

Comparing Regions of Best and Worst Liver Function Increases Sensitivity to Detect Liver Disease in Insulin Resistant Patients

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Objective: Analyze relationships between best and worst areas of liver function and liver disease severity in insulin resistant patients.

Methods: SPECT liver-spleen scans used a Siemens Ecam, iterative reconstruction and low dose, < 0.4 mCi Tc-99msulfur colloid/L extracellular fluid, $ECF \text{ in } L = (Ht \text{ in } m)(SQRT(Wt \text{ in } kg))$. Modified fractal analysis, extrapolated $LN(A/M)$ vs. $LN(I)$, for A = average counts in an isocontour I of volume V, and M, either peak (for best function) liver counts, or minimum (for worst function), to define fractal slopes, Sb for the best, and Sw for the worst, areas of liver function, both normalized for BMI, ECF, and indices of liver and spleen size. Liver function categories were assigned using ultrasound, serum transaminases, a calculated hepatic fibrosis index, abdominal CT and liver biopsy. Montreal Cognitive impairment monitored cognition.

Results or Case Presentation: Among 79 patients, Sb slopes were all positive and found in the liver right lobe. Whether calculated directly or from a quotient of the average and best slopes, the Sw slopes were all negative and found in the liver left lobe. Spleen Sb was between liver Sb and Sw, except for splenectomy or sickle cell patients. Sb and Sw are insensitive to image smoothing, variation usually < 15% for Gaussian filters from 5 mm to 10 mm using a 7mm resolution collimator. Among many ways to normalize fractal slopes, the best used $ECF/15$; $BMI/25$; liver vertical span, $L1/17$, Liver AP diameter $L2/12$ and spleen vertical span/12. Near normal patients (n =11) had HbA1c (5.9+-0.6)%, Sb 0.49+-0.04 and Sw -1.43+-0.033; NAFL patients (n=22) had Sb 0.60+-0.09, Sw -2.12+-0.67; hepatic steatosis patients (n=20) had Sb 0.66+-0.08, Sw 2.76+-1.03; liver fibrosis patients (n=25) had Sb 0.75+-0.09, Sw -3.49+-0.86. Patients (n = 23) with high HbA1c (11.1+-1.2)% had Sb 0.75+-0.11, Sw -3.52+-0.92 similar to fibrosis patients. Liver disease severity and S values trended to correlate directly with overall complications of insulin resistance, including cognitive impairment, excluding brain injured patients and Cushing's patients.

Discussion: Quantitative measure of liver function is increasingly important. The difference between Sb and Sw increases as liver disease progresses. Use of Sw increases sensitivity for early disease but Sw is more prone to attenuation artifacts and noise due to Poisson error at low count rates, which is reduced somewhat by adjusting tracer dose to ECF.

Conclusion: Abnormal liver function is fundamental to insulin resistance. Early liver disease is more sensitively detected by Sw, derived from the areas of worst liver function, or the ratio of Sb to average liver function.

1.

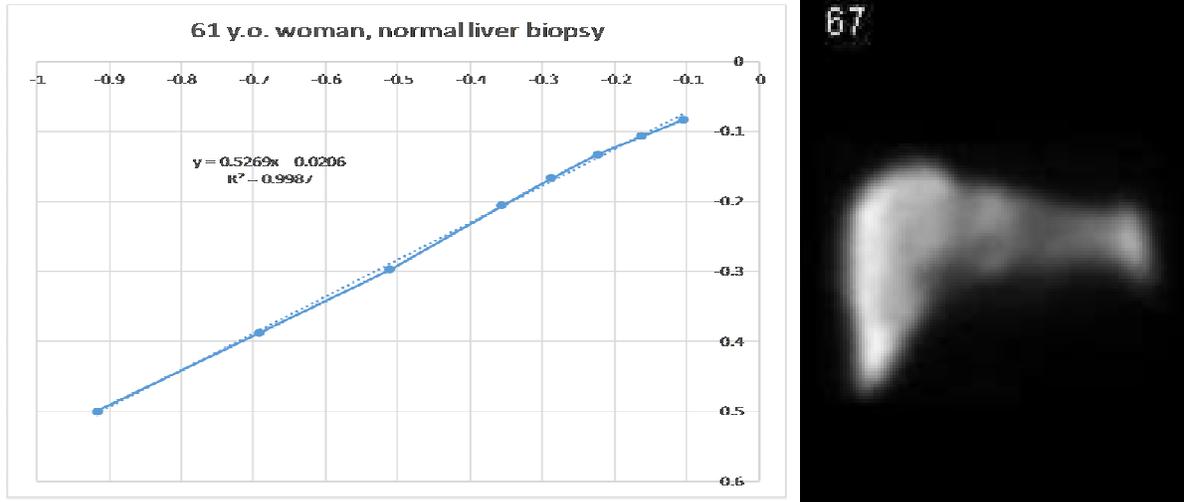
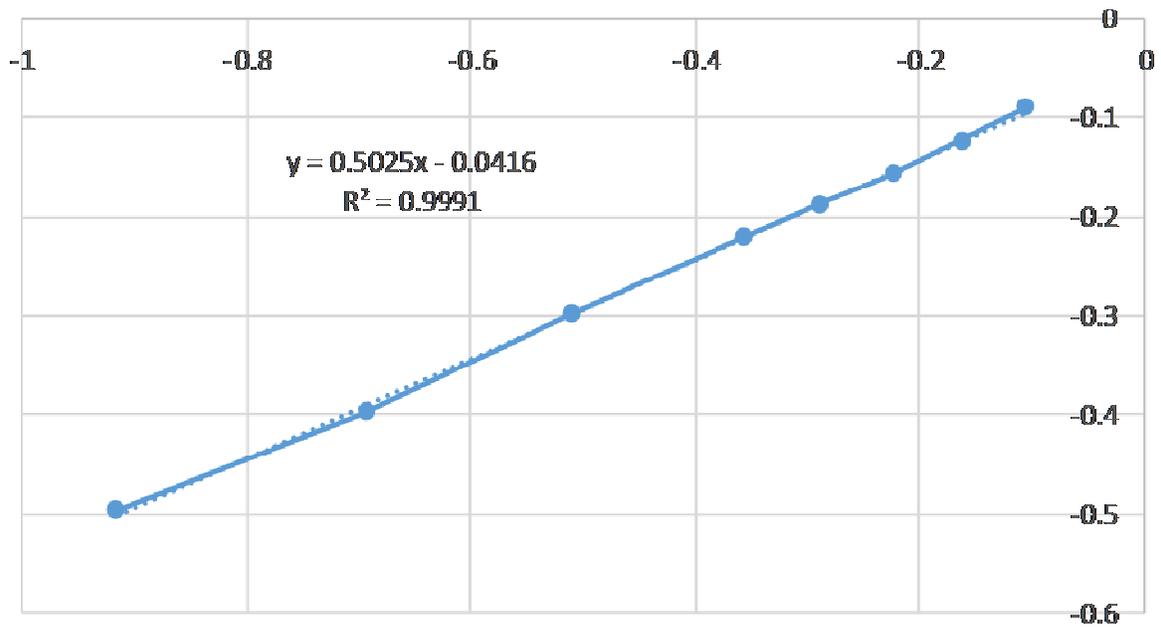
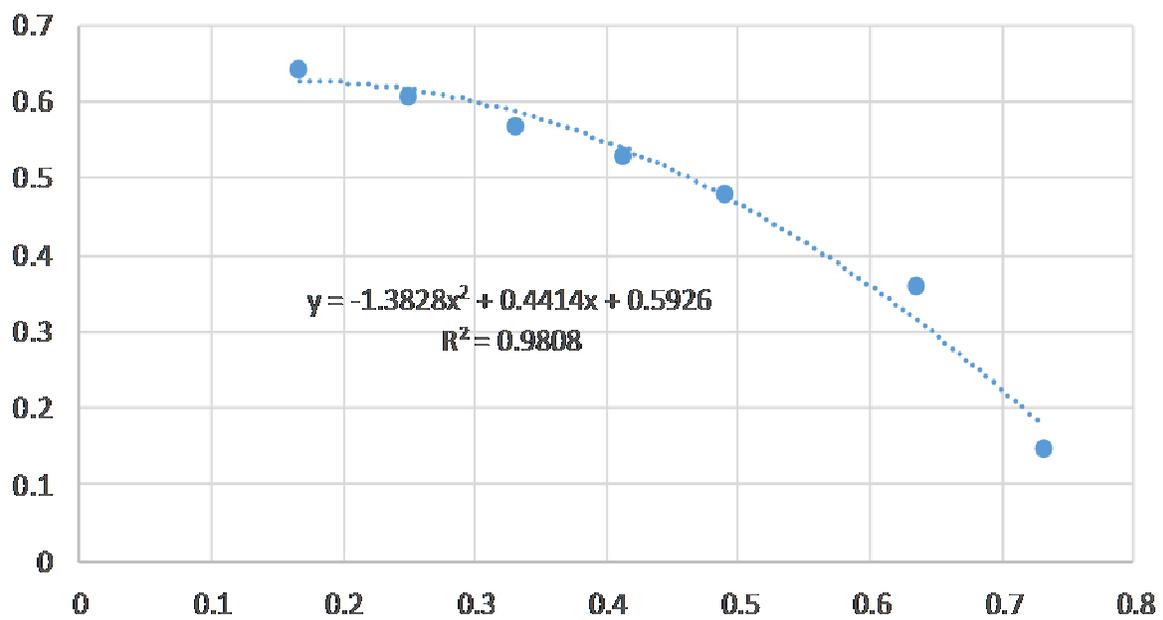


Fig. 1: Near normal patients showing nearly linear modified fractal plots for the positive (extrapolating toward maximal counts or function) but not the negative (extrapolating towards minimal counts or function) slopes. Among 20 near normal patients age 52.9+/-10.4 years, with BMI 23.7+/-3.6 and HbA1c 6.42+/-1.46, the S_n was 0.751+/-0.116, S_b 0.534+/-0.047 and S_w - 1.71+/-0.19, significantly different with $p = 5.21E-18$. For these data S_w was approximated using its isocontours as $\ln(I/40)$, where I indicates the isocontours used for S_b , which was empirically found to give $(1/3)S_w$. Weighted (for Poisson count uncertainty and/or approximate attenuation effects) and likely more accurate isocontours transform $I_w = (5/3)(I_b) - (200/3)$ where I_w is the isocontour for the negative slopes, I_b the isocontour for the positive slopes, and the 40% I_b value is taken as the entire liver area in an axial section near the mid portion of the left lobe, superior to the porta hepatis, which correlated well with anatomic measures. The patient shown below had S_b 0.537 and S_w 1.582. Since this patient had CAD, polymyositis and BMI > 25, he may not have entirely normal liver function. On the other hand, his values are quite similar to the 59 year-old woman above who had BMI 22.9 and a normal liver biopsy for reversible liver disease due to tetracycline hepatotoxicity. The Riedel's lobe (tongue-like inferior extension of the right lobe) above on the right coronal section is within normal limits.

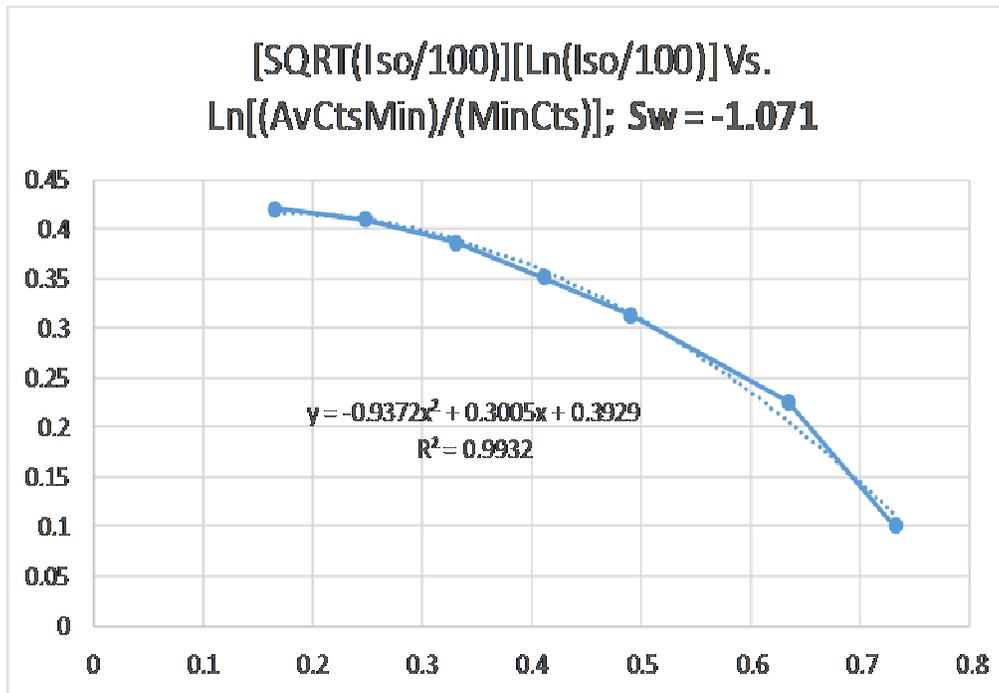
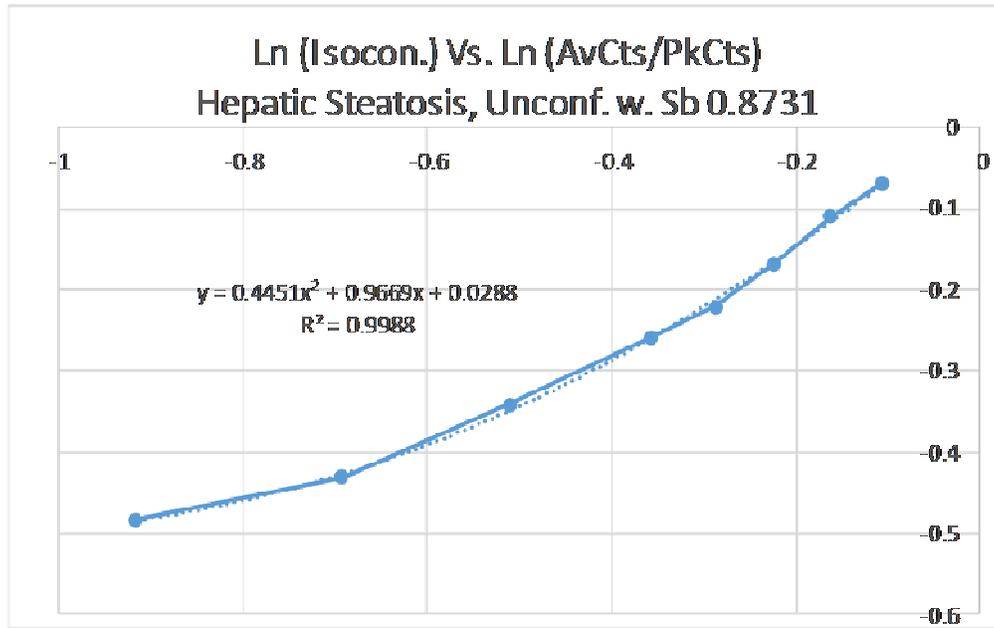
Type 2 DM man, HbA1c 7.1% BMI 26.67



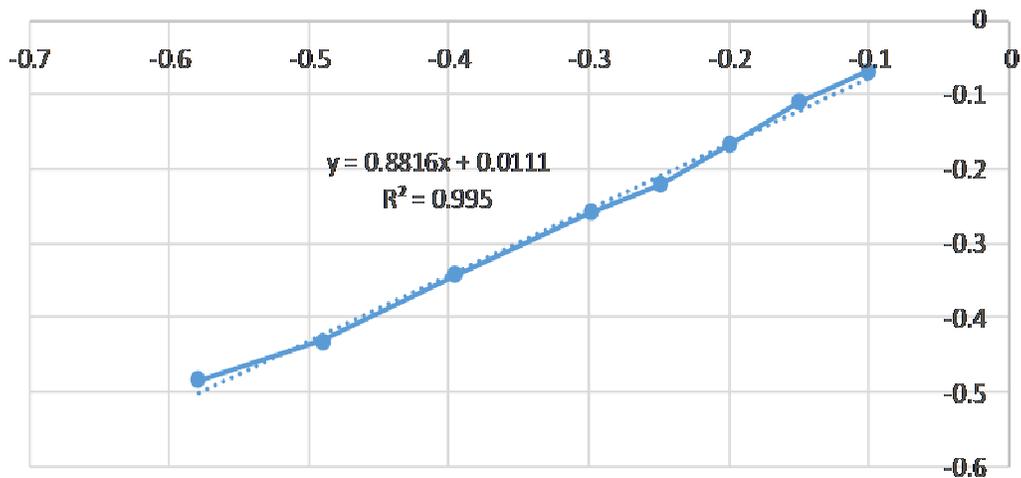
Weighted Negative Slope, $S_b -1.5815$



2.



Ln(Isocon.) Vs. Ln(AvCts/PkCts) w. wt. factor
 SQRT(Isocon); Hepatic Steatosis Unconf.
 Now Linear, nearly same Sb 0.8861



[SQRT(Iso/100)]{Ln(Iso/100)} Vs.
 [Max/AvCts][Ln(AvCtsMin/MinCts)]; Sw -2.495

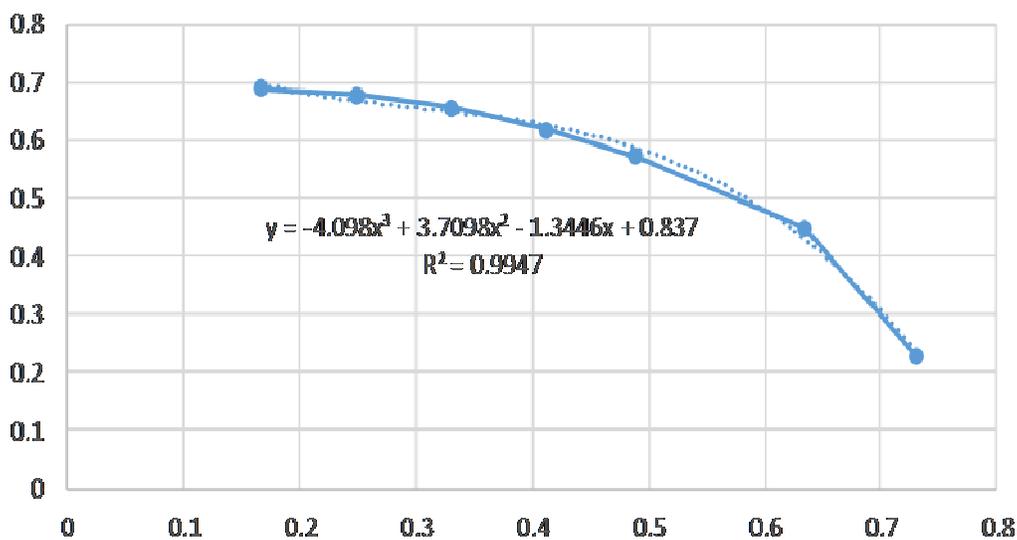
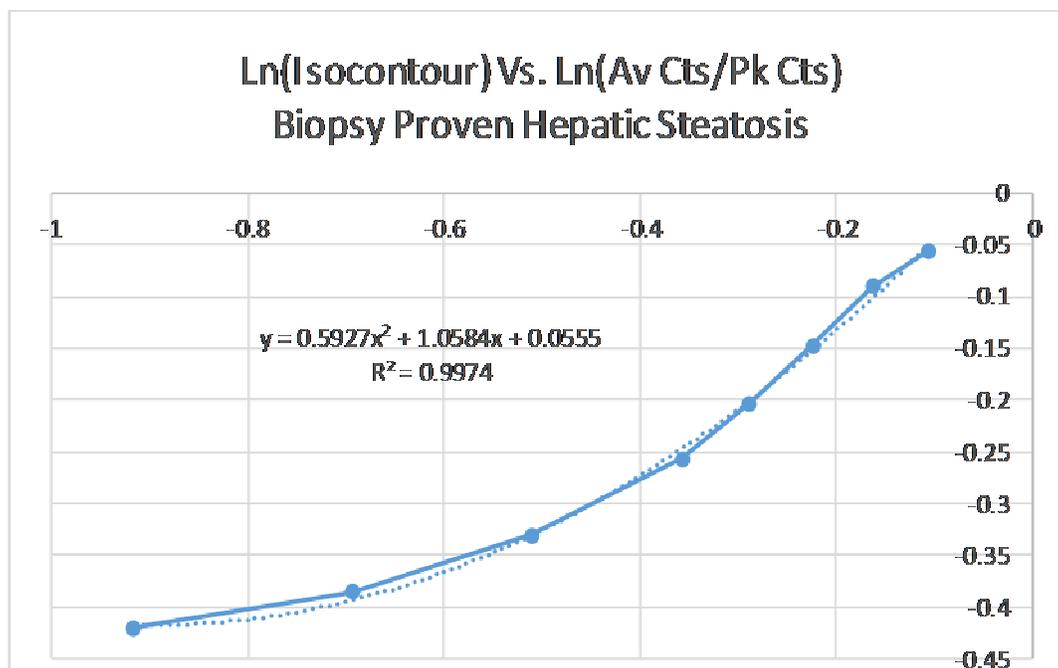
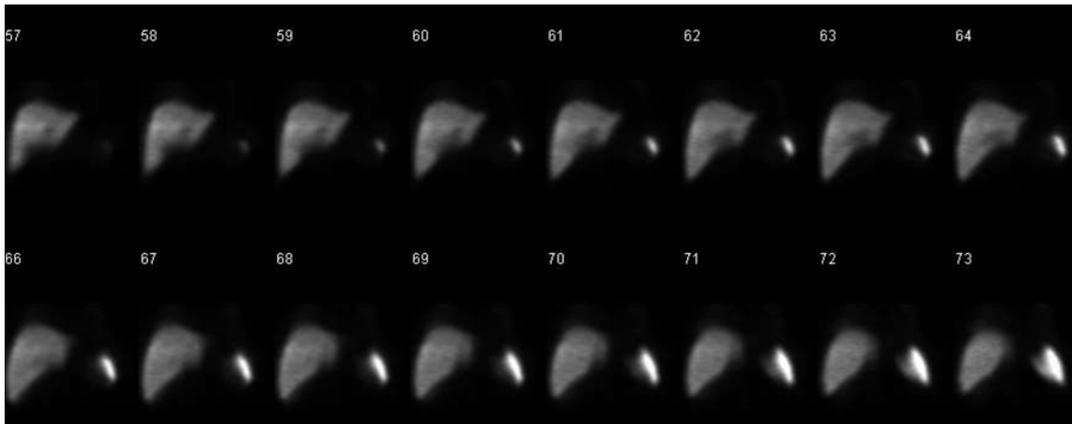
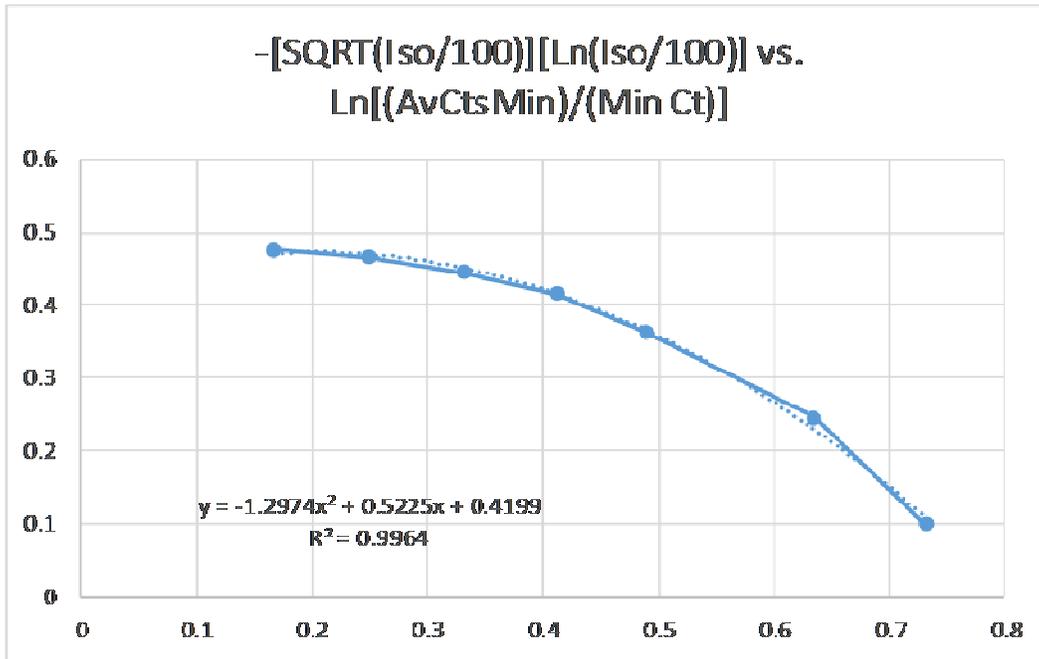


Fig. 2. Effect of weighting factors chosen is greater on Sw, shown above, right than on Sb, shown above, left, for a 73year-old type 2 diabetic man whose scan and modified fractal analysis was very similar to a biopsy-confirmed 48 year-old woman with biopsy proven hepatic steatosis (NASH). It is likely that the square root weighting factor partially corrects for attenuation as PET data (not shown) more closely follows the linear fractal pattern in patients with liver disease due to insulin resistance. The weighting factor for the ordinate is similar to the usual 1/y factor often recommended for log plots. Below is a different pattern in a patient with overt liver disease without insulin resistance showing the utility of the weighting factors chosen and their ability to sensitively detect different disease patterns. Statistical analysis based on log-log plots is not necessarily valid without further data on the nature of the original vs. the log distributions; however, the curves for the different clinical types are highly reproducible.





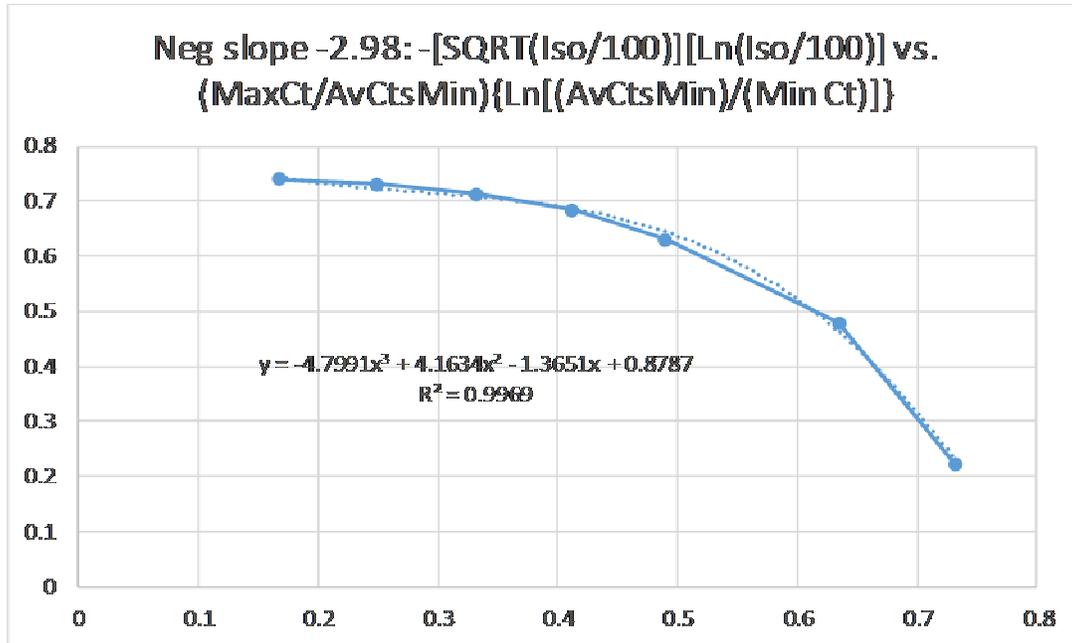
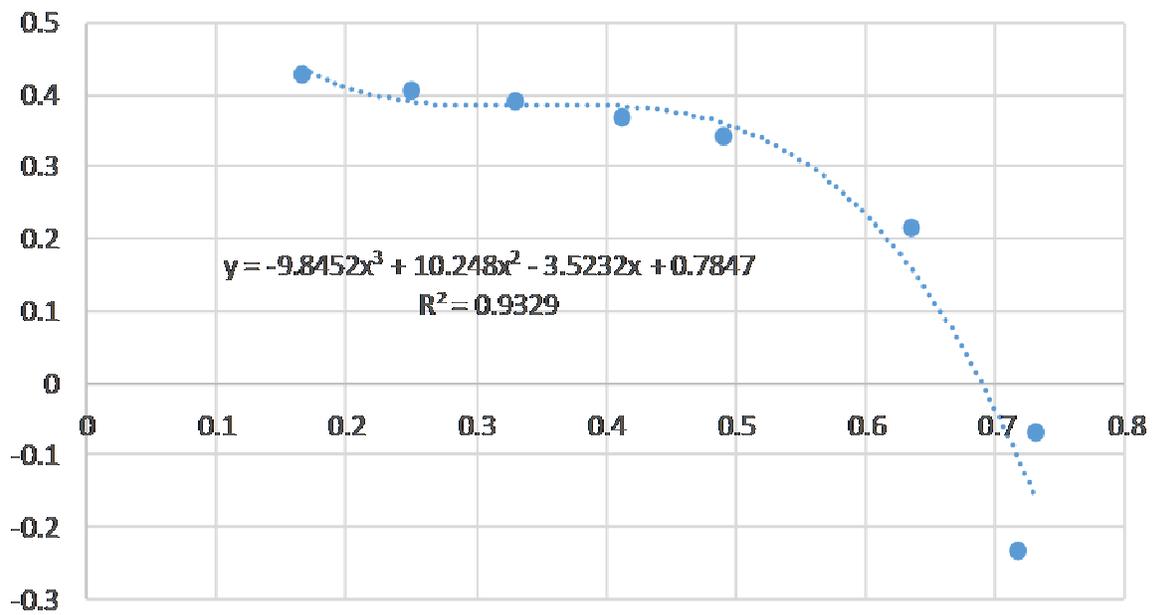


Fig. 2 Continued: The 59 year-old woman whose axial SPECT section below, at the usual mid left lobe level taken for analysis, illustrates results for a noninsulin resistant patient with multiple abnormalities, including photopenia in the left lobe consistent with an hepatic cyst and probable focal infarcts or scars in the right lobe of the liver lateral and posterior. Her Sb 0.7 was abnormal, but similar to patients with simple fatty liver (NAFL). In contrast, her Sw value, plotted on the right, shows marked abnormality reflecting the clearly visible heterogeneity in her images. Most insulin resistant patients had limited heterogeneity in the spleen; however, this patient has considerable splenic heterogeneity as well.

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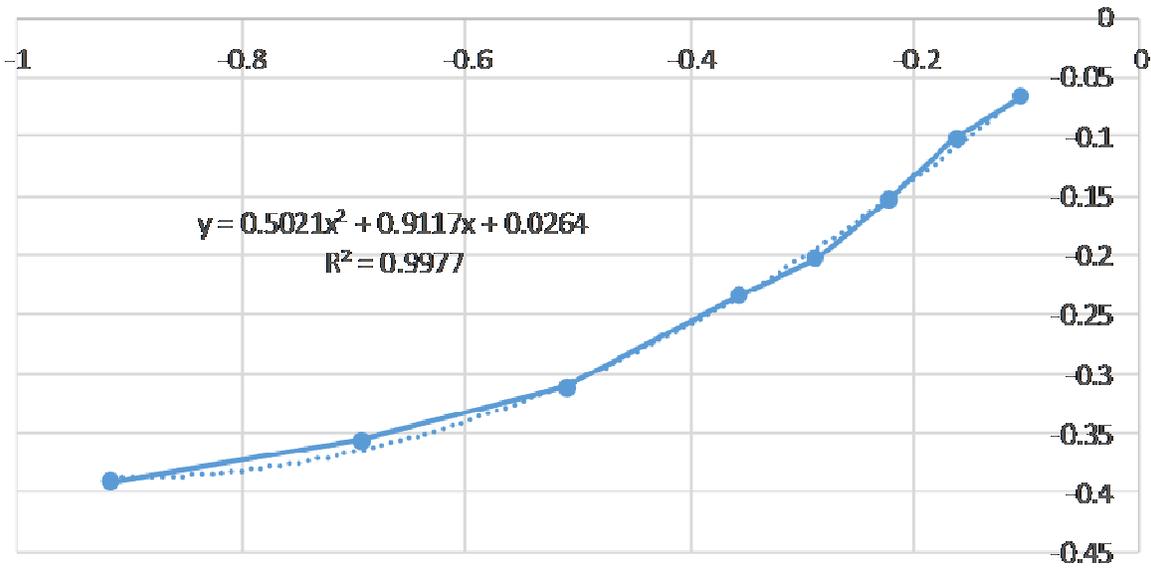


More Neg. Sw -4.02 In Thin Pt. w.o IRS



3.

75 y.o. diabetic man with splenomegaly, CHF, hi trigly, gout, CAD, former smoker, BMI 45.5



75 y.o. type 2 DM man Weighted Negative Slope

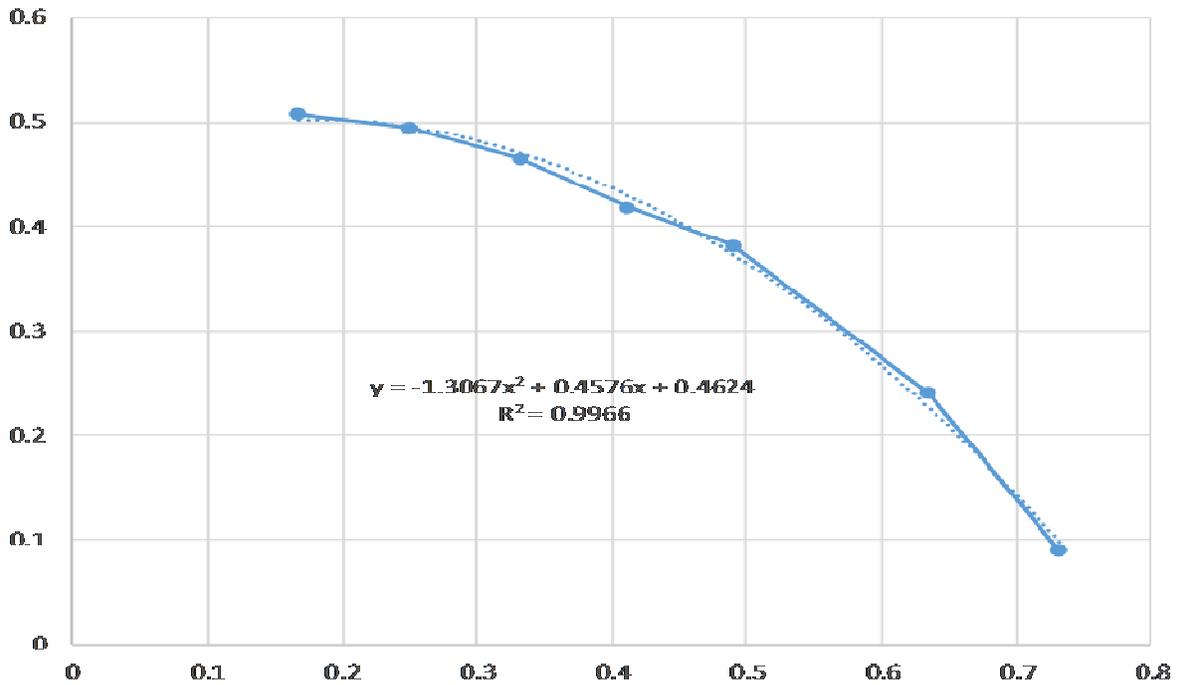
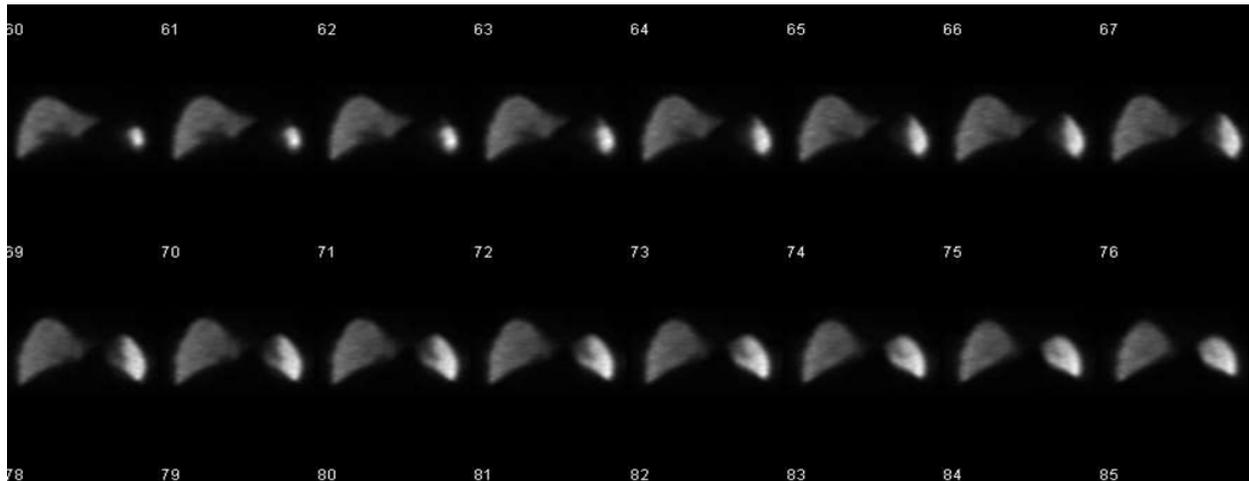


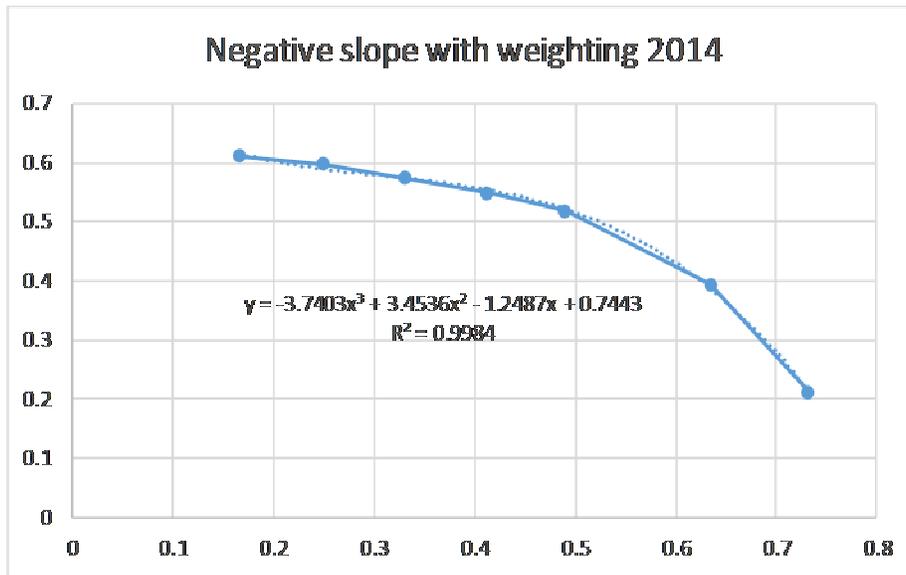
Fig 4: On the left is modified fractal slope plot for a 75 year-old hypertensive, hyperlipidemic (particularly hypertriglyceridemic), hypogonadal, type 2 diabetic man with BMI 45.5, splenomegaly, portal hypertension, CHF history with BNP 1122 (nml < 100), gout, prior cigarette smoking, abnormal ALT, normal AST, and abnormal myocardial perfusion scintigraphy pending coronary angiography . His Sn 5.01, S 0.806 and weighted neg. slope - 3.20 (shown above on the right) are typical of hepatic fibrosis as was his hepatic fibrosis index of 2.19 (95% confidence limit for fibrosis considered > 0.6). Both modified fractal plots fit well to binomials with R = 0.9988 and 0.9983. As expected, both plots give nearly the same slope if extrapolated toward the whole liver area, representing the slope near the average counts for the entire liver: - 0.112 for the left curve and -0.108 for the right curve, taking the average of the last two fitted slopes, rather than the final extrapolated value, which is nearly zero (+0.0844 on the left and -0.022 on the right) in either case. We have not discovered a simple relation of the peak positive slope, average slope and the negative slope, which vary almost independently, depending on the type of liver disease and its severity. Patients included in the present comparisons of NAFL, hepatic steatosis, and hepatic fibrosis were believed to have primarily insulin resistance related liver disease. Patients with alcoholic cirrhosis, cholestatic or viral hepatitis and other metabolic causes of liver disease, such as hemochromatosis or alpha-1 antitrypsin deficiency, were not included.



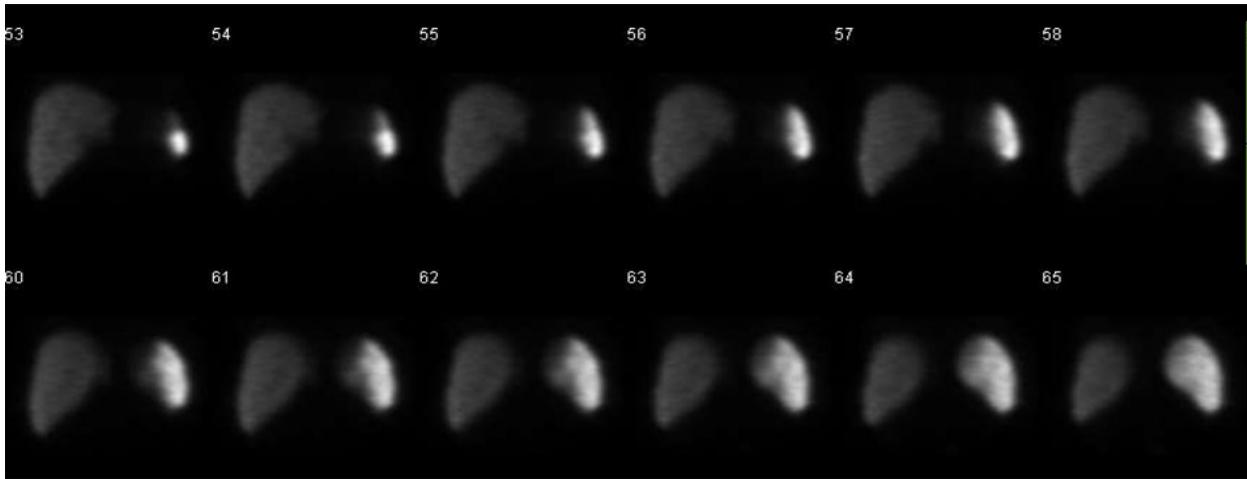
4.

Fig 4: A 34 year-old insulin-resistant woman with severe migraine and stroke-like episodes had borderline abnormal AST 40 (nml 11-38), normal ALT 37 (nml 10-47) near her first scan in Sept. 2014 with Sn 3.22 and Sb 0.756 with weight 235 lb, BMI 36.9. After omega 3 acid ethyl ester 2 grams twice daily and eventually, phentermine-topiramate ER she lost weight from an intermediate 254 lb to 230 lb and 20 months later, in May 2016, had a repeat scan with improved Sn 2.40 and Sb 0.575. Remarkably, her negative slope, Sw - 2.20 (shown on the right) only increased to -1.95 (not shown).

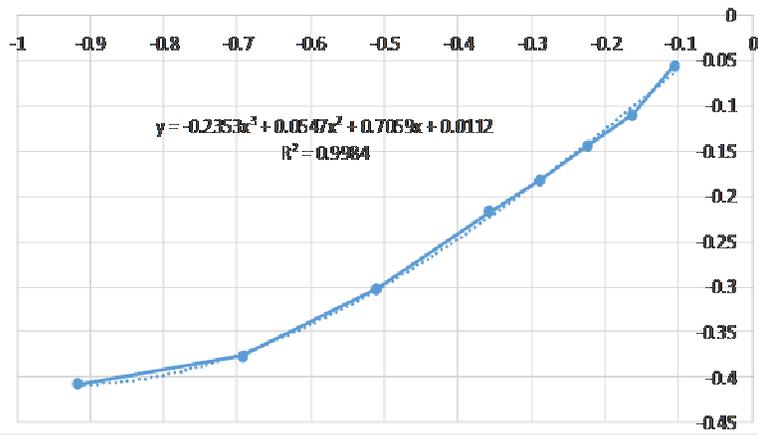
Her initial and later scans (shown below) revealed nearly constant liver and spleen size without clear visual evidence of change. Abdominal ultrasound, although technically limited, showed improvement in initial, increased, inhomogeneous echogenicity and follow-up transaminases were normal.



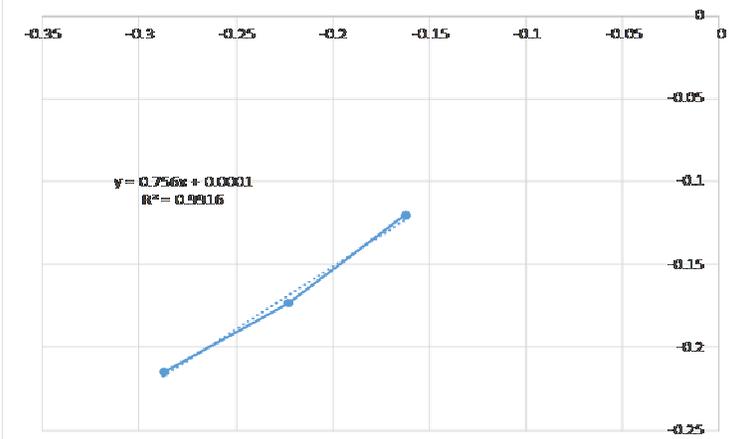
2014 Scan



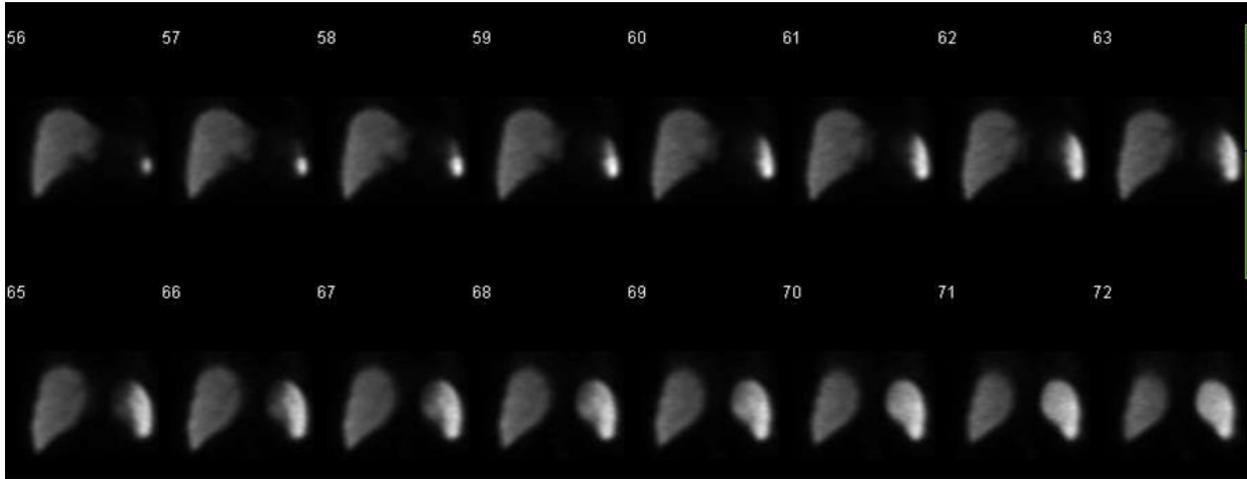
Positive Slope Sb 0.575 in 2016 After Weight Loss



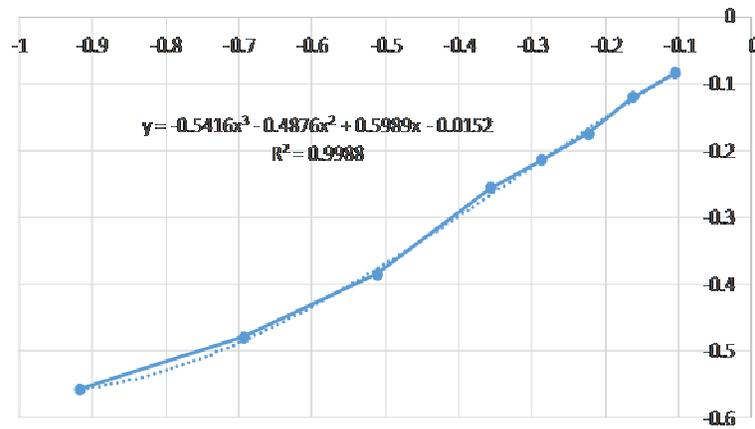
Positive Slope 2014



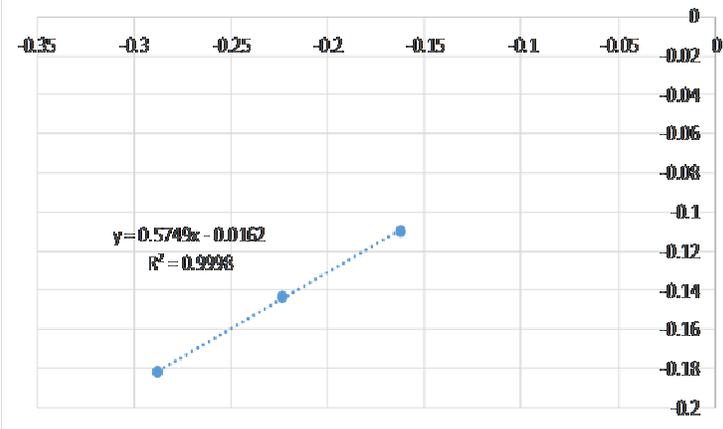
2016 Scan



Positive Slope Sb 0.756 in 2014



Positive Slope 2016; omits last point



5.

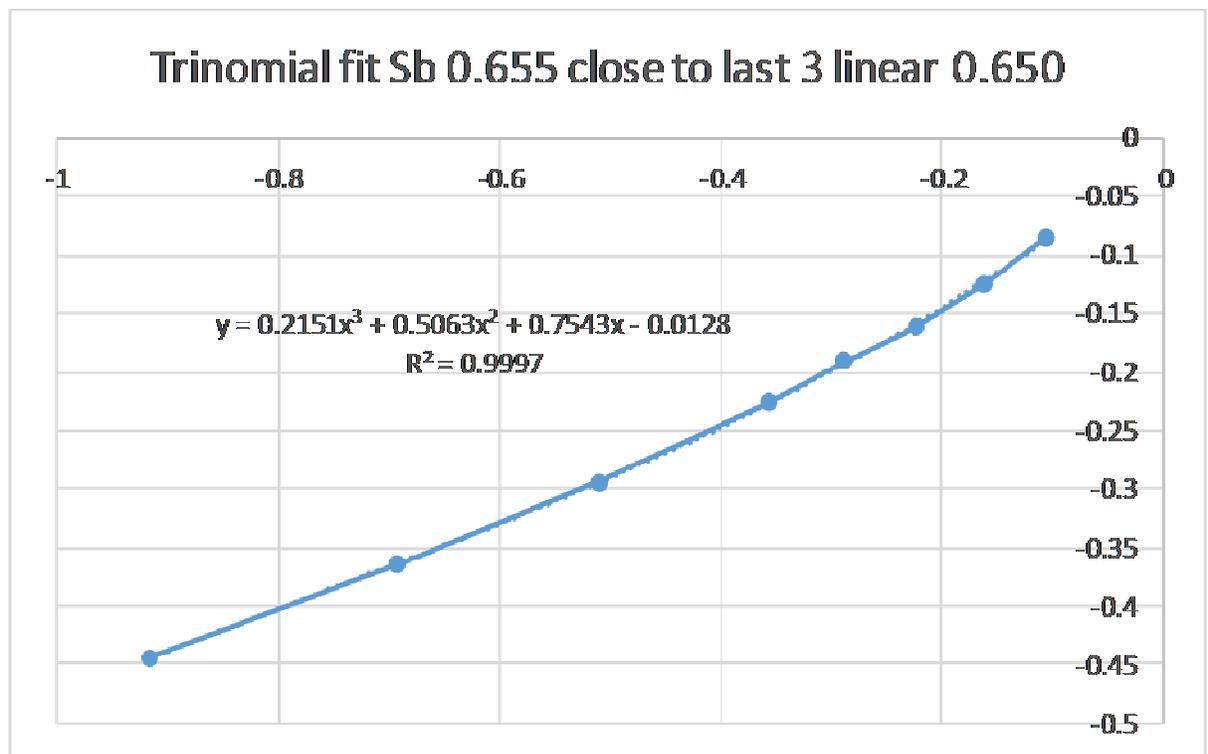
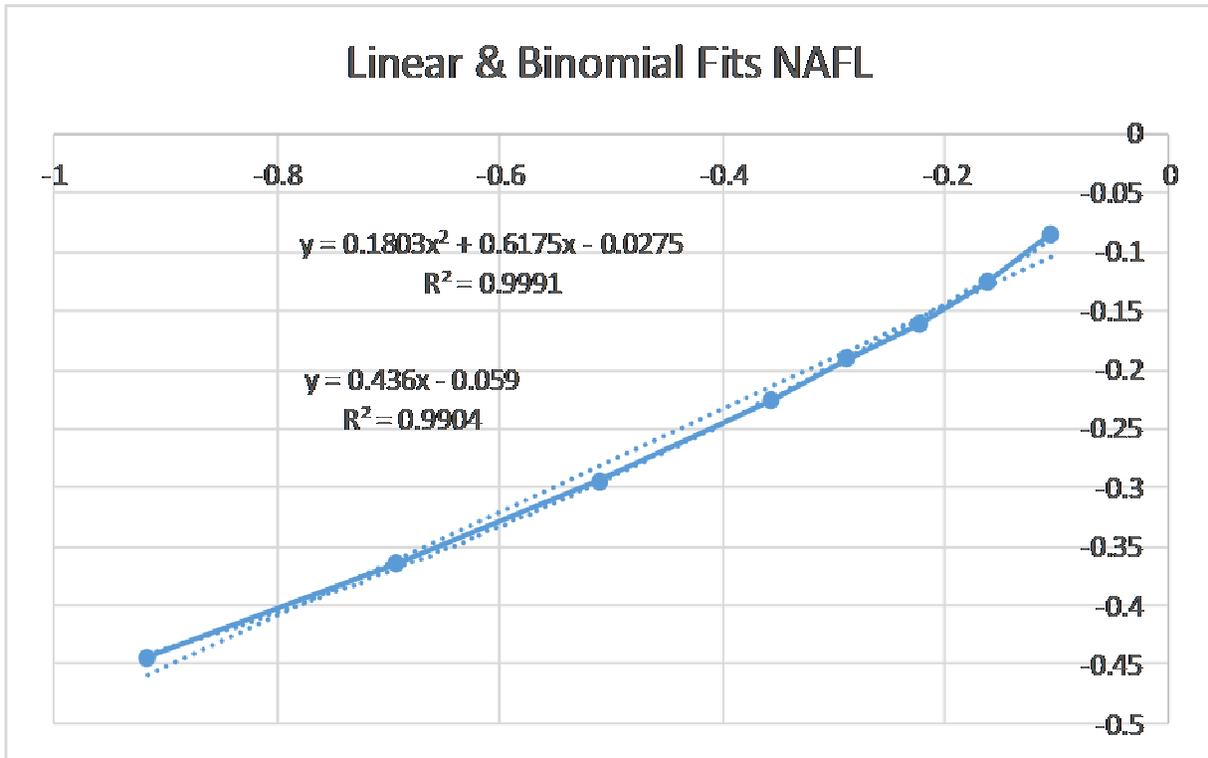
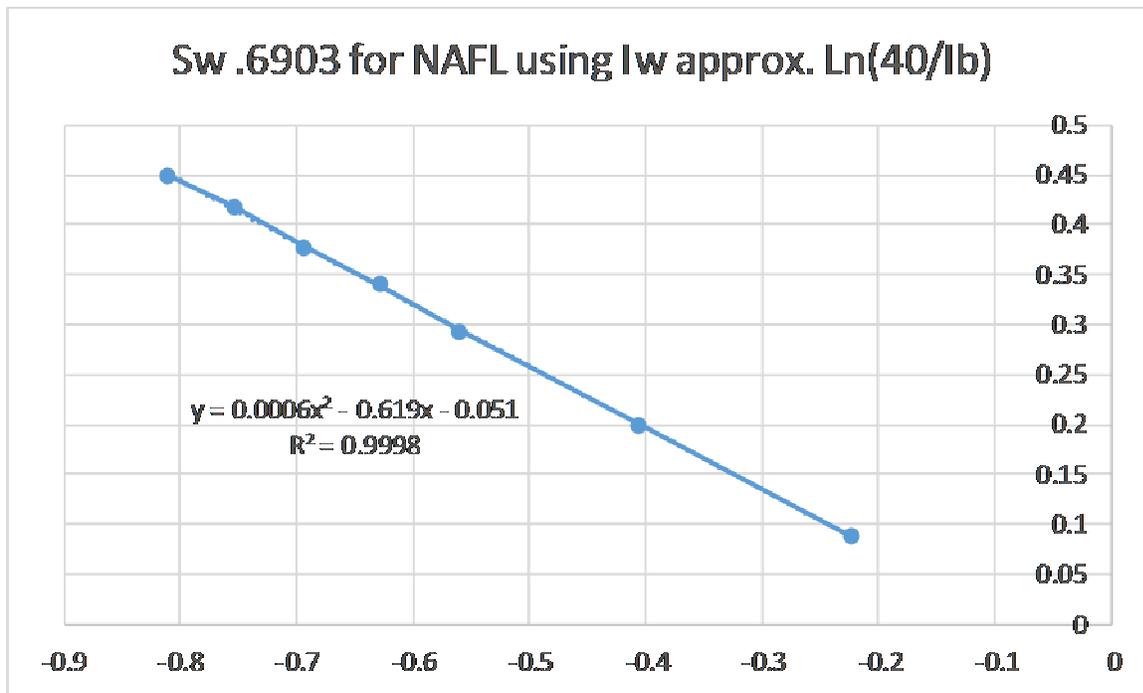
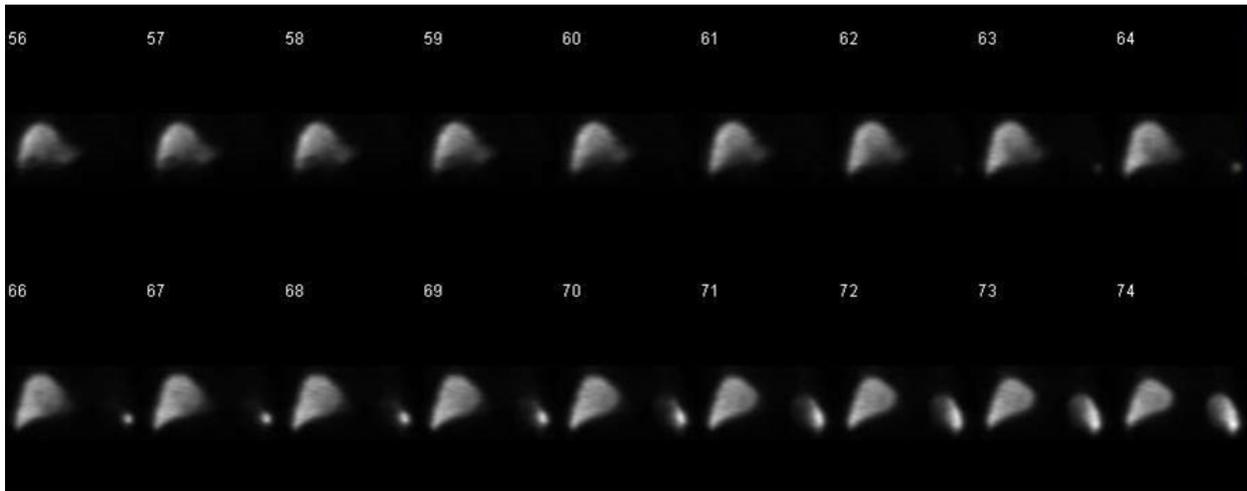
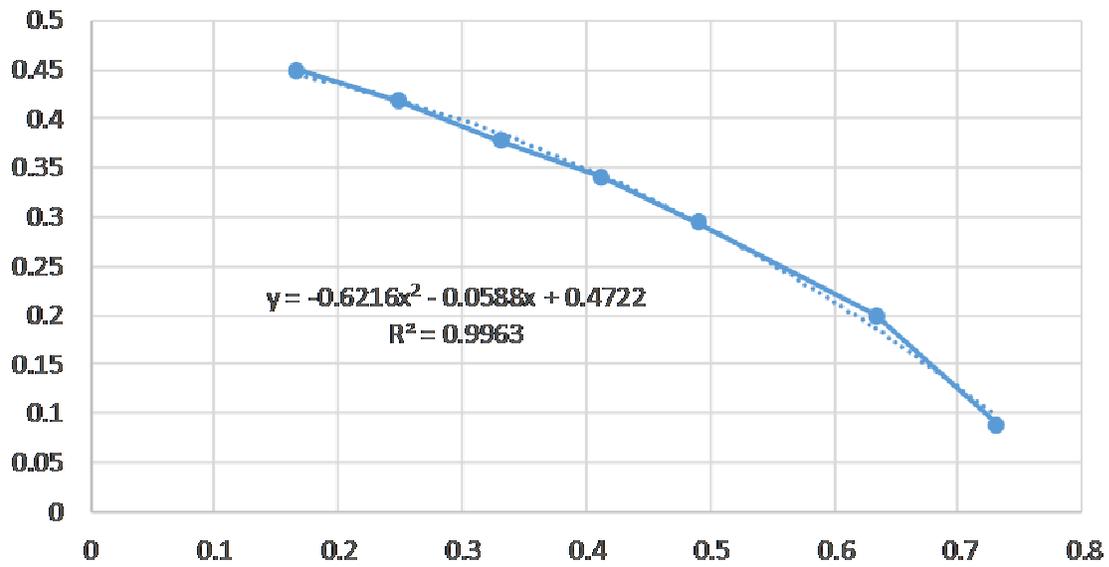


Fig 6: Positive slopes are above and negative slopes below for a 75 year-old insulin resistant man who had borderline findings of NAFL including a single borderline transaminase (only 12.4% of 123 NAFL patients had abnormal LFT's; however 13/26 = 50% of NAFL patients with abdominal CT or ultrasound confirmed fatty liver), HbA1c 5.5% (av. HbA1c among 147 NAFL 6.37+-1.38%), and Sb 0.655 (vs. 0.621+-0.065 for the NAFL group), with (1/3)Sw 0.6903 (vs. 0.769+-0.137 for the NAFL group). The difference between near normal patients (see Fig 1) with Sb 0.536+-0.045 and (1/3)Sw 0.586+-0.070 is emphasized by the difference between Sb and Sw for the NAFL group with $p = 0.000010$. For comparison of the NAFL Sb and the near normal Sb, $p = 1.68 \text{ E-}9$ and for (1/3)Sw, $p = 7.51 \text{ E-}7$. Sw values are even more different using weighted transformations as shown below on the right.



Sw 0.9682 for NAFL using $I_w = [(5/3)(I) - (200/3)]$



Conclusions

1. Modified fractal analysis of liver SPECT sensitively detects NAFL and distinguishes it from near normal.
2. Analysis of areas of worst liver function is even more sensitive than best liver function, especially with selected parameter weighting for statistical uncertainty and attenuation effects.
3. Extrapolating log plots for areas of either best or worst liver function away from their near origin intercepts yields similar, lower absolute values of the slope for heterogeneity in the average liver function area.
4. The ratio of S_b , the slope describing heterogeneity near the area of best liver function, to S_a , the slope describing heterogeneity of average liver function, is also a sensitive indicator of liver disease; however, S_b/S_a becomes unstable in severe disease (e.g. hepatic fibrosis), as S_a approaches zero.
5. Strengths of the present modified fractal slope method of analysis include:
 - A. Cost effective: only slightly more expensive than ultrasound, but much more sensitive.
 - B. Quantitative, reproducible and reveals insights not immediately apparent from visual image analysis. Helpful for monitoring therapy: e.g. areas of best function generally improve first.
 - C. Widely available: nearly all SPECT manufacturer software has isocontour (thresholding)/ROI analysis.
 - D. Relatively insensitive to processing filters, only compromised by excessive over smoothing.
 - E. Generalizes in principle to other functions, e.g. SPECT or PET perfusion, or PET metabolism tracers.
6. Areas for Further Investigation:
 - A. The S_n normalization presumes presence of the spleen; requires further calibration for splenectomy.
 - B. Areas of absent liver function, such as cysts, are straightforward in principle but more cumbersome in practice with most commercially available software.
 - C. Characteristics of the insulin resistant population are not necessarily applicable to other populations: e.g. usual type 1 diabetics without insulin resistance generally do not have fatty liver; their fractal analysis is similar to near normal patients, even though their risk of macrovascular complications is similar or greater than insulin resistant patients.
 - D. Are there new therapeutic modalities to more rapidly improve areas of more severe liver dysfunction, usually less responsive to therapy with current methods.