

#### EINSTEIN'S INSTITUTE FOR AGING RESEARCH



Staying healthy as we get older!

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#### **NMRC-2019**

## **Diabetes drives aging and other Sacred Cows**

#### Pope John Paul the 2nd



#### Things are not what they seem!

## **Provocations for Diabetes and Aging**

- Insulin resistance not only what you think
- When is T2DM is risk for CVD?
- Are microvascular complications typical to aging?
- Role of the hypothalamus and glucose metabolism in aging

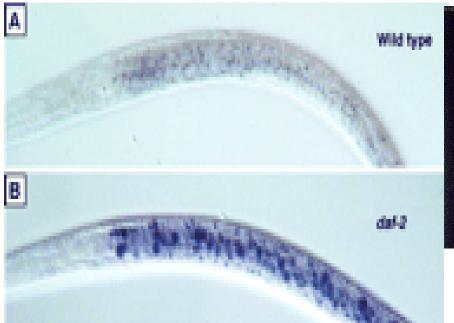
## **Great advance**

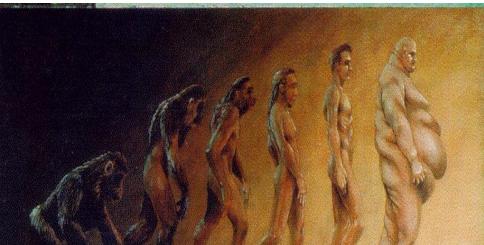
## **Great paradox**

daf-2, an Insulin/IGF Receptor-Like Gene That Regulates Longevity and Diapause in C. elegans

Kimura, Ruvkun Science 1997; 277: 942-946

Abdominal obesity is a major component of the Insulin resistance syndrome, with risk for many age-associated diseases



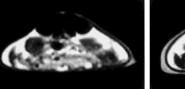


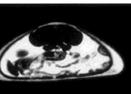
J Clin. Invest. 1998: 101:1353-1361

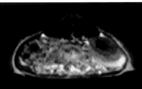


OLD

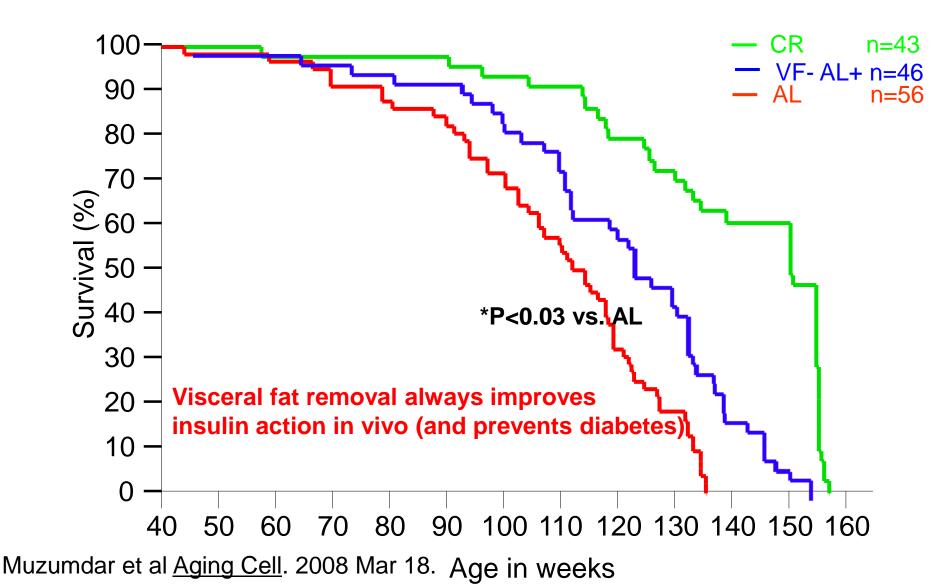
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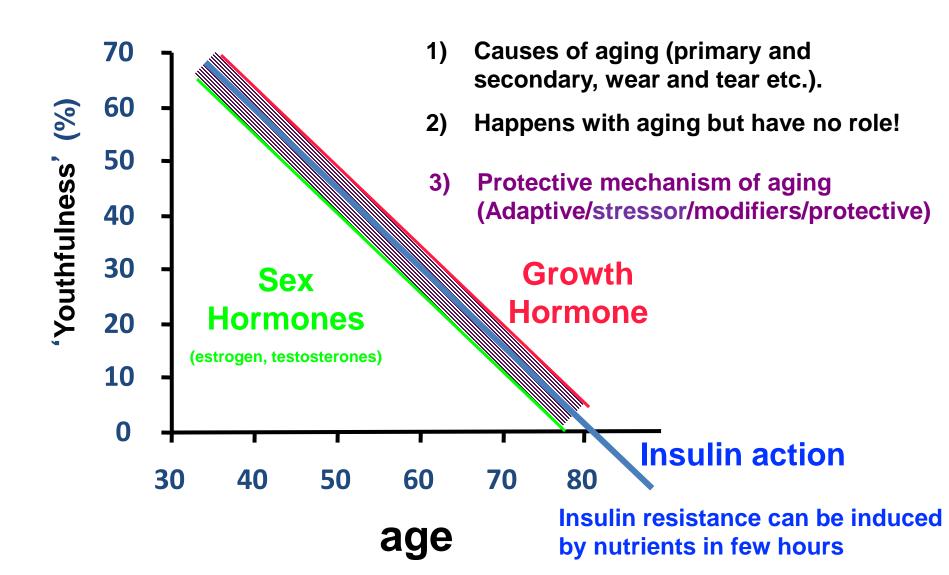




## **Does visceral fat removal extend lifespan?**



#### Phenotypes and mechanisms for aging



## Insulin Resistance and Longevity: A protective response?

Examples for decreased insulin sensitivity but with increased longevity:

IRKO+/-IR (*IrP* <sup>1195</sup> *L*/wt) IRS2+/-IRS2+/- in brain IRS1-/-Klotho transgenic mice

Rapamycin-treated mice

If we accept that insulin resistance is also a protective mechanism --we may be closer to the whole truth...

Always better for mammalians to be insulin sensitive, but if we need resistance don't just take it away

Examples for increased insulin sensitivity with decreased or unchanged longevity: PTP1B knockout mice

PGC1—a transgenic mice Resveratrol-treated mice (without high fat diet) Glut4 transgenic mice

Use of Insulin sensitizers (TZD's) have caused age-related diseases in humans!

Barzilai & Ferrucci L. J Gerontol A Biol Sci Med Sci. 2012.

### Adjusted Hazard Ratios for Death from Any Cause and from Cardiovascular Causes decrease with

Subgroup	Patients with Type 2 Diabetes	Controls		la. ۲۳' R-1 viodel 2	t <b>io (95% CI)</b> Model 3	
	no. of ev	ents		WODEL Z	WIDGEL 2	Doe an and
Death from any cause						
Before 2005	222					
<55 yr	339	606		2.81 (2.46-3.21)		an
				alor (allo blar)	2.59 (2.27-2.96)	
55–64 yr	1,227	3,501				
				1.77 (1.65–1.88)	1.57 (1.47-1.67)	and
65–74 yr ≥75 yr	3,240	10,846			1.57 (1.47-1.07)	
			I	1.52 (1.46-1.58)		
	10,399	43,890	I∳I.		1.29 (1.24–1.35)	
	10,399	43,890		1.20 (1.17-1.22)		
			*	1120 (111) 1122)	1.03 (1.01-1.06)	
During or after 2005		0.057				
<55 yr	1,066	2,289	H <b>e</b> H	2.35 (2.18-2.52)		
				2.33 (2.10-2.32)	2.18 (2.02-2.34)	
55–64 yr	4,762	13,498			()	
			IØI .	1.79 (1.73–1.85)	1 60 (1 56 1 67)	
65–74 yr	12,025	41,969	191		1.62 (1.56–1.67)	Ca
	12,025	41,505	*	1.46 (1.43-1.49)		
			•		1.27 (1.24-1.29)	
≥75 yr	44,059	189,498		1 10 /1 17 1 20)		-
			•	1.19 (1.17–1.20)	1.02 (1.01-1.03)	
Death from cardiovascular di	sease				, ,	
Before 2005		1.17				
<55 yr	97	147		3.32 (2.57-4.29)		
			⊢ <b>→</b>	1 5.52 (2.57 1.25)	2.96 (2.28-3.83)	
55–64 yr	477	1,071				
				2.24 (2.01–2.50)	1.85 (1.66-2.07)	
65–74 yr	1,520	4,117			1.85 (1.00-2.07)	
			HeH	1.88 (1.77-1.99)		
	5 43 4	01 015	H♦H		1.46 (1.37-1.55)	
≥75 yr	5,434	21,915		1.25 (1.22-1.29)		We
			÷	1.25 (1.22 1.25)	1.02 (0.99-1.06)	
During or after 2005						
<55 yr	298	476		2 15 /2 72 2 64		tha
				3.15 (2.73-3.64)	2.86 (2.47-3.31)	the
55–64 yr	1,576	3,511			,,	
			H	2.28 (2.15-2.42)	1 02 (1 82 2 05)	و الماريد
65–74 yr	4,288	12,929	H		1.93 (1.82-2.05)	whic
	1,200	12,525	101	1.69 (1.63-1.75)		
			Hel .		1.35 (1.30-1.40)	
≥75 yr	20,548	85,751		1.23 (1.21-1.24)		ac
				1.25 (1.21-1.24)	0.98 (0.96-0.99)	uu
		0.70	1.00 1.50 2.00 4	1.00	()	
		0.70	1.00 1.00 2.00 4			

s diabetes add risk to death diseases in the elderly?

n diabetes be rotective in elderly?

need to identify mechanisms by h hyperglycemia elerates aging!

Tancredi M et al. N Engl J Med 2015;373:1720-1732.

Patients with

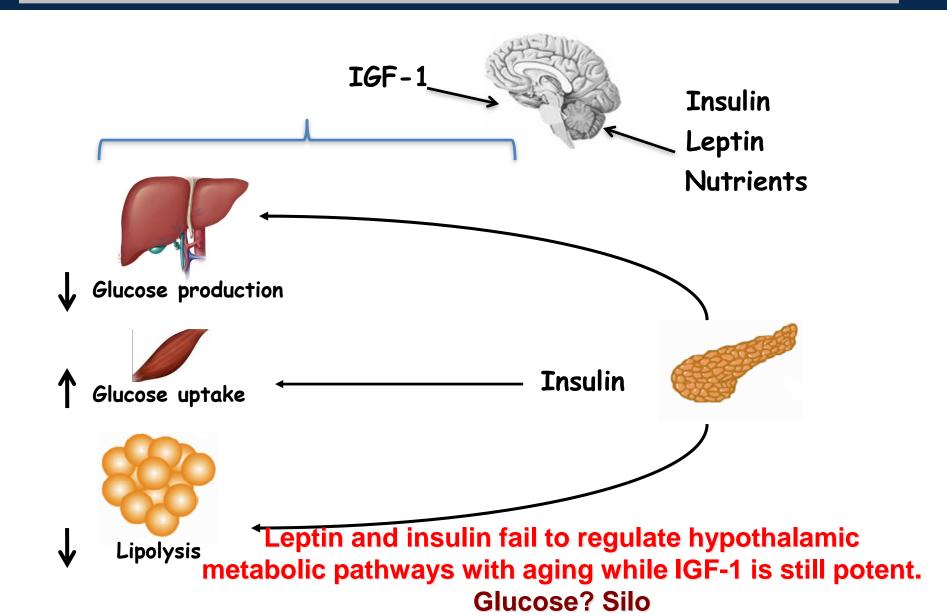
**Potential confounders:** Competing risks, survival effects, duration, metformin, statins etc

# Diabetes microvascular complications and aging (?)

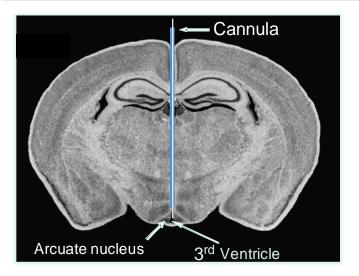
Retinopathy-Neuropathy-Nephropathy-

- It's the glycemic hypothesis that seems important.
- No data about prevalence of all those in nondiabetic elderly.
- Some overlap of nephropathy and aging, but not typical pathological kidney.

## **Regulation of glucose homeostasis**



## Hyperinsulinemic-euglycemic clamp



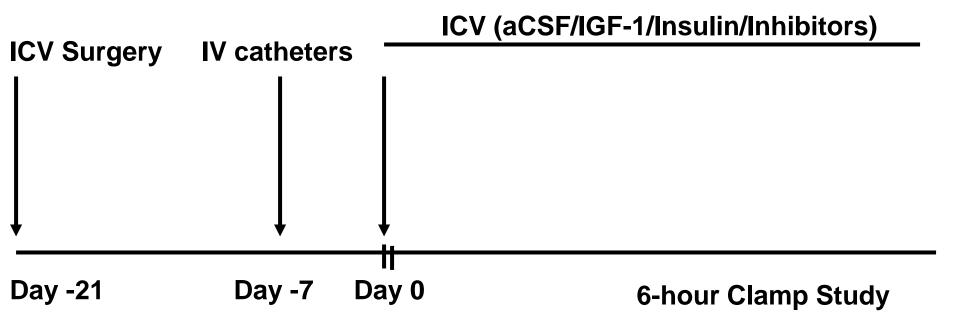
3MO and 20 MO Male Sprague Dawley Rats

25% dextrose (as needed)

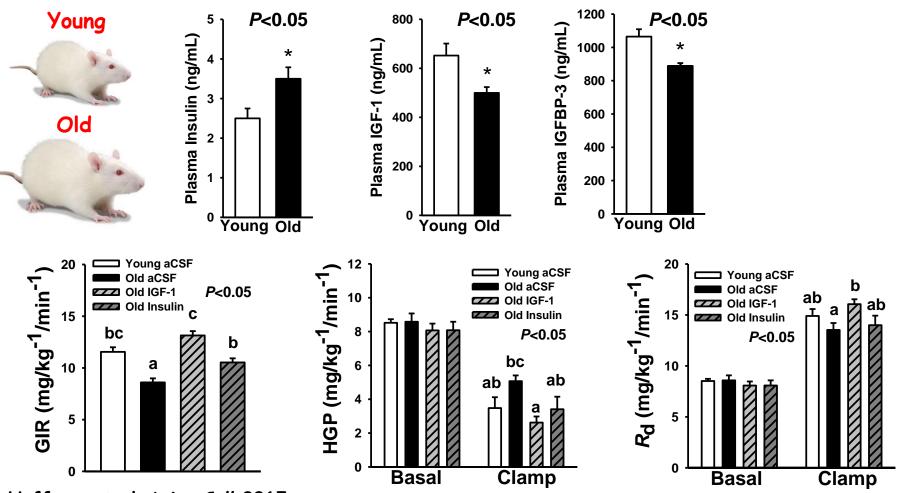
Somatostatin

Insulin 3mu/kg/min

**Tritiated glucose infusion** 



## Central IGF-1 Restores Insulin Sensitivity in an aging model



Huffman et al Aging Cell 2015

## Summary:

- The glucose hypothesis of some diabetes complications is not generally consistent with driving aging.
- Insulin resistance in aging may represent defense/ adaptation and may not necessary accelerate aging (but it does accelerate diabetes).
- Mechanisms that may fail in diabetes and aging include:
- Hypothalamic regulation of peripheral metabolism
- Insulin regulation in cognitive areas of the brain
- Proteostasis/Autophagy in a variety of tissues (beta-cells, neurons etc...), although hyperglycemia induces autophagy.
- The mechanisms by which drugs (metformin and acarbose) that target diabetes also increase longevity should be defined.
- It is a challenge is to identify the mechanisms of aging that are being accelerated with hyperglycemia!