代謝造影劑 ^{11}C-acetoacetate 未來之臨床應用潛能

常務監事　曾凱元

The role of Nuclear Medicine in AD

- HMPAO-SPECT scan
- FDG-PET scan
- Beta-amyloid PET scan
- Tau-protein PET scan
- Inflammation PET scan ?
- ????

How early is early enough?

Connection between AD & DM (T2)

- Peripheral insulin resistance and diabetes are risk factors for Alzheimer's disease;
- Hyperinsulinemia may cause the accumulation of β-amyloid in brain;
- Insulin signaling pathway are abnormal in AD brains;

AD as type III DM – by Suzanne M. de la Monte

- Deficits in glucose uptake and utilization;
- Insulin resistance down-regulated target genes needed for cholinergic function;
- Inhibition of insulin signaling mediated neurodegeneration;
- Oxidative stress, increased cell death;
- Mitochondrial dysfunction;
- Pro-inflammation and pro-apoptosis cascades.

NEJM 2010;362:329-44

Brain glucose dysregulation in AD

- Abnormalities in brain glucose homeostasis are intrinsic to AD and may begin several years before clinical symptoms;
- Decreased enzymatic activities of hexokinase, phosphofructokinase, pyruvate kinase (inside mitochondria) at lesion sites;
- Neuronal GLUT3 are reduced and parallel severity;(astrocytic GLUT1 unchanged)
- Higher tissue glucose concentration at lesion sites;
- Increases in fasting plasma glucose levels are associated with brain tissue glucose concentrations globally.

Case report

- Male, white, 51 y/o (2001), short term memory loss;
- 56 y/o (2006), gave up job, stopped driving;
- 54-58 y/o (2004-2008) MMSE score from 23 to 12;
- 2008 MRI showed diffuse involutional changes of frontal and parietal lobes and moderate left-sided and severe right-sided atrophy of amygdala and hippocampus, consistent with AD;
- *APOE* ε4-positive

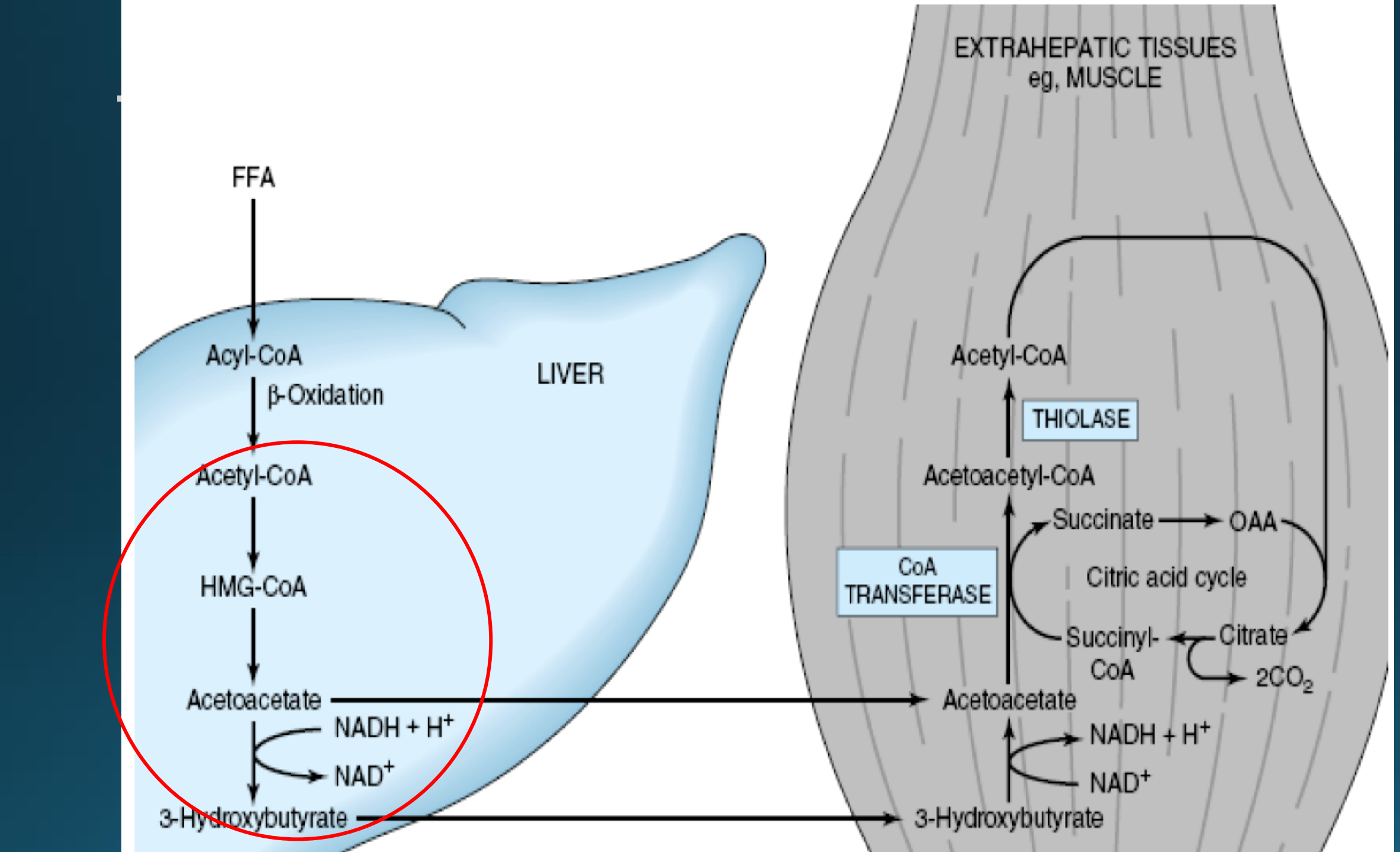
Alzheimers Dement 2015;11(1)99-103

Coconut oil-> MCTs-> ketone

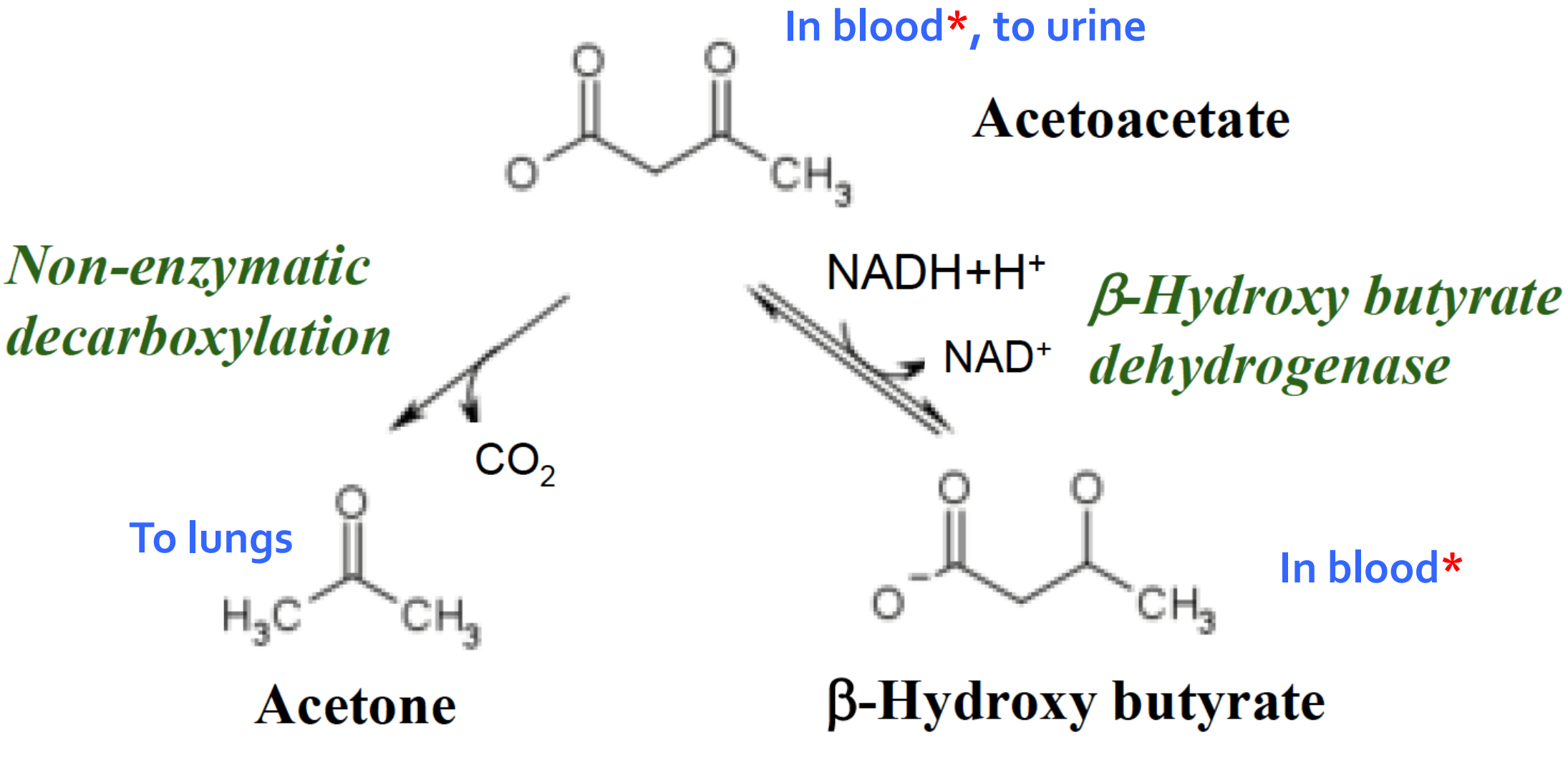
- MCTs (mid-chain triglycerides) – 6 to 12 C
  - C6:0 – Caproic
  - C8:0 – Caprylic (6%) – to ketones (most ketogenic)
  - C10:0 – Capric (9%) – to ketones
  - C12 – Lauric (>50%)
- Other LCTs (saturated)
  - C18:0 - Stearic
  - C18:1 - Oleic
  - C18:2 - Linoleic

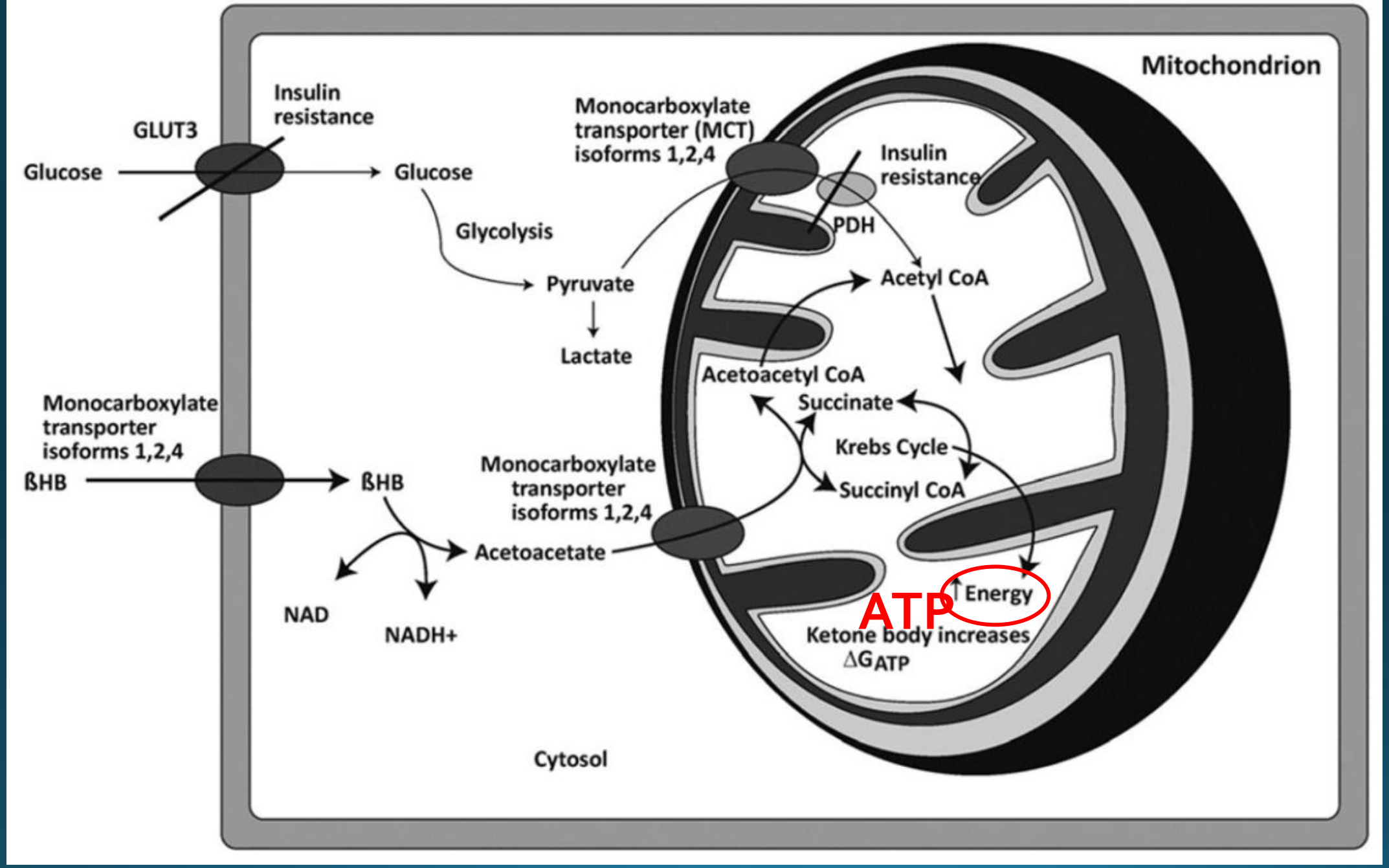
Trial courses

- 5/21/2008 starting coconut oil therapy;
- Added mid-chain triglyceride for therapy several months later;
- MMSE from 12 to 20 after 75 days therapy;
- ADAS-Cog rose 6 points, ADLs rose 14 points;
- MRI on 4/28/2010 stayed the same;
- 4/29/2010 adding keto monoester Tx;
- Improving clinically in daily activities.


EXTRAHEPATIC TISSUES
eg, MUSCLE
FFA
LIVER
Acyl-CoA
β-Oxidation
Acetyl-CoA
HMG-CoA
Acetoacetate
NADH + H+
NAD+
3-Hydroxybutyrate
Acetyl-CoA
THIOLASE
Acetoacetyl-CoA
Succinate
OAA
CoA
TRANSFERASE
Citric acid cycle
Succinyl-
CoA
Citrate
2CO2
Acetoacetate
NADH + H+
NAD+
3-Hydroxybutyrate

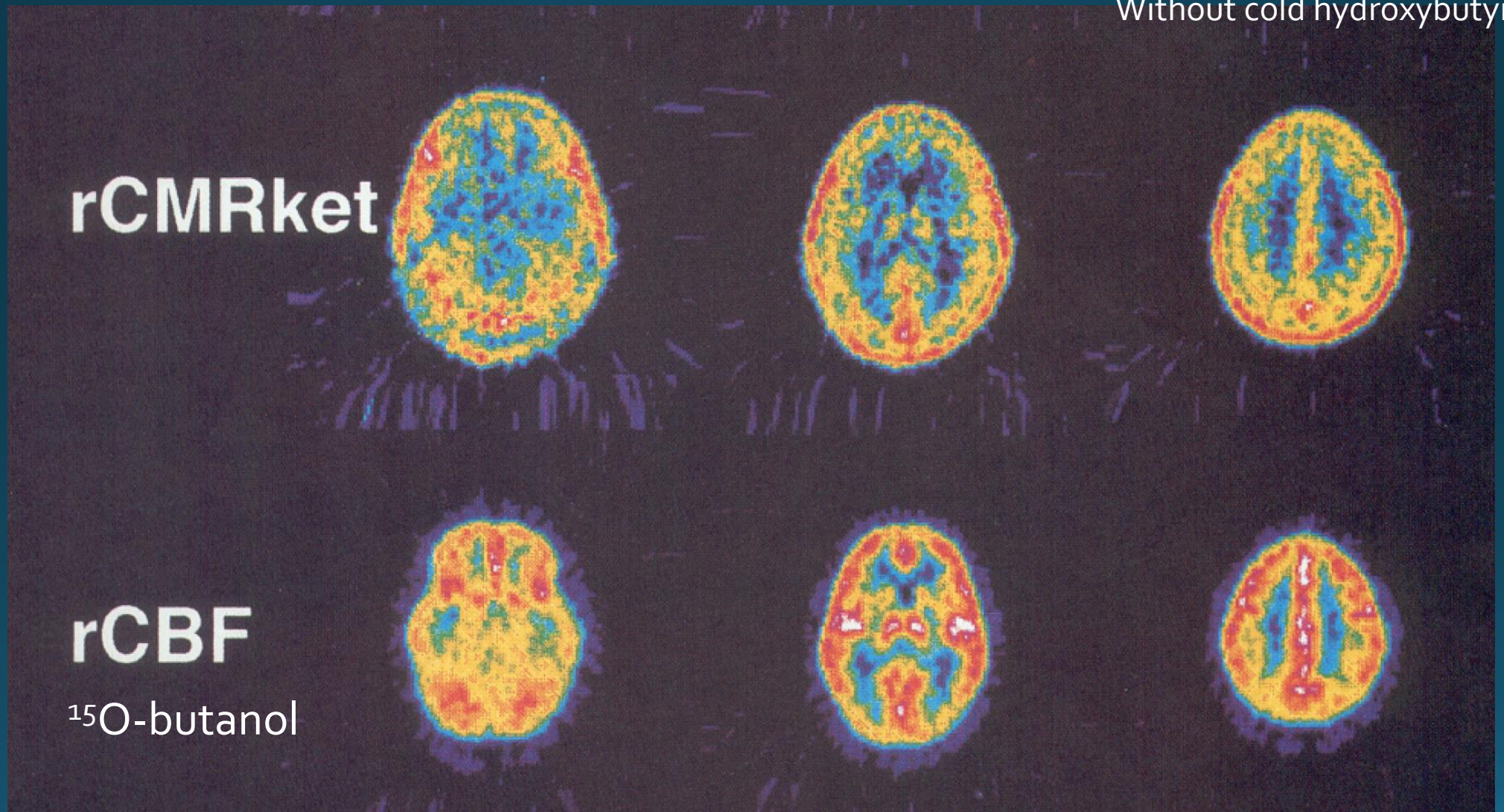
The Ketone Bodies



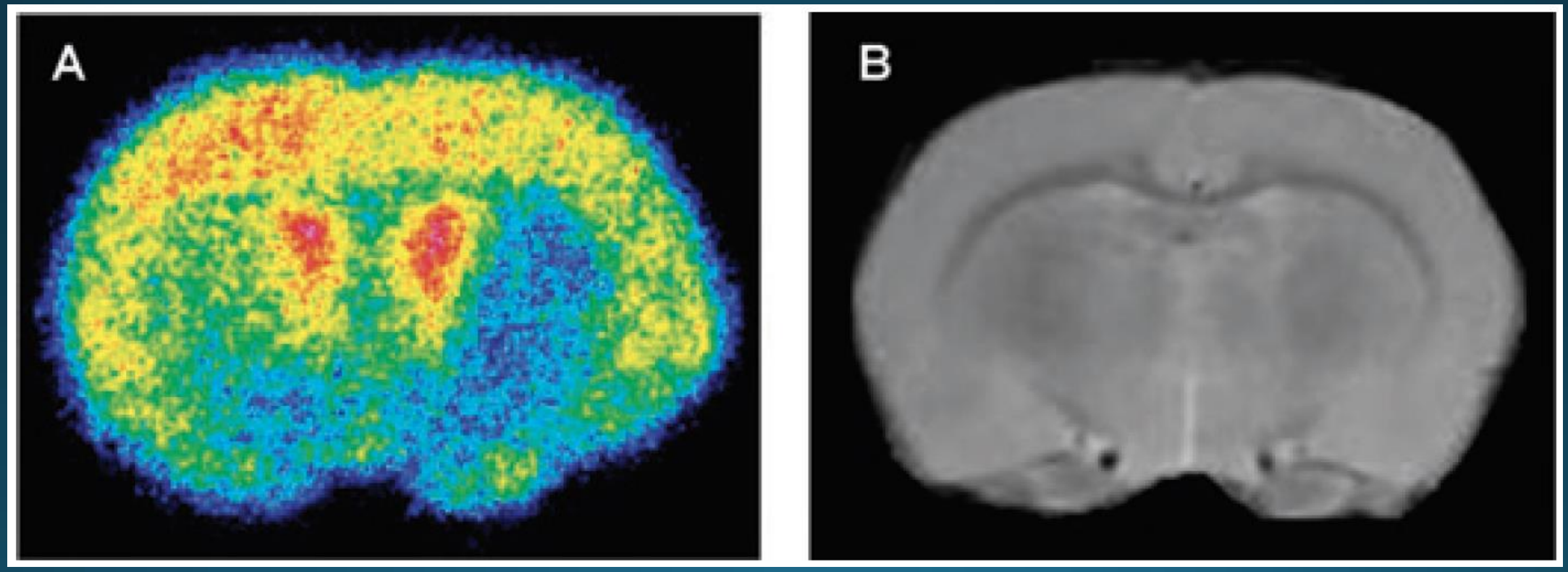

Mitochondrion
Insulin resistance
GLUT3
Glucose
Glucose
Glycolysis
Pyruvate
Lactate
Monocarboxylate transporter (MCT) isoforms 1,2,4
Insulin resistance
PDH
Acetyl CoA
Acetoacetyl CoA
Succinate
Krebs Cycle
Succinyl CoA
Monocarboxylate transporter isoforms 1,2,4
ßHB
ßHB
Acetoacetate
NAD
NADH+
ATP
Energy
Ketone body increases
ΔG ATP
Cytosol

Use of R-β-[1-^{11}C]hydroxybutyrate in PET studies of regional cerebral uptake of ketone bodies in humans

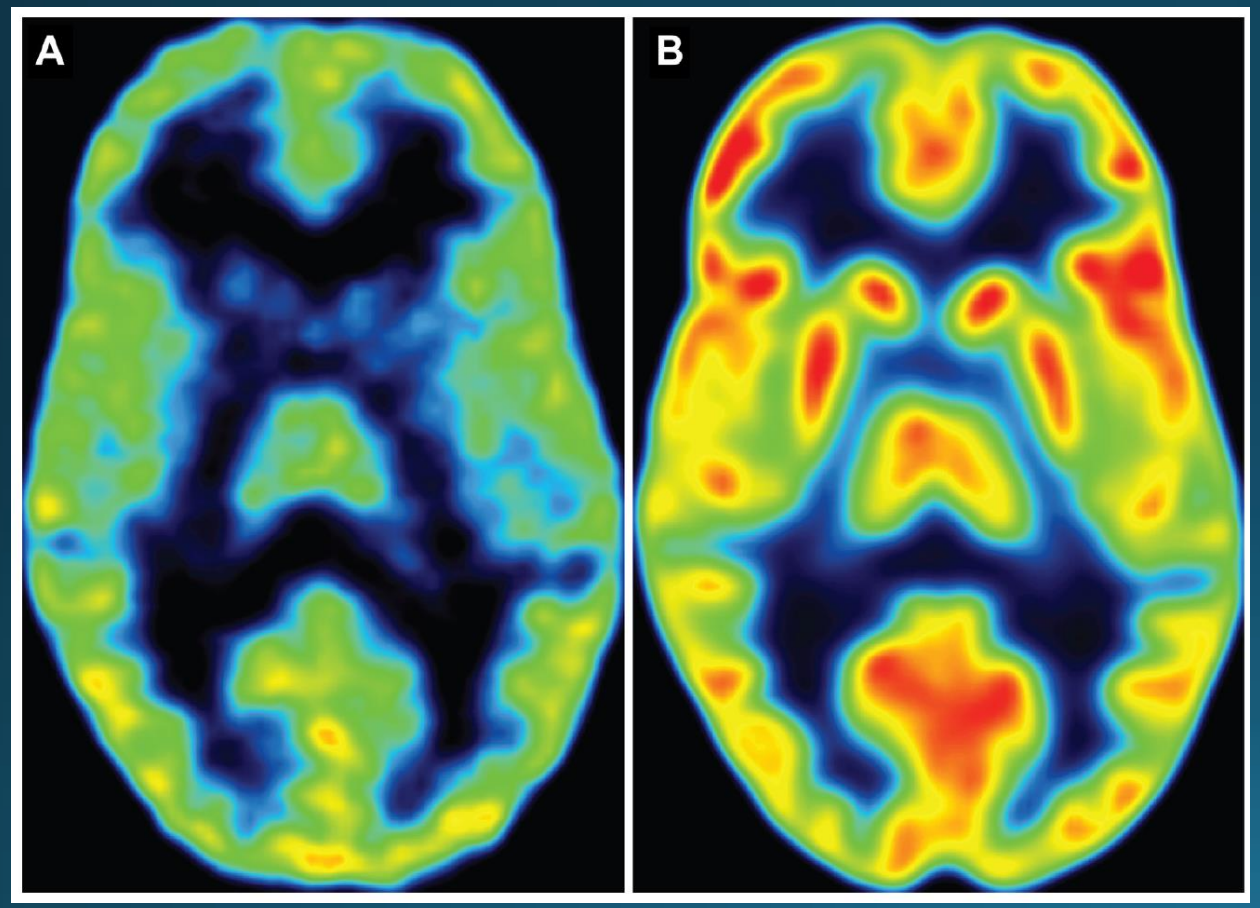
Without cold hydroxybutyrate infusion



^{11}C-Acetoacetate (AcAc)-rat



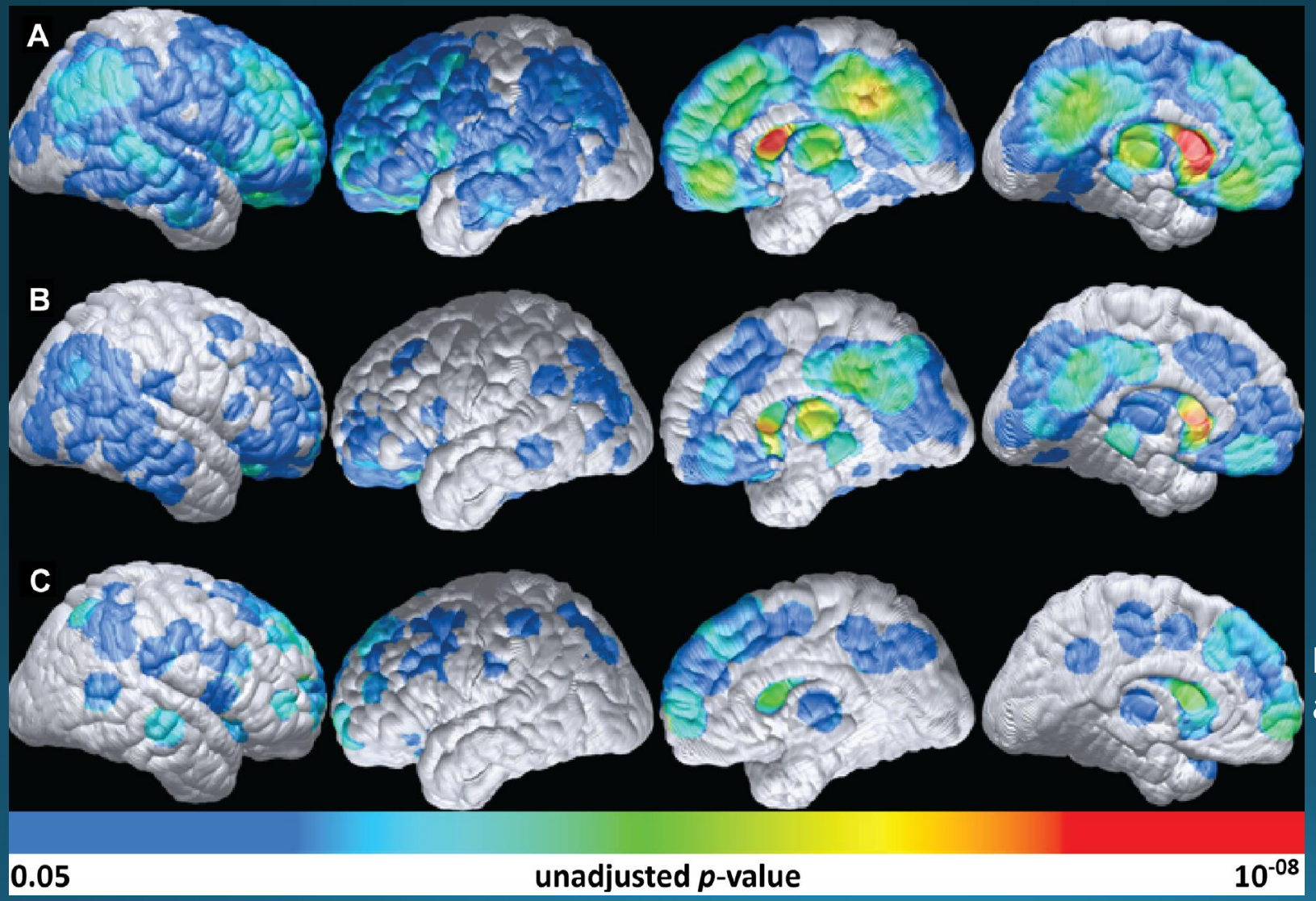
^{11}C-AcAc vs. ^{18}F-FDG young adults 26 vs. 74 y/o



- In comparison with younger adults, older adults had 8 % lower cerebral metabolic rates for glucose in gray matter as a whole.
- The effect of age on cerebral metabolic rates for acetoacetate in gray matter did not reach significance.

^{11}C-AcAc in old vs. young adults

26 vs. 74 y/o



young

old

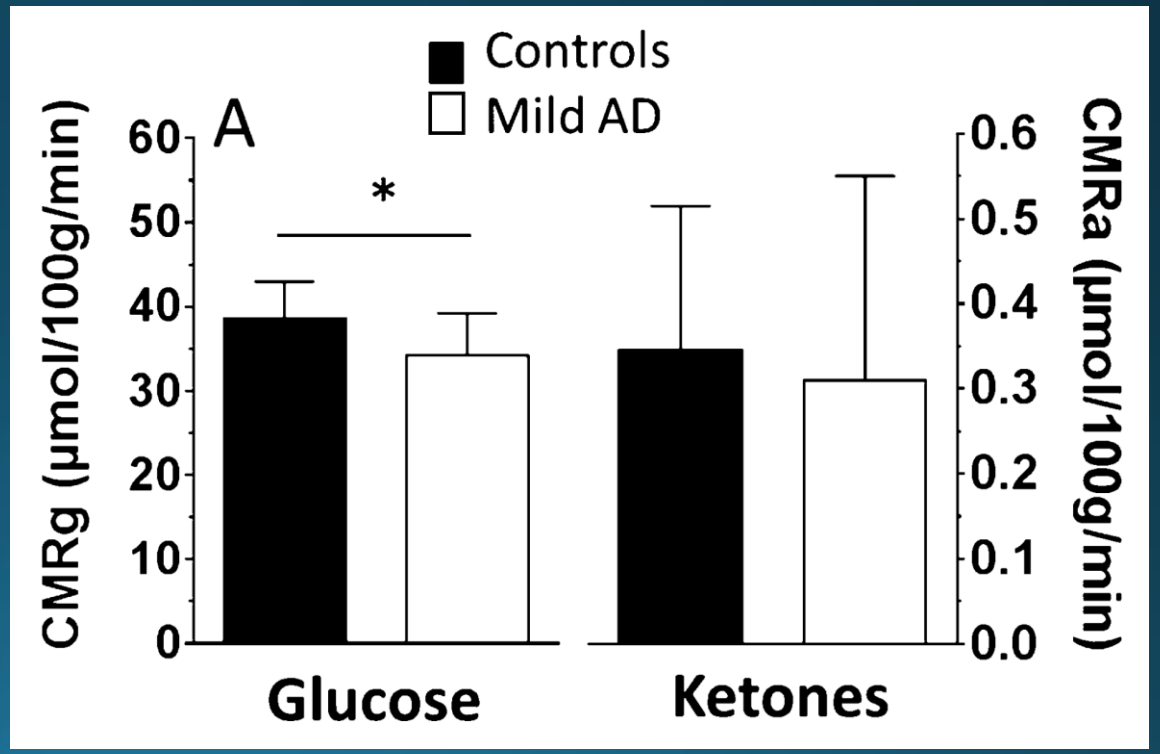
Difference at caudate

Glucose metabolism in AD brain

- Primary or Secondary?
  - Consequence of the cellular and functional degeneration in AD → glucose hypometabolism;
  - Glucose hypometabolism of brain is a critical part of the clinically asymptomatic early AD.
- Which fuel?
  - Hypometabolism to glucose only or energy substrates in general?
  - Hypometabolism affect glucose more than other substrates?

Lower Brain ^{18}F-Fluorodeoxyglucose Uptake But Normal ^{11}C-Acetoacetate Metabolism in Mild Alzheimer's Disease Dementia

- Neither global nor regional CMRa differed between the two groups.
- Regional brain energy substrate hypometabolism in mild AD may be speific to impaired glucose uptake and/or utilization.
- This suggests a potential avenue for compensating brain energy deficit in AD with ketones.



Ann NY Acad Sci 2016;1367:12-20

Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease

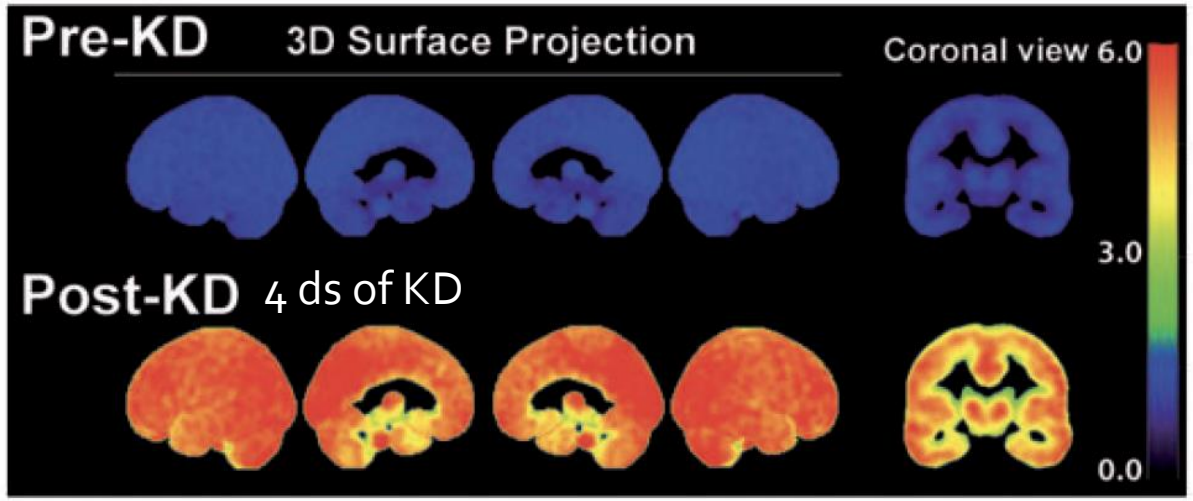
Stephen C. Cunnane,[1,2,3] Alexandre Courchesne-Loyer,[1,3] Valérie St-Pierre,[1,3] Camille Vandenberghe,[1,3] Tyler Pierotti,[1,4] Mélanie Fortier,[1] Etienne Croteau,[1] and Christian-Alexandre Castellano[1]

- AC-1202 (Axona) as "medical food" therapy;
- "Ketogenic diet" as "real food" therapy.

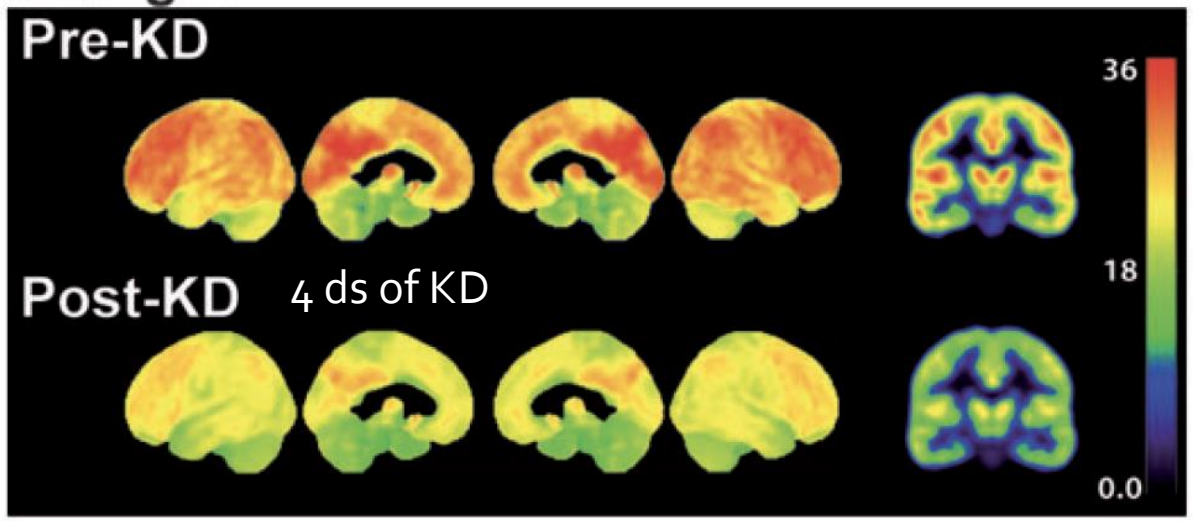
Age: 23-64, n=10

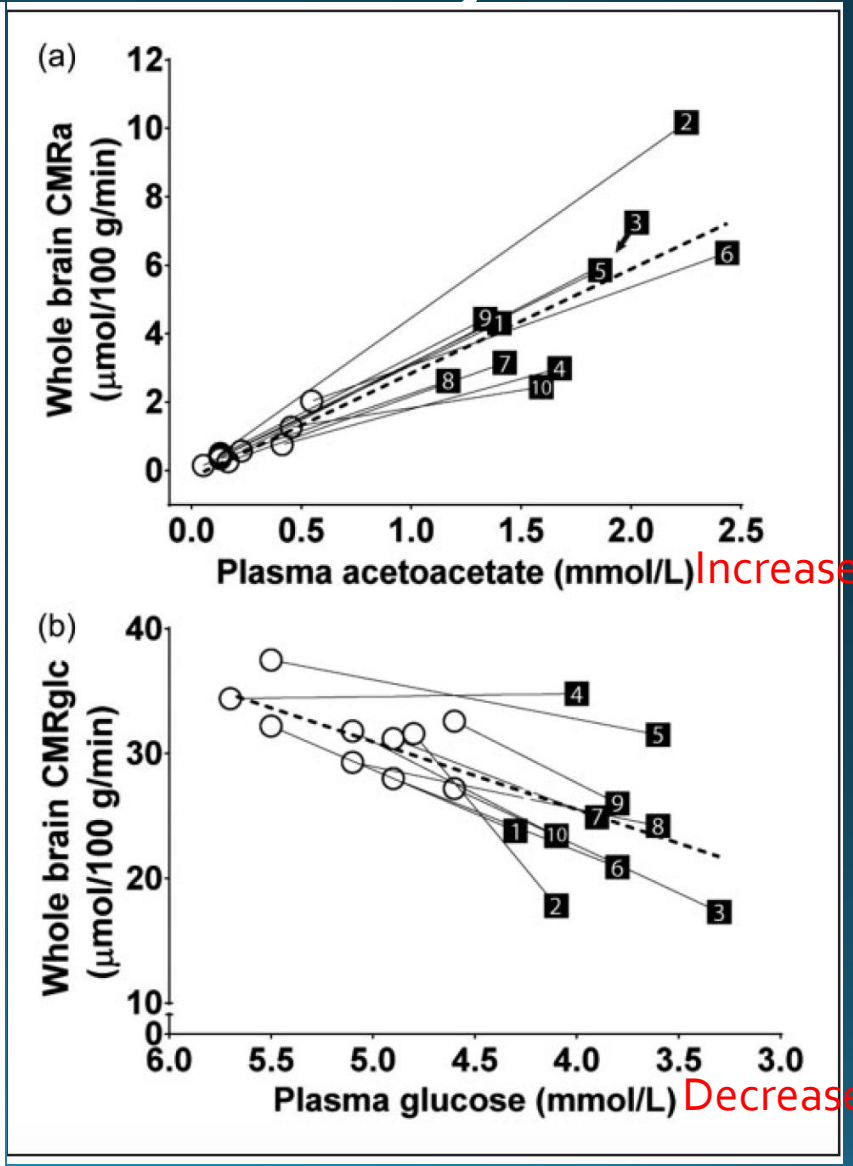
^{11}C-AcAc vs. ^{18}F-FDG vs. ketogenic diet

CMRa **^{11}C-AcAc PET increased 6-fold**



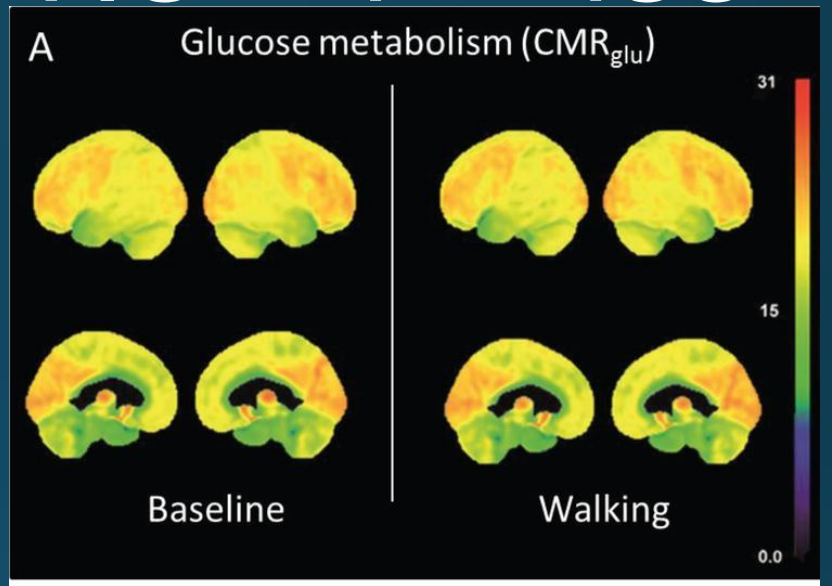
CMRglc **^{18}F-FDG PET decreased 20%**



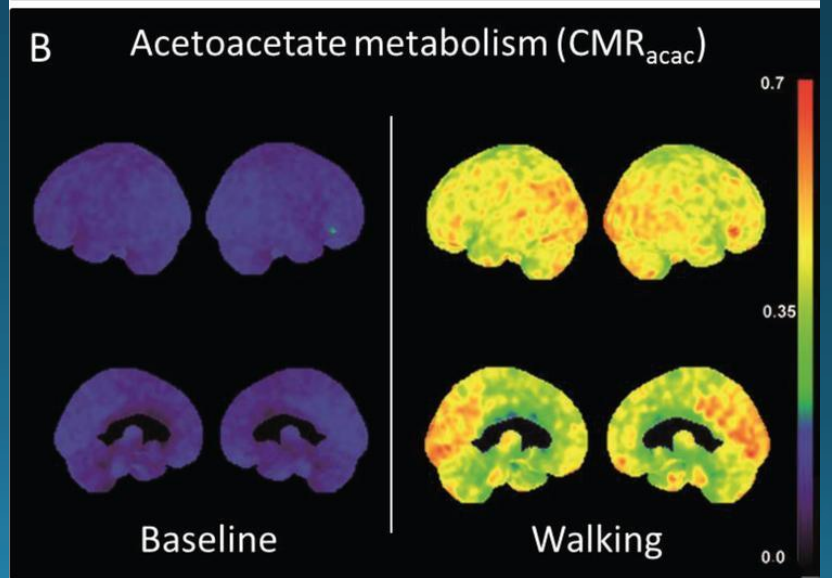


J Alzheimers Dis 2017;56(4):1459-68

- N=10, MMSE: 26/30, 73 y/o, 8 km/wk in 3 ds at 4 km/hr for 3 ms.
- Plasma acetoacetate concentration, blood-to-brain acetoacetate influx rate constant increased 2-3-fold
- Improvement in the Stroop-color naming test, Trail making A&B tests.



unchanged



Increased 3-fold

Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients

Eugene J. Fine M.D., M.S. [a,*], C.J. Segal-Isaacson Ed.D., R.D. [b], Richard D. Feinman Ph.D. [c], Silvia Herszkopf M.S., R.D., L.M.N.T. [d], Maria C. Romano M.S., R.D., C.D.N. [d], Norica Tomuta M.D. [e], Amanda F. Bontempo M.S., R.D., C.D.N. [d], Abdissa Negassa Ph.D. [f], Joseph A. Sparano M.D. [g]

[a] *Department of Radiology (Nuclear Medicine), Albert Einstein College of Medicine, Bronx, New York, USA*

Table 1
Baseline patient demographics

Patient	Age (y)/Race	Sex	Cancer diagnosis	Year*	Prior chemotherapy courses	Glucose (mg/dL)	Creatine (mg/dL)	Weight (kg)	BMI (kg/m^2)
1	61/AA	F	breast	4	5	107	1.3	77.6	29.3
2	53/H	F	fallopian tube	5	5	93	0.9	63.0	25.0
3	73/C	F	breast	14	0†	114	0.8	62.8	28.0
4	70/AA	F	colorectum	5	4	87	1.2	73.0	28.5
5	69/AA	M	lung	5	5	90	1.0	77.1	27.5
6	72/C	M	esophagus	2	6	107	1.0	103.4	29.3
7	52/As	F	colorectum	5	4	104	0.5	46.3	20.9
8	61/C	M	colorectum	6	6	95	1.1	69.9	22.7
9	64/AA	F	ovary	5	10	100	1.7	98.0	34.9
10	54/C	F	lung	4	8	93	0.9	68.0	26.1
Mean ± SEM	62.9 ± 2.5	N/A	N/A	5.5 ± 1.0	5.3 ± 0.8	99 ± 2.8	1.0 ± 0.1	73.0 ± 5.3	27.2 ± 1.2

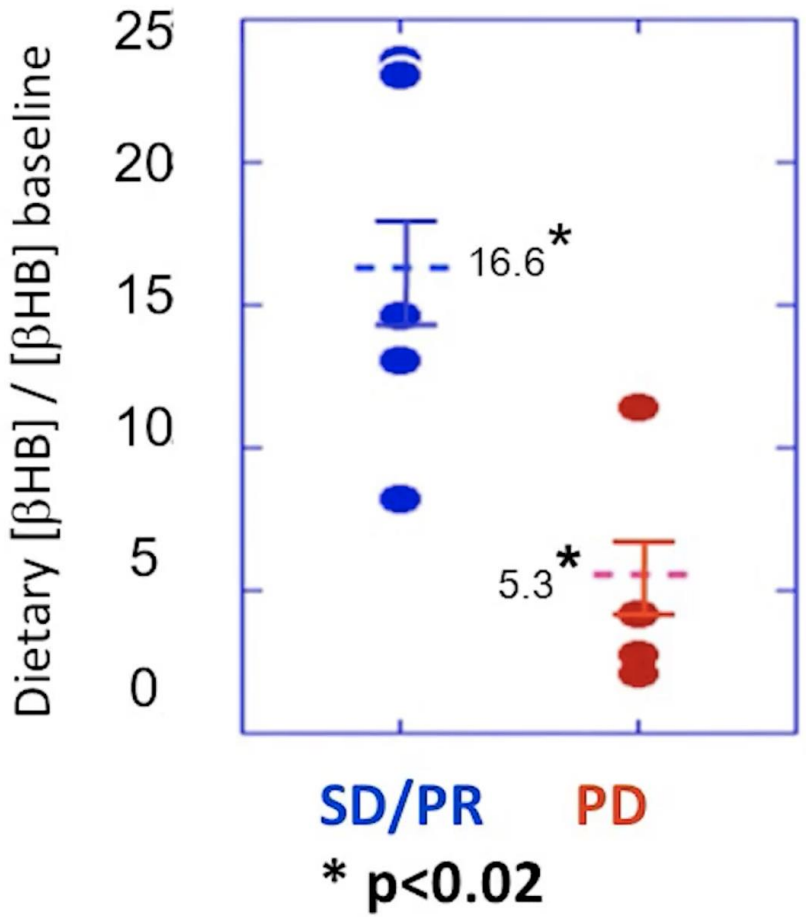
Ketosis on VLC diet vs. baseline

	Pt.	PET	$[BHB_{VLC}]$/Baseline
Stability	*3**	*SD*	*2.7 ± 1.2*
	2	PR	**23.3** ± 14.2
	5	SD	**13.1** ± 18.5
	7	SD	**14.6** ± 11.8
	8	SD	**8.2** ± 2.8
	10	SD	**23.6** ± 8.2
Progression	1	PD	**2.1** ± 1.9
	4	PD	**2.8** ± 1.2
	6	PD	**4.2** ± 2.8
	9	PD	**11.4** ± 4.5

** Pt. 3 had biologically much more indolent disease than*

Ketosis vs. PET outcome

Ketosis is 3-fold higher among stabilizers



* p<0.02

^{18}F-β-hydroxybutyrate – the next metabolic PET agent?

Conclusion

- Treat Alzheimer's disease as a metabolic disorder;
- Using ^{11}C-AcAc and ^{18}F-FDG PET scans to select suitable cases for ketone therapy in AD;
- Using ^{11}C-AcAc and ^{18}F-FDG PET scans to select suitable cases for ketone therapy in oncology;
- Possible application of ^{11}C-AcAc in other neurological disorders;
- Develop ^{11}C-AcAc , ^{11}C-β-hydroxy butyrate and ^{18}F-β-hydroxy butyrate as possible metabolic PET imaging agents in Taiwan.