MedNut Mail

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

Thiamine Transporters 1/2 (THTR1/2) and pharmaconutrition

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Editorial

The thiamine transporters Thiamine Transporter 1 (THTR1) and Thiamine Transporter 2 (THTR2) transfer thiamine and pyridoxine, and are associated with two transfer systems, being -

- THTR1 - the nutrient concentration is low and therefore uptake requires energy,
- THTR2 - the nutrient concentration is high (thiamine > 2 mmol/L), and therefore uptake involves passive nutrient diffusion.

THTR1 and THTR2 are highly expressed in the cells of various organs including skeletal muscle, heart, liver, kidney and its proximal tubules, pancreas, brain, placenta, adipose tissue, bone marrow, and retina.

THTR1 transporter is located on the basolateral membranes of the intestines, and is also highly expressed in skeletal muscle and brown adipose tissue.

THTR2 is found on the apical surface of the intestines, and also in adipose tissue, breast and placenta.

THTR1 and THTR2 are up-regulated in thiamine deficiency. THTR1/2 deficiencies can be long term or short term, and are likely due to -

1. **Inherited metabolic disorders** – examples include -
   - THTR1 deficiency which manifests as Thiamine-responsive megaloblastic anaemia (TRMA) and includes megaloblastic anaemia, sensorineural deafness, and non-type 1 diabetes), other signs such as congenital heart diseases, optic atrophy, retinal dysfunction, and cerebrovascular accidents;
   - THTR2 deficiency which manifests as Biotin-thiamine responsive encephalopathy, and Leigh Syndrome, and includes episodic encephalopathy, gait ataxia, seizures, and bulbar dysfunction (difficulty in chewing, weakness of the facial muscles, dysarthria, palatal weakness and regurgitation of fluids, drooling, dysphagia, and dysphonia);
2. **Polymorphisms (variants)** – examples include –
   a. two single-nucleotide THTR2 polymorphisms are associated with absent/minimal diabetic retinopathy and nephropathy despite long-term type 1 diabetes;
   b. potential variation in the 7 amino acid residues that are responsible for pyridoxine transport;

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3. **Environmental** – likely to manifest at any age and is dependent upon the environmental insult; thiamine and pyridoxine supplementation are likely to confer benefit in these disorders. Identified causes include -
    - ethanol impairs intestinal absorption of thiamine by inhibiting the gene expression of thiamine transporter THTR1 but not thiamine transporter THTR2 in the small intestine, and inhibits the gene expression of both THTR1 and THTR2 in the large intestine, therefore even if thiamine is present in the intestinal tract, it is not absorbed in the presence of ethanol, consequently only intravenous thiamine will be an effective intervention;
    - Chronic Kidney Disease is associated with a significant downregulation of THTR1 and THTR2 in the small intestine, heart, liver and brain;
    - pro-inflammatory cytokines such as IL-1β significantly inhibit THTR1 expression and the degree of inhibition is a function of duration of exposure; the inhibition is reversible upon removal of IL-1β;
    - neuroinflammation interferes with transcriptional mechanisms that result in dysfunctional thiamine transporters;
    - the triggers that cause thiamine to inhibit pyridoxine uptake and that cause pyridoxine to inhibit thiamine uptake are currently unclear;
    - prescription medicines that inhibit ie example of short term transporter deficiency, include -
        - THTR1 includes - Trimethoprim, Amprolium,
        - THTR2 includes (those predicted to be clinically relevant) - Amitriptyline, Amoxapine, Didanosine, Fedratinib, Hydroxychloroquine, Metformin, Penicillamine, Posaconazole, Quinidine, Quinapril, Sertraline, Telmisartan, Trimethoprim, Verapamil.

What are the consequences of THTR1/2 deficiencies?

- Thiamine is really important in the metabolism of energy, and if there is insufficient thiamine then the energy that is not metabolized is stored as fat;
- Pyridoxine -
    - enhances magnesium concentrations which is essential for thiamine activation,
    - is important in the activation of niacin and the production of NAD+; inadequate NAD+ changes energy metabolism from oxidative phosphorylation to aerobic glycolysis.

There is speculation that genetic disorders linked to THTRs may also involve defects in the pyridoxine transport function in addition to, or rather than, defects in thiamine transport, with the outcome being pyridoxine deficiency. Therefore, it may

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be worthwhile considering pyridoxine intervention if thiamine deficiency is considered to be due to transporter-related metabolic disorders or transporter polymorphisms.

What actions will you initiate when you see someone whose prescribed medications include THTR inhibitors, will you –

- clarify adequacy of dietary intake of thiamine and pyridoxine, request blood tests for thiamine and pyridoxine status, and then compare findings?
- If there is disagreement between oral intake and blood test results, will you question inhibition of the transporters?
- trial an intervention program in those with a known negative environmental impact and monitor for benefit?
- recommend nutrient interventions be administered at different times from the prescribed medicines?
- document the expressed signs and symptoms that support your request, the intervention(s) trialled, and submit as a Case Study at relevant conferences?

Conclusions

THTR downregulation has profound consequences for those with metabolic disorders and polymorphisms, and for which direct nutrient interventions may or may not confer benefit, however, in those with environmentally-induced downregulation of their THTRs, those profound consequences are reversible with either removal of the environmental insult and/or direct nutrient intervention.

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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:

Other: PPM, myasthenia gravis, hypercholesterolaemia

Biochemistry with Pharmaconutritional Consequences

Na:	137	mmol/l	Hb:	121	g/L	Albumin:	42	g/L	BSL:		mmol/l
K:	3.2	mmol/l	Lymph:	2.1		Total Protein:	66	g/L	HbA1C:		
Urea:	7.9	mmol/l	MCV:	96	mmol/l	B12:	232	pmol/L	INR:		
Creatinine:	0.086	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	1.42	mIU/L

Other: eGFR 52, vit D 71, Fe 15, TRF 2.6, satn 23%, ferritin 49, Ca 2.23, Ca corr 2.19, phos 1.2, Mg 0.83

Medications That May Adversely Affect Nutritional Status

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Drug	Vits + Mins	bpp	>90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
Atorvastatin		☑		NV	CD	↑	↓	☑				☐	☐	☐
Citalopram	Na	☐		NV	CD	↑	↕	☑		↑		☑	☑	☑
Esomeprazole	(40 mg/day) B1, B12, Ca, Fe,	☑		NV	CD	↑		☑				☑	☐	☐
FERRO-F	Ca, Mg, Zn	☐						☐				☐	☐	☐
Indapamide	Ca	☑		NV	CD		↓	☐				☑	☐	☑
MOVICOL		☐		N	D			☐				☐	☐	☐
OSTELIN	(2/day)	☐						☐				☐	☐	☐
PANADOL OSTEO		☐		NV	CD			☐				☐	☐	☐
PLAVIX		☑		N	CD	↓		☑				☐	☐	☐
Prednisolone	Ca, Cr, D, Iodine	☑		NV	CD	↕	↑	☐				☐	☐	☑
Pyridostigmine		☐		NV	D			☐				☐	☐	☐
TARGIN		☐		NV	CD		↕	☑				☑	☑	☐

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		OCT6		OCTN1		OCTN2		MATE1/2	
Nutrients - Sub	B1, choline, carnitine		B1, choline, creatinine		B1		carnitine		carnitine		carnitine		B1, creatinine	
Nutrients - Inh														
Location	intestines, liver		kidney		intestines, liver, kidney		testis, endometria		Intestines, kidney		Intestines, liver, kidney		kidney	
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Citalopram		Y		Y	S									
Esomeprazole		Y												
Clopidogrel		Y		Y										
Prednisolone				Y										
Targin				Y										
Sub – substrate, Inh – inhibitor, B1 - thiamine														

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

Data summary

Biochemistry

Recent relevant biochemistry indicates -

- low chol 2.5 - atorvastatin ceased 3 months ago;
- low vit D - commenced vitamin D intervention 3 months ago. Advisable to check

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vitamin D levels and if still low then review current vitamin D management strategy.

Glycaemia

Currently prescribed 5 medications that alter glycaemia, being aspirin, Epilim, metoprolol, paracetamol, perindopril.

Pharmaconutrition

Currently prescribed 6 medications that include nausea as a side effect.

Currently prescribed 5 medications that include anaemia, diarrhoea as a side effect.

Currently prescribed 4 medications that include vomiting as a side effect.

Currently prescribed 3 medications that include constipation, dry mouth, sweating as a side effect.

Currently prescribed 2 medications that include hyponatraemia, tremor, altered appetite as a side effect.

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.

Epilim decreases biotin and carnitine absorption, decreases availability of folic acid and vitamin D, and may decrease pantothenic acid availability.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

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

Concurrent ingestion of paracetamol and iron resulted 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.

Perindopril impairs zinc status.

Prescribed 2 medications that negatively impact riboflavin status, being metropolol and perindopril. Riboflavin is the rate-limiter in one-carbon metabolism and therefore has an important role in metabolic pathways. Advisable to clarify riboflavin status however if direct testing is unavailable then check pyridoxine and/or niacin status as both these require adequate riboflavin status so they can be activated ie functional.

Prescribed 2 medications that negatively impact zinc status, being sodium valproate and perindopril. Zinc is important in a range of body functions, including sense of taste, release of the hunger hormone Neuropeptide Y, hearing, bone development,

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protects thyroid function, 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). Advisable to monitor zinc status on a regular basis ie at least annually and if low then short term (90-120 days) intervention recommended.

Bowel management

Regular aperient prescribed.

Oral PRN aperient prescribed; administered 1 x Jun, 1 x Apr.

Nurse Initiated anal intervention administered 1 x Apr.

Staff comments

Staff advise Mr AGV eats well.

Observations

Mr AGV is a slender, pale Turkish man who had just finished eating his midday meal when I went to speak to him - he had eaten everything.

Mr AGV has remained weight stable for the last year.

Pharmaconutrition assessment

Staff expressed concern about the delayed wound-healing on Mr AGV's (L) toe. Nutritional factors that contribute to wound healing include -

- adequate vitamin D status - evidence indicates low vitamin D status is associated with delayed wound healing. Currently prescribed both a vitamin D intervention and a medicine that decreases vitamin D availability, being Epilim. Advisable to clarify current vitamin D status and if still very low then recommend reviewing current intervention with a view to increasing current dose.

- adequate vitamin and mineral intake – current combination of prescribed medications negatively impact iron, zinc, sodium, vitamin C, B12, folic acid, thiamine, biotin, carnitine, and likely pantothenic acid therefore advisable to consider either monitoring all these nutrients on a regular basis (at least annually) or commence a prophylactic intervention that is administered at a different time from the other prescribed medications (some authors are now advocating this strategy as their preferred option).

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

- loss of weight – most of the prescribed medications include side effects that negatively impact food intake either directly or indirectly;

- vitamin D – associated with muscle weakness and consequently falls; currently prescribed Epilim therefore advisable to clarify vitamin D status;

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

- low iron – currently prescribed aspirin 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 Epilim and perindopril therefore advisable to monitor status;

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

What else would you include?

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