MedNut Mail

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

Metformin and vitamin D

Y Coleman

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https://medicationsandnutrition.online

Editorial

Metformin is a commonly prescribed first line intervention in NIDDM management and its mechanisms of action include decreased intestinal sugar absorption, increased glucose uptake in liver and skeletal muscle, modulation of lactate production, inhibition of gluconeogenesis and protein synthesis, activation of fatty acid β-oxidation, and reduction in appetite.

Vitamin D deficiency is being called a pandemic disease by some authors, and further, some authors claim that its deficiency is a contributor to the increased risk of NIDDM.

Vitamin D is essential for many functions including –

- as an anti-inflammatory agent it modulates the immune system response by affecting both innate and adaptive immunity,
- regulating bone homeostasis including stimulating osteoid mineralization and regulating bone turnover,
- regulating calcium–phosphorus homeostasis such as regulating calcium absorption in the gut and maintaining serum calcium and phosphate concentrations,
- optimizing musculoskeletal system functioning such as regulating muscle function, decreasing oxidative stress, regulating muscle tone and contraction,
- optimizing mitochondrial oxidative phosphorylation (OXPHOS) by regulating mitochondrial oxygen consumption and dynamics,
- being an effective antioxidant,
- impacting occurrence and course and treatment of asthma,
- increasing insulin sensitivity and protects against high-glucose-induced ß-cell dysfunction,
- cardiovascular function,
- muscle energy metabolism.

Vitamin D deficiency manifests as decreased insulin secretion and increased insulin resistance, NIDDM, metabolic syndrome, obesity, cardiovascular risk, neurodegeneration, Alzheimers dementia, depression, inflammation, skeletal muscle atrophy, osteoporosis and rickets, increased risk of graft rejection post-transplant, and others.

One author commented that while vitamin D deficiency enhances oxidative stress (in muscles), overcorrection of vitamin D status may also negatively impact skeletal muscle.

Guidelines for Preventing and Treating Vitamin D Deficiency: A 2023 Update in Poland (https://doi.org/10.3390/nu15030695) advise these ranges for total serum 25-hydroxyvitamin D concentration indicating

- vitamin D deficiency < 50 nmol/L,
- suboptimal status 50 - 75 nmol/L,
- optimal concentration 75 - 125 nmol/L.

These ranges are noticeably different from Australia's recommended ranges – and being recent are more likely reflect recent research findings.

The research is limited in relation to transporters, and focus primarily on intestinal absorption and excretion – evidence in relation to other membrane transporters seems to be difficult to locate -

- proximal jejunum and distal ileum **to epithelium** - cholesterol membrane transporters including the scavenger receptor class B type I (SR-BI), CD36 molecule (CD36), NPC1-like transporter 1 (NPC1L1), and ATP-binding cassettes A1 and G1 (ABCA1 and ABCG1),
- **Epithelium to intestinal lumen** – MDR1 (P-gp).

MDR1 moves vitamin D out of the lumen and into the bloodstream, and moves it from the bloodstream to the lumen.

There is limited direct evidence in relation to interactions between metformin and vitamin D. The (typically) older evidence generally indicates no interaction however, in the late twenty noughties, the lower acceptable limit for vitamin D was significantly increased, and since then the evidence has more commonly indicated metformin having a negative impact on vitamin D status.

However, metformin downregulates MDR1 and upregulates MRP1, and vitamin D downregulates MDR1 and MRP1, therefore if a vitamin D intervention is to be administered then timing of administration is likely to be a consideration. Vitamin D management of MRP1 and MDR1 is likely to minimise risk of toxicity and deficiency consequently the greater risk to vitamin D status is from metformin therefore vitamin D and metformin should be administered at significantly different times from each other.

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

- recommend clarifying current vitamin D status?
- recommend regular monitoring of vitamin D status on an annual or 6-monthly basis whilst metformin is prescribed?
- recommend vitamin D interventions be administered at a significantly different time from metformin, and from food intake?

Conclusions

Metformin's negative impact on vitamin D status is quite profound and as the negative impact is on both absorption and excretion it could increase the risks of deficiency and toxicity.

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: ? Diabetes

Other: Ca rectum, delirium, AF, vertigo, CRF

Biochemistry with Pharmaconutritional Consequences

Na:	137	mmol/l	Hb:	125	g/L	Albumin:	32	g/L	BSL:		mmol/l
K:	5.2	mmol/l	Lymph:	1.8		Total Protein:	77	g/L	HbA1C:		
Urea:	12.3	mmol/l	MCV:	88	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.117	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 49, vit D 57, Fe 4, TRF 2.0, satn 8%, ferritin 337

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
DORYX	folate		☑	NV	D		↓	☑				☑	☑	☐
			▩					▩				▩	▩	▩

Transporter-mediated interactions and nutrients

Organ (transporter)	Thiamine	Folic acid	Vitamin D
Inhibitor function			
Doryx	OAT1	MDR1	MDR1

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

Biochemistry

Relatively recent biochemistry indicates

- low albumin - typical indicator of nutritional status; influenced by inflammatory response; advisable to recheck status,

- marginal vitamin D status - advisable to recheck status and if low then review current management strategy.

Pharmaconutrition

Doryx associated with negative impact on B12, D and thiamine.

Bowel management

No regular intervention prescribed,

Oral PRN aperient prescribed,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mr AGQ eats well at breakfast and has a variable, mostly minimal intake at midday and evening meals.

Observations

Mr AGQ is a tall, big-framed man who was dozing in the Day Room when I went to speak to him - he woke to his name and told me he likes mince (meat), and his eyes lit up when I asked if he likes ice cream. I asked if he was given some ice cream now would he eat it and he agreed he would - ice cream was produced and he is eating it with enjoyment.

Pharmaconutrition assessment

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

- loss of weight – doxycycline side effects include poor appetite, altered taste, dry mouth, nausea and vomiting – a combination that could significantly negatively impact food intake and consequent weigh loss;

- vitamin D – doxycycline negative impact likely due to inhibiting MDR1;

- low folate – mechanism unknown; doxycycline negatively impacts renal uptake likely due to inhibiting OAT1 which is more likely to result in higher levels rather than lower levels. However, doxycycline has a hypofolataemia effect therefore there is another mechanism of interference.

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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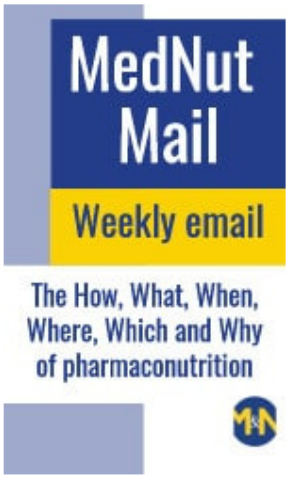

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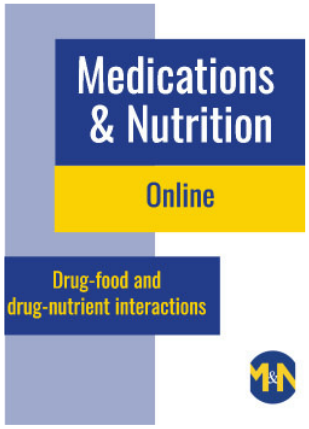

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