MedNut Mail

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

Metformin and B12

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Editorial

Metformin was developed and released in the late 1950's and within a decade was identified as a cause of B12 deficiency. More recently, other nutrients have also been identified as being negatively impacted by metformin, including magnesium, thiamine, riboflavin, folate, pyridoxine and vitamin D.

Cobalamin aka Vitamin B12 is a fully diet-dependent vitamin as it can neither be produced in the (human) body, nor produced by the gut microbiota.

Vitamin B12's range of functions include -

- formation of red blood cells,
- amino acid and fatty acid metabolism,
- modulating gut microbiota with consequent impact on the development and function of the immune system (innate and adaptive), enhancing CD4:CD8 ratio, and suppressing natural killer cells;
- DNA and neurotransmitter synthesis,
- brain and nervous system function,
- myelin sheath synthesis and maintenance,
- function of 2 enzymes, being the mitochondrial methylmalonyl-coenzyme A mutase, and the cytosolic methionine-synthase.

Vitamin B12 deficiency develops insidiously over years and often remains underdiagnosed as early symptoms are typically non-specific.

B12 deficiency occurs more frequently in those with type 2 diabetes and who are prescribed metformin for a longer duration and in higher doses, which suggests its negative impacts occur at the site of absorption.

B12 deficiency is associated with -

- neuropathy – irreversible neuropathy, peripheral neuropathy, optic neuropathy, ataxia, numbness and paraesthesia, reversible demyelinating nerve disease, aberrant neurological development such as neural tube defects, laryngeal disorders such as chronic cough, laryngeal hyperresponsiveness, vocal fold paralysis, and likely laryngeal carcinogenesis and leukoplakia;

- neuropsychiatric - dementia, suicidal behaviours, psychosis, mania, intense agitation, chronic fatigue syndrome, mood disorders, diminished cognition and increased risk of depression (these last 2 are irreversible if there is demyelination and nerve damage);
- haematologic abnormalities such as microcytosis, macrocytosis, megaloblastic anaemia, pernicious anaemia, pancytopenia;
- a reversible cause of bone marrow failure;
- impaired immune response with increased inflammation, oxidative stress and increased susceptibility to infections;
- gastrointestinal dysfunction such as glossitis, decreased appetite, mild constipation, diarrhoea, and incontinence (faecal, urinary);
- low bone mineral density ie osteoporosis;
- skin lesions such as hyperpigmentation, dyspigmentation, and hair changes;
- insulin resistance and increased risk of gestational diabetes;
- increased risk of intrauterine growth restriction (low birth weight, mall for gestational age), and consequent increased risk of pre-term birth which is a key cause of neonatal death;
- by impairing one carbon metabolism and mitochondrial aerobic respiration in pregnant T2DM and GDM women, there may also be adverse transgenerational effects such as increased risk to the offspring for cardiometabolic diseases in adulthood.
- increased plasma levels of homocysteine (Hcy) and methylmalonic acid (MMA) are associated with -
    - elevated Hcy in blood (hyperhomocysteinemia) and consequent cardiovascular and neurodegenerative diseases, peripheral neuropathy, renal failure, hypothyroidism and sarcopenia (age-related loss of muscle mass and function),
    - elevated MMA levels and consequent overall acidification of the body and defective fatty acid synthesis of neuronal membranes,
    - homocysteinuria, methylmalonic aciduria, likely “folate trap”.

Several authors recommend that physicians check vitamin B12 levels at baseline, monitor regularly, and initiate appropriate B12 interventions in a timely manner.

Vitamin B12 utilizes a range of transporters, such as -

- gut to duodenum – haptocorrin;
- duodenum to the distal ileum (to a specifical calcium-dependant cubulin receptor) – Intrinsic Factor;
- ileum to epithelium – MDR1 (P-gp);
- renal reabsorption – megalin;
- enterocyte efflux transporter - MRP1.

Carrier – Transcobalamin II (carries to various tissues; only 20% plasma B12 bound to TCII).

There are currently 3 proposed mechanisms of action to explain how metformin negatively impacts B12 status, and there is a possibility that all are relevant -

1. inhibition of the calcium dependent channel cubulin,
2. MDR1 downregulation,
3. by significantly increasing bacterial B12 accumulation from the environment, however whether this occurs *in vivo* remains unknown.

Whilst metformin's negative impact on B12 status has quite profound flow-on effects for both an individual person's health outcomes and their quality of life, it is generally not addressed until the impact is quite profound. This is exacerbated by 2 key factors, and both of which should have been addressed many years ago –

1. even after 50+ years of evidence, regular monitoring of B12 status from commencement of metformin intervention is still not included in the medical Clinical Practice Guidelines,
2. appropriate reference ranges for B12 status continue to be debated. In recent times, neuro-imaging evidence established that there was a positive response to B12 interventions once levels were < 300 pmol/L – they could see the response so let's use the evidence.

What actions will you initiate when you see someone prescribed metformin, will you -

- recommend clarifying current B12 status?
- recommend regular monitoring of B12 status on an annual or 6-monthly basis whilst metformin is prescribed?
- recommend B12 interventions be administered at a different time from metformin?

- encourage your local Care teams to use 300 pmol/L as the lower acceptable limit?
- recommend regular monitoring of B12 status (? 2-monthly) and consequent rapid B12 intervention in mums and about-to-be mums prescribed metformin?

Conclusions

After 50+ years of debate it is now accepted that metformin is a cause of B12 depletion, so how much longer will it take for regular monitoring of B12 status to become an integral component of routine diabetes management once metformin intervention commenced?

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: asthma, leg oedema

Other: CRF, scoliosis, dyslipidaemia, Ca skin lesions

Biochemistry with Pharmaconutritional Consequences

Na:	137	mmol/l	Hb:	107	g/L	Albumin:	30	g/L	BSL:		mmol/l
K:	5.1	mmol/l	Lymph:	2.2		Total Protein:	57	g/L	HbA1C:		
Urea:	11.1	mmol/l	MCV:	89	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.126	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	2.26	mIU/L

Other: eGFR 32, CRP < 0.7, ESR 10, Ca 2.17, Ca corr 2.32, phos 1.26, Mg 0.76

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
AVANZA		☐	N	D	↑	↑	☐				☑	☐	☐
Frusemide	(20 mg/day) Ca, Cl, K, Mg, Na,	☑	NV	CD		↓	☐				☑	☐	☑
MOTILIUM		☑	N	CD		↕	☐	↓			☑	☐	☐
PANAMAX		☐	NV	CD			☐				☐	☐	☐
Prednisolone	Ca, Cr, D, Iodine	☑	NV	CD	↕	↑	☐				☐	☐	☑
Risperidone		☑	NV	C	↑		☐		↑		☐	☐	☐
TARGIN		☐	NV	CD		↕	☑				☑	☑	☐
TEMAZE		☑	NV	C			☑		↕		☑	☐	☐

Extra drug:

Transporter-mediated interactions and nutrients

Organ (transporter)	Thiamine	Choline
Inhibitor function		
Liver	Risperidone (OCT1)	Risperidone (OCT1)
Into kidneys	Mirtazapine (OCT2) Prednisolone (OCT2) Risperidone (OCT2) Targin (OCT2)	Mirtazapine (OCT2) Prednisolone (OCT2) Risperidone (OCT2) Targin (OCT2)

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

FLUID RESTRICTION 1.5 L/DAY

Data summary

Biochemistry

Relatively recent relevant available biochemistry indicates -

- low albumin + total proteins - typical indicators of nutritional status; may alter the effectiveness of five of the prescribed medicines; advisable to recheck status;

- low magnesium – there is a recommendation that lower acceptable lower be 0.80 mmol/L; currently prescribed frusemide; advisable to consider an intervention and that it be administered at a different time from frusemide.

- elevated TSH – there is a recommendation that TSH > 2.5 mIU/L is diagnostic for altered thyroid function in the elderly, and currently prescribed prednisolone therefore advisable to clarify thyroid function.

Glycaemia

Currently prescribed 3 medications that alters glycaemia, being frusemide, prednisolone and risperidone.

Pharmaconutrition

Currently prescribed 8 medications that include nausea as a side effect.

Currently prescribed 6 medications that include vomiting, diarrhoea and constipation as side effects.

Currently prescribed 5 medications that include hyperglycaemia and dry mouth as side effects.

Currently prescribed 4 medications that include hyponatraemia and hypercholesterolaemia as side effects.

Regular monitoring sodium levels recommended whilst avanza prescribed.

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

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

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.

Prednisolone may decrease iodine uptake and protein-bound iodine concentrations.

Vitamin D enhances anti-inflammatory effects of prednisolone.

Prednisolone prescription is associated with lower vitamin D levels; proposed mechanism steroids may enhance inactivation of vitamin D-2 by upregulating 24-hydroxylase activity.

Bowel management

No regular intervention prescribed,

No PRN interventions prescribed,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs AGO has a variable appetite ie eating well some days but not others.

Observations

Mrs AGO is a small, slender lady with definitely swollen ankles, who was dozing in a wheelchair in the Day Room - she woke to her name. Mrs AGO told me she eats well, sleeps well, and does not feel upset in the tummy.

Mrs AGO has remained weight stable since admission.

Pharmaconutrition assessment

Currently prescribed prednisolone which is associated with low vitamin D levels, and as Mrs AGO does not go outside for adequate duration nor on a regular basis it is therefore likely vitamin D levels may be compromised. Advisable to check vitamin D levels and if low then intervention recommended.

Nutritional factors that contribute to wound healing include -

- plasma proteins within acceptable range - status currently low therefore advisable to recheck status,

- adequate iron status - was prescribed a proton pump inhibitor until recently and PPIs associated with reduced iron absorption; since Hb is low advisable to clarify iron status,

- adequate B12 status - was prescribed a proton pump inhibitor until recently and PPIs associated with reduced B12 absorption therefore advisable to clarify B12 status,

- adequate magnesium status - was prescribed a proton pump inhibitor until recently and PPIs associated with reduced iron absorption, and is also currently prescribed frusemide which increases magnesium excretion; since magnesium levels are low advisable to consider an intervention,

- adequate vitamin C - important in collagen formation and the strength of the collagen; was prescribed a proton pump inhibitor until recently and PPIs associated with reduced vitamin C availability therefore may benefit from a short term (60-90 days) vitamin C intervention.

Mrs AGO's diagnoses include falls - nutritional factors that may be useful to consider in falls management include -

- low potassium - important in muscle function, was recently prescribed a PPI and is currently prescribed frusemide therefore advisable to monitor status;

- low calcium - more likely to be low if potassium or magnesium low; important in muscle function, was recently prescribed a PPI and is currently prescribed frusemide therefore advisable to clarify status;

- vitamin D – associated with muscle weakness and consequently falls; was recently prescribed a PPI and is currently prescribed prednisolone therefore advisable to clarify vitamin D status;

- low B12 - is important in the righting reflex when a person stumbles; was recently prescribed a PPI therefore advisable to check status;

- low Hb – is low; was recently prescribed a PPI therefore advisable to consider a short term iron intervention, and preferably administered non-orally;

- low iron – was recently prescribed a PPI therefore advisable to check status;

- low zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass; was recently prescribed a PPI and is currently prescribed frusemide therefore advisable to check status;

- low magnesium – currently low status; magnesium is important in vitamin D activation and muscle function, amongst other functions. Also was recently prescribed a PPI and is currently prescribed frusemide both of which significantly decrease magnesium availability. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status.

What else would you include?

Medications have profoundly and positively changed health outcomes however they do generally come with some nutritional harms. By identifying and addressing the nutritional harms, optimal health outcomes are closer to being achieved.

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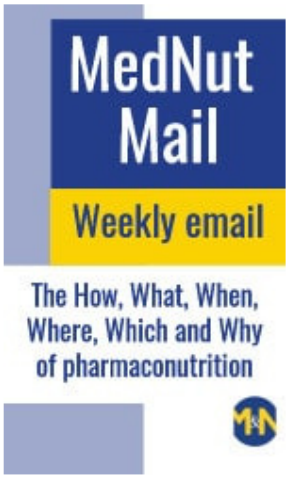

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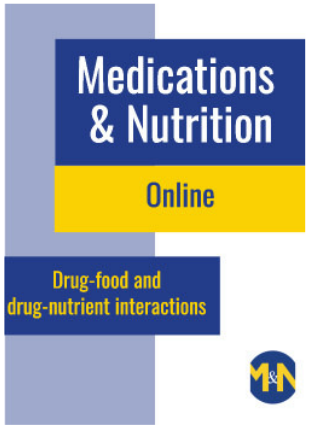

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