MedNut Mail

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

Metformin and vitamin B3

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Editorial

The mechanisms by which metformin exerts its effects are not fully understood and current concepts are currently being challenged. However, it is known that metformin inhibits glucose production in the liver and increases glucose uptake in peripheral tissues thereby lowering blood glucose levels.

Metformin's accepted function is that it slows mitochondrial respiration by inhibiting -

- NADH-ubiquinone oxidoreductase in complex 1 of the respiratory chain by facilitating the transfer of electrons from NADH to coenzyme Q10 (CoQ10) and moving protons across the inner mitochondrial membrane; the ultimate outcomes is decreased NAD levels;
- glycerol-3-phosphate dehydrogenase (GPD2) which ultimately reduces gluconeogenesis.

Niacin confers its benefits by activation of downstream signalling and by NAD generation and its important activities include anti-oxidant, anti-inflammatory, anti-apoptotic, energy production, neurogenesis, protection of DNA and mitochondrial function, and reduction in carcinomas.

Pyridoxine, and indirectly riboflavin, is essential for niacin activation.

Niacin deficiency, aka pellagra, is primarily known for its 4 Ds – dermatitis, diarrhoea, dementia, death. Other symptoms include intestinal inflammation, depression, paranoid behaviours, suicide and aggression.

Rate and extent of niacin excretion is dose-dependent ie finely-tuned homeostasis.

Niacin can cross the Blood-Brain-Barrier but some of its precursors such as quinolinic acid cannot.

NAD functions include regulation of cellular redox status; energy metabolism; co-substrate for enzymes such as sirtuins, poly-ADP-ribose-polymerases (PARPs) and some catalytic membrane proteins; regulating essential biological processes such as gene expression, DNA repair, calcium signalling, circadian rhythms, mitochondria biogenesis, cellular stress response and cellular communication, insulin secretion, apoptosis and aging.

Altered NAD homeostasis is associated with diseases such as cancer, cardiovascular, neurodegeneration and metabolic disorders including diabetes.

NAD can be either excreted in the urine or recycled as a substrate for sirtuins.

Exogenous sources of niacin include dietary intake and gut microbiota production whilst endogenous sources include production in the liver. Reaction rate can be slowed by inadequate availability of pyridoxine, riboflavin, thiamine, iron and haem, and tryptophan.

Niacin is associated with a range of transporters and several authors believe there are more to be found.

Intestinal

OAT10 – substrate niacin; at physiological concentrations;

SMCT1 (sodium-coupled monocarboxylate transporter) – substrate niacin; at pharmacological doses;

SMCT1 – substrate nicotinate (apparently speculative);

OCTN2 – substrate niacin;

CCC9 (Cation-Chloride Cotransporter 9) - substrate NMN (nicotinamide mononucleotide);

Liver

SMCT1 – substrate nicotinate (apparently speculative);

MATE1 efflux – substrates metformin;

Renal

OCTN1 – substrate metformin; located on the brush-border membrane (urine side) of proximal tubule cells;

OCTN2 – substrate niacin; expressed in the apical brush-border membrane of renal proximal tubules;

OAT10 – substrate niacin; renal reabsorption;

OCT2 – substrates NMN, metformin;

MATE1/2 – substrates NMN, metformin;

SMCT1 – substrate nicotinate (apparently speculative);

Respiratory

OCTN1 – substrate metformin; is located on the luminal (air) side of airway epithelial cells;

Skeletal muscle

OCTN2 – substrate niacin; expressed in the skeletal muscle, heart, lung, liver;

OAT10 – substrate niacin; heart;

MCT1 -substrate nicotinate; highest expression in the heart and also expressed in retina;

Pancreas

CCC9 (Cation-Chloride Cotransporter 9) - substrate NMN;

Retina

OCTN2 – substrate niacin;

Cellular uptake

SMCT/2 (sodium-dependent monocarboxylate transporter) – substrate niacin;

MCT1 (monocarboxylate transporter-1) – substrate niacin;

Other

OAT10 – substrate niacin; brain;

Gpr109a (G-protein coupled receptor 109a) - endogenous receptor for niacin; located in adipocytes, spleen, some immune cell types including neutrophils, macrophages, keratinocytes and Langerhans cells;

Niacin transporter inhibitors include short chain fatty acids (e.g. acetate), monocarboxylate drugs (e.g. salicylates), lactate and pyruvate.

Finding recent evidence that metformin directly impacts niacin status has proven to be particularly challenging. However, there seem to be 3 likely mechanisms of action -

1. **metformin as a substrate for transporters OCT2, MATE1, MATE2**. This will likely delay niacin excretion with resultant higher niacin levels in the blood and for a longer duration. If lactate inhibits niacin transporters, then the effect is much more profound ranging from absorption, to distribution and excretion;
2. **by significantly altering gut microbiota population**. Proposed mechanisms include preferentially altering microbiome population in favour of those that produce lactate in the colon and those that produce Short Chain Fatty Acids and that there is a consequent change in the production and absorption of nutrients – especially the B vitamins;
3. **by decreasing riboflavin and pyridoxine availability.** There is a chain reaction – riboflavin is essential for the activation of pyridoxine, and pyridoxine is essential for the activation of niacin ie niacin's availability is dependent upon the availability of pyridoxine.

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

- recommend clarifying niacin status if there is low pyridoxine status?

Conclusions

Whilst niacin is acknowledged to have an increasingly important role in both physiological function and as a treatment in physiological mal-function, our knowledge in relation to its range of functions, transport, and elimination is remarkably limited. Metformin has a range of mechanisms in which it can directly and indirectly impact niacin availability.

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: pork

Other: seizures, DVT, delirium

Biochemistry with Pharmaconutritional Consequences

Na:	144	mmol/l	Hb:	136	g/L	Albumin:	43	g/L	BSL:		mmol/l
K:	5.1	mmol/l	Lymph:	1.6		Total Protein:	70	g/L	HbA1C:	5.9	
Urea:	8.7	mmol/l	MCV:	93	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.061	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	0.83	mIU/L

Other: GFR > 60, chol 4.8, Tg 2.0, HDL 1.2, LDL 2.7, nonHDL 3.6, chol:HDL 4.0, vit D 112, Fe 12, TRF 2.8, satn 17%, ferritin 3

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
Atorvastatin			☑	NV	CD	↑	↓	☑				☐	☐	☐
Cholecalciferol	(500 mcg/day - incorrect orde		☐					☐				☐	☐	☐
Clopidogrel			☑	N	CD	↓		☑				☐	☐	☐
Esomeprazole	(20 mg/day) B1, B12, Ca, Fe,		☑	NV	CD	↑		☑				☑	☐	☐
Gliclazide	(08:00)		☑	NV	CD	↑	↕	☑				☐	☐	☑
Lamotrigine	carnitine, D		☐	NV	D		↓	☐				☐	☐	☐
Levetiracetam	D		☐	NV	D	↑	↑	☐				☑	☐	☐
Metformin	(08:00) B12		☐	NV	D	↓	↓	☑				☐	☐	☑
Paracetamol			☐	NV	CD			☐				☐	☐	☐
Sertraline	Na		☑	NV	CD	↑	↑	☐				☑	☐	☐

Transporter-mediated interactions and nutrients

Organ (transporter)	Thiamine	Choline	Pyridoxine	Carnitine
Inhibitor function				
From gut	Metformin (ThTr2) Sertraline (ThTr2)		Metformin (ThTr2) Sertraline (ThTr2)	
Liver	Clopidogrel (OCT1) Esomeprazole (OCT1) Lamotrigine (OCT1) Metformin (OCT1) Sertraline (OCT1)	Clopidogrel (OCT1) Esomeprazole (OCT1) Lamotrigine (OCT1) Metformin (OCT1) Sertraline (OCT1)		
Into kidneys	Clopidogrel (OCT2) Lamotrigine (OCT2) Sertraline (OCT2)	Clopidogrel (OCT2) Lamotrigine (OCT2) Sertraline (OCT2)		
Into muscles				
Substrate function				
From gut	Metformin (ThTr2)		Metformin (ThTr2)	
Into muscles	Metformin (OCT3) Sertraline (OCT3)	Metformin (OCT3) Sertraline (OCT3)		Metformin (OCT3) Sertraline (OCT3)
Liver	Lamotrigine (OCT1) Metformin (OCT1)	Lamotrigine (OCT1) Metformin (OCT1)		
Into kidneys	Metformin (OCT2)	Metformin (OCT2)		
Urine	Metformin (MATE)	Metformin (MATE)		

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

Data summary

Biochemistry

Relatively recent available biochemistry indicates

- marginal ferritin - likely due to the ongoing proton pump inhibitor prescription

Glycaemia

Currently prescribed 2 medication that alters glycaemia, being atorvastatin and sertraline.

BSLs (May)

- before breakfast - 5.5-6.9; recommended range 4-6,
- daily range - 4.7-7.7; recommended range 4-10,
- tested weekly x 2,
- reportable limits: < 3 and > 20,
- last HbA1c indicates very good overall glycaemic control.

Diabetes drugs

- gliclazide (08:00) has a duration of 18-24 hours,
- metformin (08:00) has a duration of 12 hours.

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous morning's gliclazide; no coverage from previous morning's metformin,
- before evening meal BSLs - covered by current morning's gliclazide; some coverage from current morning's metformin.

Mrs AGR’s glycaemic control is sufficiently tight that she may be at risk of hypoglycaemia in the afternoons therefore advisable to review current management strategy particularly with regard to number of prescribed drugs and/or their current doses.

Pharmaconutrition

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

Currently prescribed 7 medications that include nausea and altered weight as side effects.

Currently prescribed 6 medications that include vomiting and altered appetite as side effects.

Currently prescribed 5 medications that include constipation and altered taste as

side effects.

Currently prescribed 3 medications that include anaemia, hyponatraemia, tremor and dry mouth as side effects.

Esomeprazole decreases B12, vitamin C, magnesium, zinc and iron absorption and may decrease calcium absorption.

Gliclazide decreases B12 levels.

Lamotrignine decreases availability of carnitine and vitamin D.

Levetiracetam decreases vitamin D availability.

Metformin decreases B12, B1 and B6 absorption - regular monitoring recommended.

Concurrent administration of metformin and esomeprazole is associated with lower B12 levels – the authors suggest there is an additive effect.

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

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

Regular monitoring sodium levels recommended whilst sertraline prescribed.

Currently prescribed vitamin D 500 mcg/day (equivalent to 20 x 25 mcg tabs/day) however administered 2 x 25 mcg tabs/day. Evidence indicates 50 mcg vitamin D per day is a maintenance dose; vitamin D tabs typically provide 25 mcg vitamin D per tab (25 mcg vitamin D is equivalent to 1000 IU vitamin D). Recommend amending current vitamin D intervention.

There is increasing evidence that proton pump inhibitors such as esomeprazole 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.

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

- conversion of sun-skin contact to vitamin D – current vitamin D status within acceptable range,

- 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 AGR is fully assisted with her meals and eats well.

Observations

Mrs AGR is a small, grey-looking lady who was about to have morning tea - she advised she eats well and does not feel upset in the tummy.

Mrs AGR has slowly gained weight during the last year.

Pharmaconutrition assessment

Mrs AGR has been prescribed a proton pump inhibitor since admission (2 years 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)

Several of Mrs AGR's diagnoses fit within the metabolic syndrome cluster. Metabolic syndrome is characterised by insulin resistance and consequent hyperinsulinaemia - there are a number of strategies to improve insulin sensitivity or reduce insulin resistance including -

- magnesium – is important in glycaemic control; currently prescribed esomeprazole and metformin which significantly decreases magnesium absorption, and currently no intervention. Advisable to monitor status;

- thiamine - is important in glycaemic control and currently prescribed esomeprazole and metformin therefore advisable to monitor status;

- TNF-α – evidence indicates TNF- α has systemic effects that result in insulin resistance and NIDDM; low B12 status exacerbates elevated TNF- α. Currently prescribed esomeprazole, gliclazide and metformin therefore advisable to monitor B12 status;

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

- low B12 – important in the righting reflex and currently prescribed esomeprazole, gliclazide and metformin therefore advisable to monitor B12 status. There is disagreement between pathology ranges and research findings with regard to appropriate B12 levels - neuro-imaging research indicates B12 interventions are effective once levels are less than 300 pmol/L.

Nutritional factors that may be useful to include UTI management include -

- vitamin C – 100 mg/day found to confer benefit however esomeprazole prescribed;

- vitamin D – recurrent UTIs associated with vitamin D deficiency and currently prescribed atorvastatin however current levels within acceptable range;

- zinc – recurrent UTIs deplete immune system and consequently zinc status therefore advisable to check zinc status and if low then short term (90-120 days) intervention recommended however esomeprazole prescribed;

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

- loss of weight – prescribed 9 drugs with side effects that negatively impact food intake;

- low potassium - important in muscle function, currently prescribed esomeprazole therefore advisable to monitor status;

- low calcium - more likely to be low if potassium or magnesium low; important in muscle function, currently prescribed esomeprazole therefore advisable to monitor status;

- vitamin D – associated with muscle weakness and consequently falls; currently prescribed atorvastatin and metformin therefore advisable to monitor vitamin D status;

- low B12 - is important in the righting reflex when a person stumbles; prescribed esomeprazole, gliclazide and metformin therefore advisable to monitor status;

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

- low magnesium - magnesium is important in vitamin D activation and muscle function, amongst other functions. Also currently prescribed esomeprazole and metformin which significantly decreases magnesium availability. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to monitor magnesium status;

- low carnitine - carnitine is both absorbed and produced de novo, and is important in a range of muscle functions; lamotrigine decreases carnitine absorption; magnesium is important in de novo carnitine production. Advisable to monitor status.

What else would you include?

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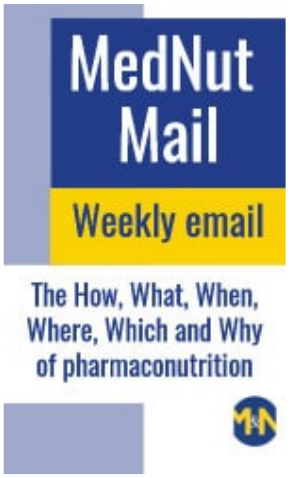

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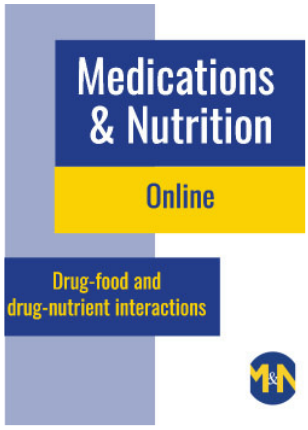

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