Metformin and benefits Beyond diabetes

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Disclaimer

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Objectives

1

Review popular new claims regarding metformin

2

Review the data on metformin and morbidity/mortality benefit

3

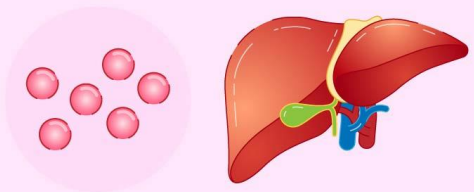
Discuss potential implications of above

Case scenario

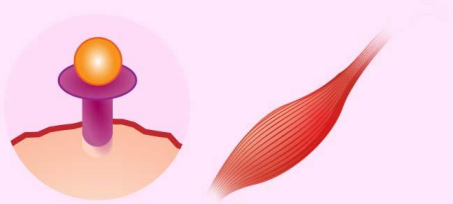
- Dennis is a 69yo M with diet-controlled diabetes(6.9%). His wife Jeanine is a healthy 67yo F(6.0%).
- They have heard about this old miracle drug metformin is investigated as “anti-aging” drug. What are your thoughts?
- They ask several questions!

What is Metformin?

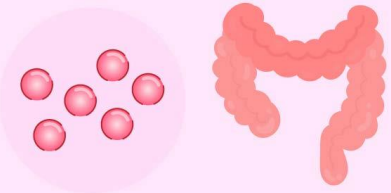
- Biguanide, approved for use in Type 2 Diabetes
- FDA approved for DM2 since 1994



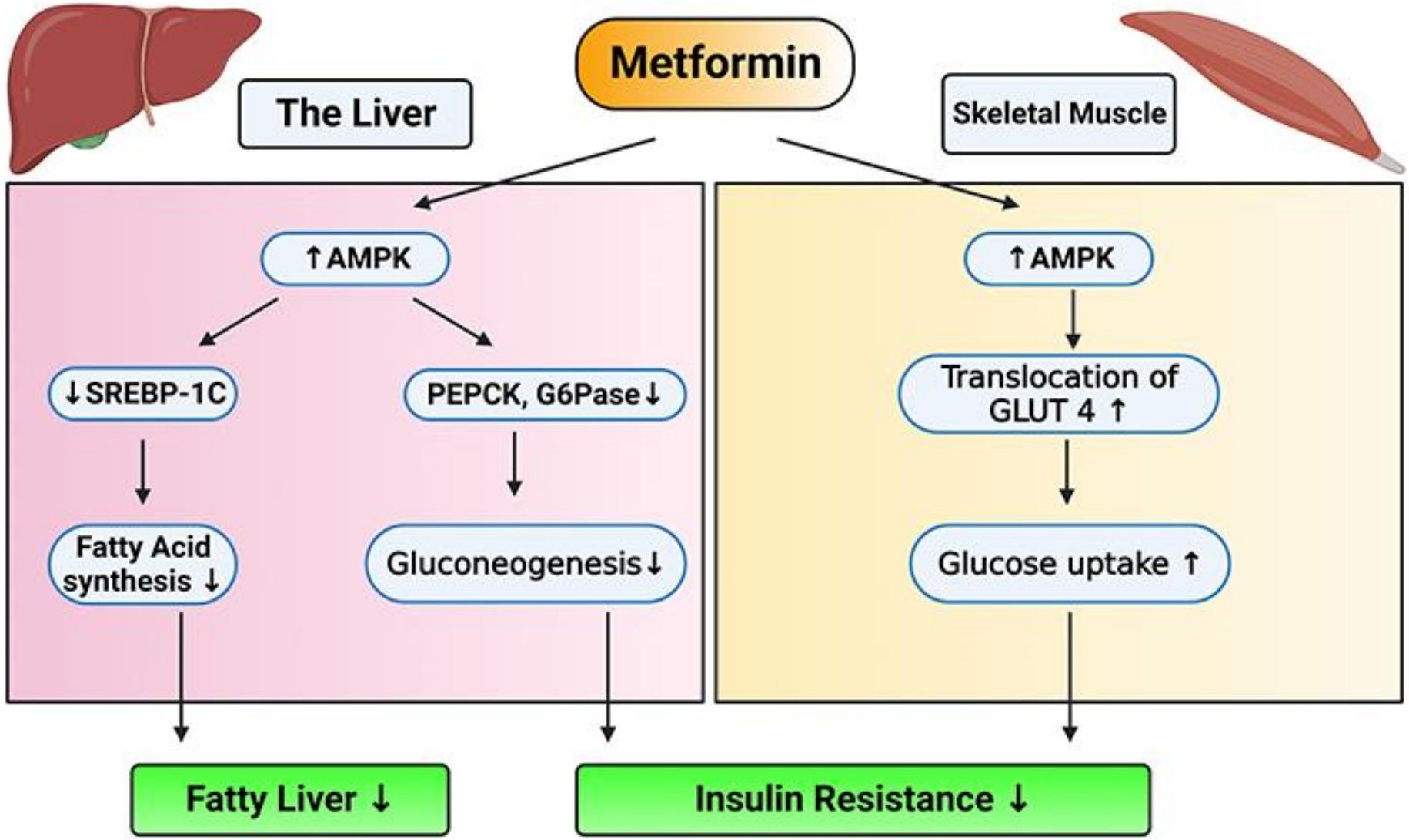
Reduce glucose production in the liver



Increase insulin receptors in muscle



Delay the absorption of glucose in the intestine


Metformin
The Liver
Skeletal Muscle
↑AMPK
↓SREBP-1C
PEPCK, G6Pase↓
Fatty Acid synthesis ↓
Gluconeogenesis↓
↑AMPK
Translocation of GLUT 4 ↑
Glucose uptake ↑
Fatty Liver ↓
Insulin Resistance ↓

What are recent popular claims for metformin?

Cognitive protective benefits

Increasing healthy lifespan

Anti-inflammatory effect

Cancer prevention

Does metformin work for diabetes?

Proven by landmark trial UKPDS(Unite Kingdom Prospective Diabetes Study)

20yr Randomized prospective study

-Glucose lowering effect A1c reducton 1-2%

-Reduced MI(33% RRR P.005)

-Mortality related to diabetes and all cause mortality (27% P=0.002)

Can Metformin prevent diabetes?

Diabetes Prevention

The New England
Journal of Medicine

VOLUME 346 FEBRUARY 7, 2002 NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

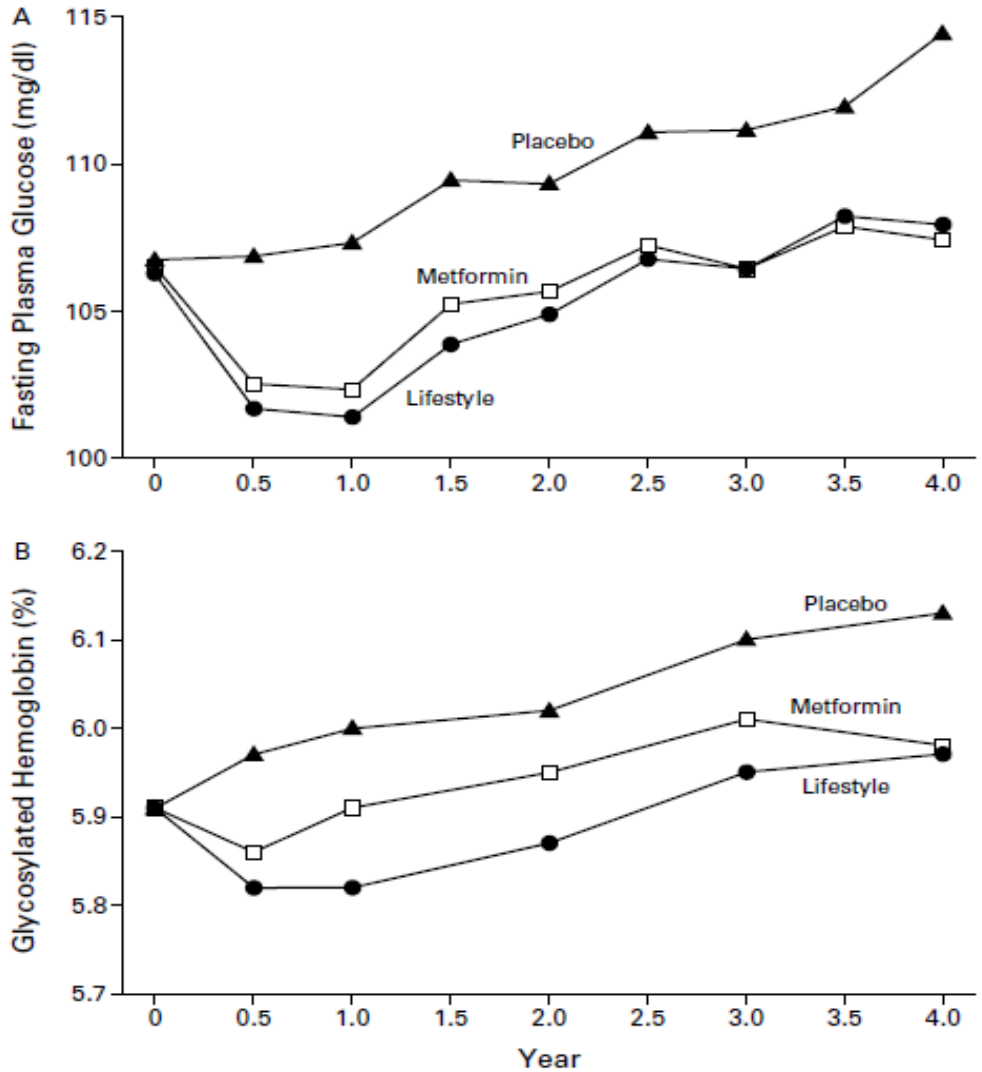


Figure 3. Fasting Plasma Glucose Concentrations (Panel A) and Glycosylated Hemoglobin Values (Panel B) According to Study Group.

The analysis included all participants, whether or not diabetes had been diagnosed. Changes in fasting glucose values over time in the three groups differed significantly ($P<0.001$). Glycosylated hemoglobin values in the three groups differed significantly from 0.5 to 3 years ($P<0.001$). To convert the values for glucose to millimoles per liter, multiply by 0.05551.

Can metformin prevent dementia?

frontiers | Frontiers in Neuroscience

TYPE Systematic Review
PUBLISHED 25 August 2022
DOI 10.3389/fnins.2022.984559

Metformin use is associated with a reduced risk of cognitive impairment in adults with diabetes mellitus: A systematic review and meta-analysis

Jia-Hao Zhang[1†], Xin-Yang Zhang[1*†], Yan-Qiu Sun[2†], Ren-Hua Lv[3], Mei Chen[1] and Meng Li[1]

Results: A systematic search identified 1,839 articles, of which 28 (17 cohort, 8 case-control, and 3 cross-sectional studies) were included in the meta-analysis. Metformin reduced the occurrence of cognitive impairment in patients with diabetes [unadjusted hazard ratio (*HR*) = 0.67, 95% *CI*: 0.62–0.73; adjusted hazard ratio (a*HR*) = 0.92, 95% *CI*: 0.85–0.99]. In addition, the use of metformin was associated with a decreased risk of dementia (*HR* = 0.64, 95% *CI*: 0.59–0.69; a*HR* = 0.90, 95% *CI*: 0.84–0.96), while a random-effects meta-analysis indicated no significant effect of metformin on the risk of Alzheimer's disease (AD) (*HR* = 0.85, 95% *CI*: 0.60–1.22; a*HR* = 1.10, 95% *CI*: 0.95–1.28).

- Massive prospective cohort trial
- Duration 8 years
- Annual neuropsychiatric assessment(Not just MMSE)
- N=3029
- Actual autopsy data available for 1584

Metformin, age-related cognitive decline, and brain pathology

Ajay Sood[1], Ana W. Capuano[1], Robert S. Wilson[1], Lisa L. Barnes[1], Alifiya Kapasi[1], David A. Bennett[1], Zoe Arvanitakis[1]

- Metformin group showed reduced rate of cognitive decline

And less microvascular damage on autopsy

Table 2. Relationship of metformin* with cognitive function at baseline and over time

Outcome	Estimate (SE, *p*-value)	
	Metformin	Metformin x time in study
Global Cognition	-0.007 (0.037,0.84)	**0.017 (0.007,0.027)**
Cognitive domains		
Episodic Memory	-0.010 (0.048,0.840)	**0.021 (0.009,0.017)**
Semantic Memory	-0.032 (0.047,0.550)	**0.022 (0.011,0.041)**
Working Memory	-0.026 (0.045,0.566)	0.006 (0.006,0.305)
Visuospatial abilities	-0.023 (0.046,0.620)	0.006 (0.005,0.312)
Perceptual speed	-0.052 (0.049,0.286)	0.002 (0.007,0.741)

Six separate linear mixed effects models (one per row) controlling for age at study baseline, sex, and years of education

* Using metformin at any time during the study

Longevity benefits

- Longevity trials are very difficult to do

-Need LONG trial period. Preferably over a lifespan

-Need prospective trial in non-diabetic population.

So far animal models are easiest

-Mice, flies etc

E.g. Mice model shows metformin increased lifespan by 14%.

Are these benefits of diabetes management or metformin itself?

Do the benefits extend to non-diabetic population?

RESEARCH Open Access

Comparison of long-term effects of metformin on longevity between people with type 2 diabetes and matched non-diabetic controls

oshua Stevenson-Hoare[1], Ganna Leonenko[2] and Valentina Escott-Price[1*]

- Conclusion
- Healthy control still has longer lifespan than well controlled diabetic on metformin

Metformin In LongEvity Study (MILES) 2014

- N=14 elderly with pre-diabetes
- 6weeks in duration.
- Genetic and biochemical study
- Outcomes
- Metformin showed altered genetic expression in many aging biochemical pathways
- Eg .collagen, extracelluar matrix, MSH genes etc.

Upcoming trial

TAME trial(Targeting Aging with Metformin)

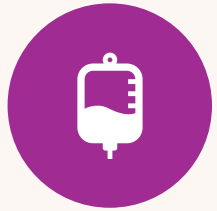
- Longitudinal prospective blinded trial.
- N=3000 non-diabetic patients. Randomized to metformin vs plaebo
- Outcome measures:
- 1. New age related chronic diseases;
- 2.Mobility : gait speed over 10 meters
- 3. Cognitive impairment
- 4. Biomarkers of aging such as for inflammation and senescence .

Conclusion

METFORMIN IS EXCELLENT FOR TREATING DIABETES

-IMPROVES MORTALITY, CARDIOVASACULAR AND COGNITIVE OUTCOMES

METFORMIN MAYBE BENEFICIAL IN REDUCING PROGRESSION INTO DIABETES



FROM PRE-DIABETES(A1C 6.0-6.4%)

METFORMIN'S BENEFIT IN NON-DIABETICS IS NOT PROVEN. NEW STUDY (TAME) IS SET TO ANSWER THIS QUESTION.

LET'S DISCUSS. SHOULD WE PRESCRIBE METFORMIN TO NON-DIABETICS? WHY OR WHY NOT?

Questions