MedNut Mail

The How, When, Where, Which and Why of pharmacotnutrition

Metformin and pharmaconutrition

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Editorial

Metformin's role in healthcare management is expanding and is now being considered as a treatment for some cancers, bone health, neurodegeneration, and probably others, as well as its long-recognised role in diabetes management.

The mechanisms by which metformin exerts its effects are still not fully understood but it is currently accepted that metformin inhibits glucose production in the liver and increases glucose uptake in peripheral tissues thereby lowering blood glucose levels. However, many authors admit that even after 60 years, the full range of metformin's mechanisms of action for remain unknown.

Known mechanisms of action include -

1. Change in energy pathway. Metformin's inhibition of mitochondrial NADH dehydrogenase means a significant change in energy metabolism from the usual oxidative phosphorylation pathway to the aerobic glycolytic pathway ie a much less energy efficient pathway; presumably this alters the nutrients required and demand on their availability.

2. One carbon metabolism. One-carbon metabolism comprises a complex network of enzymes and contributes to many pathways that fuel a range of processes including biosynthesis, amino acid homeostasis, epigenetic maintenance, NADPH pools, and ultimately regulates metabolism, growth, and physiological function via multiple strategies.

Dietary constituents that mediate one-carbon metabolism as essential substrates or cofactors, include riboflavin, pyridoxine, folate and cobalamin – metformin alters the availability of each of these nutrients.

3. Change in gut microbiota. Metformin alters gut bacteria by -

- inhibiting NAD which results in decreased Bacillus, Lactobacillus, Bifidobacteria and Eubacteria, and a consequent increase in lactate production in the colon;
- increasing lactate producing bacteria through unabsorbed glucose and glucose polymers availability;
- changing the microbiota population and thus altering the production and absorption of nutrients, especially B vitamins;

- potentially increasing the bacterial population that produces Short Chain Fatty Acids.

4. Stimulates ferroptosis. Metformin induces ferroptosis which is a form of regulated cell death, by increasing the intracellular iron and lipid ROS (Reactive Oxygen Species aka Reactive Substances) levels.

5. Substrate and/or inhibitor of a range of transporters. Metformin Transporters include -

- **Metformin as a Substrate** - OCTN1 (intestinal uptake, other tissues uptake and excretion, renal uptake and excretion), OCT2 (renal uptake), MATE1/2 (renal excretion), ThTr2 (intestinal absorption), OCT1/3 (intestinal absorption), OCTN2 (intestinal absorption), PMAT (intestinal absorption), SERT (intestinal absorption);
- **Metformin as an Inhibitor** - MDR1, ThTr2, OCT1.

Metformin is now deemed the universal probe for thiamine transporters.

Metformin's intestinal uptake is estimated to be - THTR2 (22.2%), OCT3 (9.77%), PMAT (9.68%), SERT (1.52%) and OCTN2 (0.66%) and that passive diffusion is about 54.6%. The authors comment it is possible there other currently unidentified transporters that may also be involved in the intestinal uptake of metformin.

6. Nutrients affected by Metformin. Decreased absorption of magnesium, folate, riboflavin, cobalamin, vitamin D - both directly and indirectly due to decreased magnesium absorption, thiamine – both directly and indirectly due to decreased magnesium absorption, pyridoxine both directly and indirectly due to decreased riboflavin availability, niacin – indirectly due to decreased pyridoxine availability, vitamin K – indirectly due to decreased riboflavin availability, de novo synthesis of vitamin C – indirectly due to decreased riboflavin availability.

Metformin negatively impacts nutritional factors via a range of strategies, many of which are still in the early stages of research. Given the increasing evidence that a range of nutrients and biological pathways are negatively impacted, it is probably time we invoked First Principles (do no harm, or minimize potential harm) and start initiating interventions to moderate the negative nutritional impact. Our big issue is identifying the sweet point for intervention that confers greatest benefit.

What actions will you initiate when you see someone whose prescribed medications include metformin – will you -

- recommend regular monitoring of thiamine, pyridoxine, folic acid, B12, vitamin D and levels?

- if pyridoxine levels are low, will you recommend checking riboflavin and niacin levels?
- if there are low or elevated nutrient levels, will you question whether metformin may be inhibiting some of their transporters?
- If nutrient levels are low, will you recommend interventions and will you recommend administration time to be different from metformin administration time?

Conclusions

Metformin's pharmaconutrition impacts are varied and far-reaching, ranging from negatively impacting absorption, availability and excretion of several nutrients, to altering energy metabolism, one-carbon metabolism, and even to altering our gut microbiota populations – nutrient interventions are likely to confer therapeutic benefit.

Case study

Medical History with Nutritional Aspect

Amputation	☐	Constipation	☐	Dysphagia	☐	MND	☐
Anaemia	☐	CVA	☐	Enteral Feed	☐	MS	☐
Arthritis	☑	CVD	☐	Falls	☐	Osteoporosis	☐
Cancer	☐	Dementia	☐	Fracture	☐	PD	☑
CCF	☐	Dentures	☐	Frailty	☐	Pressure Area	☐
Chest Infection	☐	Depression	☑	Gout	☐	Renal	☐
COAD	☐	DM Type 1	☐	Hypertension	☐	Ulcer	☐
Confusion	☐	DM Type 2	☑	Incontinent	☐	UTI	☐

Food Allergies:

Other: joint pain, AF, PPM, hypothyroidism

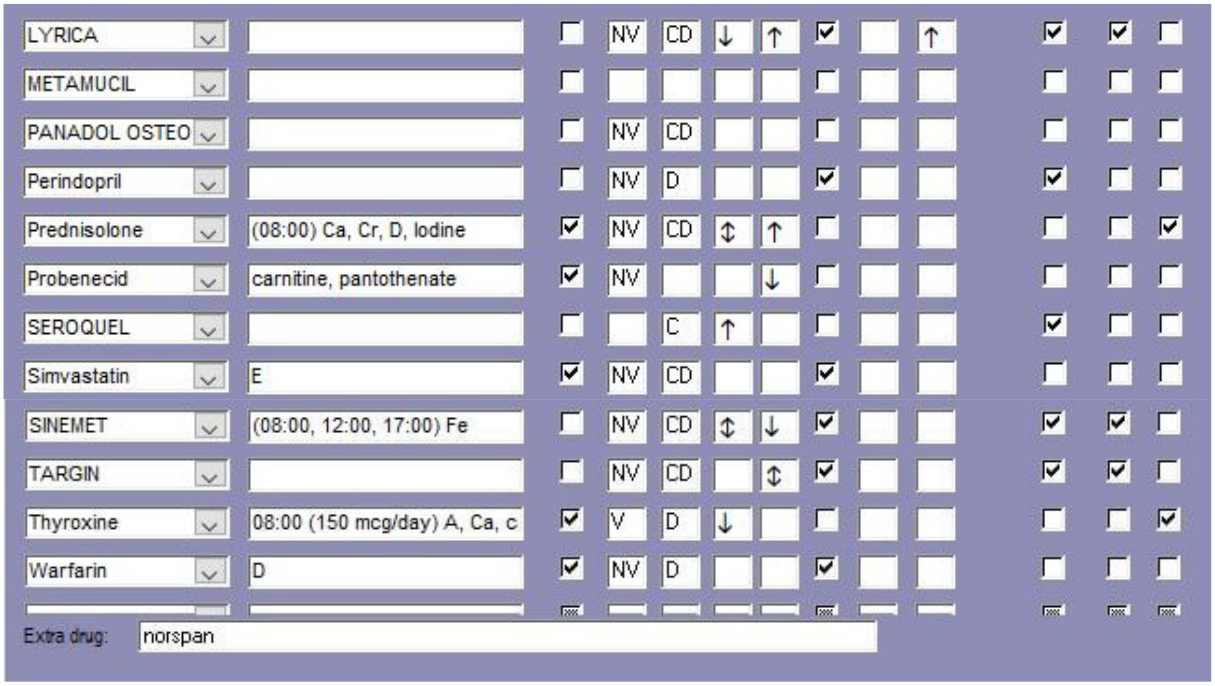
Biochemistry with Pharmaconutritional Consequences

Na:	137	mmol/l	Hb:	135	g/L	Albumin:		g/L	BSL:		mmol/l
K:	4.2	mmol/l	Lymph:	2.5		Total Protein:		g/L	HbA1C:	7.6	
Urea:	17.4	mmol/l	MCV:	87	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.100	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 46, CRP 53.2, urate 0.53

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp	>90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
Colchicine	B12	☐		NV	D	↑		☐				☐	☐	☐
DIABEX XR	(08:00) B12, B1, B6, Mg, B2, \	☐		NV	D	↓	↓	☑				☐	☐	☑
DIAMICRON MR	(08:00)	☑		NV	CD	↑	↕	☑				☐	☐	☑
Escitalopram		☐		NV	CD	↕	↓	☑				☑	☐	☑
Esomeprazole	(40 mg/day) B1, B12, Ca, Fe,	☑		NV	CD	↑		☑				☑	☐	☐
FERRO-F	(17:00) Ca, Mg, Zn	☐						☐				☐	☐	☐
FOSAMAX	Ca	☐		NV	CD	↑		☑				☐	☑	☐
Frusemide	(80 mg/day) Ca, Cl, K, Mg, Na,	☑		NV	CD		↓	☐				☑	☐	☑



Transporter-mediated interactions and nutrients

Organ (transporter)	Thiamine	Choline	Carnitine	Pyridoxine
Inhibitor function				
From gut	Metformin (ThTr2) Metformin (OCT1)	Metformin (OCT1)		Metformin (ThTr2)
Liver	Escitalopram (OCT1) Esomeprazole (OCT1) Probenecid (OCT1) Quetiapine (OCT1)	Escitalopram (OCT1) Esomeprazole (OCT1) Probenecid (OCT1) Quetiapine (OCT1)		
Into kidneys	Escitalopram (OCT2) Prednisolone (OCT2) Naloxone (OCT2)	Escitalopram (OCT2) Prednisolone (OCT2) Naloxone (OCT2)		
Substrate function				
From gut	Metformin (ThTr2) Metformin (OCT1)	Metformin (OCT1)		Metformin (ThTr2)
Into muscles	Metformin (OCT3)	Metformin (OCT3)		
Into kidneys	Metformin (OCT2)	Metformin (OCT2)		
Into urine	Metformin (MATE)	Metformin (MATE)		

Comments – medication and nutrition impacts (direct and indirect) only

Data summary

Biochemistry

Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for eight of the prescribed drugs and hypoproteinaemia may alter their effects and side effects.

Glycaemia

Currently prescribed 9 medications that may alter glycaemia.

BSLs

- before breakfast - 6.9-10.8; recommended range 4-6,
- tested daily before breakfast,
- reportable limits: < 3 and > 20,

Diabetes drugs

Diabex XR has a duration of 24 hours,

Diamicron MR has a duration of 24 hours.

Diabetes drugs coverage

Before breakfast BSLs - minimal, if any, coverage from previous morning's Diabex XR or Diaformin MR;

Before evening meal BSLs - covered by current morning's Diabex XR or Diaformin MR.

Pharmaconutrition

Currently prescribed 16 medications that include vomiting as a side effect.

Currently prescribed 15 medications that include nausea and diarrhoea as side effects.

Currently prescribed 11 medications that include constipation as a side effect.

Currently prescribed 10 medications that include altered taste as a side effect.

Currently prescribed 8 medications that include anaemia and dry mouth as side effects.

Currently prescribed 7 medications that include decreased appetite as a side effect.

Currently prescribed 5 medications that include hyponatraemia, hypokalaemia and hyperlipidaemia as side effects.

Colchicine decreases B12 absorption.

Diabex XR decreases B12 absorption - there is now a recommendation for regular monitoring B12 status ie at least annually.

Esomeprazole decreases B12, vitamin C, magnesium, zinc and iron absorption, maybe decrease calcium absorption, and decreases thiamine availability.

Ferrous fumarate decreases zinc absorption.

Ferro-f has been prescribed prior to admission 6 months ago. Since evidence indicates iron deficiency anaemia is unlikely to resolve whilst a proton pump inhibitor is prescribed, advisable to clarify current status.

Adequate calcium and vitamin D intake recommended whilst Fosamax prescribed.

Frusemide increases urinary excretion of calcium, magnesium, zinc, potassium, sodium and thiamine.

Dietary levels of caffeine intake in conjunction with paracetamol inhibit antinocieception.

Concurrent ingestion of paracetamol and iron resulted in increased rate of iron absorption and decreased extent of drug absorption; the authors advise drug and iron to be administered at different times from each other.

Perindopril impairs zinc status.

Probenecid inhibits carnitine transport and uptake, and decreases urinary excretion of pantothenic acid.

Evidence indicates that glucocorticoids such as prednisolone are associated with lower vitamin D levels; proposed mechanism steroids may enhance inactivation of vitamin D-2 by upregulating 24-hydroxylase activity. Vitamin D enhances the anti-inflammatory effects of glucocorticoids such as prednisolone.

Since vitamin D enhances anti-inflammatory effects of prednisolone and prednisolone decreases vitamin D availability, advisable to clarify current vitamin D status and if low then intervention recommended.

Ferro-f is administered at the same time as Sinemet in the evenings - there is a potential drug-nutrient interaction between iron and levodopa therefore advisable to review administration time of iron intervention in relation to Sinemet administration.

Three drugs, being colchicine, Diabex and esomeprazole, decrease B12 absorption therefore advisable to clarify B12 status.

Three drugs, being metformin, frusemide and esomeprazole, decrease magnesium availability. Magnesium deficiency manifests as confusion, disorientation, personality changes, loss of appetite, depression, muscle cramps, tingling, numbness, hypertension, cardiac dysrhythmia, seizures. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of

status. Advisable to clarify magnesium status, and administer any interventions at a different time from metformin; concurrent administration with esomeprazole indicates oral interventions are unlikely to be effective.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sunlight-on-skin to vitamin D - vitamin D intervention recommended,

- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended,

- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Bowel management

No regular intervention prescribed,

Oral PRN aperient prescribed,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs AGS eats well but not excessively.

Observations

Mrs AGS is a pale, charming lady who was lying in bed when I went to speak to her - she told me she has a poor appetite, often sweats during the night, usually feels unwell, and doesn't often go outside.

Mrs AGS has gained weight since admission – advisable to clarify that the gain is not due to undermedication with frusemide and consequent fluid retention.

Mrs AGS has a dubious ranking - she falls within my top 10 as she is prescribed 20 different medications.

Pharmaconutrition assessment

Mrs AGS's sweating may be a consequence of the current diabetes drugs combination.

Mrs AGS's BSLs are only checked before breakfast however there seems to be minimal drug effect at that time. As both prescribed drugs are effective in the afternoons, and because prednisolone is known to cause afternoon hyperglycaemia, advisable to check BSLs before evening meal for 3 days and clarify glycaemic status.

Mrs AGS's diagnoses include hypothyroidism - thyroxine dose is directly related to weight status. Since Mrs AGS has had a significant change in weight status she is at risk of undermedication therefore advisable to check thyroid function and clarify

current status.

Mrs AGS has been prescribed a proton pump inhibitor since admission 9 months ago and likely before then. There is increasing evidence that longterm (3+ years) proton pump inhibitor prescription is associated with -

- altered gut microbiome;

- increased risk of food sensitivities at a level of peanut allergy, due to partial protein digestion;

- increased risk of coeliac disease due to partial protein digestion;

- increased risk of scurvy;

- generalised malnutrition due to impaired absorption of a range of nutrients such as B12, vitamin C, magnesium, zinc, iron, etc;

- altered gastric pH which reduces absorption dynamics of a range of drugs and nutrients. Altered drug availability is relatively easily identified however reduced nutrient absorption is rarely identified due to the non-specific nature of their signs and symptoms.

Consequently, advisable to reconsider reviewing current proton pump inhibitor prescription and consider -

- whether proton pump inhibitor prescription is still required,

- if suppression of gastric acidity is still required then could it be managed with an H2 antagonist such as ranitidine (there is a general belief that they cause less nutritional harm than proton pump inhibitors).

Mrs AGS's diagnoses include arthritis and joint pain both of which are associated with chronic pain - nutritional factors that may be useful to consider in pain management include -

- vitamin D – currently no intervention; evidence indicates increasingly brittle pain control with decreasing vitamin D levels. Currently prescribed metformin and prednisolone both of which decrease vitamin D status. Advisable to clarify vitamin D status and commence intervention if low.

- vitamin C - pain increases the reactive substances (formerly Reactive Oxygen Species) within cells. Vitamin C is important in quenching reactive substances and if there is insufficient vitamin C then cell status becomes compromised and the cells typically die which also causes pain. Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit. Currently prescribed esomeprazole which decreases conversion of vitamin C to its active form therefore any intervention to be administered at a different time from esomeprazole.

- low B12 exacerbates elevated TNF- α which is an inflammatory response marker; elevation of the inflammatory response can include a pain response; currently prescribed metformin and esomeprazole therefore advisable to clarify B12 status and commence a non-oral intervention if low.

- magnesium – proposed mechanism magnesium blocks the NMDA receptor channels in the spinal cord and thus limits the influx of calcium ie reduces the risk of excitotoxicity and consequent exacerbation of pain. Currently prescribed esomeprazole, frusemide and metformin which decrease magnesium availability. Advisable to clarify magnesium status and consider an intervention if levels are low, however advisable to administer intervention at a different time from metformin, and it is unlikely oral interventions will be effective whilst esomeprazole prescribed.

What else would you include?

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