MedNut Mail

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

Metformin and riboflavine

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https://medicationsandnutrition.online

Editorial

A throw-away comment in a relatively recent paper that metformin was associated with diminishing riboflavin status prompted this post.

Although metformin can be prescribed for decades there is remarkably limited evidence in relation to its negative impacts on various nutrients, and especially riboflavin.

Riboflavin is important in cancer therapy, malarial infection control, angiogenesis, erythropoiesis, male fertility [by disrupting the transporter (important for sperm motility and fertility) and by reducing energy availability for sperm], immune system function, metabolism of xenobiotics and toxins, cholesterol and vitamin D metabolism, the synthesis of cofactors such as coenzyme A and coenzyme Q, has anti-inflammatory, anti-pain and antioxidant properties, modifies histamine response (to itch) by regulating TRPV1, and reduces the risk of osteoporosis, cataracts, reperfusion oxidative injury, migraine and premenstrual syndrome.

Riboflavin deficiency is associated with cheilosis and glossitis, loss of hair, swollen tongue, sore throat, oedema of oral and mucous membranes, impaired renal function, cataract development, anaemia, inflammation of skin, malabsorption, impaired nerve function, growth retardation, neurodegeneration, some cancers, hyperhomocysteinaemia, impaired immunity and ineffective viral clearance, low haemoglobin, dysfunctional mitochondria, and likely others.

Riboflavin transporter impairment is associated with deafness, weakness, feeding difficulties, respiratory symptoms, cranial nerve deficit, sensory symptoms (ataxic gait, lower limb muscle weakness).

Sources of riboflavin include diet, supplements, gut microbiota.

Currently three riboflavin transporters have been identified, being –

- **RFVT1** (SLC52A1) primarily expressed in duodenum, placenta, small intestine, skin, and very limited expression elsewhere,
- **RFVT2** (SLC52A2) broadly expressed across many different tissues including colon, stomach, placenta, testis,
- **RFVT3** (SLC52A3) primarily expressed in testis, lesser expression in small intestine, duodenum, colon, prostate, kidney, and very limited expression elsewhere.

Carriers - bound to albumin and immunoglobulins.

The throw-away line that was cited elsewhere came from a paper with this conclusion - metformin use in diabetes was inversely associated with vitamin B12 and, to a lesser extent, vitamin B2.

Hopefully this finding will be sufficient to generate curiosity in a researcher somewhere in the world to conduct further research and clarify both the extent of metformin's impact on riboflavin status and whether it is of clinical significance, and also clarify the proposed mechanisms of action.

What actions will you initiate when metformin is one of the prescribed medications, will you –

- recommend regular monitoring of riboflavin and pyridoxine levels ie at least 12-monthly, possibly 6-monthly, or even 3-monthly until their trends are identified?
- question whether there is excessive intake, and/or whether there is inhibition of excretion if riboflavin levels are elevated?
- check adequacy of dietary intake and whether prescribed medicines are inhibiting absorption or increasing excretion if riboflavin levels are low?
- question riboflavin status in the presence of normal Serum Iron Studies and low Haemoglobin?
- clarify B6 status?

Given riboflavin's profound importance in physiological function, especially neurological function. it may be worthwhile including riboflavin in your regular checklist when assessing those prescribed metformin, and routinely monitoring riboflavin levels for a sufficient period to ascertain whether there are any trends in status.

Conclusions

There is an early hint that metformin may negatively impact riboflavin status – hopefully further research will be conducted soon to clarify whether the hint is of clinical significance, in the meantime it is best to act as though it is clinically significant.

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: asthma

Biochemistry with Pharmaconutritional Consequences

No recent relevant results available.

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
Aspirin	C, Fe	☑	NV				☐				☐	☐	☑
COLOXYL WITH S		☐		D			☐				☐	☐	☐
Mirtazapine		☐	N	D	↑	↑	☐				☑	☐	☐
OSTELIN	(1/day)	☐					☐				☐	☐	☐
PANAMAX		☐	NV	CD			☐				☐	☐	☐
PARIET	(20 mg/day) B1, B12, Ca, Fe,	☑	NV	CD	↑	↓	☑				☑	☐	☐
Risperidone		☑	NV	C	↑		☐		↑		☐	☐	☐
		▩					▩				▩	▩	▩

Extra drug: cranberry, enprocal tds

Transporter-mediated interactions and nutrients

Organ (transporter)	Thiamine	Choline	Carnitine
Inhibitor function			
Liver	Rabeprazole (OCT1) Risperidone (OCT1)	Rabeprazole (OCT1) Risperidone (OCT1)	
Into kidneys	Risperidone (OCT2) Rabeprazole (OCT2) Risperidone (OCT2)	Risperidone (OCT2) Rabeprazole (OCT2) Risperidone (OCT2)	
Into muscles	Rabeprazole (OCT3)	Rabeprazole (OCT3)	Rabeprazole (OCT3)

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

Data summary

Biochemistry

No recent relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for three of the prescribed drugs and hypoproteinaemia may alter their effects and side effects.

Glycaemia

Currently prescribed 2 medicines that alters glycaemia, being aspirin and risperidone.

Pharmaconutrition

Currently prescribed 5 medications that include nausea as a side effect.

Currently prescribed 4 medications that include vomiting as a side effect.

Currently prescribed 3 medications that alter iron status as a side effect.

Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury.

Chronic use of coloxyl + senna may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

Pariet decreases B12, vitamin C, magnesium, zinc and iron absorption, may decrease calcium absorption, and decreases thiamine availability.

FDA Safety Announcement recommends checking magnesium levels prior to commencement of rabeprazole and ongoing checking for duration of the intervention.

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

Concurrent ingestion of paracetamol and iron resulted 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.

Currently prescribed ostelin (1/day). Evidence indicates 50 mcg vitamin D per day is a maintenance dose; ostelin provides 25 mcg vitamin D per tab (25 mcg vitamin D is equivalent to 1000 IU vitamin D). Some of the leading international vitamin D researchers are now saying vitamin D levels should be > 100 nmol/L. Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

There is increasing evidence that proton pump inhibitors such as Pariet significantly impair magnesium absorption. 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. Cellular magnesium status is unknown whilst magnesium levels within acceptable range however if magnesium levels are low then typically indicates significant cellular depletion and intervention recommended

Bowel management

- regular aperient prescribed
- no PRN interventions prescribed
- Nurse Initiated oral aperient administered x 1

Staff comments

Staff advise Mrs AGM eats well and that she is fully assisted with her meals.

Observations

Mrs AGM is a small, pale, frail lady who was asleep in bed when I went to speak to her - she did not stir to her name, and staff advise that is her usual state.

Mrs AGM has progressively lost weight since admission.

Pharmaconutrition assessment

Mrs AGM has been prescribed a proton pump inhibitor since admission (4 years previously) 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 AGM's diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include

- vitamin D - current intervention may not be adequate to attain adequate range therefore advisable to check vitamin D levels and if still low then review current vitamin D management strategy;

- 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. Advisable to consider a vitamin C intervention - the optimal intervention is 500 mg vitamin C/day (if more than 500 mg vitamin C administered at a time then the excess above 500 mg is not absorbed as the vitamin C transporters are overloaded). 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 Pariet which decreases conversion of vitamin C to its active form;

- low B12 exacerbates elevated TNF- α which is an inflammatory response marker; elevation of the inflammatory response can include a pain response and currently

prescribed Pariet therefore advisable to check B12 status and if low then intervention recommended;

- 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 Pariet which decreases magnesium absorption.

Three of the prescribed medications negatively inhibit thiamine and choline uptake - given inhibition prevents organ and cellular uptake of these nutrients it is likely blood tests will indicate normal, high-normal or even high levels of thiamine and choline which is misleading from a diagnostic aspect as it would be assumed status is acceptable.

What else would you include?

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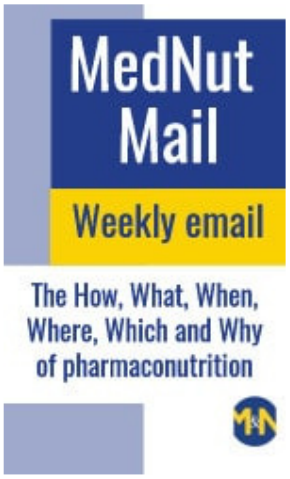

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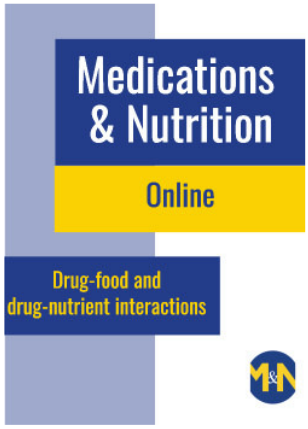

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