MedNut Mail

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

B6 and metformin

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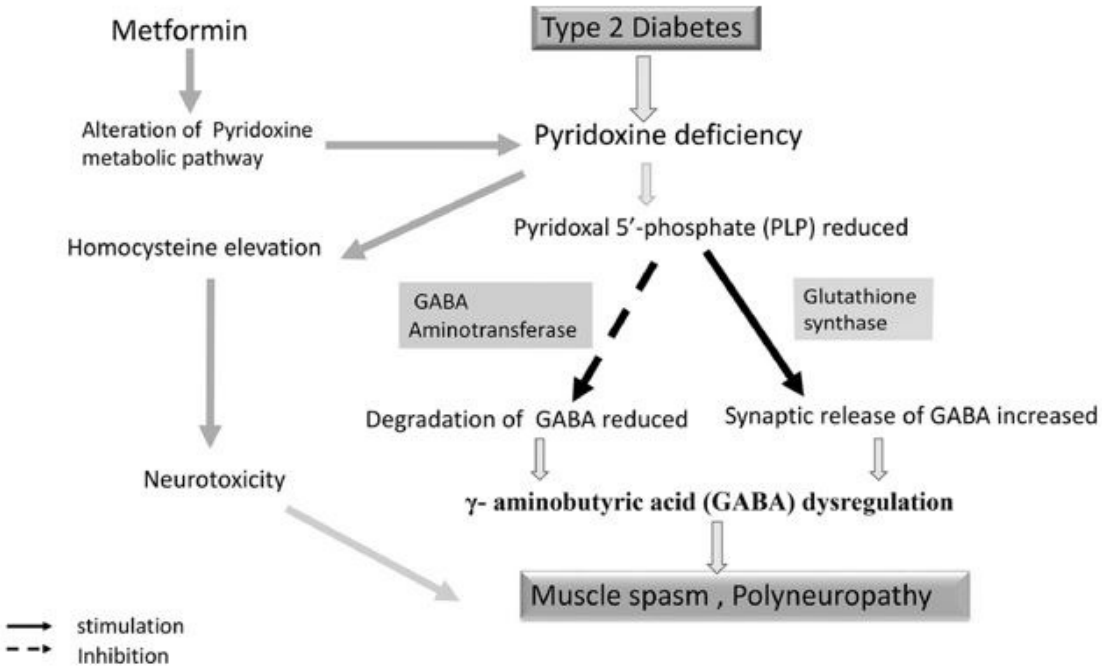
https://medicationsandnutrition.online

Commentary

Whilst researching a related topic for a soon-to-be-published MedNut Mail email, I came across this diagram and asked the question “what are the likely mechanisms of action for metformin to alter pyridoxine’s (vitamin B6) metabolic pathway?”



Zhou J. & Effiong, U. 2021. Isolated Pyridoxine Deficiency Presenting as Muscle Spasms in a Patient with Type 2 Diabetes: A Case Report and Literature Review. The American Journal of Medical Sciences. 2021 361(6):791-794.

There is now early evidence that metformin use is associated with a higher risk of B6 deficiency, with one study estimating a risk increase of about 48% - the authors did not propose any mechanisms of action; needless to say the authors recommended more studies to identify the relevant mechanisms.

Recent evidence also indicates that both B6 and metformin are involved in tryptophan metabolism via its kynurenine component and that metformin normalizes tryptophan metabolism, speculatively by decreasing utilization of the kynurenine pathway.

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Some recent research suggests metformin may also negatively impact riboflavin (vitamin B2) status - the authors identified a degree of inverse association between metformin and B2 status. B2 is required for the generation of the active form of B6 ie perhaps low B2 contributes to or exacerbates B6 deficiency.

Given the evidence is recent but steadily increasing, what interventions will you initiate when you see someone whose prescribed medications include metformin and diagnoses include diabetes – will you -

- request vitamin B6 status be clarified?
- ensure vitamin B2 levels are within acceptable range?
- recommend a small pyridoxine intervention and that it be administered at a different time from metformin?
- review all prescribed medications for a negative impact on B6 and/or B2?
- recommend regular monitoring of pyridoxine status?

Conclusions

Given metformin is the fourth most commonly prescribed drug in the world it is surprising its negative impact on B6 status has only recently been identified.

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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: IDA, schizophrenia, parkinsonism, AF

Other: psychosis, DVT, paraproteinaemia, GORD, B12 def

Biochemistry with Pharmaconutritional Consequences

No recent relevant results available that may have a pharmaconutrition component.

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
COLOXYL WITH S		☐			D			☐				☐	☐	☐
DIAMICRON MR	(08:00)	☑		NV	CD	↑	↕	☑				☐	☐	☑
FERROGRADUMET	Ca, Mg, Zn	☐		NV	CD			☐				☐	☐	☐
Metformin	(08:00, 17:00) B12	☐		NV	D	↓	↓	☑				☐	☐	☑
PANADOL		☐		NV	CD			☐				☐	☐	☐
Paroxetine	Na	☑		NV	CD	↑	↓	☑				☑	☑	☑
SOMAC	(20 mg/day) B1, B12, Ca, Fe,	☑		NV	CD		↓	☑				☑	☐	☐
Warfarin	D	☑		NV	D			☑				☐	☐	☐
ZYPREXA		☑			C	↑	↑	☐				☑	☐	☐

Extra drug: lantus (38 U mane)

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

No recent, relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for five of the prescribed drugs and hypoproteinaemia may alter their effects and expression of their side effects.

BSLs (May-Jun) –

- before breakfast - 5.0-9.6; recommended range 4-6

- daily range - 5.0-15.1; recommended range 4-10

- reportable limits: < 4 and > 18

- tested daily bd

- PRN actrapid 4U if BSLs > 20.0

- advisable to check HbA1c and clarify overall glycaemic control.

Diabetes drugs

- lantus has a time to onset of 1hour, minimal peak and duration of 20-26 hours
- diamicron MR has a duration of 24 hours
- metformin has a duration of 12 hours

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous morning's lantus, diamicron MR or metformin, nor from previous evening's metformin
- before evening meal BSLs - no coverage from previous evening's metformin; covered by current morning's lantus, diamicron MR and limited coverage from current morning's metformin.

Prescribed 2 drugs that alter glycaemic control, being paroxetine and Zyprexa.

Chronic use of coloxyl + senna may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

Ferrogradumet decreases zinc absorption.

Metformin decreases B12 and thiamine absorption - there is now a recommendation for regular monitoring (at least annually) of B12 status whilst metformin prescribed, and regular monitoring thiamine status is now advisable.

Annual measurement of B12 levels in those on longterm meformin therapy has been recommended since the 1970's; annual injections of 1 mg B12 recommended for those prescribed longterm metformin therapy.

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

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Concurrent ingestion of paracetamol and iron results in 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.

Regular monitoring of sodium levels recommended whilst paroxetine prescribed.

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

Ferrogradmet - time to dissolution at pH 1.2 (ie gastric environment) about 48 minutes, and at pH 5.8 (ie intestinal environment) about 362 minutes; gastric emptying time for adults is 3-6 hours, therefore any undissolved tablet will pass into the large intestine and be excreted. As Mrs ABI is prescribed Somac time to dissolution is extended and there is an altered gastric pH which means much lower amount absorbed therefore advisable to check SIS.

Two drugs prescribed that decrease B12 absorption, being metformin and Somac - the authors suggest an additive effect on B12 malabsorption.

There is increasing evidence that proton pump inhibitors such as Somac 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. Since a proton pump inhibitor has been prescribed for at least 12 years, advisable to check magnesium levels and clarify current status.

Bowels –

- regular aperient prescribed

- no PRN interventions prescribed

- no Nurse Initiated interventions administered

Staff advise Mrs ABI eats all that is offered, and has also been observed to take food from elsewhere.

Mrs ABI is a small, pale lady of size who was participating in an activity when we went to speak to her - we did not disturb her.

Mrs ABI is pale and is prescribed both Somac which decreases iron absorption and ferrogradument which is an iron supplement. Advisable to check SIS and if not within acceptable range then consider why it is not - options being -

- delayed dissolution of ferrogradumet, and or

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- minimally available absorbable iron due to Somac's impact on gastric pH.

From staff comments Mrs ABI is chronically hungry which is likely exacerbated by insulin resistance and hyperinsulinaemia. Physiologically the body only releases insulin when glucose is present in the bloodstream - the chronic presence of insulin in the bloodstream results in the hunger hormone being continually stimulated and therefore a constant desire to consume more food; currently prescribed lantus.

The combination of falls and incontinence indicates an increased risk of low B12 status, and currently prescribed 2 drugs, being metformin and Somac, that are likely to exacerbate B12 depletion, therefore advisable to check B12 levels.

Commencement of metformin indicates prudent clinical practice for B12 management as outlined -

- establish B12 status at commencement of drug treatment, and monitor on a regular basis, or
- commence a prophylactic B12 intervention with oral supplements as they are not protein-bound and therefore do not require gastric acidity for absorption.

Mrs ABI has been prescribed warfarin for an unknown duration; warfarin antagonises vitamin K availability and a stable intake is required. Vitamin K is important in a range of body functions including the clotting cascade, bone health, glycaemic control, lipid metabolism, and production of myelin sheaths and neuronal membranes; and low vitamin K status is now being associated with cognitive impairment. It is likely Mrs ABI is low in vitamin K and has probably depleted her vitamin K stores. Advisable to check vitamin K status – either by blood test or by dietary record.

Currently prescribed paracetamol and diagnoses include arthritis therefore increased likelihood 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. 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 Somac which decreases conversion of vitamin C to its active form.
- evidence indicates substantial relief of neuropathic pain by thiamine, pyridoxine and B12 separately, and in combination there was a synergistic benefit. Currently prescribed metformin (thiamine,

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pyridoxine, B12), Somac (thiamine, B12, possibly B6).

- 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 metformin and Somac which both decrease B12 availability therefore advisable to check B12 status.
- vitamin D – currently no intervention. Evidence indicates increasingly brittle pain control with decreasing vitamin D levels. Currently prescribed warfarin which decreases vitamin D status. Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.
- vitamin K - has been found to suppress the inflammatory cytokines and NF-kappaB and prevent oxidative, hypoxic, ischemic injury to oligodendrocytes and neurons – vitamin K deficiency therefore results in classic expression of the inflammatory response and consequently pain. Currently prescribed warfarin which interacts with warfarin.
- 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 Somac which decreases magnesium absorption.

Many of Mrs ABI's diagnoses fit within the metabolic syndrome cluster. Metabolic syndrome is characterised by insulin resistance and consequent hyperinsulinaemia - hyperinsulinaemia is associated with increased appetite and consequent weight gain which then compounds the insulin resistance. Physiologically the body releases insulin once glucose is present in the bloodstream - the presence of insulin in the bloodstream at other times increases the risk of insulin resistance. There are a number of nutritional interventions to improve insulin sensitivity or reduce insulin resistance including -

- vitamin D within acceptable range - current intervention may not be adequate to attain adequate range. Early evidence indicates low vitamin D is a predictor of peripheral insulin resistance and elevated inflammatory response markers and currently prescribed warfarin.
- magnesium – is important in glycaemic control and inadequate intake may impair insulin synthesis, secretion and signalling pathways; in fact there is evidence of an inverse correlation between magnesium status and diabetes incidence. Currently prescribed Somac which significantly decreases magnesium absorption, and currently no intervention. Advisable to review status.
- thiamine - people with diabetes have a significantly increased urinary excretion of thiamine;

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thiamine is important in glycaemic control; currently also prescribed metformin and Somac which further decreases thiamine availability.

- TNF-α – evidence indicates TNF- α has systemic effects that result in insulin resistance and NIDDM; low B12 status exacerbates elevated TNF- α and currently prescribed metformin and Somac therefore advisable to check B12 status.
- zinc – is integral to insulin formation, and enhances insulin sensitivity through stimulation of insulin receptors; inadequate intake may impair insulin synthesis, secretion and signalling pathways. It is important in the glucose metabolism, protects the mitochondria from oxidative stress and glycation, and altered glomerular function, as well as modifying the inflammatory response pathway and activation of the polyol pathway (a part of intracellular signalling and metabolism) and currently prescribed Somac therefore advisable to check status.
- potassium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways, and currently prescribed Somac.
- calcium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways, and currently prescribed Somac.

Mrs ABI's diabetes management includes 3 drugs administered before breakfast, of which 1 drug has a duration of about 24 hours, 1 drug has a duration > 24 hours, and 1 drug administered bd has a duration of 12 hours; effectively there is minimal before-breakfast coverage. Mrs ABI's afternoon glycaemia is curious - realistically she should have very low BSLs because all 3 prescribed diabetes drugs administered before breakfast are maximally effective in the afternoons, however Mrs ABI's BSLs are mostly high therefore one should ask why and there seem to be 5 options -

1. the hyperglycaemic effects of the afternoon tea snack food, caffeine, and chlorogenic acid in the caffeine are sufficient to offset the hypoglycaemic effects of the drugs;
2. current medication management strategy is undermedicating glycaemic control;
3. current medication management strategy is overmedicating glycaemic control and causing the liver to release stored glucose as a physiological response to hypoglycaemia;
4. current medication management strategy is overmedicating glycaemic control and Mrs ABI is grazing to offset the hypoglycaemic effect;
5. current medication management strategy is overmedicating glycaemic control and causing both the liver to release stored glucose and Mrs ABI to graze.

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Therefore advisable to review current diabetes management strategy.

Mrs ABI's large body size is likely due to a number of factors including limited activity, healthy appetite, and prescribed drugs such as metformin and Somac:-

- metformin, paroxetine, Zyprexa - decrease thiamine availability. Thiamine is important in glycaemic and lipid control, neurological function and energy production; when there is insufficient thiamine then food is converted to alternatives such as fat stores, cholesterol and triglycerides.
- Somac - decreases magnesium absorption and thiamine availability. Magnesium converts thiamine to its active form.
- Lantus - increases food intake both directly by stimulating hunger and indirectly by dropping BSLs and so the person eats to increase BSLs to acceptable levels again. If insulin resistance is addressed then hunger is also controlled. If Mrs ABI is hyperinsulinaemic then the excess insulin in the blood will stimulate hunger and consequently she will eat - by addressing insulin resistance then hunger is also being addressed albeit indirectly.

Thiamine status is negatively impacted by 4 prescribed medications, being metformin, paroxetine, Somac, Zyprexa and intervention may be advisable – intervention best administered at least one hour before or two hours after administration times of the identified drugs.

What else would you include?

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