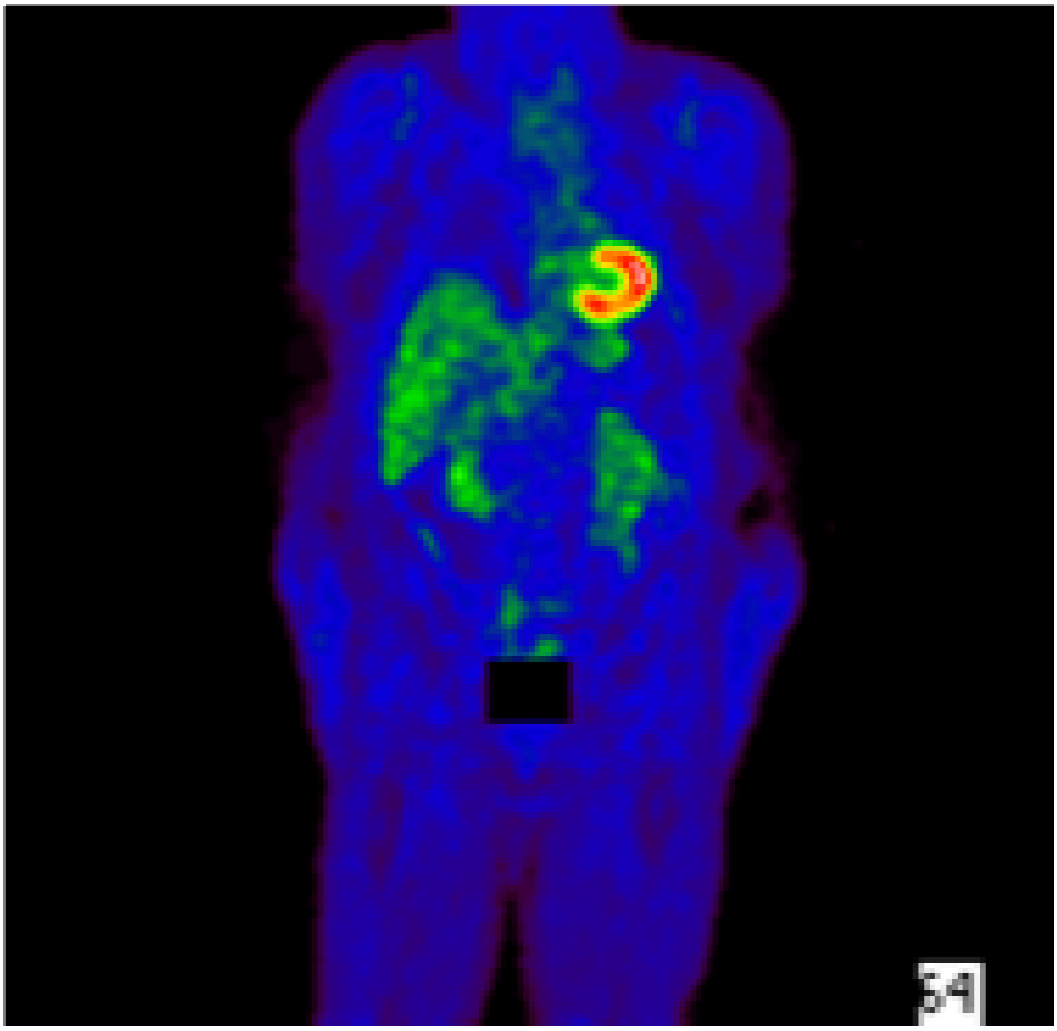


Fig. 3: FDG PET for a 69 year old female with chronic thyroditis and Type 2 DM. Patient has a history of depression and a HbA1c 8.1% with squamous lung cancer in remission post video thorascoscopic resection. The PET data yields Sn 1.94 and her fibrosis index is 0.82, consistent with probable hepatic steatosis or early fibrosis (values > 0.65 fibrosis index are consistent with fibrosis), despite normal AST 14 and ALT 16 (normal < 40). Also, despite minor hyperglycemia, blood sugar 157 mg/dl fasting, myocardial activity is prominent, consistent with minor cardiomyopathy, confirmed on an earlier PET as well and by mildly reduced LVEF 48%. Patients with abnormal adrenal function have a tendency to develop hepatic inflammation and elevated Sn: this patient's baseline AM cortisol was 5.4, borderline low. Remarkably, the methodology used for PET apply also to FDG PET studies: this patient's value would be only slightly above the regression line in Fig. 5 for Ln Sn (on y axis) and the fibrosis index (on x axis).

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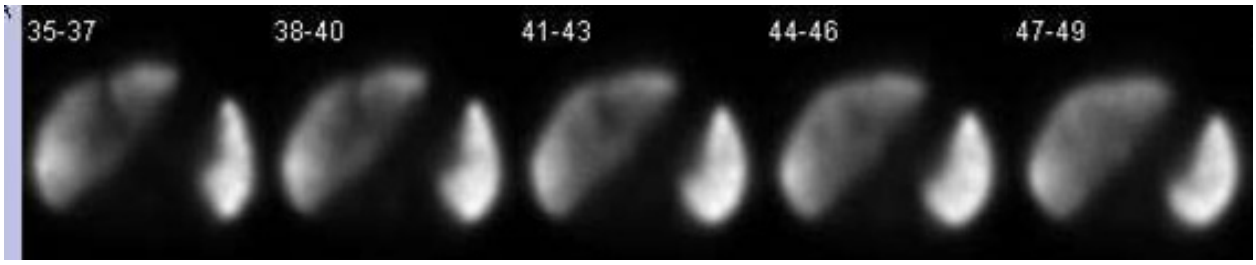

Fig. 4: Transaxial SPECT images for a 66 year-old type 2 diabetic woman with hepatic fibrosis index 1.73 (> 0.65 consistent with fibrosis) and Sn 2.52. Note evidence of portal hypertension with increased spleen concentration of tracer. Additional factors possibly contributing to hepatic fibrosis in this patient included history 18 months of breast cancer chemotherapy. Her FDG PET showed remission without liver or other metastasis. Patients with hepatic fibrosis have Sn 2.66+-1.5, comparable to patients with either severe type 2 DM (HbA1c 10.9%+-1.3%) or splenomegaly as shown in Fig 8B.

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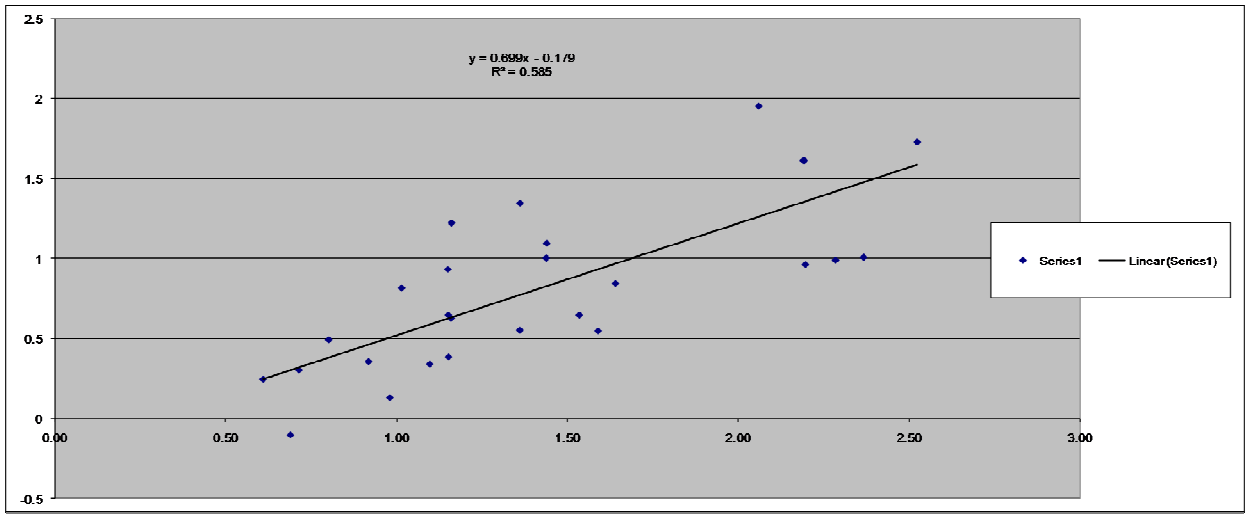

Fig. 5: Semi log plot of Ln(Sn) on the y axis vs. fibrosis index on the x axis. A significant correlation of 0.765
was obtained for patients age <19 to 74 years and BMI 25 to 44, without abnormal steroid levels and without coincident cholecystitis or hepatitis (viral or chemical) together with IR or DM.

6.

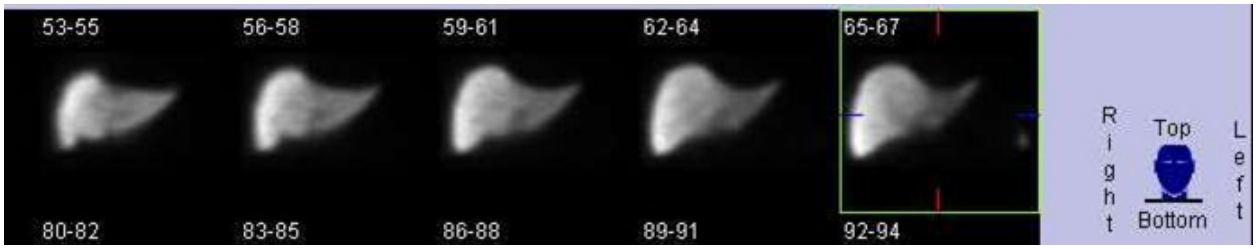

Fig 6A: A 46 year-old man with opiate and other analgesic dependent chronic low back pain has IR with HbA1c 5.8% and history of significant alcohol consumption. His abnormal liver transaminases and mildly elevated Sn 1.44 were consistent with early hepatic steatosis. Patients with hepatic steatosis had average Sn 3.0+-2.1.

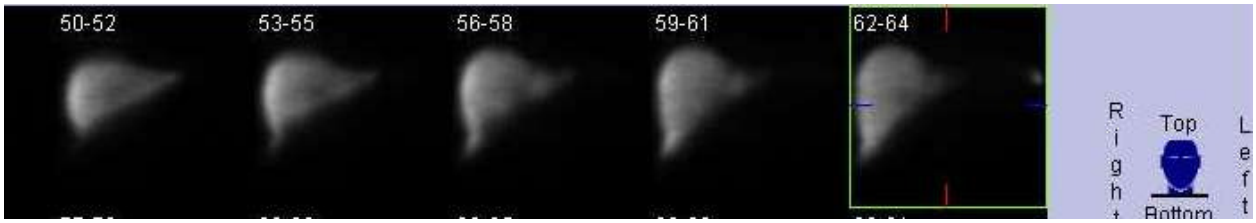

Fig 6B: A 73 year-old hypertensive, hyperlipidemic, type 2 diabetic man with chronic thyroiditis, diabetic neuropathy and history of stroke three years earlier had abnormal liver enzymes consistent with hepatic steatosis and Sn 2.08. The natural history and genetic component of RELD is emphasized by this patient being the father of the one illustrated above in Fig 6A.

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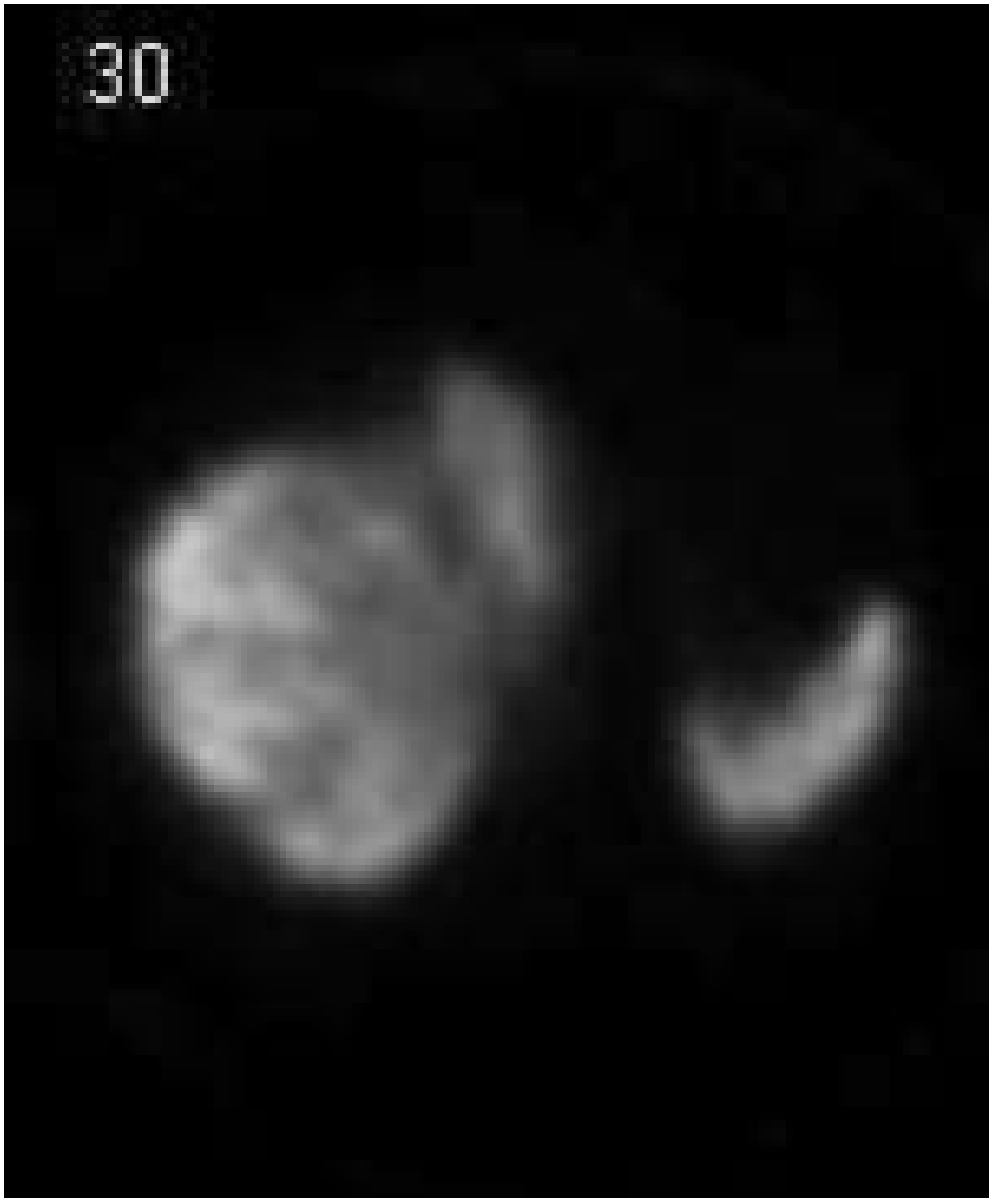

Fig. 7: A 66 year-old type 2 diabetic, acromegalic man has evidence of more prominent hepatic inhomogeneity than expected, both visually and from graphical analysis, his Sn of 2.56 (Ln = 0.94) exceeding expected for fibrosis index only 0.61 (cf. Fig 5). Besides hepatomegaly with liver span 19.5 cm vs. < 17 cm for normal, possibly due to acromegaly, the patient had hepatotoxin exposure.

8.

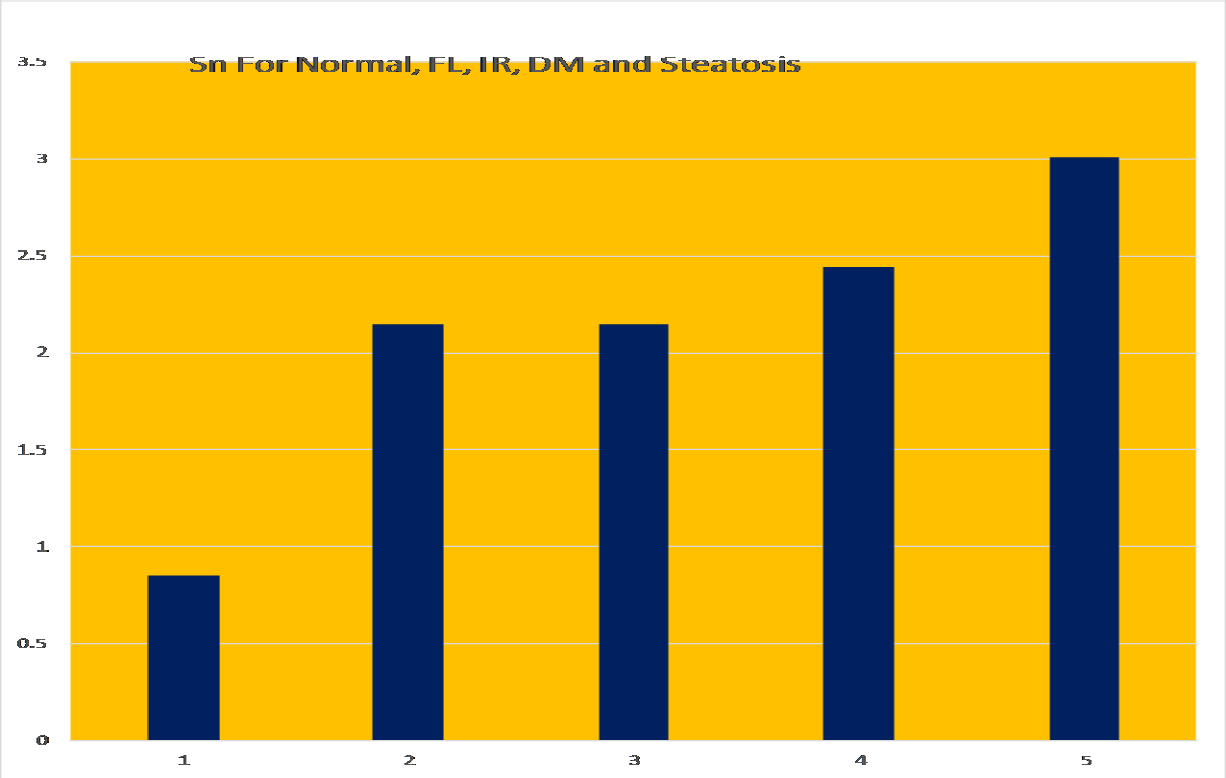

Fig 8A: Sn values from left to right for near normal, 0.822+-0.133, IR 2.15+-0.98, Fatty liver, 2.15+-0.12, type 2 DM 2.44+-1.33 and hepatic steatosis 3.0+-2.1. hepatic

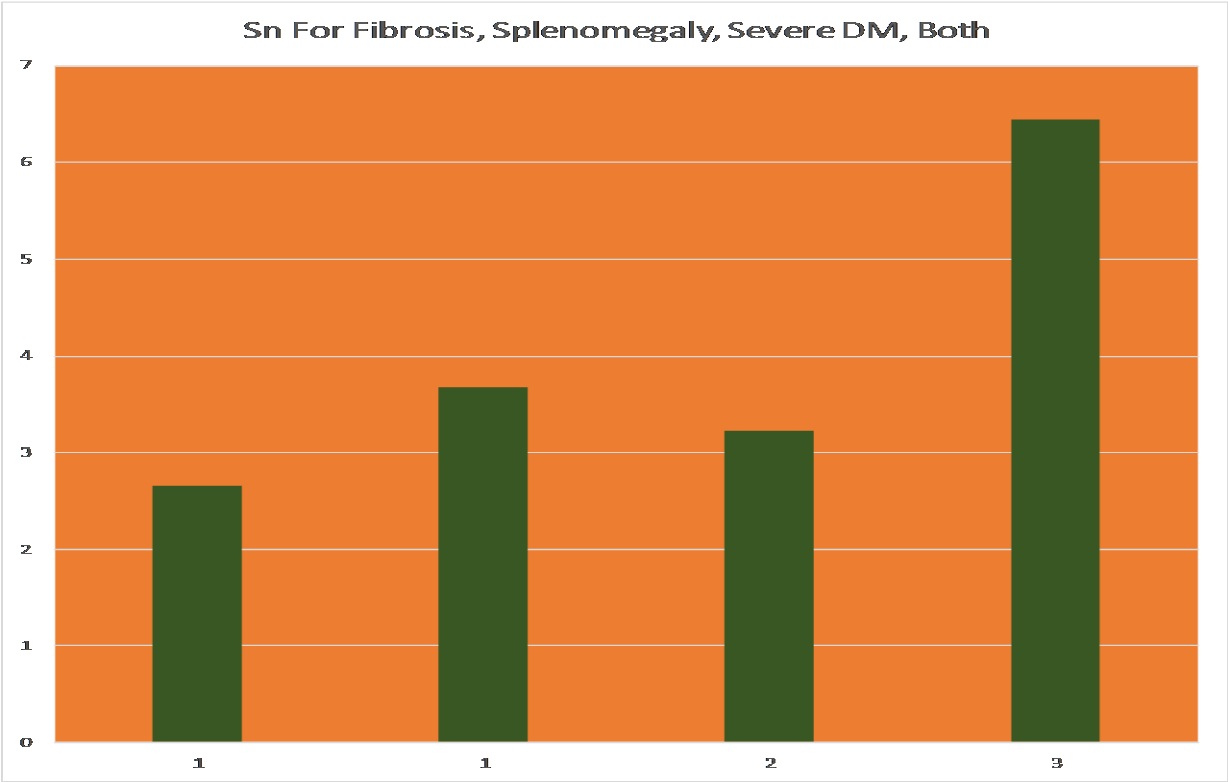

Fig 8B: Sn values from left to right for hepatic fibrosis 2.66+-1.5; splenomegaly 3.08+-1.43; severe type 2 DM 3.22+-1.98 and patients with both severe DM and splenomegaly 6.44+-1.31. The patients with both severe DM and splenomegaly were significantly different ($p < 0.01$).

Conclusion

Modified fractal analysis of liver spleen scans is:

1. Highly sensitive, near 90% for detecting fatty liver (FL), if 100% of IR patients have FL.

2. Widely available and likely can be generalized to other modalities such as FDG PET.

3 Correlates well with extent of disease, more severe or combined causes of liver disease generally increasing Sn values exponentially.

4. Is an economically feasible method to detect and monitor the fundamental, hepatocentric aspect of the metabolic syndrome.

5. RELD: Reversible Liver Disease potentially includes nearly all liver disease, with one patient in this series showing significant recovery after hospice referral for apparently terminal cirrhotic liver failure due to alcoholism and uncontrolled type 2 diabetes mellitus

Among 401 Patients in this Series ,Liver and selected, treatable, related diseases included:

1.	Obesity (BMI > 25)	377 94.0%
2.	Insulin Resistance (IR)	205 51.1%
3.	Diabetes mellitus (DM)	176 43.9%
4	Hyperlipidemia	227 56.6%
5.	Hypertension > 140/90)	199 49.6%.
6.	Thyroid disease	156 38.9%
7.	Depression (Psychiatric)	131 32.7%
8.	Adrenal (mainly Cushing's syn)	63 20.9%
9.	Alcohol related	36 9.0%
10.	Viral hepatitis & metabolic synd.	>6 >1.5%