Insulin Resistance, Diabetes Mellitus and Low Cerebral Flow Reserve: Fuel to the Fire of the Dementia Epidemic

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Abstract Body:

Objective: Clarify insulin resistance (IR), diabetes mellitus (DM) and low cerebral flow reserve contributions to stroke (S) and dementia (D).

Methods: Among 300 patients with cerebral ischemia symptoms, brain SPECT indices of basal metabolism (CMi), stimulated perfusion (CPi) and cerebral flow reserve (FRi = CPi – CMi and FRr = net stimulated/basal counts) used parabolic renal corrections. Same day scans for FRi and FRr correlations had background < 30%. Test Your Memory (TYM) dementia cutoff was < 41/50.

Results: In 34 near normal patients age (51.8+-14.6) years, CMi was (57.3+-4.4)%, FRi (10.0+-2.5)% and TYM 47.6+-1.5. For 43 patients with FRr calculations: (20- FRi) = 45.83(1.4- FRr)+0.87 with r = 0.93. In 128 IR cases, age (52.4+-14.2) years, FRi was -(0.24+-6.71)%, TYM (43.4+-3.6), S 14.1%, D 16.5%; similarly, in 172 DM cases, age (56.5+-12.3) years, FRi was -(0.16+-9.0)%, TYM (43.8+-5.6), S 11.6%, D 19.7%, Age of S+D patients was (56.4+-12.2) years for IR cases and (57.9+-11.7) years for DM cases. For IR patients, males were a similar 25.8% (33/128) of the total and 26.3% (5/19) of D cases; however, males comprised more, 47.7% (82/172) of total and 63.3% (19/30) of D cases among DM patients.

Conclusions: Total S and D are similar in IR and DM, hence IR (prevalence > > DM) likely contributes predominantly to overall cognitive impairment. Cost effective blood tests for amyloid fragments (Pesini P, 2012) and focused brain uptakes (Pretorius, 2005) may further clarify if DM predisposes even more to dementia in men than periemenopausal women.

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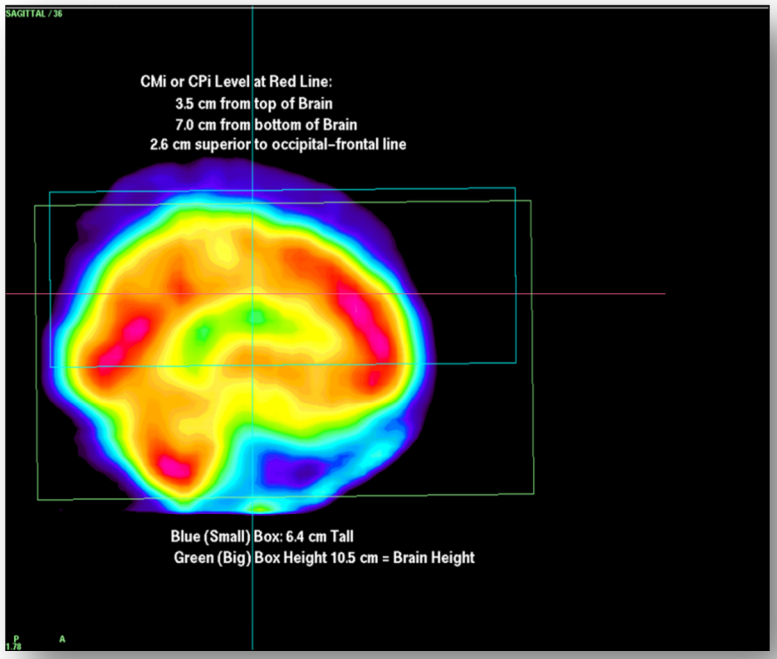

Fig. 1A. Axial SPECT slices are defined parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMi), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of the normal-sized lateral ventricles. Activity display uses a Sokoloff color scale, with white for peak brain, black for zero and spectral colors for intermediate activities. Computer-selected isocontours (see Fig. B) define areas that contain activity > a certain fraction of the peak activity. The 30% isocontour represents total brain activity in an axial slice, chosen slightly outside the actual external edge of the brain to correct for attenuation. The 60% isocontour approximates the cortex. The Cortical Metabolic index (CMi), the ratio of activity within the 60% isocontour to that within the 30% isocontour is a measure of cortical brain function. The Cortical Perfusion index (CPi) is similarly calculated from 60% and 30% isocontours after the patient receives a cerebral perfusion stimulant such as 0.5 to 1 g acetazolamide IV or 0.4 to 0.8 mg nitroglycerin sublingual. The difference between CPi and CMi is a measure of cerebral flow reserve (CFi).

10.20	2.78	Normals
-5.93	25.81	Pituitary
0.3	12.93	Diabetics
1.17	11.01	Thyroid Disease
-0.5	19.00	Lo GFR
-2.24	22.81	Hi GFR
0.67	11.81	TBI
-0.06	13.79	IRS

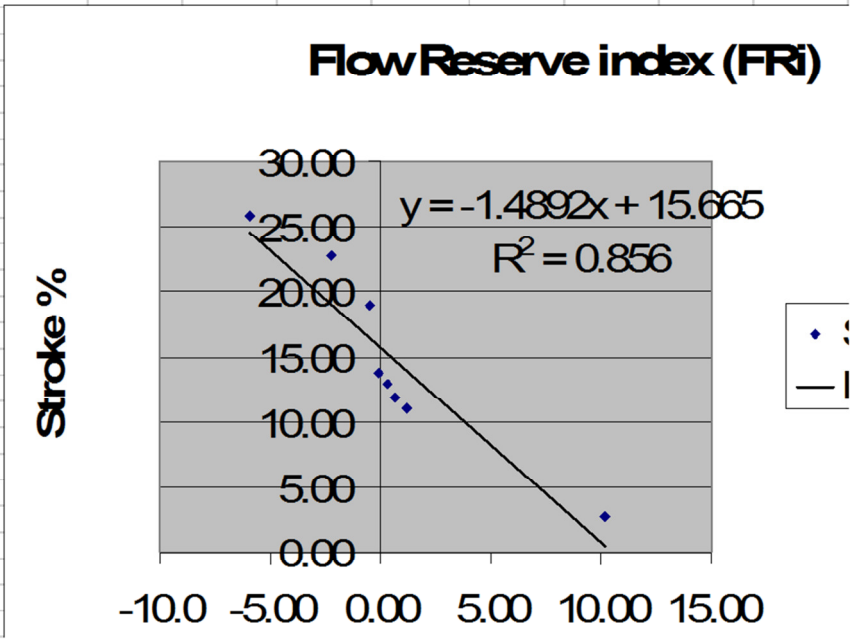

Fig 1B Graph of Flow Reserve Index (FRi) shown on the x axis above, vs. Stroke prevalence shown on the y axis above for 36 near normal patients age 52+-14 years, with 2.77% stroke prevalence, for whom FRi = (10.2+-2.6)% and other interrelated groups. The post stroke Brain SPECT to the single near normal patient who eventually had a stroke is noted in Fig 2B to the right. The regression line is given by:

S = 15.67 - (1.49) FRi.
with correlation coefficient –0.925.

Parabolic renal corrections were employed but could be further optimized. Using GFR uncorrected for body surface area in part takes account of increased patient size increasing stroke incidence. The concept is that increased body size does not increase brain size but does increase risk of compromised cerebral circulation.

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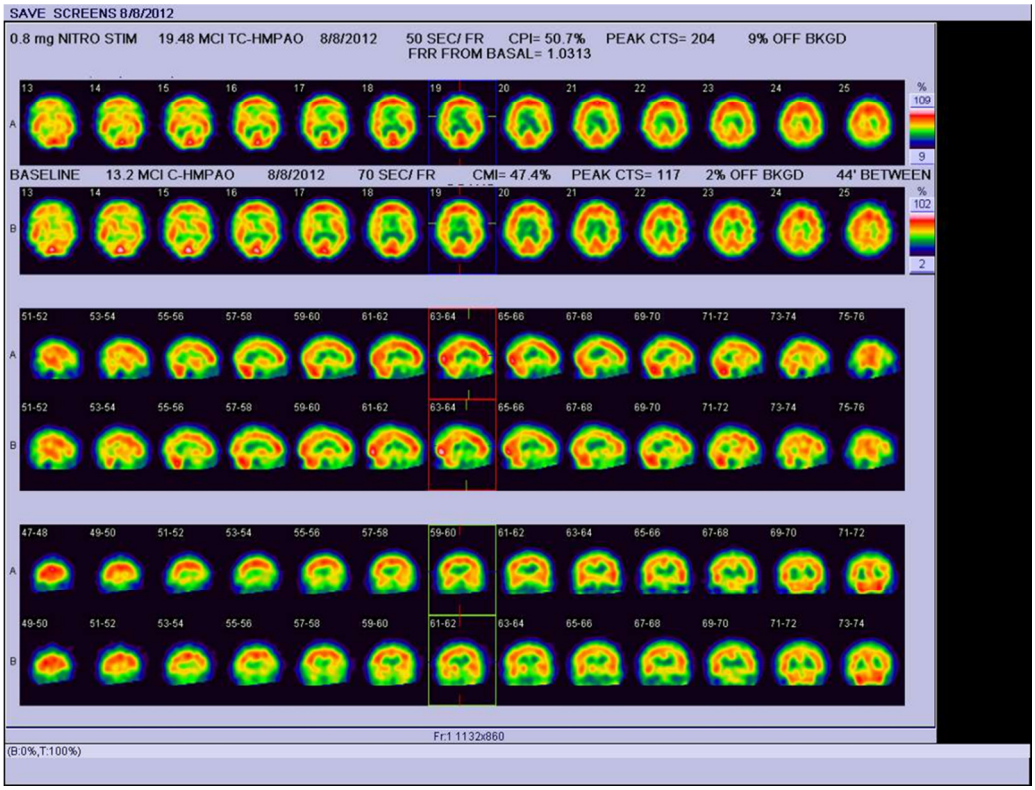


Fig. 2A: A 66 year-old hypertgensive, hyperlipidemic, insulin resistant (HbA1c 6.0%) and cognitively impaired (TYM 33) woman who has recovered well physically from a minor stroke she suffered at age 59 years. In this study women were much more likely to suffer cognitive impairment within 6 years of menopause. An additional risk factor for cognitive impairment in this patient was a distant concussion in an automobile accident the patient suffered at age 46 years. Mildly elevated cystatin C of 1.03 with normal serum creatine of 0.68 and eGFR of 89 ml/min/1.73 metersq may also be a risk factor for stroke and cognitive impairment.

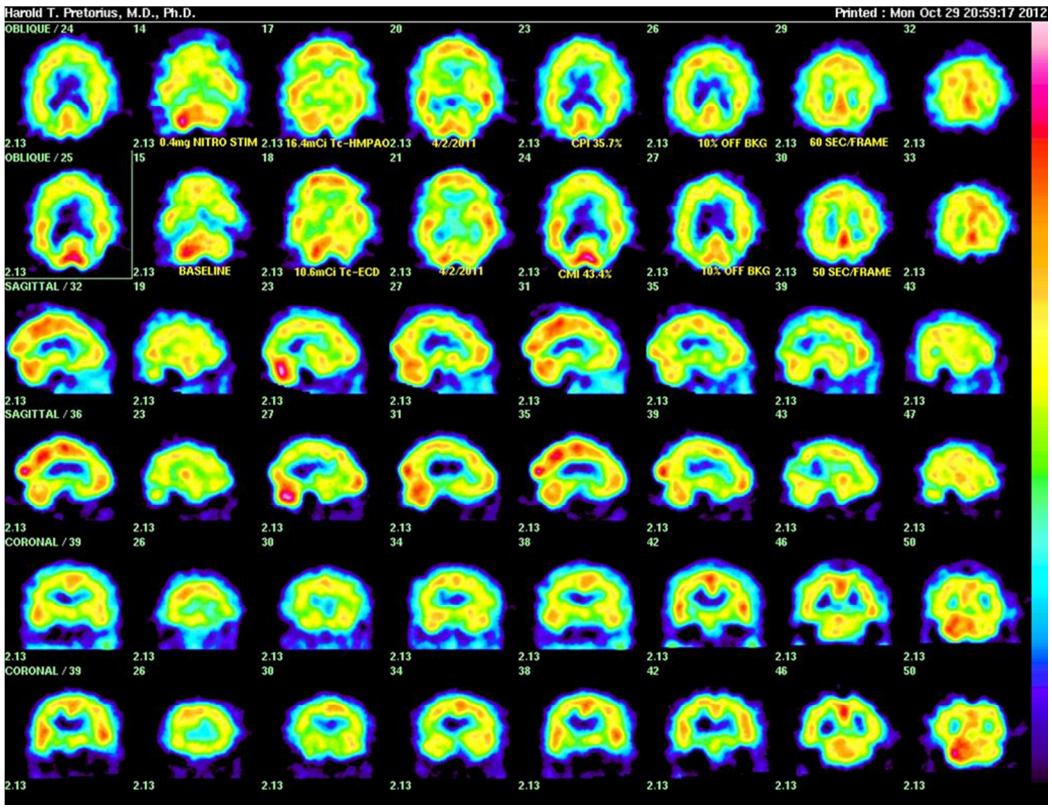


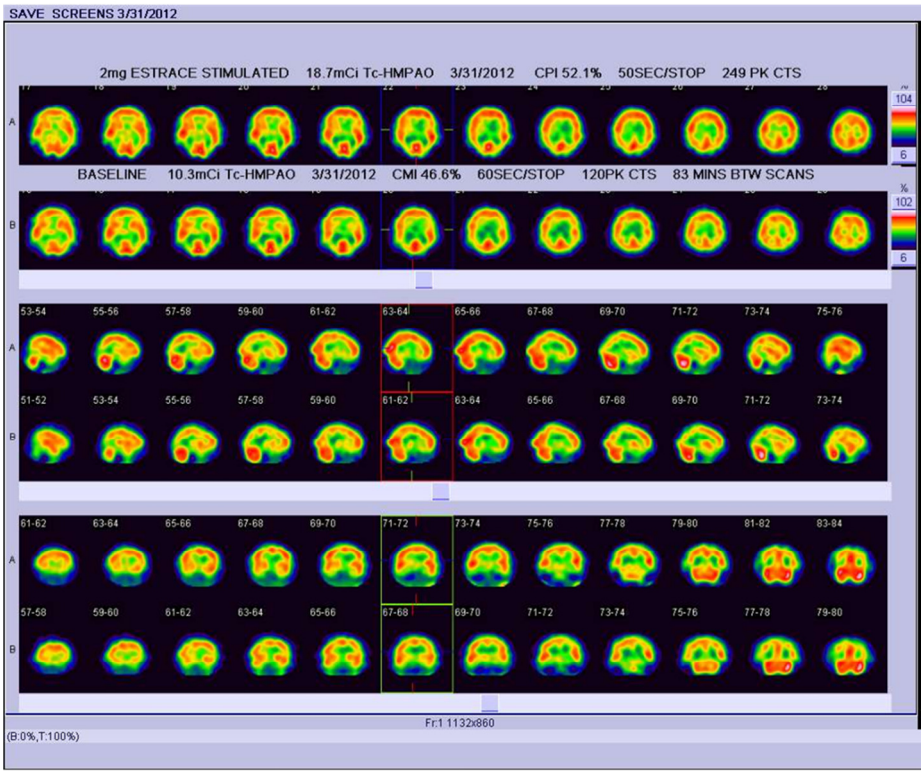
Fig 2B: Brain SPECT for a 52 year-old diabetic man after a left hemispheric stroke shows compromised FRi –7.7%. This patient is the only one in our entire experience to have a stroke after a normal scan with normal FRi 12.9, CMi 59.6%, CPi 71.4% two years before his stroke. In addition to uncontrolled type 2 diabetes mellitus (HbA1c 11.0%) with frequent hypoglycemic episodes, this patient's additional stroke risk factors included greater than 4 packs per day cigarette smoking, hyperlipidemia, coronary artery disease requiring angioplasty, renal hyperfiltration with low serum creatinine 0.7 (normal 0.9-1.3) and nonadherence to medical therapy including antiplatelet therapy (aggrenox).

Table

Category	n	Age	CMi	FRi	TYM	% Stroke	% Dementia	Male	Female
Near Normal	36	52+-14	57.3+-4.4	10.2+-2.5	47.6+-1.5	2.8	0	14	22
Insulin Resistant	128	52+-14	52.3+-7.6	-0.24+-6.7	43.4+-3.6	14.1	16.5	33	95
	24	58+-16						7	17
Diabetes Mellitus	172	56+-12	53.8+-6.8	-0.16+-9.0	43.8+-5.6	11.6	19.7	82	90
	60	59+-14						32	28
Dementia	84	59+-15					100	39	45
Stroke	39	60+-10	54.7+-7.0	-2.37+-8.1	42.3+-5.5	100	21.1	12	27

Fig 3A: Above is a table showing male and female IRS and DM patients with or without dementia defined as TYM 40 or less and partially stratified by age. As noted in the abstract, in diabetics with dementia males predominate; however, among insulin resistant cases as young as 52 years and among both IRS and DM by age 59 years, dementia affects women predominately.. Thus there is a suggestion that men may be affected cognitively at an earlier age by diabetes; however, within about 7 years post the usual menopause at age 52 years, dementia cases in women have overtaken those in men.

Fig 3B: The single case shown below suggests that even though estrogen may help retard dementia in perimenopausal women, it is not likely to do so by improving cerebral perfusion. The same perimenopausal woman received 2 mg estradiol oral on the left and has no increase in FRi, while stimulation with coconut oil, which is similar to other established perfusion stimulants, such as sublingual nitroglycerin or IV acetazolamide, produces a normal response in background-corrected FRi > 7% on the right.



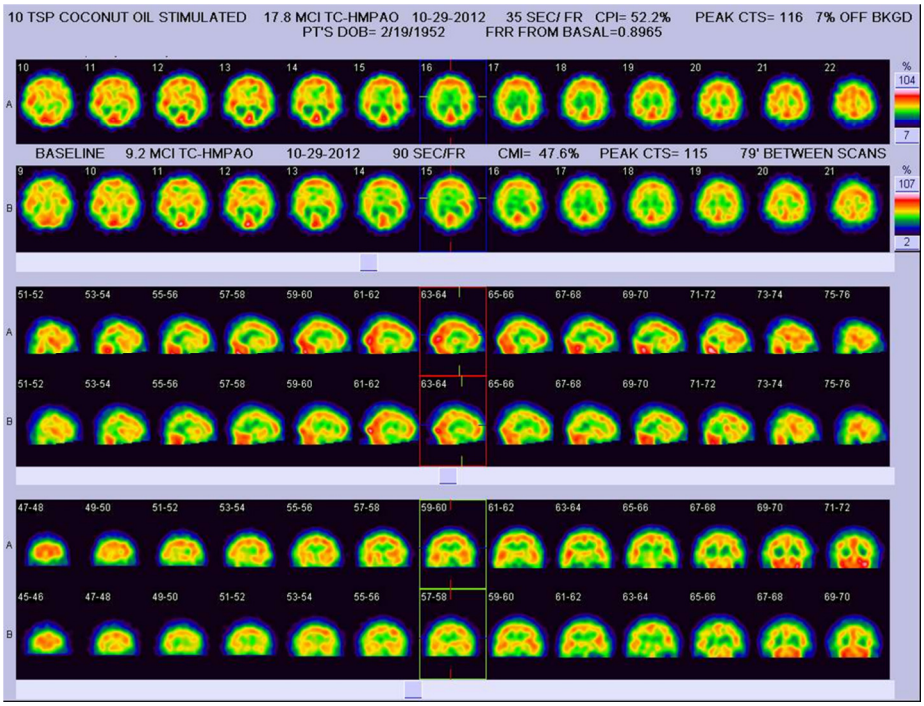


Fig. 4: Brain SPECT for a year-old man with a clinical diagnosis of Alzheimer's disease (TYM score 22) whose brain SPECT below suggests cerebrovascular disease affecting the right parieto-occipital area and more advanced neurodegeneration affecting the left parieto-occipital area, quite possibly amounting to mixed dementia. Such a pattern is typical (affects over 70%) of patients presenting with memory loss.

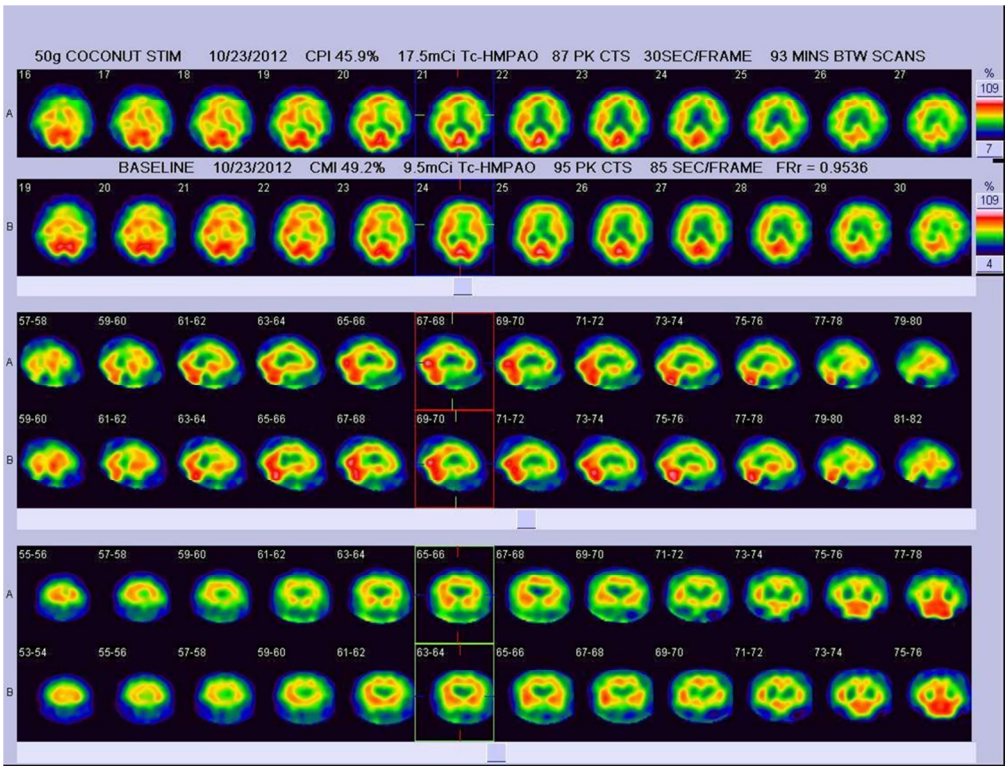


Fig 5: The biodistribution of TYM scores for diabetics complaining of cerebrovascular symptoms, particularly memory loss, is shown above. Although the largest peak identifiable corresponds to normal TYM 47+-2, there are clearly many patients seen in everyday practice who are significantly cognitive impaired, with amnestic mild cognitive impairment (MCI) near TYM 43 predominating and more severely impaired individuals, likely representing early dementia, being more uncommon than usually recognized in patients averaging only 52 years old.

Although the TYM test is straightforward, concerns about its appropriate cutoff for dementia (score of 32 vs. 42) have arisen and it is likely that further progress could be afforded with quantitative, noninvasive tests such as the evolving blood test for total amyloid fragments or the quantitative brain uptake which uses a modified thyroid uptake probe to obtain perfusion-metabolism ratios in focused, critical brain regions.

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