

MedNut Mail

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

Metformin and magnesium

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<https://medicationsandnutrition.online>

Commentary

Metformin is the fourth most commonly prescribed medicine in the world therefore it's negative impacts on nutritional factors affects a significant percentage of the global population.

Hypomagnesaemia in people diagnosed with diabetes is reported to be about 31%, based on a lower acceptable limit for magnesium of 0.70mmol/L. There is a recommendation for a universal lower acceptable limit for magnesium of 0.80 mmol/L which therefore noticeably increases the percentage of diabetics with hypomagnesaemia.

Hypomagnesemia occurs when intake does not meet body requirements and so there is a sustained demand on body stores which ultimately results in depletion – it may take years to get to this point.

Hypomagnesemia is due to a number of factors including a negative effect on magnesium availability from some commonly prescribed medications including metformin.

Magnesium is involved in more than 600 different functions including being a cofactor of several important enzymes including energy production, regulation of ion channels, the binding of calcium to specific proteins such as calmodulin, cell membrane stability, mitochondrial function, cell proliferation control, maintenance of the tertiary structure of DNA and RNA, many major metabolic and signalling pathways, protein, lipid and carbohydrate synthesis and metabolism, insulin/glucose metabolism, nervous and immune system functioning, heart function, muscle formation and contraction, bone and calcium metabolism, and activation of the nutrients thiamine, vitamin C, vitamin D, and iodide.

Magnesium deficiency is associated with diseases such as cardiovascular diseases including arrhythmia, preeclampsia, heart failure, hypertension; neurological diseases including headache, seizures, stroke; respiratory diseases including bronchial asthma, chronic obstructive pulmonary disease; depression, overweight and obesity, insulin resistance and type 2 diabetes mellitus, and changes in lipid metabolism.

Magnesium transporters include –

- TRPM6/7 channels - large intestines (caecum and colon), magnesium absorption,

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- Magt1 – magnesium transport across plasma membranes,
- Cyclin M2 (Cnm2) – renal magnesium resorption,
- Cyclin M4 (CNNM4) – liver magnesium exporter,
- Mitochondrial channels such as Mrs2 (influx), Slc41a3 mRNA levels (efflux),
- Slc41a1 – predominantly heart and testis; also permeable to other divalent cations such as cobalt, copper and zinc; efflux channel.

Metformin impacts magnesium effect via a number of different mechanisms including -

- short-term treatment increases the activity and cell surface expression of TRPM6 and consequently increases magnesium uptake,
- long- term treatment downregulates TRPM6 gene expression and consequently reduces magnesium uptake,
- disturbing magnesium intestinal absorption and renal re-absorption,
- decreasing mRNA levels and/or expression of Magt1, cyclin M2, Slc41a3,
- has not been found to impact cyclin M4.

There seems to be a trade-off between the importance of long-term administration of metformin in improving glycaemic control and its negative impact on magnesium status – a nutrient that is itself important in glycaemic control. The risk of hypomagnesaemia to the diabetes-diagnosed population caused one author with particularly relevant findings, to recommend routine measurement of magnesium levels as a management strategy to prevent hypomagnesaemia.

One 2021 Conference poster presentation proposed a metformin + magnesium intervention as a strategy to minimise insulin resistance and a couple of cancers – given the above findings, hopefully the intervention would not be administered concurrently!

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

- recommend regular monitoring of magnesium status ie at least 6 monthly?
- recommend interventions be initiated once magnesium status is < 0.80 mmol/L?
- ensure magnesium intervention is not administered concurrently with metformin?

Conclusions

Ultimately, the evidence is steadily increasing that metformin interferes with many aspects of magnesium's absorption and excretion.

Case study

Medical History with Nutritional Aspect

Amputation	<input type="checkbox"/>	Constipation	<input type="checkbox"/>	Dysphagia	<input type="checkbox"/>	MND	<input type="checkbox"/>
Anaemia	<input type="checkbox"/>	CVA	<input type="checkbox"/>	Enteral Feed	<input type="checkbox"/>	MS	<input type="checkbox"/>
Arthritis	<input checked="" type="checkbox"/>	CVD	<input type="checkbox"/>	Falls	<input type="checkbox"/>	Osteoporosis	<input type="checkbox"/>
Cancer	<input type="checkbox"/>	Dementia	<input type="checkbox"/>	Fracture	<input type="checkbox"/>	PD	<input type="checkbox"/>
CCF	<input type="checkbox"/>	Dentures	<input type="checkbox"/>	Frailty	<input type="checkbox"/>	Pressure Area	<input type="checkbox"/>
Chest Infection	<input type="checkbox"/>	Depression	<input checked="" type="checkbox"/>	Gout	<input type="checkbox"/>	Renal	<input type="checkbox"/>
COAD	<input type="checkbox"/>	DM Type 1	<input type="checkbox"/>	Hypertension	<input type="checkbox"/>	Ulcer	<input checked="" type="checkbox"/>
Confusion	<input type="checkbox"/>	DM Type 2	<input type="checkbox"/>	Incontinent	<input type="checkbox"/>	UTI	<input checked="" type="checkbox"/>
Food Allergies:	<input type="text"/>						
Other:	<input type="text" value="leg ulcers, hernia"/>						

Biochemistry with Pharmaconutritional Consequences

Na:	<input type="text" value="142"/>	mmol/l	Hb:	<input type="text" value="116"/>	g/L	Albumin:	<input type="text" value="41"/>	g/L	BSL:	<input type="text"/>	mmol/l
K:	<input type="text" value="4.9"/>	mmol/l	Lymph:	<input type="text" value="1.5"/>		Total Protein:	<input type="text" value="72"/>	g/L	HbA1C:	<input type="text"/>	
Urea:	<input type="text" value="9.3"/>	mmol/l	MCV:	<input type="text" value="92"/>	mmol/l	B12:	<input type="text"/>	pmol/L	INR:	<input type="text"/>	
Creatinine:	<input type="text" value="0.112"/>	mmol/l	Zn:	<input type="text"/>	umol/l	Folate:	<input type="text"/>	nmol/L	TSH:	<input type="text"/>	mIU/L
Other:	<input type="text" value="eGFR 41, Fe 12, TRF 2.8, satn 17%, ferritin 181, ESR 56"/>										

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp >90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drig	d m	Dys	BSL
Aspirin	C, Fe	<input checked="" type="checkbox"/>	NV								<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
CALTRATE	Fe	<input type="checkbox"/>		C							<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cholecalciferol	(1/day)	<input type="checkbox"/>									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
COLOXYL WITH S		<input type="checkbox"/>		D							<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
MOVICOL		<input type="checkbox"/>	N	D							<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
NEXIUM	(20 mg/day) B1, B12, Ca, Fe,	<input checked="" type="checkbox"/>	NV	CD	↑		<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Strontium ranelate		<input type="checkbox"/>	N	D							<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Summary of medications, nutrients and transporters

Organ (transporter)	Thiamine	Choline	Carnitine
Inhibitor function			
Liver	Nexium	Nexium	

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

Data summary

Biochemistry

Relevant biochemistry mostly within acceptable ranges however B12 status is marginal and likely high risk of ongoing depletion due to Nexium prescription.

Glycaemia

Currently prescribed 1 medication that alters glycaemia, being aspirin.

Pharmaconutrition

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.

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

Calcium carbonate requires gastric acidity for absorption however Nexium prescribed therefore advisable to consider calcium citrate which does not require gastric acidity for absorption.

Bowel management

Regular aperients prescribed

Oral + anal PRN interventions prescribed

No Nurse Initiated interventions administered

Staff comments

Staff advise Mrs AGK eats well, that she sleeps until about 10:00 am is showered and has breakfast. Staff also commented Mrs AGK has frequent chest infections and has recently ceased (yet another) course of antibiotics.

Observations

Mrs AGK is a small, pale, frail lady with cold hands and who was lying in bed when I went to speak to her - she responded to my presence but not my questions.

Currently weight stable.

Pharmaconutrition assessment

Since Mrs AGK is pale, advisable to check iron levels especially since Nexium is prescribed as it is associated with decreased iron absorption.

Mrs AGK is reported to have frequent chest infections which are treated with antibiotics. Frequent infections decrease the immune system especially zinc status.

Metformin and magnesium

Zinc is important in a range of body functions, including sense of taste and release of the hunger hormone Neuropeptide Y. Advisable to check zinc levels especially since Nexium is prescribed as it is associated with decreased zinc absorption.

Mrs AGK has been prescribed a proton pump inhibitor for more than 4 years. There is increasing evidence that long-term (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 consider 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 AGK's diagnoses include arthritis which is a cause of chronic pain - nutritional factors that may be useful to consider in pain management include

- 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 - 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 Nexium 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 Nexium therefore advisable to check B12 status.

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- 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 Nexium which decreases magnesium absorption.

Mrs AGK's diagnoses include falls - nutritional factors to consider in falls management include -

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

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

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

- low magnesium - magnesium is important in vitamin D activation and muscle function, amongst other functions. Also currently prescribed Nexium 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.

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

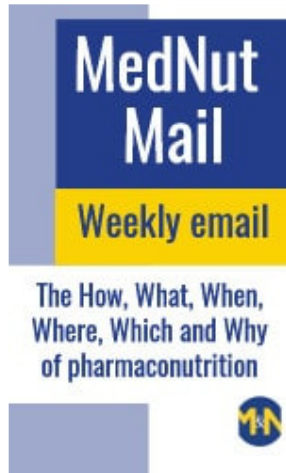
- B12 and/or folate - associated with deafness; currently prescribed Nexium therefore advisable to check B12 status and if low then intervention recommended;
- vitamin C - inadequate dietary intake associated with deafness; currently prescribed Nexium which reduces conversion of vitamin C to its active form;
- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed Nexium therefore advisable to check zinc status and if low then intervention recommended;
- thiamine – associated with bilateral hearing loss and proposed mechanism of action is that thiamine transporter OCT2 is expressed in the hair cells of the cochlea therefore interruptions to thiamine accessibility are likely to impact hair cell function; currently prescribed Nexium which decreases thiamine availability both directly and indirectly.

What else would you include?

Metformin and magnesium

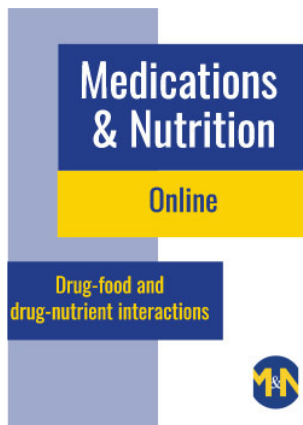
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