Insulin Resistance in Adult Type 1 Diabetics: An Increasing Problem With More Severe Liver Disease than Type 2 Diabetics

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Objective: NAFLD is characteristic of insulin resistance (IR) in diabetes type 2 (DM2) but not noninsulin resistant type 1 (DM1); however, coexisting IR and DM1 (IRDM1) are increasingly recognized. Here we compare IR effects on NAFLD in DM1 and DM2.

Methods: NAFLD severity was quantified by analyzing Tc-99m-sulfur colloid liver SPECT from a Siemens e.cam with SCINTRON software. A sensitive fractal parameter, F, combined effects of best (Sb) and worst (Sw) liver function. F was calibrated by liver biopsy and ultrasound and normalized (Fn) for effects of liver and spleen size, BMI, BSA and ECF.

Results: In 14 near normal patients F 1.54+- 0.20 was similar to uniform activity phantoms. Among 823 patients with liver SPECT, age 52+-15 years, 43 (5.2%) had DM1 and 25 (58.1%) of these, including 3 (12%) with LADA, also had IR, using > 50 units insulin/day. Fn for patients with IR alone was similar to DM2 with HbA1c < 9.5%. Excluding patients with liver disease risks other than IR or DM2, Fn for IRDM1 was > Fn for DM2: in near normal (3.73+- 0.13) > (2.56+-0.45); in NAFL (7.13+- .99) > (4.48+-0.46); in NASH (10.54+-1.22) > (7.15+-.69) and in fibrosis (12.84+-0.32) > (10.83+-1.71); p < 0.03. Patients with IRDM1 had HbA1c (8.1+-1.7)% > (6.8+- 1.2)% in DM2 or IR (p < 0.02). Patients with either DM2 or IRDM1 who had uncontrolled HbA1c (11.2+-1.5)% had similar Fn (9.2+-2.9). Decreasing HbA1c to normal in 4 months did not change Fn in IRDM1; however, among 221 DM2 patients with follow-up studies of 4 to 48 months, Fn improved in 92 (41.6%), was unchanged in 78 (35.3%) and worsened in 51 (23.1%). DM2 patients with hepatic metastasis had significantly (p < 0.003) increased Fn (20.5+- 4.7).

Discussion: The fractal parameter, F the sum of absolute values of Sb, and Sw, reflects overall liver function inhomogeneity; greater values indicate worse function. Normal patients or phantoms with uniform activity had similar Sb (0.61+-0.05) and Sw - (0.93+-0.01). Not surprisingly, such control Sb and Sw are nonzero and unequal without image attenuation correction or log plot weighting factors. Since the BMI of IRDM1 and DM2 patients was taken account of in normalizing Fn, attenuation is not likely causing greater Fn in IRDM1 than DM2. Prior studies suggest greater diabetic complications in patients with worse NAFLD. Higher Fn in IRDM1 likely indicates a high risk category, and patients with hepatic metastasis and even higher Fn are at even higher risk.

Conclusion: Liver dysfunction in increasingly recognized IRDM1 is more severe than in DM2 or DM1 without IR, but similarly exacerbated in IRDM1 or DM2 patients who have uncontrolled
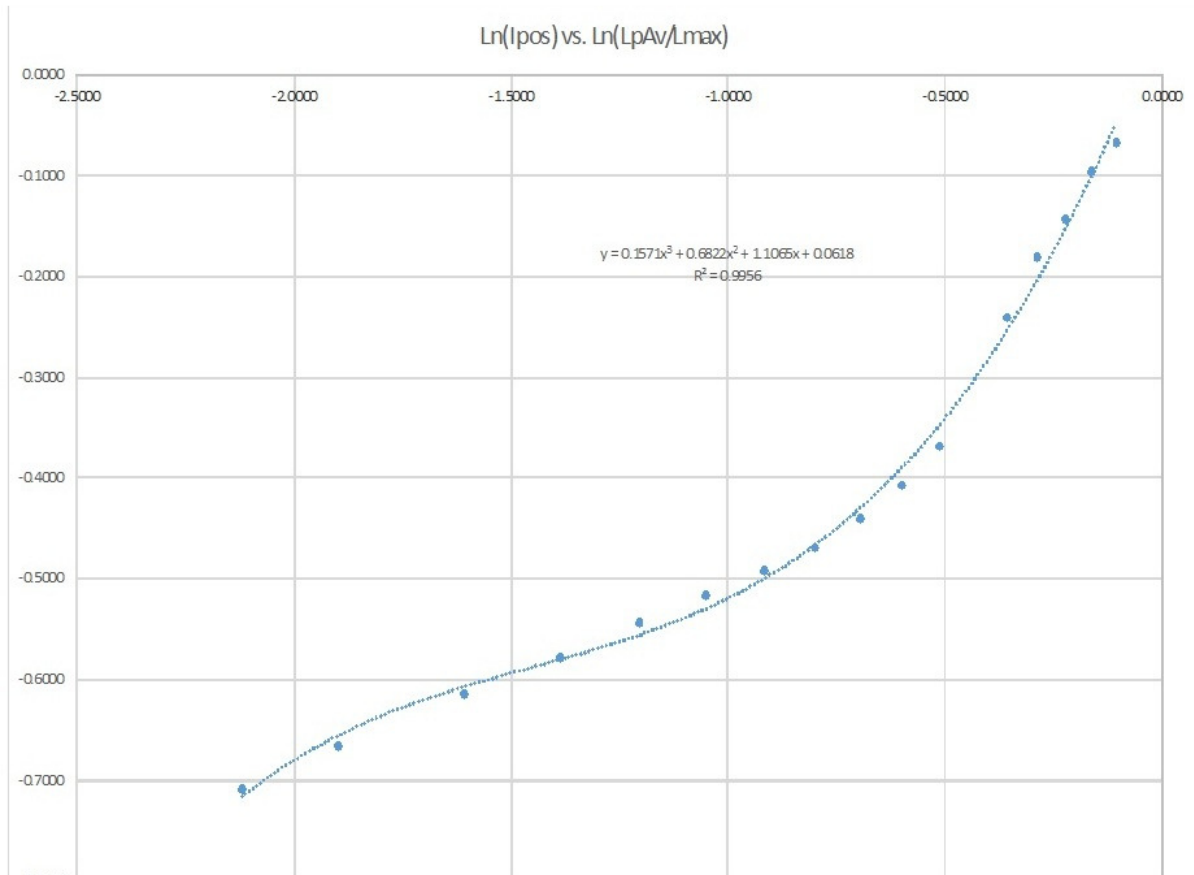
HbA1c.

1.

Ln(Ipos) vs. Ln(LpAv/Lmax)

$y = 0.1571x^3 + 0.6822x^2 + 1.1065x + 0.0618$
$R^2 = 0.9956$

Fib 1: Positive Slope, Sb Concept: Plotted above are Ln(Ipos) vs. Ln(LpAv/Lmax) where Ipos is the % isocontour of maximal liver counts, Lmax. This graph plots in the third Cartesian quadrant since the average count in the Ipos isocontour, written as LpAv, is always less than the maximal count and hence the y axis, Ln of a fraction is always negative; likewise the Ln(Ipos) is always a fraction < 100%. This graph extrapolates to the origin (0,0) since the maximal Ipos isocontour is 100% whose Ln(1) = 0, for the x axis, and also the maximal y axis occurs when LpAv approaches Lmax near a 100% isocontour, and hence Ln(LpAv/Lmax) also approaches Ln(1) = 0. The slope, Sb (0.6325, r = 0.9973, above) near the origin (last 4 points) represents heterogeneity in the area of greatest hepatic tracer uptake, taken as the area of best hepatic reticuloendothelial function. We use a linear extrapolation to avoid a tendency to lower Sb values in small regions of interest with high isocontour values. Nonetheless, Sb is often less than the maximal slope (0.7973, r = 0.9979, above) which is often in an area of greater inhomogeneity between left and right lobe of the liver function (illustrated by the break in the curve above, the first 5 points corresponding to the right lobe and the next 5 to the left lobe of the liver. At low values of Ipos the curve slopes down again as Ipos extends beyond the liver boundary. One measure of the boundary is the minimum of the second derivative of the above polynomial fit

which is visually near the 5th point from the left. Besides comparing to anatomic (e.g. CT or Ultrasound) other measures of the appropriate Ipos for the boundary may be found by analyzing Sw, the negative slope, representing heterogeneity in the area of least liver tracer uptake, as explained in Fig 2.
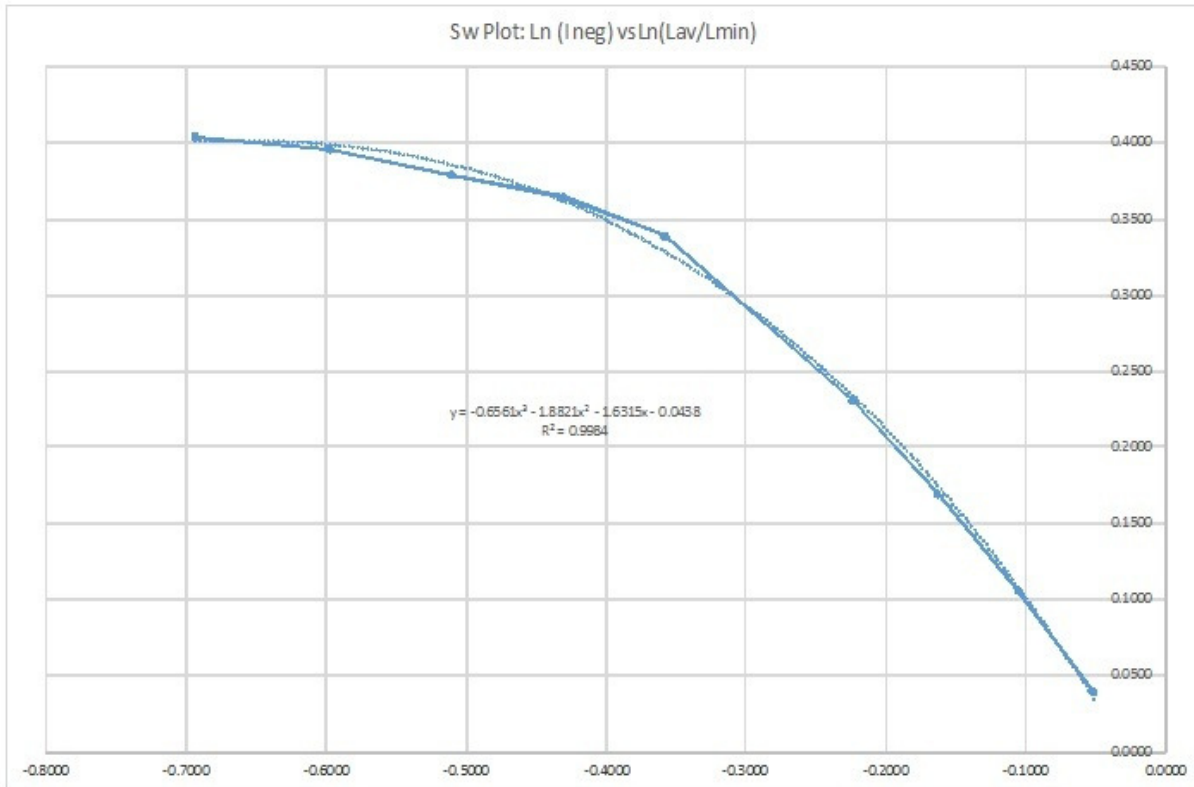
2.

Fig 2A: Negative Liver Slope, Sw, concept involves calculating counts included within the boundary of the liver but not within a positive isocontour, I pos, so that the % negative isocontour, Ineg = (100 + Ibound) - Ipos. When Ipos = 100% I neg is at the liver boundary, Ibound, which was 40% in the above example, the x asix being Ln(Ineg). To avoid statistical error with small regions of interest and low counts in Ipos we typically use a peak Ipos value of 90 to 95%: in the example above, 90% so that Ineg = 140 - 90 = 50% and the most negative Ineg is Ln(0.5) = - 0.69314. The y axis is Ln(Av/Lmin) where Av is the average counts NOT in the Ipos isocontour, but still within the liver boundary. When Ineg = Ibound this Av = Lav, the average counts in the entire liver in the analyzed axial slice. Hence the peak y axis value becomes Ln(Lav/Lmin) = Ln(74.55/48.8) = Ln(1.5277) = 0.4238 in the example above. As this maximal y axis value increases, meaning that the Lav is increasingly > Lmin, there is more heterogeneity in the liver count distribution and Sw, the slope extrapolated near (0,0) is steeper., i.e. more negative. Conversely, when Lmax and Lmin are closer, so that Lav is closer to Lmin the activity is more uniform and Sw is less steep. Hence, oversmoothing of the images makes Sw less steep; however, we empirically observe that Sw is relatively insensitive to data smoothing (varies by < 10%) in the usual range of visual image analysis. A corollary is that the slope near Ineg= Ibound generally approaches zero, i.e. the left side of the above graph looks flat. Interestingly, Sw , the slope extrapolated toward (0,0) for uniform liver activity, is not zero

as might be thought intuitively. Recently 10 near normal patients had Sw - 0.94+-0.10., similar to Sw - 0.93 obtained for SPECT of a phantom filled with uniform activity.   In the example shown all the points are fitted to a polynomial; however, more precise extrapolation involves fitting the statistically most significant points near the origin. The curve extrapolates to (0,0), since when Ipos = Ibound, Ln(Ineg) = Ln(100%) = 0, for the x axis. For the y axis, Ln(Lav/Lmin) approaches Ln(Lmin/Lmin) which is also 0, since the Lav counts not in the Ipos isocontour, but still inside the boundary, approaches Lmin as Ipos approaches the boundary. In Fig 2B the behavior of such plots extrapolated to low values of Ipos, outside the liver boundary is explained further.

Ln(Ineg) Extrapolated toward Ipos = 0 & Ineg = (100+Ibound)

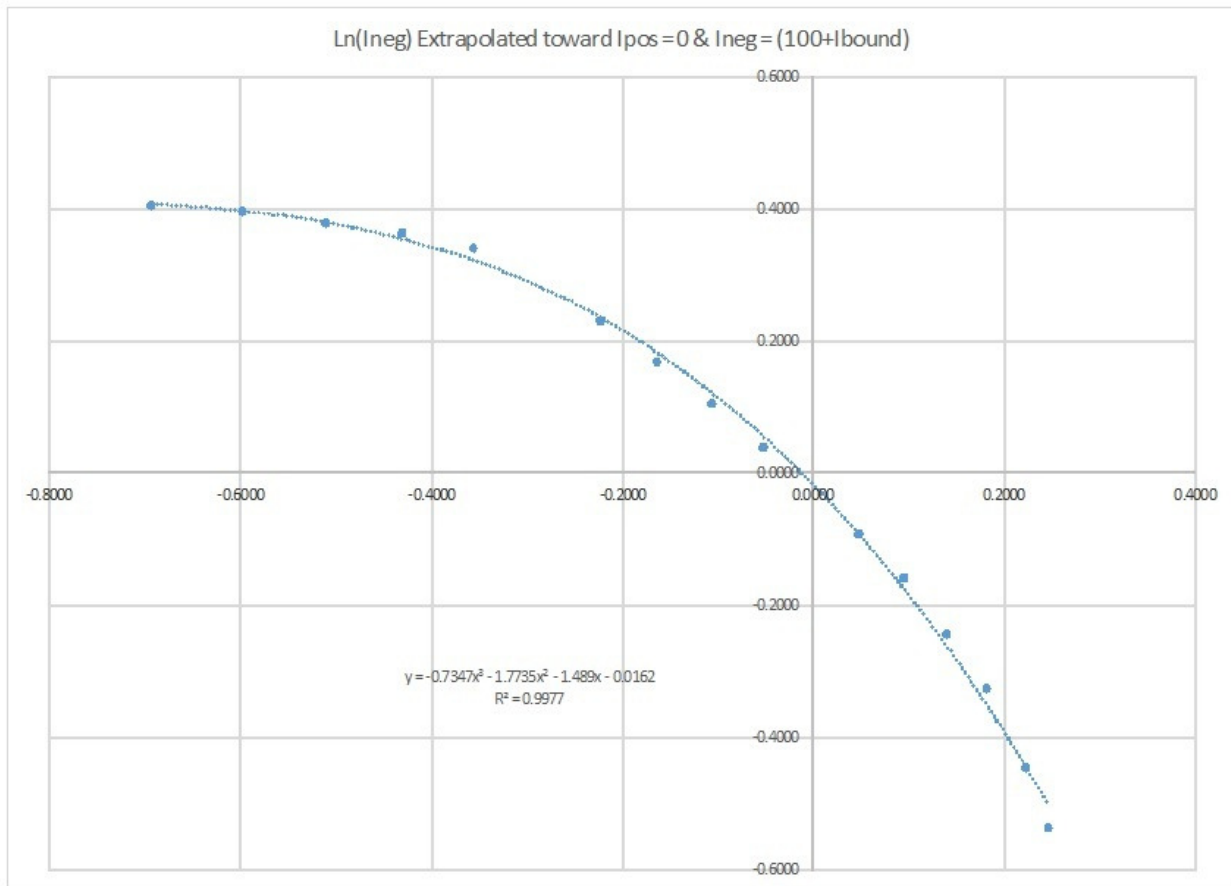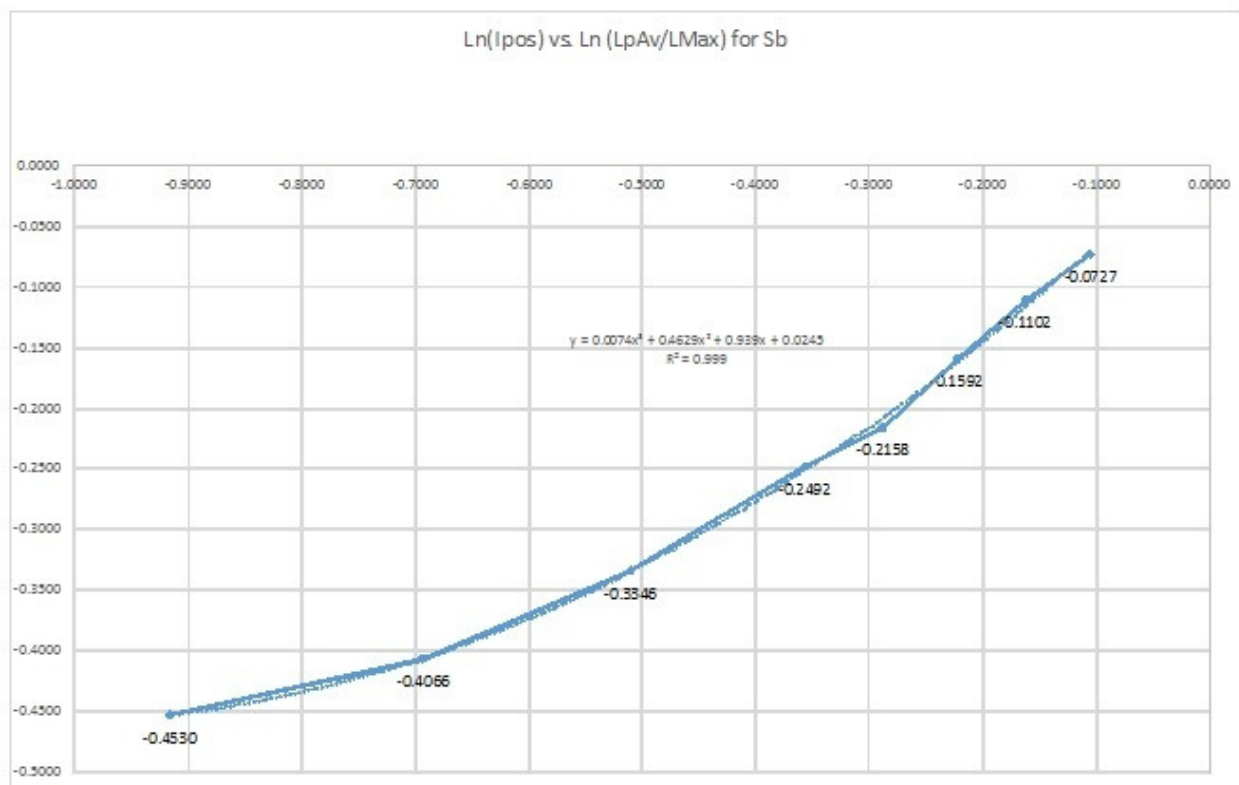$y = -0.7347x^3 - 1.7735x^2 - 1.489x - 0.0162$
$R^2 = 0.9977$

Fig 2B: Graphical analysis for a 62 year-old woman with biopsy proven NASH (nonalcoholic steatohepatitis) in 1997, whose recent (2017) liver-spleen SPECT suggests progression to hepatic fibrosis after she became depressed and began drinking daily 500 to 1000 ml of wine. Her calculated Sbn 3.231 and Fn 9.59 are similar to Sbn 3.65+-0.68 and Fn 10.75+-1.56 for 17 patients with hepatic fibrosis. The liver boundary, Ibound, was 40% of peak liver activity in the frame analyzed, which was a third of the way from the most superior axial frame, to include a good representation of both the right and left lobes of the liver.   Graphical analysis of background is given by the extrapolation toward negative isocontour Ineg = ln(140%) and yields calculated background 23.5 counts per 3.9 x 3.9 mm pixel, while measured region of interest analysis for background was 28.5 counts per pixel. Since Ineg = (100 + Ibound) - Ipos, when

Ipos is near zero, corresponding to an infinitely wide outer margin, I neg is near (100 + Ibound) = 140% whose ln = 0.3365. The ordinate approaches negative infinity or ln(zero/Lmin), where Lmin is the minimum liver count, if there is no background, but ln(Bkg/Lmin) if there is background. Such analysis confirms appropriate boundary selection, as does agreement (usually within 5%) of the organ sizes with anatomical imaging such as CT or ultrasound. This patient had moderately severely compromised cognition with Montreal Cognitive Assessment 18/30. We previously found that hypercorticolism, which affects 21.0 % of our series of 710 evaluable patients, and three of the fibrosis patients. preserves cognition in liver disease patients: average MoCA 22.9 +-3.1 in 12 hepatic fibrosis patients, excluding those with hypercorticolism..

3.

Ln(Ipos) vs. Ln (LpAv/LMax) for Sb

$y = 0.0074x^4 + 0.4629x^2 + 0.939x + 0.0243$
$R^2 = 0.999$

Data labels: -0.0727, 0.1102, 0.1592, -0.2158, -0.2492, -0.3346, -0.4066, -0.4530

Binomial Fit for Sw

$y = -0.9115x^2 - 1.6037x - 0.0297$
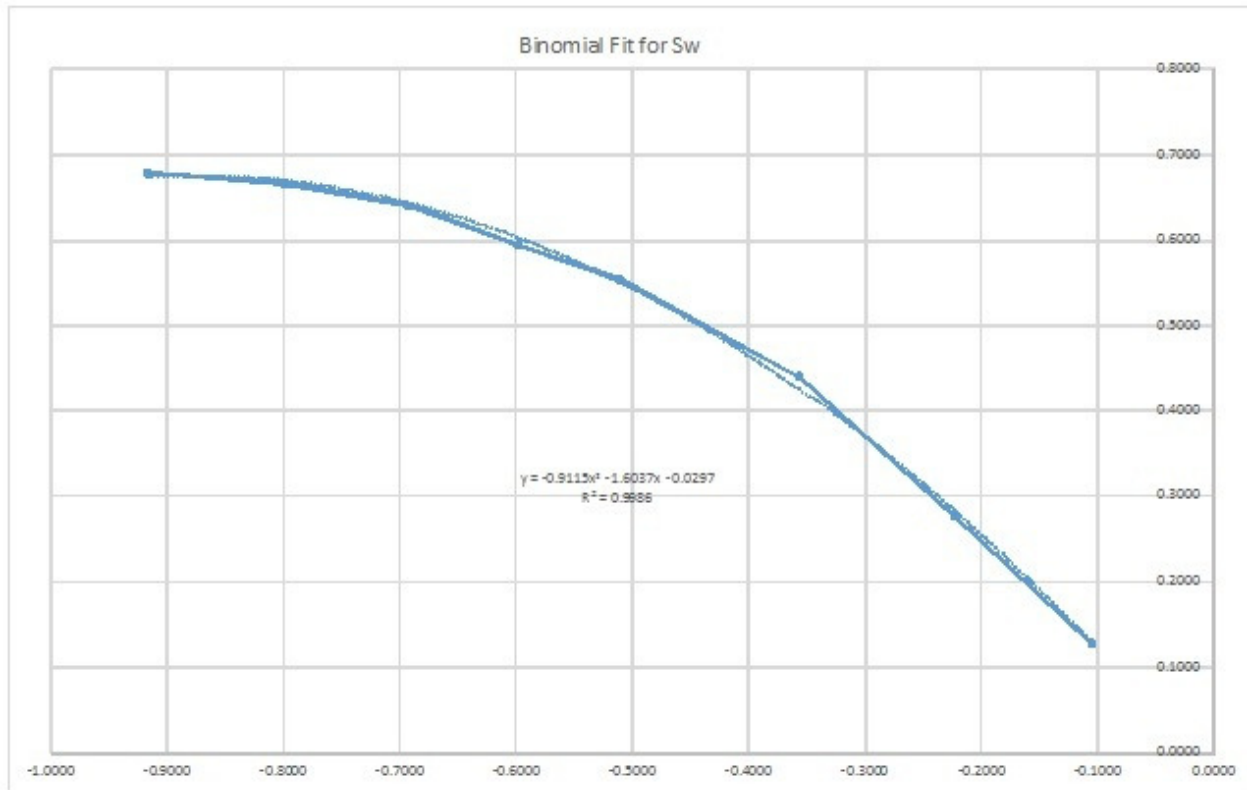$R^2 = 0.9986$

Fig3A   An insulin resistant type 1 diabetic woman age 73 years has positive, Sb, and negative, Sw, slopes suggestive of hepatic fibrosis in 2016, evolving from diffuse fatty liver on CT of 2007. Note the smoothly curving slope of this patient's Sb plot.. Normal patients have a straighter Sb plot with a lower slope, 0.554+-0.045 for 13 near normal vs. Sb 0.788, r = 0.9980 for the patient above. The negative slope, above on the right, looks visually similar; however, Sw –1.601 is different and of greater absolute value than Sb, indicating more heterogeneity in the area of least liver function.   An axial SPECT image (B below) shows prominence of the Falciform ligament, which appears hypertrophied and extends into the left lobe, and also linear hypofunction between the left and right lobes of the liver, a pattern frequently seen in patients with hepatic fibrosis. Greater spleen than liver uptake, consistent with portal hypertension is also evident.

Show BELOW image axial 38 with division of R &L lobes and prominent Falciform and hot spleen with CT correlation
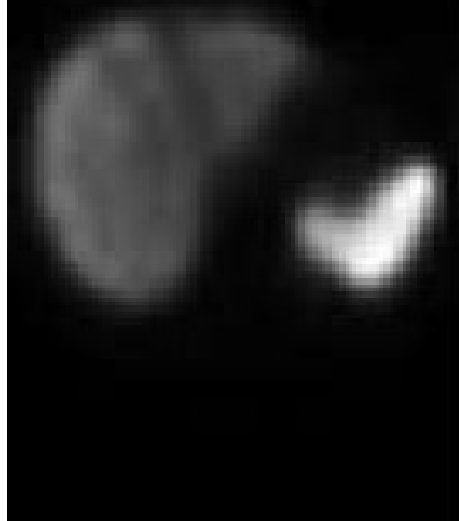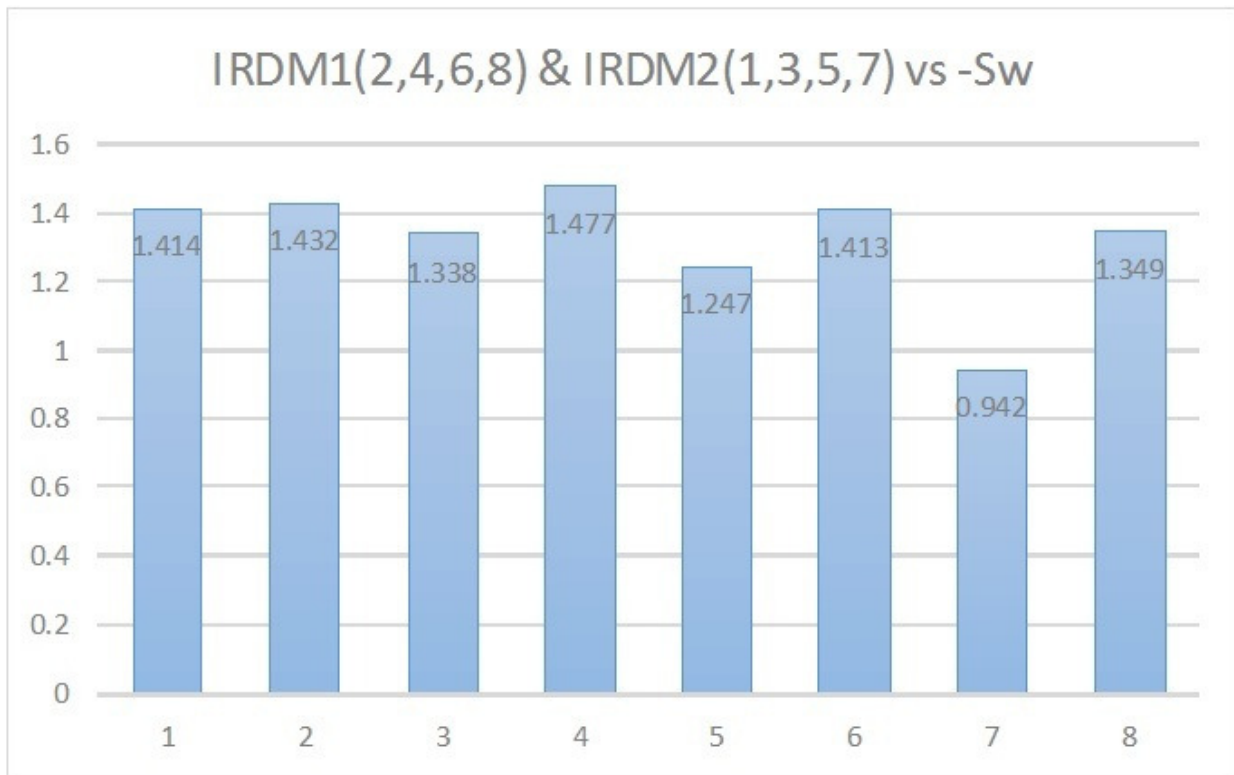
4.

Fig 4: Values of Sw, the negative slope representing functional inhomogeneity near the area of least liver reticulothelial function (least tracer uptake) for hepatic fibrosis (1 and 2), NASH (3 and 4), NAFL (5 and 6) and Near normal (7 and 8). The p value (0.97) for hepatic fibrosis was insignificant, for NASH, p = 0.20 was also insignificant, bot for NAFL p = 0.000927 was significant and for Near normal p = 2.87 E-7 very significant.. The tentative conclusion is that initial injury in IRDM1 tends to affect areas of least liver function more significantly while there is little difference in areas of least liver functional heterogeneity in more advanced disease between IRDM1 and IRDM2. Since the patient numbers are smaller for more advanced disease it is also possible that potential differences for more advanced disease were less sensitively detected. We found a similar pattern previously for IRDM2 patients with or without abnormal thyroid function.
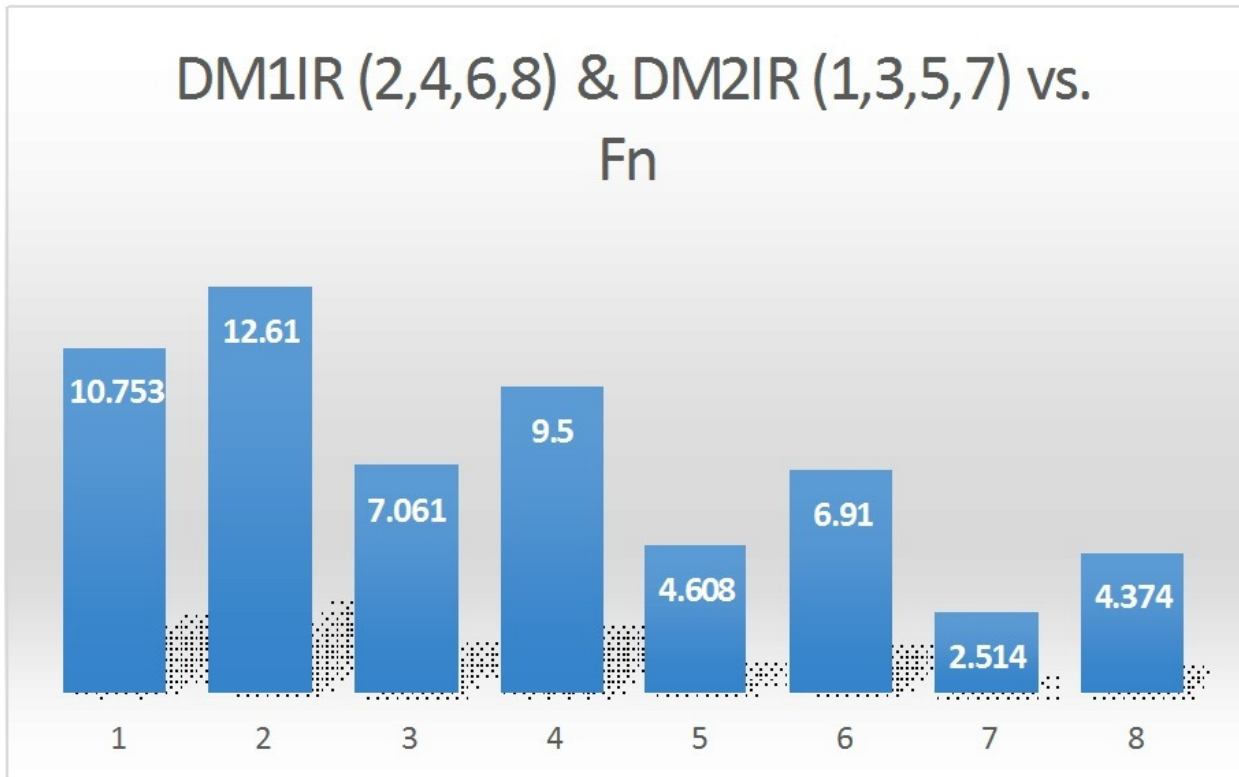
5.

Fig 5: Values of Fn = (Norm Fact)(Sb-Sw) for patients with hepatic fibrosis (1 and 2), NASH (3 and 4), NAFL (5 and 6) and near normal (7 and 8). In each case DM1IR values are greater than DM2IR values: for hepatic fibrosis p = 0.0023, for NASH p = 0.00250, for NAFL p = 1.038 E – 10, for Near normal p = 1.377 E –7.

Conclusions

1. Modified fractal analysis is an intuitively simple but statistically robust method which is less affected in our experience by image filtering (smoothing) than visual image analysis.
2. Normal or near normal liver reticuloendothelial function, revealed by heterogeneity of Tc-99m-sulfur colloid liver uptake, has similar Sb 0.55+-0.45 for the right and left lobes of the liver.
3. Abnormal liver function typically has a higher Sb and greater difference between absolute values of Sb and Sw.
4. A normalized factor, F, combining effects of Sb and Sw as well as body size (BMI), shape (BSA) and composition (ECF) together with Liver and spleen size detects significant differences between IRDM1 and IRDM2 patients throughout the NAFLD spectrum from near normal to NAFL (simple fatty liver), NASH (steatohepatitis with liver injury) and hepatic fibrosis.
5. Insulin resistance in type 1 diabetics, whether LADA or not, is common and affects over half of type 1 diabetics in an endocrine referral practice.
6. Although the long term prognosis of liver disease associated with type 1 DM is unknown it is likely to be worse than type 1 DM alone since progression of NAFLD in type 2 patients is clearly associated with increased risk of complications, particularly macrovascular complications which have the worst prognosis. Moreover, combined hepatitis C, which untreated produces liver disease similar to progressive NAFLD, clearly has a worse prognosis when associated with diabetes.
7. Multiple approaches can slowly (often at a rate of about 20% improvement in SBn per year) reverse NAFLD, including diet and exercise, medical weight loss therapy, bariatric surgery, GLP-1 agonists, omega 3 fish oil 4 g daily, especially with 8 or more g added medium chain triglycerides, natural vitamin E 400 units daily, pioglitazone, mifepristone, potent statins and possibly multiple other agents/methods to improve glycemic control, including correction of thyroid dysfunction and hypogonadism.   We have no experience with obeticholic acid (approved for primary biliary sclerosis) but prior studies suggest it may also be promptly effective for NAFLD.