MedNut Mail

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

Metformin and folate

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15th February 2023

https://medicationsandnutrition.online

Editorial

In many countries, metformin is the first prescribed therapeutic intervention for those diagnosed with Type 2 diabetes. Metformin primarily increases insulin sensitivity, promotes weight loss, lowers death rates from all causes, decreases cancer risk, and lowers risk of atherosclerosis and heart disease.

Folate or folic acid, is an essential vitamin with multiple functions including being essential for -

- proper cognitive function, especially during periods of rapid growth and brain development such as during infancy and childhood;
- the formation of DNA;
- blood-brain barrier function;
- promotion of axon regrowth;
- inhibition of apoptosis (programmed cell death) in astrocytes. The proposed mechanism of action is that folic acid decreases oxidative stress and thereby prevents telomeric DNA oxidative damage and telomere attrition (reduction in numbers, size, or strength). Further, mitochondrial central carbon metabolism in astrocytes regulates overall brain bioenergetics (energy flow), neurotransmitter homeostasis and redox balance;
- oligodendrocyte development and maturation. In fact, folate rescues oligodendrocyte defects caused by methotrexate-induced dihydrofolate reductase (DHFR) inhibition;
- protecting and/or rescuing OAT1 expression in the presence of Uric Acid Nephropathy (UAN).

Red Blood Cell folate is a good indicator of long-term folate status and has good correlation with tissue stores.

Folate absorption is highly pH-dependent, with higher uptake at acidic pH than at neutral or alkaline pH.

Folate deficiencies can occur for many reasons, including -

- reduced folate intake,
- decreased absorption – intestinal and/or renal tubular,
- increased metabolism,
- increased requirements – eg wound healing,

- xenobiotics (medications, toxic metals, pesticides, herbicides) with antifolate capacity,
- genetic defects,
- chronic use of ethanol-folate malabsorption, derangement of hepatobiliary metabolism, and⁄or increased renal excretion of folate,
- intestinal resection,
- drug interactions,
- potentially - transporter occupancy and inhibition.

There is some evidence that metformin has antifolate capacity.

Low folate status is associated with deafness, cognitive decline, impaired lipid metabolism and myelin lipid abnormalities, impairment to neuronal function and physiology, neural tube defects (NTDs) during gestation, increased risk of spontaneous abortion and stillbirth, increased prevalence of small for gestational age (SGA) births, restricted foetal growth, smaller placentas and reduced nutrient transport to the foetus, and maternally - lower foetal weight.

Folate reduction by pharmacological DHFR inhibition results in oligodendrocyte death and differentiation defects.

Primary folate transporters include -

- folate receptor α (FRα/FOLR1),
- reduced folate carrier (RFC) – jejunum.
- proton-coupled folate transporter (PCFT) – intestine, liver, kidney, placenta; mediates folate uptake in both acidic and neutral pH environments,
- folate-binding protein (FBP),
- organic anion transporters (OATs1-3) - folate is an OAT1 substrate,
- P-glycoprotein (MDR1) – low affinity efflux (out of cells) transporter of folates.

Metformin significantly inhibits MDR1 expression by several factors including blocking MDR1 gene transcription, activating AMPK and suppressing MDR1 expression in MCF-7/adr cells, and by inhibiting the activation of NF-κB and CREB.

There is a direct correlation between cellular folate concentration and transport activity of Multidrug Resistance Protein 1 (MRP1) and Breast Cancer Resistance Protein (BCRP).

The currently limited evidence on metformin-folate interactions consistently demonstrates that metformin has a negative impact on folate status, and that it is reasonably consistent in relation to duration of metformin administration and

metformin dose. The evidence also indicates an inverse relationship between folic acid and glucose levels. Some authors now recommend folate supplements for all those prescribed metformin – and especially in both metformin-managed mums and metformin-managed about-to-be-mums.

There is a potential risk of folic acid over-supplementation – with early evidence indicating (high) choline intake is likely to modify some of the negative effects of high folate levels.

However, the mechanisms of action on how metformin induces low folate status is yet to be established.

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

- recommend clarifying current folic acid status?
- recommend regular monitoring of folic acid status on an annual or 6-monthly basis?
- recommend regular monitoring of folic acid whilst a proton pump inhibitor is concurrently prescribed?
- suggest trialling a folic acid intervention if there is a concurrent UAN diagnosis?
- suggest trialling a folic acid intervention for those diagnosed with chronic alcoholism?

Conclusions

Metformin's negative impact on folic acid status is a currently overlooked aspect of care for those diagnosed with diabetes. Inadequate folic acid status may explain some of the negative outcomes in those with diabetes.

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: blindness, diverticulosis

Biochemistry with Pharmaconutritional Consequences

Na:	139	mmol/l	Hb:	131	g/L	Albumin:	28	g/L	BSL:		mmol/l
K:	4.4	mmol/l	Lymph:	2.4		Total Protein:	63	g/L	HbA1C:		
Urea:	18.4	mmol/l	MCV:	85	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.197	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 23, CRP 116.5

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				☐				☐	☐	☑
Frusemide	(40 mg/day) Ca, Cl, K, Mg, Na,	☑	NV	CD		↓	☐				☑	☐	☑
MOVICOL		☐	N	D			☐				☐	☐	☐
NEO-B12	fortnightly	☐	NV	D			☐				☐	☐	☐
OSTEVIT-D	(1/day)	☐					☐				☐	☐	☐
Pantoprazole	(40 mg/day) B1, B12, Ca, Fe,	☑	NV	CD		↓	☑				☑	☐	☐

Transporter-mediated interactions and nutrients

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

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

Data summary

Biochemistry

Relatively recent biochemistry indicates

- low albumin - typical indicator of nutritional status; may alter the effectiveness of three of the prescribed medicines; advisable to recheck status;

- elevated CRP - inflammatory response marker; associated with increased resting metabolic rate and consequent increase in energy (food) requirements; influenced by vitamin D status and currently prescribed a vitamin D intervention.

Glycaemia

Currently prescribed 2 medications that alter glycaemia, being aspirin and frusemide.

Pharmaconutrition

Currently prescribed 2 medications that include nausea, vomiting, constipation, diarrhoea and poor appetite as side effects.

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

Caffeine increases aspirin absorption.

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

Ostevit + thiazide diuretic increases risk of hypercalcaemia.

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

A B12 intervention has been prescribed since admission 3 years ago and likely before then; fortnightly interventions were commenced 6 months. Evidence indicates elevated B12 levels diminish cognitive function. Advisable to check B12 levels and if well within acceptable range then advisable to review frequency of administration and consider 3-monthly or even 6-monthly interventions and

monitor status.

Currently prescribed Ostevit (1/day). Ostevit provides 25 mcg vitamin D per tab (25 mcg vitamin D is equivalent to 1000 IU vitamin D). Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

Currently prescribed the daily double ie two drugs that decrease magnesium availability, being - pantoprazole and frusemide. Magnesium is important in muscle function, especially cardiac muscle, amongst other functions. 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. Advisable to clarify magnesium status and if low then consider a magnesium intervention however unless administered non-orally, magnesium interventions are unlikely to be effective whilst a proton pump inhibitor is prescribed.

Bowel management

Regular aperient prescribed,

Oral + anal PRN interventions prescribed; oral administered 1 x Feb, 2 x Jan,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mr AGN usually eats breakfast, and otherwise has a limited range of food choices, being soup, ice cream and weetbix, and an overall variable intake.

Observations

Mr AGN is a tall, slender man who was asleep in bed when I went to speak to him - I did not disturb him; staff advise he often feels cold - a person will feel cold if there is inadequate food intake.

Mr AGN has been losing weight for the last 6 months.

Pharmaconutrition assessment

Advisable to review necessity for continued prescription of frusemide and pantoprazole as there are no supporting diagnoses and both have diminished appetite as a side effect.

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

- loss of weight – prescribed 2 drugs with side effects that negatively impact food intake;

- potassium - important in muscle function, currently prescribed frusemide and pantoprazole therefore advisable to clarify status;

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

- vitamin D – associated with muscle weakness and consequently falls; currently prescribed Ostevit therefore advisable to clarify vitamin D status (and therefore effectiveness of the intervention);

- B12 - is important in the righting reflex when a person stumbles; prescribed pantoprazole therefore advisable to check status;

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

- magnesium - magnesium is important in vitamin D activation and muscle function, amongst other functions. Also currently prescribed frusemide and pantoprazole which significantly decreases magnesium absorption. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to clarify magnesium 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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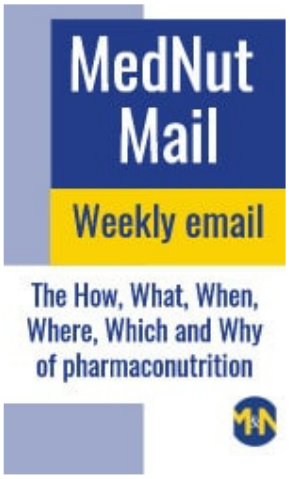

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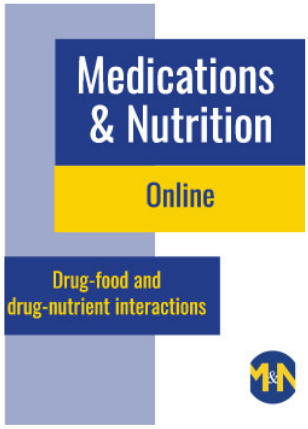

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