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

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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

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

Metformin: Structural Derivation

Metformin: Uses
• Diabetes Mellitus
• Prevention of Diabetes Mellitus
• Polycystic Ovary Syndrome
• Others?
  – Anti-inflammatory
  – Microbiome
  – Cancer
  – Aging
**Metformin: Anti-inflammatory**
- Affects multiple pathways for inflammation
- ROS
- Decreases – PAI-1, – TNF-alpha, – IL-6
- Decreases oxidized LDL
- “Polarization” of inflammatory macrophages

**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


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**Metformin: SLE*\(^\text{a}\)**
- China-113 with SLE randomized to add metformin to their regimen or placebo
- Well matched at baseline- target dose 500mg three times a day

\(^{a}\)Systemic lupus erythematosus

**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 Gut**
- 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
Metformin, “Mucus” and Health

DISEASES
Genes vs. Environ

Villi
Mucosal layer
Mucosal microbes
Inflammation
Bacteria can enter through "gaps in mucus"

INFLAMMATION!!!

Metformin-Akkermansia?
• Akkermansia=red bars
• These maps show "abundance" of a certain bacteria
• Mouse Model:
  – Green is high-fat diet plus metformin
  – Induces a large increase in Akkermansia

Metformin and Microbiome

• Akkermansia muciniphila is a Gram-negative, strictly anaerobic, non-motile, oval-shaped bacterium.
• Lives in the mucus of our gut and uses it as a source of energy
• Thin mucus layer low # of these bacteria at increased risk of inflammation
  – Upregulated by metformin
  – Improved glycemic 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 it healthier
  – Propionate and acetate→liver
• ↑ Intestinal 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

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 ~90 strains of bacteria in the gut
• Major change in Bifidobacterium adolescentis
  – This is a probiotic bacterium highly abundant just after birth, but levels may decrease with age
  – Correlated weakly with change in A1C

Metformin-Bifidobacterium adolescentis
• Akkermansia also increased-but no correlation with change in A1C
• Transfer of effect
  – Fecal microbiota transplant to germ free mice from 3
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 a added bonus of metformin, but not yet a compelling reason
  - Take probiotics if you would like

*Mortality from Common Malignancies*

- Photo: bel and organic food

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

Proposed actions of metformin in cancer

  - Nat. Rev. Endocrinol. doi:10.1038/nrendo.2013.256

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

- 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
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

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

Metformin: Breast Cancers

• 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

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

Zhang X et al. Mayo Clinic Hepatology 2014
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,

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

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(3): 750-758

Primary Aim

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

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

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!

“Aging”

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

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.

Koepke 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

Aging explained simply

http://www.totalrestitution.com/articles/telomerase.html
www.meresearch.org.uk
**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

**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

**Metformin: Rodent models extend life and Health**

- May be dose response, but hard to tell from rodent model to human-drug initiated at week 54

**Metformin: and Nematodes (C. Elegans)**

- CABRERO F. Cell 2013;153:228-39

**Metformin: Rodent models extend life and Health**

- *Health*

- Performance on A treadmill
- How fast ran, on average in open field testing

- *p<0.05

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### Metformin: Advise to patient
- Probably not for aging or healthspan yet.
- Rodent and human trials not always congruent

### 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"