MedNut Mail

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

Biotin and pharmaconutrition

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Commentary

Biotin is a B vitamin that helps the body break down fats, carbohydrates, and proteins and is important in cell growth, the metabolism of fats and amino acids, and energy production; roles include –

- cofactor for a small group of enzymes catalyzing carboxylation, decarboxylation, and transcarboxylation reactions in fatty acid, glucose and amino acid metabolism and which include -
  1. **acetyl-CoA carboxylase 1** - converts acetyl-CoA to malonyl-CoA during fatty acid biosynthesis;
  2. **acetyl-CoA carboxylase 2** - converts acetyl-CoA to malonyl-CoA during fatty acid biosynthesis;
  3. **methylcrotonyl-CoA carboxylase** - involved in leucine degradation;
  4. **propionyl-CoA carboxylase** - involved in gluconeogenesis starting from lactate, glycerol, or amino acids; and
  5. **pyruvate carboxylase** - forms oxaloacetate from pyruvate for citrate formation during the anaplerotic reaction.
- regulating cellular oxidative stress;
- regulating gene expression [impacts the expression of over 2,000 human genes];
- regulating cell signalling pathways;
- regulating mitochondrial function;
- maintaining a normally functioning immune system – important in the activity, generation, maturation, and/or responsiveness of immune cells;
- maintaining normal intestinal integrity and homeostasis;
- influencing the colonization/invasiveness of certain entero-pathogenic bacteria;
- mediating the effect of probiotic bacteria on gut microbial community;
- haemoglobin formation;
- glycaemic control.

Sodium Multivitamin Transporter (SMVT) transports biotin from

- small intestine - dietary sources
- large intestine - the microbiota

Human biotin deficiency is rare because the microbiota can produce biotin in excess of the body's daily requirements. Biotin deficiency and suboptimal levels occur due to factors such as -

- long-term prescription of some medications such as isotretinoin, antibiotics, or antiepileptics,
- alcoholism,
- Inflammatory Bowel Disease,
- exposure to avidin – an egg protein,
- mutations in the *SMVT* gene and other inborn errors of biotin metabolism,

- deficiency in the carboxylase synthetase enzyme that covalently links biotin onto biotin-dependent carboxylases or biocytinase that facilitates biotin reutilization,
- the inhibitory effect of the bacterial endotoxin Lipopolysaccharide on colonic biotin via a decrease in cell surface expression of the hSMVT protein,
- malnutrition,
- rapid weight loss,
- long-term parenteral feeding,
- achlorhydria – including partial gastrectomy,
- possibly smoking – by increasing biotin catabolism,
- possibly pregnancy complications in humans however this is quite contentious.

Biotin deficiency causes

- increases in the levels of proinflammatory cytokines such as tumour necrosis factor-α, interleukin-1β, and interferon-γ, immune dysfunction and cutaneous and neurological features,
- a number of neurological disorders, including ataxia, developmental delay, hypotonia, seizure, and sensory and motor deficits, depression, lethargy, hallucination, and numbness and tingling of the extremities,
- seborrheic-like dermatitis - scaly, red rash around the eyes, nose, and mouth and perineum,
- alopecia,
- conjunctivitis,
- impaired immune system - including increased susceptibility to bacterial and fungal infections,
- ketolactic acidosis and acidurua,
- secondary carnitine deficiency due to carnitine loss as urinary acylcarnitines (animal studies).

Measurement of circulating biotin in serum and plasma is not a reliable measure of status because depressed serum biotin is not consistently observed in biotin deficiency.

Biotin is transported by -

- sodium-dependent multivitamin transporter (SMVT) - a low-affinity transporter that also transports pantothenic acid, lipoic acid and iodide,
- biotin transporter - a high-affinity transporter and only transports biotin,
- monocarboxylate transporter 1 - facilitates the acquisition of biotin into Peripheral Blood Mononuclear Cells (PBMC).

Drugs that inhibit the uptake of biotin by SMVT

Strong inhibitory activity*		Weak inhibitory activity		No inhibitory activity	
≥ 70%	%	31% - 69%	%	≤ 30%	%
indomethacin	88	Meloxicam	62	Aspirin	-4
ketoprofen	83	Pravastatin	60	Methotrexate	-5
diclofenac	83	Salicylic acid	45	Enoxacin	-7
ibuprofen	80	Alacepril	44	Lomefloxacin	-9
phenylbutazone	78	Piroxicam	39	Lomefloxacin	-13
flurbiprofen	77.5	enalapril	33	6-mercaptopurine	-16
		Cefmetazole	22		
		Captopril	20		
		Norfloxacin	7		

*- clinically meaningful

Consequences of dysfunctional SMVT include phenotypic heterogeneity such as failure to thrive, developmental delay or early normal development followed by developmental regression, seizures, diarrhea or vomiting, immunodeficiency, pleomorphic motor neuropathies that have both axonal and demyelinating features and/or osteopenia.

Both directly and via its various metabolites, chronic alcohol exposure has been found to cause significant inhibition in both SMVT biotin uptake of the microbiota-generated biotin, and the degree of expression of SMVT.

Evidence regarding the interactions between the drugs carbamazepine, primidone and phenytoin and the nutrients biotin and pantothenate concluded they (prescribed medications) specifically and competitively inhibit biotin absorption via intestinal brush border membranes (Said et al, 1989), and that there is competitive inhibition of absorption between carbamazepine, biotin and pantothenic acid (Said, 1999). Sadly, there do not seem to be any further studies investigating this important area – where are our nutrition scientists?

Biotinylated prodrugs and polymeric nanoparticles that utilize the SMVT and biotin transporters are being developed because there is enhanced

permeability of drugs. Further the evidence indicates biotin-decorated polymeric nanoparticles enhance the uptake of poorly soluble drugs such as doxorubicin, SN-38, and 15,16-dihydrotanshinone.

Some concerns come to mind about the use of biotinylating drugs and prodrugs to enhance permeability of drugs – such as -

- what is the impact of the presence of excessive levels of biotin in areas unaccustomed to a sustained oversupply?
- if SMVT is the preferred transporter of choice then what strategies will be developed to ensure ongoing adequate availability of pantothenate, lipoate and iodide to negatively impacted cells?
- who will develop guidelines to guide clinical decision-making with regard to monitoring status and timing of interventions?

Biotin supplementation may interfere with some analytical assays and result in incorrect results therefore there is a recommendation for all healthcare providers to include biotin intake in their nutritional history, especially if biotin-containing supplements are consumed.

Some research has found that people with diabetes are more likely to develop epilepsy, however the reverse does not seem to have been investigated. If a person with epilepsy has brittle diabetes control, then perhaps a low biotin dose (to a maximum of 10 x recommended dose ie ~ 300 mcg biotin/day) may confer benefit without causing further harm – we need the evidence.

There is very limited evidence regarding the negative impact of prescribed medications on biotin status with only a limited number of identified medications – being carbamazepine, phenobarbital, phenytoin, primidone, sodium valproate, isotretinoin, antibiotics, and likely diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, phenylbutazone. This seems to indicate drug-biotin interactions have neither been fully investigated and are not being investigated on an ongoing basis even although biotin is important in so many metabolic processes. Consequently it may be worthwhile becoming familiar with biotin deficiency symptoms and, from a first principles perspective, start considering whether there may be a biotin deficiency and whether to address it.

What interventions will you initiate when you see someone whose prescribed medications include any of those listed above – will you -

- request biotin status be clarified?
- ensure carnitine, pantothenate and iodide levels are within acceptable ranges?
- recommend a biotin intervention and that it be administered at a

different time from the anti-epileptic drugs?
- recommend regular monitoring of glycaemic status and thyroid function?

Conclusions

Given the extent of biotin function are we already seeing biotin deficiency without recognizing it?

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: vit D def

Other: (L) THR, cholecystitis due to biliary colic

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
Cholecalciferol	(1/day)	☐					☐				☐	☐	☐
COLOXYL WITH S		☐		D			☐				☐	☐	☐
Domperidone		☑	N	CD		↕	☐	↓			☑	☐	☐
KINSON	Fe	☐	NV	CD	↕	↓	☑				☑	☑	☐
Lactulose		☐	NV	D		↓	☐				☐	☐	☑
MADOPAR	Fe	☐	NV	CD	↑	↓	☑				☐	☑	☑
Mirtazapine		☐	N	D	↑	↑	☐				☑	☐	☐
Paracetamol		☐	NV	CD			☐				☐	☐	☐
SOMAC	(40 mg/day) B1, B12, Ca, Fe,	☑	NV	CD		↓	☑				☑	☐	☐

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 two of the prescribed drugs and hypoproteinaemia may alter their effects.

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

Both kinson and madopar complex with iron to decrease drug availability.

Regular monitoring B12 and homocysteine recommended whilst kinson prescribed.

Mirtazepine associated with delayed-onset hyponatraemia therefore regular monitoring sodium levels recommended.

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

Concurrent ingestion of paracetamol and iron resulted 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.

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

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 and intervention recommended.

Commencement of the drug 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.

Mr ABD is a small, slender, pale man who was sitting in the Day Room when we went to speak to him - when asked if he likes ice cream his whole face lit up and he had a huge smile.

Since Mr ABD is pale, advisable to check iron levels and if low then short term (90-120 days) intervention

recommended. It is unlikely oral iron interventions will be effective whilst paracetamol and a proton pump inhibitor are prescribed therefore advisable to consider a non-oral intervention.

Loss of weight is associated with depletion of zinc status and zinc is important in a range of body functions, including sense of taste and release of the hunger hormone Neuropeptide Y. Currently prescribed kinson and somac – both of which are associated with depletion of zinc status. Advisable to check zinc levels and if inadequate then short term (90-120 days) intervention and recheck status prior to cessation of the intervention.

Mr ABD has been prescribed a proton pump inhibitor since September 2009, and likely before then. There is increasing evidence that longterm proton pump inhibitor prescription is associated with

- altered gut microbiome;
- increased risk of food sensitivities at a level of peanut allergy;
- increased risk of coeliac disease;
- increased risk of scurvy due to impaired absorption of vitamin C;
- generalised malnutrition due to impaired absorption of a range of nutrients such as B12, 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.

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).

Mr ABD's diagnoses include chronic pain - pharmaconutritional 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 - the optimal intervention is 500 mg vitamin C/day (if more than 500 mg vitamin C administered at a time then the excess above 500 mg is not absorbed as the vitamin C transporters are overloaded). 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.

- **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 somac therefore advisable to check B12 status. There is disagreement between pathology ranges and research findings with regard to appropriate B12 levels - recent neuro-imaging research shows a direct causal link between B12 status and damage to the brain, and recommend B12 interventions once levels are less than 300 pmol/L
- **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.

Mr ABD's diagnoses include depression which is commonly associated with poor appetite and he has been losing weight. Mr ABD is prescribed 6 medications that also include decreased appetite as a side effect and 3 medications that also alter the sense of taste.

Both inhibit various thiamine transporters. Advisable to consider a thiamine intervention and for it to be administered either one hour before or 2 hours after administration times of mirtazapine and somac.

What else would you include?

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