

An In Depth Look at Metformin: Potential New Uses for an Old Drug

Curtis Triplitt, PharmD, CDE
Diabetes Research Center,
Texas Diabetes Institute
Associate Professor of Medicine, University of Texas
Health Science Center at San Antonio

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Metformin: Overview

- Anti-inflammatory effects
- Microbiome
- Cancer
- Aging

**Word of Caution: I am an expert in none of the above!
So I approached as a Pharmacist Diabetes Educator
And the question: What do I tell my patients about this?
It is All Off-Label Use**

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Metformin: Botanical Background



- Galega officinalis
- “Goat’s rue”
- “French Lilac”
- Rich in guanidine, but too toxic for direct diabetes treatment, derivatives were synthesized
- “First” synthesis
 - Jean Sterne- Aron Pharmaceuticals-France

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Metformin: Structural Derivation

Guanidine	$\text{NH}_2 - \text{C}(\text{NH}_2) = \text{NH}_2$
Galegine	$\text{CH}_2 - \text{C}(\text{NH}_2) = \text{CH} - \text{CH}_2 - \text{NH} - \text{C}(\text{NH}_2) = \text{NH}_2$
Synthetin A	$\text{NH}_2 - \text{C}(\text{NH}_2) - \text{NH} - (\text{CH}_2)_{10} - \text{NH} - \text{C}(\text{NH}_2) = \text{NH}_2$
Synthetin B	$\text{NH}_2 - \text{C}(\text{NH}_2) - \text{NH} - (\text{CH}_2)_{12} - \text{NH} - \text{C}(\text{NH}_2) = \text{NH}_2$
Biguanide	$\text{NH}_2 - \text{C}(\text{NH}_2) = \text{NH} - \text{C}(\text{NH}_2) = \text{NH}_2$
Metformin	$\text{CH}_2 - \text{N}(\text{NH}_2) = \text{C}(\text{NH}_2) - \text{NH}_2$
Phenformin	$\text{C}_6\text{H}_5 - (\text{CH}_2)_2 - \text{N}(\text{NH}_2) = \text{C}(\text{NH}_2) - \text{NH}_2$
Buformin	$\text{CH}_3 - (\text{CH}_2)_3 - \text{N}(\text{NH}_2) = \text{C}(\text{NH}_2) - \text{NH}_2$

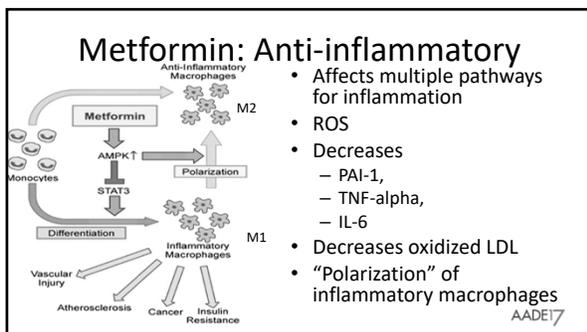
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Metformin: Uses

- Diabetes Mellitus
- Prevention of Diabetes Mellitus
- Polycystic Ovary Syndrome
- Others?
 - Anti-inflammatory
 - Microbiome
 - Cancer
 - Aging



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Metformin and Acute Diverticulitis

- Retrospective Case Control Trial
- Rates of acute diverticulitis in metformin treated patients with diabetes (n=175)
- Results
 - Metformin 44% vs. No-metformin 60% p=0.002
 - Insulin and other orals used not associated with a lower risk

Scandinavian Journal of Gastroenterology, 2017, 52:969-972

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Metformin: SLE*

- China- 113 with SLE randomized to add metformin to their regimen or placebo
- Well matched at baseline- target dose 500mg three times a day

A

Patients at Risk
Metformin add-on: 56 56 56 52 49 48 44 44 44 43 43 43
Conventional treatment: 57 56 56 52 49 48 44 43 39 39 38 33

B

Patients with DQW reduction
Metformin add-on (n=56)
Conventional treatment (n=57)

May help in a complex way through the interferon-alpha pathway

Wang J et al. Arthritis Rheumatol 2015;67:3190

*Systemic lupus erythematosus

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Anti-inflammatory Summary

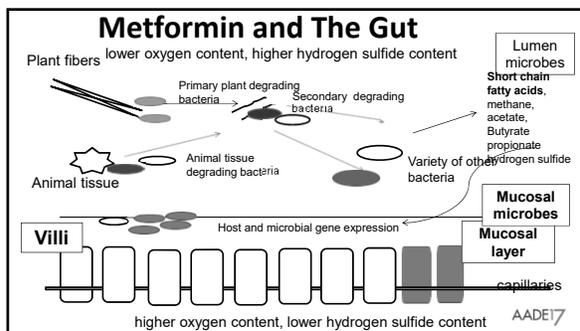
- Mechanism- may convert to "anti-inflammatory macrophages"
- Helps to decrease damage from neutrophil "bombs"
 - Fancy name- neutrophil extracellular traps
- Rheumatoid arthritis
 - Very limited data- not much research planned
- SLE -Interesting pilot study
 - Multicenter trial now recruiting via same center in China
 - Not being extensively studied for other similar issues via www.clinicaltrials.gov
- What to tell our patients? It is too early to recommend metformin for any chronic inflammatory condition, but if you happen to have T2DM, it is worth a try

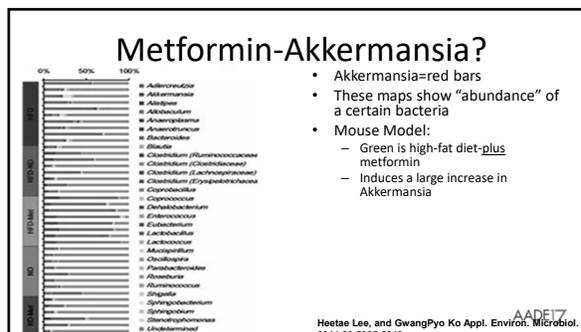
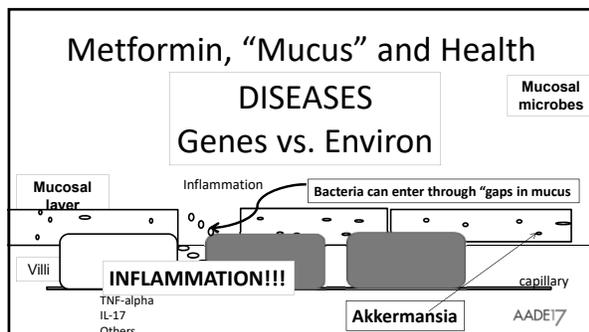
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Metformin and the Microbiome

- A small number of bacteria make it past stomach and influence bacteria in gut (microbiome)
- The gut condition influences the bacteria that can flourish
- Mix of bacteria- influenced by a large number of issues, inputs, and disease states
- Early on body trains itself to distinguish self from non-self- these are called dendritic cells and Tregs
 - Inflammation can occur if seen as foreign

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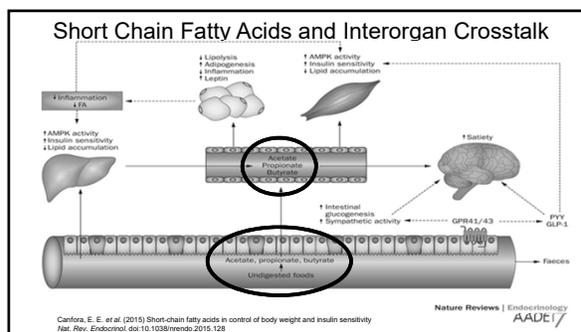


Metformin and Microbiome

- *Akkermansia muciniphila* is a Gram-negative, strictly anaerobic, non-motile, oval-shaped bacterium.
- Lives in the mucin of our gut and uses as a source of energy
- Thin mucus layer=low # of these bacteria=at risk of inflammation
 - Upregulated by metformin
 - Improves glycaemic control
 - May improve intestinal integrity
 - Helps keep other harmful bacteria out of contact with gut by mass exclusion
- Short-chain fatty acid producing bacteria
 - May come from bacterial source or mucin breakdown
 - Butyrate- feeds the enterocyte making in healthier
 - Propionate and acetate=liver
 - ↑ intestine making glucose, which may decrease the liver's production of glucose
 - Resistant starch- help with satiety, lowering blood glucose, and lowering cholesterol through these pathways

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Carlson, E. E. et al. (2015) *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2015.128
Forslund K. *Nature* 2015;528:262-266

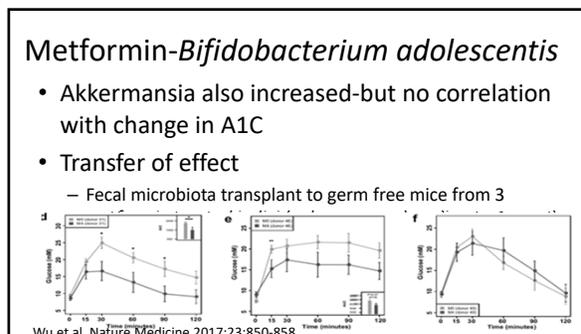


Metformin- One More Bacteria!

- 1700mg/day (n=22) or placebo (n=18) for 4 months in DM Med drug-naïve T2DM patients
- Small group of placebo switched to metformin 6 months later to see if same effect as active group
- Metformin changed the abundance of **~80 strains** of bacteria in the gut
- Major change in *Bifidobacterium adolescentis*
 - This is a probiotic bacteria highly abundant just after birth, but levels may decrease with age
 - Correlated weakly with change in A1C

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Wu et al. *Nature Medicine* 2017;23:850-858



How to Improve Your Gut?

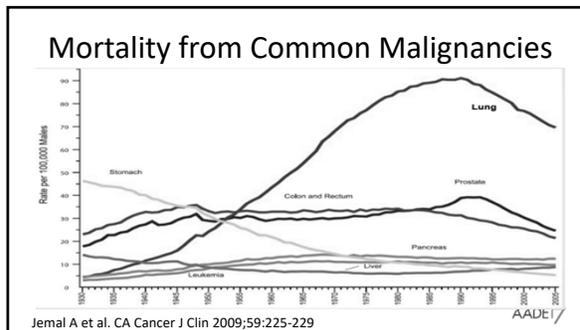
- **Take in plenty of probiotics**
 - Yogurt, non-frozen dairy, soy based drinks, sauerkraut, many pickles etc.
 - Supplement? Perhaps but poor evidence helps...but does not hurt
 - A1C lowering effect ~0.4%
- **Increase poly-phenol rich foods**
 - Cranberries, other berries including blueberries
 - Others
- **Consider metformin?** Ahhhhh.....no.....not yet.
- **Unless you have PreDM or Type 2 DM**



- **What to Tell Patients:**
 - This is not the same effect as GI side effects
 - This is an added bonus of metformin, but not yet a compelling reason
 - Take probiotics if you would like

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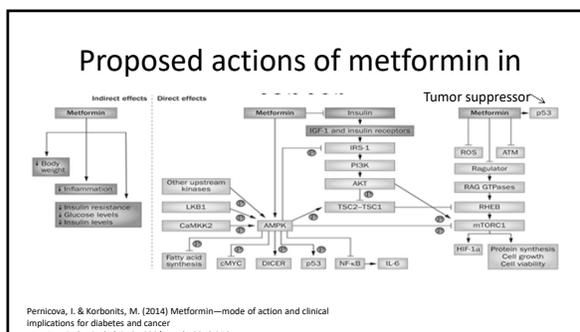
*Wang et al. J Pediatr Endocrinol Metab 2017;30:6-11-622. Photo:belandorganicfood



Metformin and Cancer

- Cancer survival rates continue, in most cases, to improve
- Mechanism of action is still under investigation
 - Direct Effects – through AMPK and mTOR pathways
 - Indirect- blood glucose lowering/anti-inflammatory
- Test tube data—Be Careful!
 - Often at very high levels of metformin or really high glucose which can affect some cancer growth
 - What is tissue metformin concentration at site of cancer?
 - Example: Hepatic levels 4-6 times plasma

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Intensified Glycemic Control

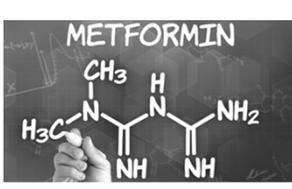
- Cancer mortality and cancer incidence from major randomized controlled trials that intensified glycemic control did not improve
- UKPDS 33, UKPDS 34, ACCORD (Action to Control Cardiovascular Risk in Diabetes) and VADT (Veterans Affairs Diabetes Trial) was of

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Johnson JA, Bowker SL. Diabetologia. 2011; 54: 25-31.

Metformin: Potential Adjuvant Treatment in Select Cancers

- Evidence Level Varies Per Cancer
- More Data
 - Colorectal
 - Prostate
 - Breast
 - Liver
- Less Data
 - Bladder
 - Renal Cell Carcinoma
 - Pancreas
 - Lung
 - Endometrial
 - Gastric



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Metformin: Others Cancers

- Renal cell carcinoma
 - May help with localized RCC only
 - Metastatic RCC, may increase survival time by a few months when used in combo therapy, but not survival
- Pancreas- may help with resectable tumors but not if metastatic disease

Clin Genitourin Cancer. 2016 Apr;14(2):168-75

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Metformin: Cancers

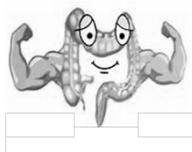
- Prostate
 - At least 7 meta-analysis
 - Not all congruent but clear about the following:
 - May decrease risk of occurrence, but does not decrease death
 - Recurrence rate- no effect to 20% reduction
 - May work better in those who use radiotherapy by improving tumor response rate to therapy

He XX et al. Medicine (Baltimore). 2016 Feb;95(7):e2749
 Ann Oncol. 2016 Dec;27(12):2184-2195
 Diabetes Metab Res Rev. 2015 Sep;31(6):595-602
 Br J Clin Pharmacol. 2015 Dec;80(6):1464-72.

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Colorectal

- 151 on-DM patients with single or multiple colorectal adenomas removed were randomized to metformin 250mg daily or placebo in Japan
- Metformin at 1 year F/U had less:
 - Adenomas plus “pre-adenoma”
 - 27 metformin vs. 35 placebo p=0.034
 - Relative Risk Ratio 0.67 (95% CI 0.47–0.97)
 - Well tolerated
- Colorectal
 - Meta-analysis Data- Users vs. Non-Users
 - Incidence: OR = 0.90, 95% CI: 0.85-0.96
 - Survival: HR = 0.68, 95% CI: 0.58-0.81



The Lancet Oncology 2016;17:475-483
 PLoS One. 2013 Aug 23;8(8):e71583

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Metformin: Breast Cancer

- Given before resection of tumor “Neoadjuvant Therapy”
- New Dx of breast cancer in non-DM patients- started on metformin 500mg TID until surgery
- In variety of breast cancers with markers (HER2, estrogen receptor etc) but in general “mild to moderate”
- Results:
 - Decreased Ki-67- INTERPRETATION- decreased division of breast CA cells
 - Increased TUNEL staining- INTERPRETATION-more breast CA cells were dying

Breast Cancer Research and Treatment 2012;135:821-830

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Metformin: Breast CA

# of women	Study population	Setting	Design	Metformin dosing
22	Early BC patients; insulin >45 pmol/L	Adjuvant	Single arm	500 mg tid x 6 mos
47	Operable invasive BC	Neoadjuvant window	Metf versus ctrl (no metf)	500 mg qd x 1 wk, then 1000 mg bid x 1 wk
200	Operable BC	Neoadjuvant window	Metf versus ctrl (placebo)	850 mg bid x 4 wks
35	Ov/Ob invasive BC or DCIS versus matched untreated historical ctrl	Neoadjuvant window	Single arm	500 mg am and 1000 mg pm, 2-4 wks (avg = 22 days)
3,649	Treated early BC	Adjuvant	Metf versus ctrl (placebo)	850 mg bid x 5 yrs (results reported after 6 mos)
39	Operable BC	Neoadjuvant window	Single arm	500 mg tid 13-40 days (avg = 18)

No Data To Date (That I could find)
 That metformin Improves cure Rates etc.

Patient info:
 Not going to hurt you- Worth a try, but have Reasonable expectations

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Continuation of Metformin Use After a Diagnosis of Cirrhosis Significantly Improved Survival of Patients with Diabetes

Zhang X et al. Mayo Clinic Hepatology 2014

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Hepatologists May Know....

- “Metformin can be used in patients with liver cirrhosis without renal insufficiency.”
 - Unreferenced in article

Amarapurkar DN
Prescribing Medications in Patients with
Decompensated Liver Cirrhosis
International Journal of Hepatology
Volume 2011 (2011), Article ID 519526,

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Hepatocellular Carcinoma (HCC)

- Cirrhosis increases risk
 - Increase in risk is more with Hep C or B than DM
 - NAFLD cirrhosis- 7-12% HCC over 10 year
- NAFLD may increase HCC without cirrhosis
 - In HCC with “no” underlying etiology, a high percent had steatosis (~50%) or portal inflammation (79%)
- 1/3 of HCC patients have type 2 DM

Baffy et al. J of Hepatology 2012; 56:1384

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Background Study: Met Likely Decreases HCC

- 610 HCC patients compared with 618 matched cirrhotic patients and 1696 Controls
- HCC Risk-In those with T2DM upon Multivariate analysis reported metformin treatment vs. SU or Insulin treatment
 - (OR 0.15; CI 0.04–0.50; $P=0.005$)

-Confounder always health of patient

Liver International 2010; 30(5): 750-758

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Primary Aim

- Assess survival between diabetic patients who continued metformin versus those who discontinued after diagnosis of cirrhosis



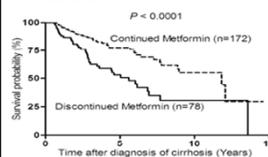
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Methods

- Retrospective cohort study
 - Diagnosed cirrhosis (Jan 2000 to DEC 2010)
 - Cirrhosis- by histology (n=124) and/or clinical features-portal HTN, morphologic-radiologic imaging
 - DM- by self-report, taking DM meds, by A1C or random glucose
 - On Metformin at cirrhosis diagnosis
 - 2 groups- continue metformin (MET) or discontinue
 - Continue= took at least 3 months
 - Discontinue= cessation within 35 months after diagnosis (arbitrary)
- Exclusion-history of malignancy except non-melanoma skin CA, less than 18 y.o., incomplete hx, stop metformin prior to dx or start after dx of cirrhosis

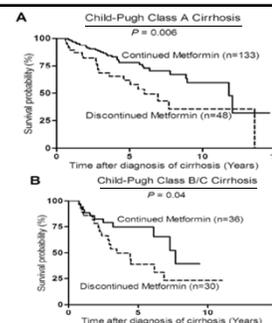
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Results



After Cirrhosis Diagnosis
Median Survival of patients who:

Continued metformin=11.6 year
Discontinued metformin=5.6 years,
($P < 0.0001$)



Discussion

- Metformin in NASH
 - No Lactic Acidosis
 - Child-Pugh B and C
 - “No life-threatening complications”
- Prolonged survival!!!!
- To my patient:
 - Take it!

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“Aging”

- Neurodegenerative diseases
- Extending Life
- Extending “Healthspan”
- Or both!

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Alzheimer Disease (AD)

- 20 non-DM patients with mild AD
- Pilot study, R, DB, PC
- Metformin 2000mg/day X 16 weeks
- Cognitive functioning at baseline and end of treatment period
- Metformin levels were found in CSF
- Functioning neuroimaging-no change
- Executive function only, improved significantly
 - The High level coordination of activity and thinking
 - Multitasking-staying to social norms etc.

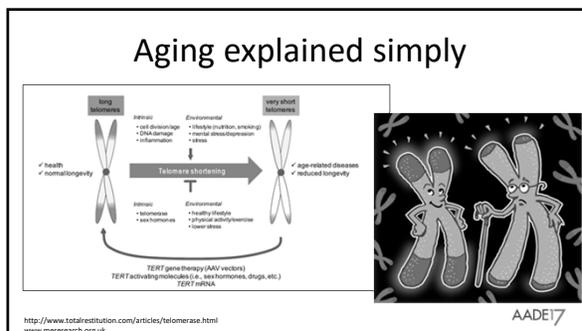
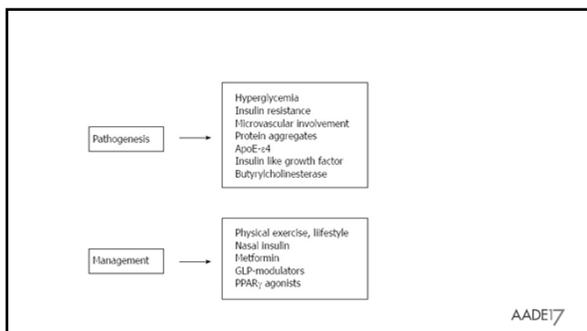
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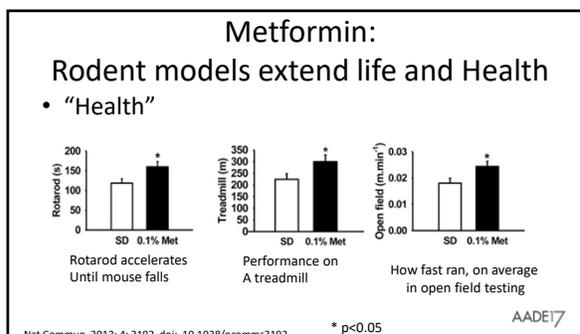
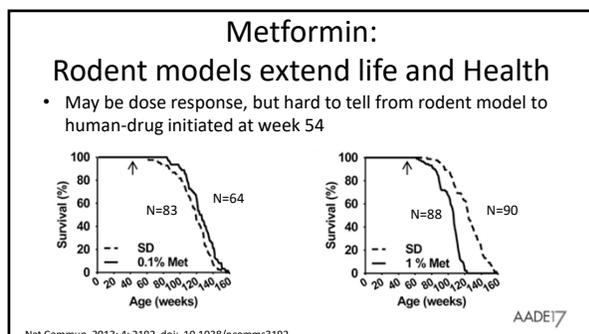
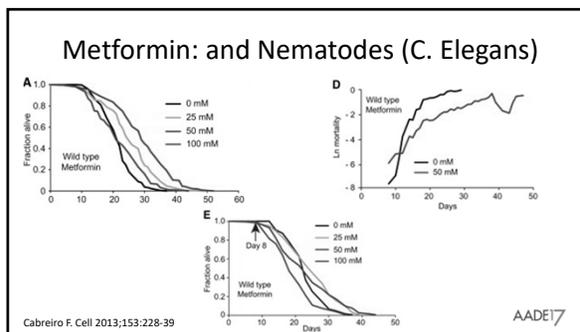
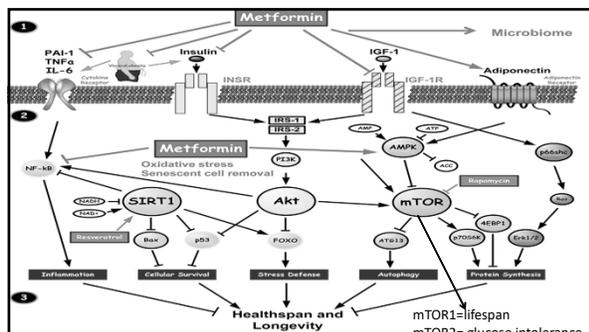
Koenig AM, Et al. Alzheimer Dis Assoc Disord 2017;31:107-113

Metformin and Cognition: DPP/DPPOS

- At 8 and 10 years f/u in the DPP/DPPOS
- Placebo (n=749) versus metformin (n=746) compared
- No significant difference in cognition outcomes
- Higher glycemia associated with poorer cognition outcomes

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Targeting Aging with Metformin (TAME)

- Delay the onset of age-related diseases and conditions including cancer, cardiovascular disease and Alzheimer's disease with metformin?
- Dose? Protocol? Likely R, DB, PC trial in ~3000 older adults
- FDA has "signed off" on looking at metformin for aging
- NIH earlier this year had R01 grants for this purpose
- Not in clinicaltrials.gov

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Metformin to Augment Strength Training Effective Response in Seniors (MASTERS)

- 120 subjects ≥65 years of age
- Progressive resistance training program
- Metformin 850mg BID or placebo in addition to resistance training
- Outcomes
 - Muscle biopsies
 - Balance and gait tested
 - Physical activity ability
 - Physical strength
 - Quality of life

Trials 2017;18:192

Metformin: Advise to patient

- Probably not for aging or healthspan yet.
- Rodent and human trials not always congruent

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Conclusion: Metformin

- Should it go in our drinking water?
- Probably not yet!
- Holds promise for certain immune diseases, cancers, and as a healthspan/aging agent
- Hopefully well conducted trials to come as evidence to date is encouraging but not "solid"



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