METFORMIN AND CKD

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DISCLOSURES

- None

WHAT'S THE CONCERN?

- Metformin:
- Continues to be in the top ten drugs prescribed in the United States.
- Has been considered first-line therapy for type 2 diabetes since 1995.
- Large portion of patients with chronic kidney disease have diabetes, and more than a 1/3rd of type 2 diabetic patients develop chronic kidney disease.
- Metformin belongs to the biguanides family.

HISTORY OF BIGUANIDES

- Discovered as a end result of the burnt out phenomenon…

BURNT OUT…DIABETES

THE USEFULNESS OF BIGUANIDES

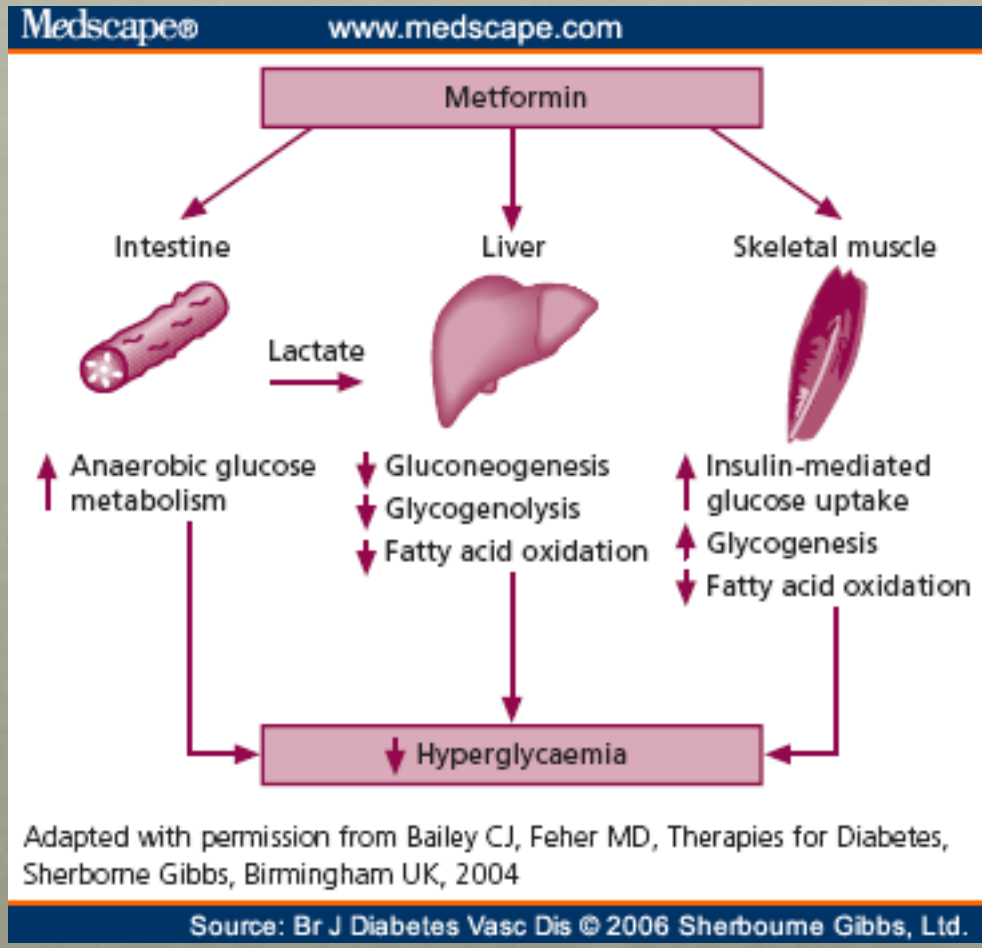
- The term “burnt-out diabetes” is a phenomenon that occurs due to decreased renal/hepatic insulin clearance, decline in renal gluconeogenesis, diminished food intake due to anorexia, protein-energy wasting, and hypoglycemic effect of dialysis treatment.
- The result appears to be improved diabetic control.

BIGUANIDES METABOLITES

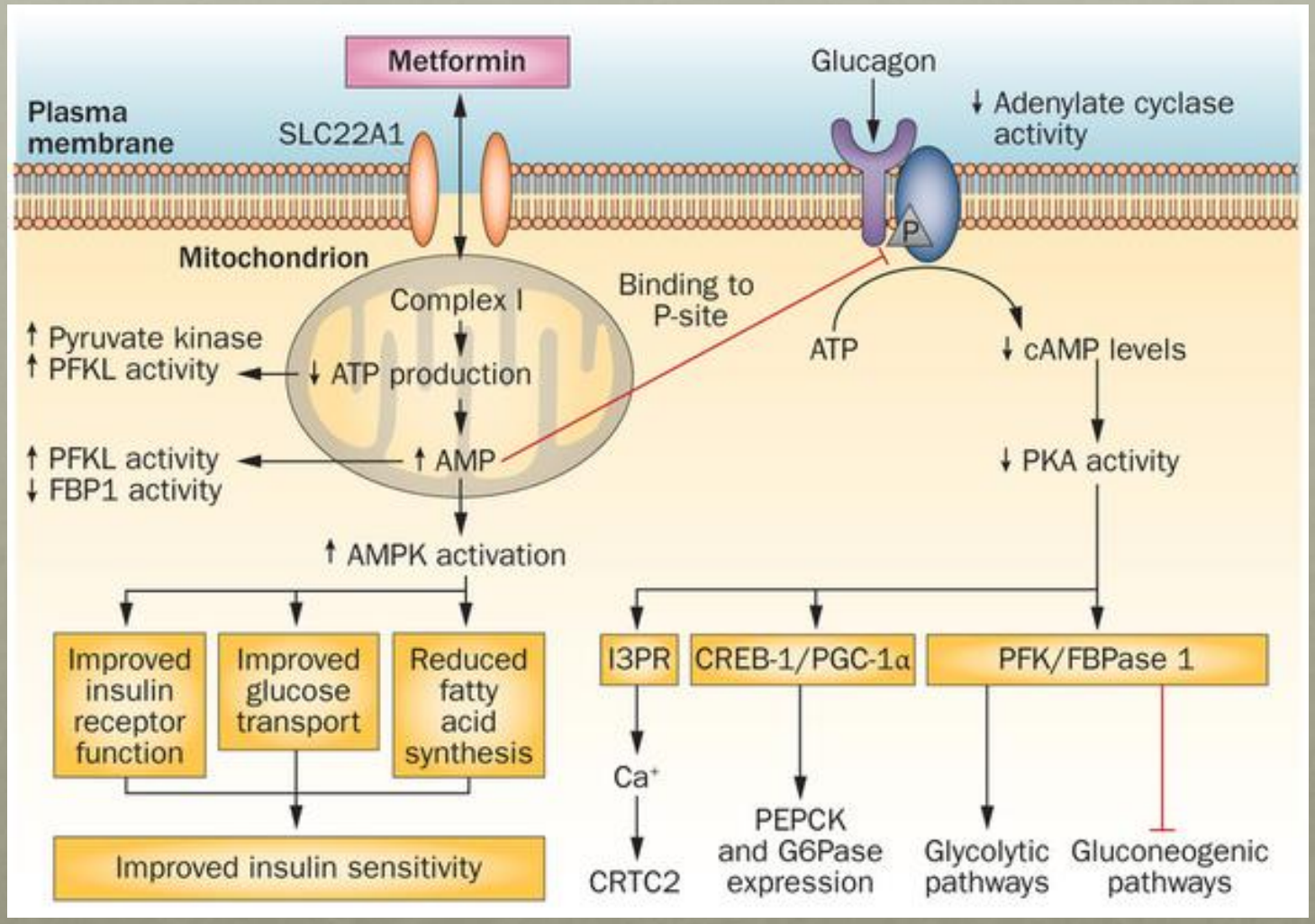
- In addition, Kalantar-Zadeh et al. reported on finding increased levels of guanidino compounds in renal failure from amino acid metabolism. Suggesting its possible role in diabetes control.
- Guanidino extracts were discovered in 1920s, eventually leading to its wide spread use in 1970s as the primary treatment for adult onset diabetes.

BIGUANIDES

- Increases the activity of the AMP-dependent protein kinase (AMPK)
- Activated AMPK stimulates fatty acid oxidation, glucose uptake, and non-oxidative metabolism, and it reduces lipogenesis and gluconeogenesis.
- Increase insulin sensitivity
- Increased glucose uptake
- Decreased hepatic gluconeogenesis



AMPK AND METFORMIN



Side Effects of Metformin

- Diarrhea
- Vomiting
- Abdominal pain
- Drowsiness
- Headache
- The most feared complication is also the least understood complication: Metformin Associated Lactic Acidosis (MALA)

LACTIC ACIDOSIS

- Broder and Weil reported in 1964 that lactate levels > 4 was associated with poor outcomes.

- LA has become an obligatory diagnostic criteria for septic shock.

LACTIC ACIDOSIS (LA)

- Elevated serum lactate is associated with increased mortality, independent of organ failure and shock.
- Type A LA is anaerobic, caused by lactate overproduction in the absence of oxygen usually seen in circulatory collapse.
- Type B LA is aerobic, caused by underutilization of lactate due to impaired removal/metabolism seen in liver disease, diabetes, alcohol and with metformin.

TYPE B LA

- Lactate accumulation is usually due to enhanced pyruvate production, reduced pyruvate conversion to carbon dioxide and water, an altered redox state in the mitochondria leading to increased lactate production. Metformin induced LA production is type B.

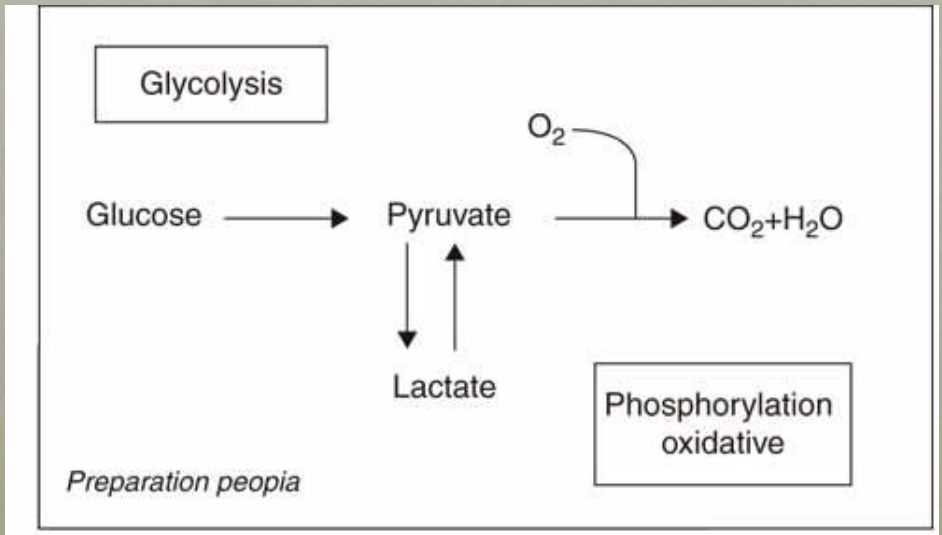
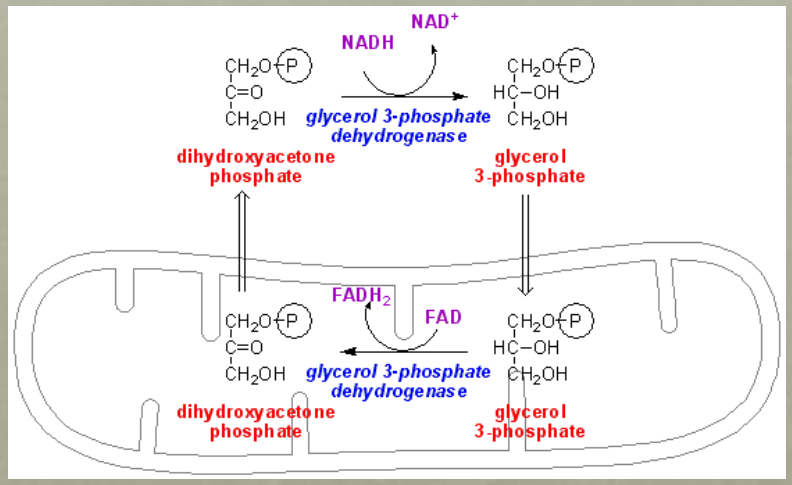


Fig. 1 – Glucose metabolism.
Source: Authors'.

MITOCHONDRIAL INHIBITION

- Metformin selectively inhibits the mitochondrial glycerophosphate dehydrogenase , which results in accumulation of NAD, which in turn inhibits conversion of lactate to pyruvate.
- But, it started with Phenformin.



PHENFORMIN

- High affinity for mitochondrial membranes
- Powerful inhibitory effect on functioning of the mitochondrial respiratory chain
- Inhibits lactate oxidation/increases lactate concentration in plasma
- Half-life of 7–15 h
- Metabolized by CYP2D6 in the liver
- Increased risk of lactic acidosis, with a mortality rate of 30–50% 0.4–0.64 cases per 1,000 patient-years

METFORMIN VS PHENFORMIN

- How does metformin provide protection from type B lactic acidosis that was so commonly seen with phenformin?
- Metformin concentrates in the **cytosol** so has less effect on the mitochondria and less protein binding and shorter half-life than phenformin, therefore has less LA formation.

METFORMIN

- Lower affinity for mitochondrial membranes than phenformin
- Less powerful inhibitor of the mitochondrial respiratory chain
- Not metabolized
- Half-life of 1.5–6.5 h
- Incidence of LA is 0.03 cases per 1,000 patient-years
- Reported cardiovascular benefit-which resulted in promotion of the use of Metformin in congestive heart failure patients.

METFORMIN

- Metformin plasma levels should not exceed 5mg/L
- The therapeutic range for metformin is 0.7 to 5 mg/L

METFORMIN ASSOCIATED LACTIC ACIDOSIS (MALA)

- 2-5 cases per 100,000 patients receiving Metformin.
- Similar to diabetic patients not receiving metformin.

MALA

- Metformin results in increased anaerobic metabolism, leading to increased lactic acid production. Which again is type B LA.

- The GI tract has also been shown to have increased LA production, reduced liver uptake of LA.
- Metformin accumulates in hepatocytes that express an Organic Cation Transporter. OCT knock out mice did not develop lactic acidosis.

MALA-PLATELETS

- **In vitro**, metformin increased lactate production and glucose consumption in human platelets in dose dependent and time dependent manner.
- Therapeutic doses did not alter human platelet mitochondrial function.

Is the concern real for MALA?

- https://youtu.be/36Ux2cmHCL8

Clinical Diabetes Journal: Belgium &Denmark

- 1. "…there is little, if any, theoretical justification for the claims that metformin contributes to the incidence of LA and that epidemiological evidence is lacking. If there is any impact, it is probably rather low."
- 2. "It is suggested that introduction of metformin therapy to more advanced stages of CKD may bring therapeutic benefits that outweigh the possible risks."

- 1. Clinical Diabetes, 2011
- 2. Peritoneal Dialysis International, 2014

Tabel 1. Epidemiology of Lactic Acidosis

Author	Location	Treatment	Year	Cases *(n)*	Patient-Years *(n)*	Incidence Per 100,000 Patient-Years
Brown[13]	United States	No biguanides	1993–1994	4(7)	41,426	9.7 (16.9)
Bergman[3]	Sweden	Metformin	1975–1977	2(3)	20,548	9.7 (14.6)
Wilholm[30]	Sweden	Metformin	1977–1991	18	249,400	7.2
Stang[31]	Canada	Metformin	1080–1995	2	22,296	8.9
Misbin[32]	United States	Metformin	1995–1996	47	Approx. 1,000,000	4.7
Bodmer[15]	United States	Metformin Sulfonylurea	1994–2006	5	50,048	3.3 4.8
Aguilar[14]	Mexico	Metformin Sulfonylurea	1987–1990			0.0* 2.9*
Salpeter[18]	World	Metformin	1959–2002	0	36,893	0.0

*Data in parentheses indicate possible cases included. *Per 100 acute admissions.*

- A total of 194 studies from 1959 to 2002 reported no cases of LA.
- The true incidence on a repeat investigation in 2010 calculated MALA to be < 4.2/100,000 patient-years.

META-ANALYSIS-UK

- "…no clear effect of metformin on lactate levels was seen. Diabetes itself is a more important risk factor for LA…which occurs in association with acute illness. The current guidance adopts a cautious approach but may overemphasize the role of metformin in diabetic patient with LA."
- Harvey & Scale, Clinical Endocrinology 2011

Table 3. Numbers of patients with the various risk factors for lactic acidosis in patients with diabetes on and not on metformin and patients without diabetes. Cohen and Woods class A (tissue hypoxia because of cardiorespiratory disease) and B (no significant acute cardiorespiratory disturbance) are shown

	Cohen and Woods classification Class A			Cohen and Woods classification Class B			
	Patients with type 2 diabetes			Patients with type 2 diabetes			
	On metformin	Not on metformin	No diabetes	On metformin	Not on metformin	No diabetes	ANOVA Type B patients
N	10	9	57	18	11	38	
Male	3	8	32	9	4	19	
Deceased	7	5	33	10	5	19	
Age (years)	60·9 ± 3·4	74·2 ± 2·4	67·3 ± 2·4	71·4 ± 3·0	72·1 ± 5·7	60·4 ± 3·3*	$F = 3·2$, $P = 0·049$
H^+ (10^{-9} M)	97·1 ± 10·8	105·1 ± 10·6	84·4 ± 3·3	93 ± 8·2	87·6 ± 8·1	83·4 ± 3·2	$F = 1·3$, $P = 0·28$
Base excess	−14·3 ± 3·0	−18·3 ± 1·4	−14·1 ± 0·8	−20·3 ± 1·7***	−10·1 ± 1·6**	−16·4 ± 0·8*	$F = 11·0$, $P < 0·001$
Lactate (mM)	10·7 ± 1·5	11·6 ± 1·1	9·9 ± 0·5	10·6 ± 1·1	8·4 ± 0·8**	13·6 ± 0·8*	$F = 6·9$, $P = 0·002$
Acute renal failure	6	2	26	15	5	16	
Chronic renal failure	1	2	8	3	4	5	
eGFR (ml/min)	35·7 ± 10·8	37·7 ± 5·8	44·6 ± 3·7	20·4 ± 3·7**	42·4 ± 5·9	48·3 ± 5·2	$F = 6·6$, $P = 0·003$
Ischaemic heart dis	8	9	24	8	6	9	
Sepsis	4	4	23	8	6	19	
Seizure	0	0	1	1	3	13	
Alcoholism	0	0	6	2	0	10	
Hypothermia	0	1	5	1	1	2	
Cancer	0	2	7	5	1	4	
Liver disease	0	0	4	0	1	8	

- Considering specifically diabetic patients without cardiopulmonary insufficiency, lactate levels were slightly higher in patients with type 2 diabetes but there was no difference between those on metformin compared with diabetic patients not on metformin.
- Cohen and Woods, UK, 2012

COCHRANE ANALYSIS 2010

- "There is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other anti-hyperglycemic treatments…if the drugs are prescribed under study conditions, taking into account contraindications."

CONTRAINDICATIONS

- impaired renal function (GFR < 45)
- liver failure
- severe hypoxia
- *heart failure*
- Surgery
- alcohol use

HEART FAILURE

- Metformin has shown improved cardiac outcomes in diabetics and CHF patients.

- No longer listed as a contraindication.

METFORMIN

- The Other Side of the Story…

AUSTRALIAN STUDY 2016

- A series of 10 patients with MALA.
- Higher rate of LA in patients on metformin. Significant increase in the relative risk of LA in patients on metformin compared to the general population.
- MALA leads to increased mortality but not as high as in LA associated with sepsis.
- Advise to reduce dose of Metformin until GFR < 20, then to stop altogether.

- World Journal of Nephrology, 2016

TAIWAN STUDY

- Prior to restriction of Metformin in CKD patients, metformin users had a 29% higher mortality than nonusers over a 2 year period.
- There was a dose dependent relationship between metformin and death.
- Metformin users did have a 23% increased risk of LA, but did not correlate with death.

METFORMIN AND AKI

- Metformin is eliminated rapidly and actively by the kidneys.

- Any AKI may lead to metformin accumulation.

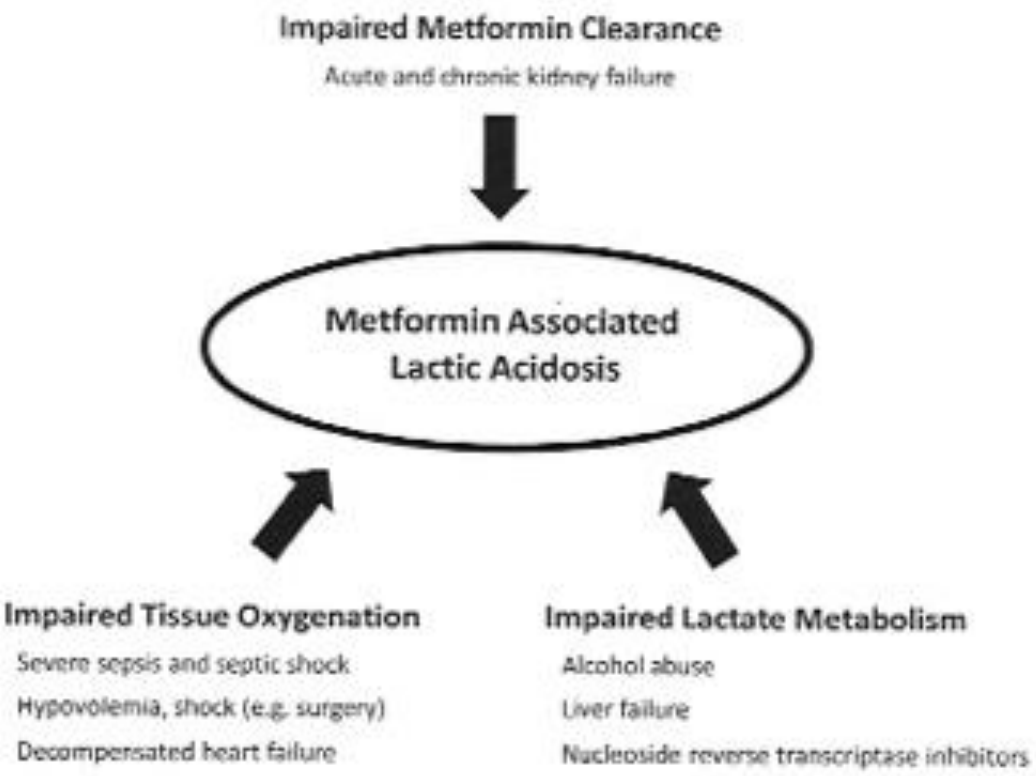


FIGURE 1. Pathogenesis of metformin-associated lactic acidosis.

AJMS, March 2015

PROTTI ET AL. CC 2012

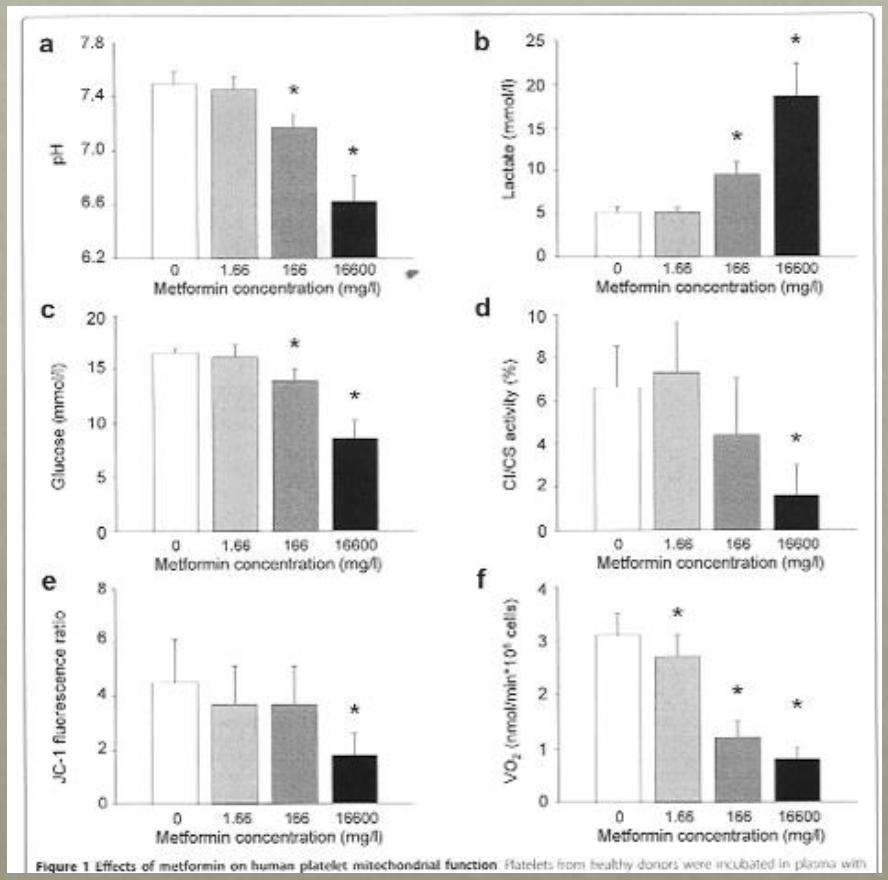


Figure 1 Effects of metformin on human platelet mitochondrial function Platelets from healthy donors were incubated in plasma with

In Pigs, severe metformin intoxication causes mitochondrial dysfunction in platelets. As well as other vital organs like the heart, kidney and skeletal muscle.

Human platelets exposed to toxic dose of metformin, both in vitro and in vivo, have clear signs of mitochondrial dysfunction.

METFORMIN AND THE MITOCHONDRIA

- Human platelet respiration diminishes during metformin-induced lactic acidosis from drug accumulation, rather than lactic acidosis from circulatory collapse.
- Human RBCs that lack mitochondria did not have any alteration in cellular metabolism with high doses of metformin.
- If analogous changes occur in other organs, they will likely contribute to the pathogenesis of lactic acidosis.

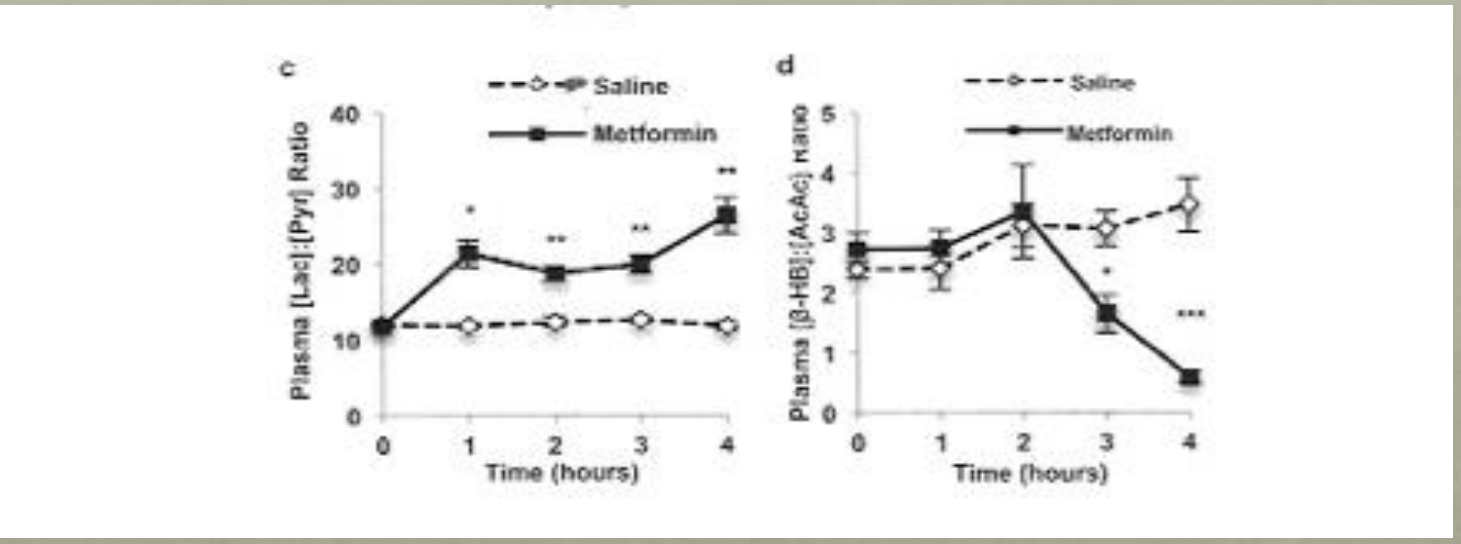
METFORMIN AND THE MITOCHONDRIA

- Metformin toxicity also was dependent on the duration of metformin infusion.
- Patients who acutely ingest large doses have very high initial serum drug levels, but only mild lactic acidosis.
- As opposed to those who get intoxication over a few days, have a lower serum drug level but extremely elevated lactic acidosis.

MORE MITOCHONDRIA

- Metformin treated rats at doses that achieve comparable human metformin therapeutic doses inhibits mitochondrial glycerophophate dehydrogenase noncompetitively
- Resulting in reduced endogenous glucose production. This was also associated with increased lactate production.

NATURE 2014, YALE



Metformin treated of rats at doses that achieved comparable plasma concentrations in type 2 diabetic patients inhibits mitochondrial redox state, leading to lactic acidosis.

MALA

- It was acute rather than chronic renal failure that was associated with lactic acidosis.

- However, patients with CKD are at a higher risk for AKI leading to metformin accumulation.

- MALA is rare and is observed in association with an acutely worsening clinical condition.

- Interestingly, metformin concentration were, on average, three times higher in patients who survived.

MALA AND SEVERE SEPSIS

- In patients admitted to the ER with severe LA and sepsis, the rate of mortality was lower for those who were actively treated with Metformin.
- Metformin has anti-inflammatory and anti-thrombotic effects. Metformin can also induce activation of AMP-activated protein kinase, which results in increased use of ATP-generating pathways. Thus useful in times of increased stress.

DOSE ADJUSTMENT?

- United Kingdom: reduced dose for GFR < 45, stop when GFR < 30
- Canada: stop with GFR < 30, no reduction
- Australia, similar to Canada.
- US: still adhere to serum creatinine of 1.5 mg/dL males and 1.4 mg/dL females

DOSE ADJUSTMENT

- Metformin is restricted to:
- 500mg in GFR< 15 (Controversial)
- 1000 mg with GFR < 30
- 2000mg with GFR < 60
- 3000 mg with GFR >60

SO, WHAT DID WE LEARN?

- Metformin is toxic to the mitochondria.
- It does accumulate in renal failure.
- But debate exists as to whether there is significant MALA in comparison to non-metformin diabetic patients.
- Current US guidelines are too conservative.
- May be appropriate to adapt to the dose adjustment guidelines.

THANK YOU

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