MedNut Mail

The How, What, Which, Where, When and Why of pharmaconutrition

Albumin and vitamins

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Editorial

Albumin and vitamins are essential for body function as albumin is either a primary or secondary carrier for most vitamins. Many factors can alter albumin's structural shape and therefore its ability to carry nutrients, pharmaceuticals and other compounds.

Vitamins are essential for the metabolism of proteins, fats and carbohydrates, and to support energy production, growth and cell maintenance.

Human and bovine albumin commonality

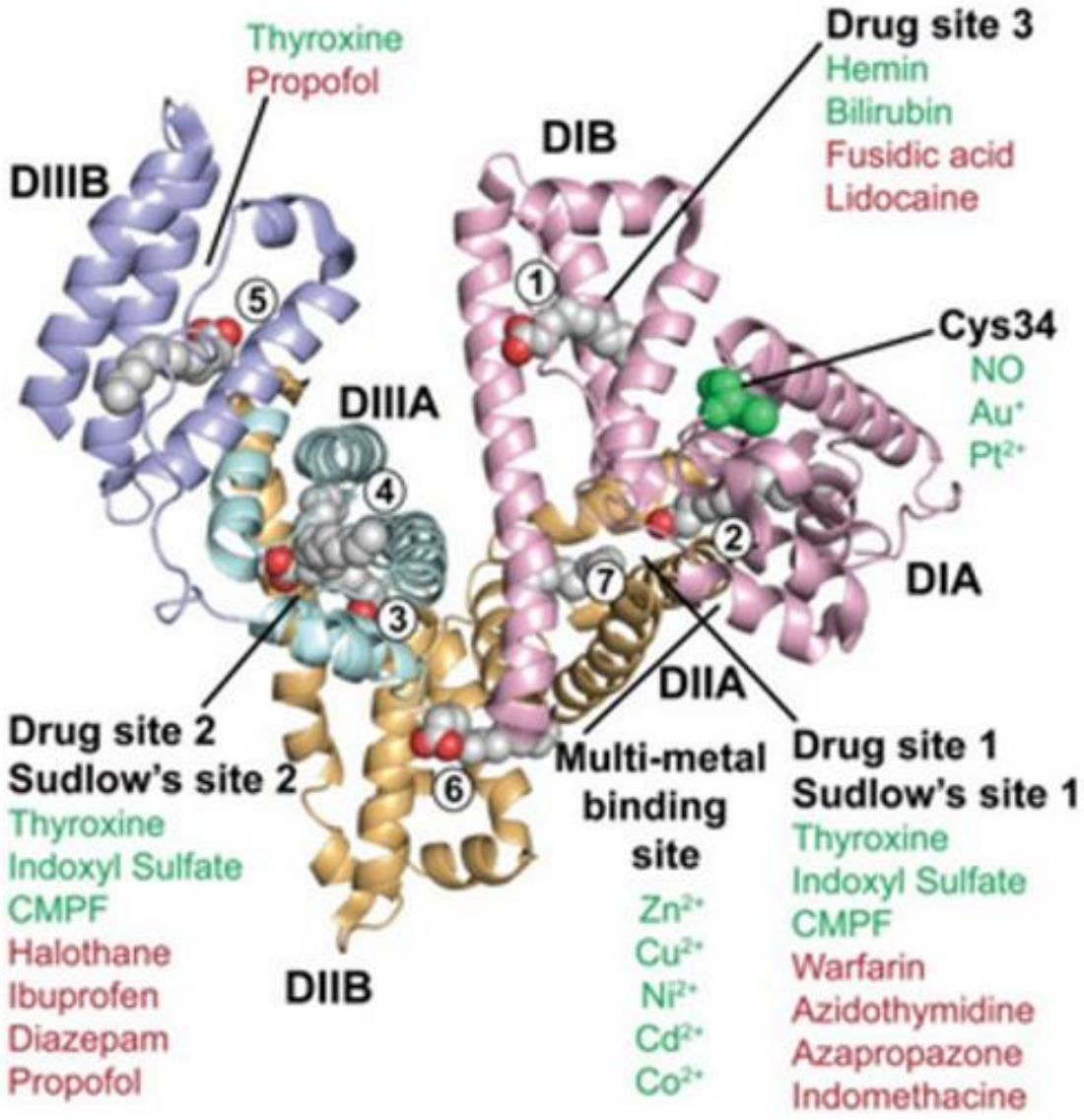
Human (HSA) and bovine (BSA) albumins have 76% commonality and similarity in their 3D structures. A significant differentiator is the number of tryptophan binding sites –

- Human - one tryptophan site - Trp-214 in subdomain IIA;

- Bovine - two tryptophan sites - Trp-134 (subdomain IIA), Trp-212 (subdomain IIIA).

Co-operative drug-nutrient interactions

Subdomain IIA is the preferred binding site for both folate and methothrexate, however folate only binds to IIA whilst methothrexate binds to IIA and IIIA. When both drugs are present, folate binds to IIA and methotrexate binds to IIIA -this is deemed a cooperative interaction to minimize alteration to albumin's structure. https://doi.org/10.1021/acsomega.7b01437



The crystal structure of human albumin

From - Unraveling the Interaction between FcRn and Albumin: Opportunities for Design of Albumin-Based Therapeutics

https://doi.org/10.3389/fimmu.2014.00682

Distribution of vitamins and their binding sites

Table of vitamins and their known binding sites on albumin	
Vitamin	**Binding site**
Thiamine	Subdomain IIA – Trp-214
Riboflavin	Subdomain IIA
Niacin	Sudlow site 1 Subdomain IIA
Pantothenate	No apparent evidence of carriage by albumin.
pyridoxine	Subdomain IIA - Lys-190
biotin	No apparent evidence of carriage by albumin.
Folate	Sudlow site I Subdomain IIA - on or near Tyr-214
Cobalamin	Subdomain IIA
Vitamin C	Binding site I (Sudlow site 1) Subdomain IIA
Vitamin A/retinol	Subdomain IIA – Trp-214 Subdomain IIIA – Asp-451
Vitamin D	Metabolites - calcitriol and cholecalciferol Domains 2 + 3, preferred option domain 2
Vitamin E	α-tocopherol – Fatty Acids 3+4 sites, Subdomain IIIA Tocopherol - Site II Subdomain IIIA
Vitamin K	Unable to verify domains, subdomains or binding sites

Note - Vitamin E is a generic name that refers to two tocochromanols, tocopherol (Toc) and tocotrienol (T3). Albumin mediates the difference in the cellular uptake of Toc and T3.

Bilirubin binding to albumin at subdomain IB inhibits lipid peroxidation, and protects α-tocopherol from peroxyl radicals

Table of vitamin binding sites on albumin, by domain and subdomain

Table of domains and subdomains and their vitamin distribution	
Subdomain	**Vitamins**
IA	
IB	
IIA	B1, B2, B3, B6, B9, B12, Vit C, Vit A
IIB	
IIIA	Vit A, Vit E
IIIB	
Domain	
II	Vitamin D metabolites (calcitriol, cholecalciferol)
III	Vitamin D metabolites (calcitriol, cholecalciferol)

Clinical concerns

The evidence in relation to albumin-based drug-nutrient interactions is remarkably limited. A range of factors, including nutrients and pharmaceuticals, can alter albumin structure and therefore it's carrying capacity. Our knowledge of albumin-based vitamin binding sites and vitamin-induced changes to albumin structure, is in dire need of further clarification.

There may also be nutrient-nutrient competition for some of albumin's binding sites, and their access process also requires clarification. Is nutrient access based on first-come, or is there a pecking order and if so what is it?

How can we apply the likely albumin-based drug-nutrient interactions evidence in our clinical reports? At this stage I suggest increased monitoring of nutrients that share the same subdomain as each prescribed medicine. The limitations with this suggestion are that it does not take into account -

- drug-induced, or possibly nutrient-induced, impacts on the domain(s) and/or subdomain(s) it is, and is not, occupying;

- some nutrients and drugs being able to share the same subdomain as they access different binding sites.

Albumin-based drug-nutrient interactions also further emphasize the importance of a comprehensive Diet History that includes nutrient supplements. If there is contradiction between oral intake and blood test findings, then external causes of the anomaly should be considered. The mechanisms of action of external sources likely include inhibiting transporters, and/or altering access to albumin.

Clinical Questions

What actions will you initiate as you a review a person whose prescribed medications profile includes one or more drugs that utilize albumin as a carrier, will you -

- clarify and monitor adequacy of intake of nutrients carried by albumin that are potentially affected by their prescribed medicines?

Conclusions

Albumin and vitamins are both directly and indirectly impacted by a broad range of prescribed medicines as they can alter their effectiveness and availability.

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: GORD, SMOKER, ETOH abuse, smoker, PA (L) heel

Other: hypothyroid, Ca bowel -> colostomy, ABI

Biochemistry with PharmacoNutrition Consequences

Na:	143	mmol/l	Hb:	129	g/L	Albumin:	32	g/L	BSL:		mmol/l
K:	4.6	mmol/l	Lymph:	0.8		Total Protein:	60	g/L	HbA1C:	5.9	
Urea:	4.9	mmol/l	MCV:	99	mmol/l	B12:	152	pmol/L	INR:		
Creatinine:	0.049	mmol/l	Zn:	11.1	umol/l	Folate:	10.1	nmol/L	TSH:	0.57	mIU/L

Other: Ca corr 2.44, phos 1.05, Mg 0.72, chol 3.3, Tg 1.4, HDL 0.83, LDL 1.8, LDL:HDL 2.2, chol:HDL 4.0, Fe 7, TRF 2.3, satn

Prescribed medications side effects - biochemistry

Drug	Y-yes		↑↓									
	BPP	ana	Alb	BSLs	Na	K	Ca	Mg	Zn	Cr	pho	UA
Caltrate							↑					
Colecalciferol							↑					
Coloxyl + senna						↓						
esomeprazole	Y				↓	↓		↓	↓			
fludrocortisone	Y			↑		↓						
Jardiance				↓								
Lexapro		Y		↑	↓							
mirtazepine		Y			↓							
paracetamol		Y	↓	↑		↓					↓	
Reandron							↑					
rosuvastatin	Y											
Thyroxine	Y											
Trajentamet	Y			↓								↑
BPP – binding to plasma proteins ≥ 90%, ana – anaemia, alb – albumin, glyc – glycaemia, Na – sodium, K – potassium, Ca – calcium, Mg – magnesium, Zn – zinc, Cr – chromium, pho – phosphates, UA – uric acid												

Prescribed medications side effects profile

Drug	N/V	C/D	Wt	App	AT	DM	Thir	Dys	SW	Tre			
Caltrate		C											
Colecalciferol													
Coloxyl + senna	N	D											
esomeprazole	N/V	C/D	V		Y	Y			Y				
fludrocortisone				↑					Y				
Jardiance													
Lexapro	N/V	C/D	↑↓	↓	Y	Y	Y		Y	Y			
mirtazepine	N/V	C/D	↑↓	↑	Y	Y	Y		Y	Y			
paracetamol	N/V	C/D											
Reandron	N	D											
rosuvastatin	N	C			Y								
Thyroxine	V	D	↓						Y	Y			
Trajentamet	N/V	D	↓	↓									
N – nausea, V – vomiting, C – constipation, D – diarrhoea, Wt – weight, App – appetite, AT – altered taste, DM – dry mouth, Thir – thirst, Dys – dysphagia, SW – sweating, Tre - tremor													

Prescribed medications affected nutrients profile

Drug	Nutrients affected (Y = yes)													
	B12	B9	B1	B2	B6	VC	VD	VK	K	Mg	Zn	Ca	Fe	Na
Caltrate													Y	
Colecalciferol														
Coloxyl + senna														
esomeprazole	Y		Y							Y	Y	Y	Y	
fludrocortisone									Y			Y		Y
Jardiance														
Lexapro														
mirtazepine														
paracetamol													Y	
Reandron														
rosuvastatin														
Thyroxine										Y		Y	Y	
Trajentamet	Y	Y	Y		Y					Y	Y			
fludrocortisone - Cr														
B12 – cobalamin, B9 – folate, B1 – thiamine, B6 -pyridoxine, VC – vitamin c, VD – vitamin D, VK – vitamin K, K – potassium, Mg – magnesium, Zn – zinc, Ca – calcium, Na – sodium														

Transporter-mediated interactions and nutrients matrices

Transporter	OCT1		OCT2		OCT3		TEE (OCTN1)		OAT1		OATP1A2		OATP2B1		GLUT4	
Nutrients - Substrates	B1, choline		B1, choline		B1, choline, carnitine		Carnitine, choline		B9, B5, pyridoxic acid (B6), B7		Retinoids		Vit D		vit C	
Nutrients - Inh							Vit D, choline						Vit D def			
DRUG	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh
Caltrate																
Colecalciferol																
Coloxyl + senna																
esomeprazole		Y														
fludrocortisone																
Jardiance																
Lexapro		Y		Y												Y
mirtazepine				Y												
paracetamol										Y						
Reandron																
rosuvastatin											Y		Y			
Thyroxine																
Trajentamet	Y	Y	Y		Y		Y									
Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide																

Transporter	THTR1		THTR2		MATE1		MATE2		BCRP		P-gp		OAT3	
Nutrients - Sub	B1, B6		B1, B6		B1, B2, carnitine		B1, B2		B2, B9, B5, vit K3		B12, vit D, B6, B3, B5		B5, B6, B9, carnitine, B2	
Nutrients - Inh			B1						vit D2		vit A			
Biomarker									B2					
DRUG														
Caltrate														
Colecalciferol														
Coloxyl + senna														
esomeprazole														
fludrocortisone														
Jardiance									Y		Y		Y	
Lexapro														
mirtazepine														
paracetamol														
Reandron					Y									
rosuvastatin														
Thyroxine														
Trajentamet			Y	Y	Y		Y							

Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide, TYR - tryptophan

Comments – medication and nutrition effects only

Data summary

Biochemistry

Relatively recent available biochemistry indicates

- low Hb - associated with increased risk of falls, and poor appetite. Currently prescribed 4 drugs that alter iron availability and therefore haemoglobin status. Advisable to monitor iron status on an ongoing basis;

- low albumin - indicates increased risk of pressure area formation. Currently prescribed paracetamol which decreases albumin status;

- elevated MCV + low B12 - currently prescribed esomeprazole and trajentamet therefore B12 intervention recommended. Neuro-imaging research found B12 interventions are effective once levels are less than 300 pmol/L;

- marginal zinc - currently prescribed esomeprazole and trajentamet therefore advisable to monitor status on a regular basis;

- low magnesium – currently prescribed esomeprazole, thyroxine and trajentamet, plus magnesium intervention that provides 74.4 mg elemental magnesium/day. Advisable to recheck magnesium levels and if still low then review current magnesium intervention and consider an intervention that provides about 300 mg elemental magnesium per day;

- low cholesterol – currently prescribed rosuvastatin. There is variability between pathology laboratories with regard to appropriate lower acceptable cholesterol level. Some pathology ranges have set the lower acceptable limit at 3.5 units, others 3.0 units, and some do not set a lower limit. Cholesterol is important in brain structure and function amongst many other roles. Advisable to review necessity for continued prescription of rosuvastatin.

Glycaemia

BSLs

- daily range - 6.7-8.2; recommended range 4-10;

- now checked three-monthly by HbA1c;

- no reportable limits;

- old HbA1c indicates good overall glycaemic control; advisable to clarify current status

Diabetes drugs

- Jardiane/empagliflozin (08:00);

- trajentamet (08:00, 17:00) has a duration of 24 hours.

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous morning's trajentamet; some coverage from previous evening's trajentamet;

- before evening meal BSLs - minimal, if any, coverage from previous evening's trajentamet; covered by current morning's trajentamet and jardiance/empagliflozin.

Currently prescribed 3 medicines that include hyperglycaemia as a side effect – fludrocortisone, Lexapro, and paracetamol.

Currently prescribed 3 medicines associated with increased risk of diabetes, being mirtazepine, levothyroxine and rosuvastatin.

Pharmaconutrition

Calcium carbonate may interfere with the absorption of iron.

Calcium carbonate requires gastric acidity for absorption however esomeprazole prescribed. Advisable to consider calcium citrate which does not require gastric acidity for absorption.

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

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

Coffee inhibits vitamin D uptake by inhibiting the osteoblasts (bone builders) vitamin D receptors, consequently decreasing calcium and zinc absorption. Advisable to monitor vitamin D and zinc levels.

Vitamin D enhances the anti-inflammatory effects of glucocorticoids such as fludrocortisone. Glucocorticoid dose and duration associated with lower vitamin D levels.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

Mirtazepine and paracetamol are CYP1A2 substrates (can be carried by the transporter). CYP1A2 substrates include caffeine, retinol, melatonin, phosphatidylcholine, inhibitors include grapefruit juice and inducers include coffee. Mirtazepine and paracetamol metabolism inhibited by caffeine therefore they will remain active in the body for longer.

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 absorption of paracetamol. Consequently, the authors advise different administration times from each other for the drug and iron.

Thyroxine-coffee interaction – coffee sequesters thyroxine resulting in a 55% reduction in drug absorption.

Thyroxine administration with grapefruit or orange juice may reduce drug

effectiveness.

Metformin component of trajentamet decrease impact on B12 status is not transitory, but is progressive ie the decrease persists and grows.

Magnesium is administered at the same time as thyroxine. As there is a potential drug-nutrient interaction (complexing of thyroxine and magnesium resulting in reduced availability of each) advisable to review current administration times and administer at separate times from each other, with a gap of at least 2 hours.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sun to vitamin D - vitamin D intervention currently prescribed however advisable to check it's effectiveness;

- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended;

- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Membrane transporters

Some of the identified membrane transporters alter the absorption and/or organ and cellular uptake of a range of nutrients. Inhibition of membrane transporters means blood test results may be unreliable. To clarify nutrient status advisable to conduct blood tests at least one hour before administration of relevant prescribed medicines. A concurrent detailed Diet History is also essential to corroborate adequacy of intake of all affected nutrients. Further, all affected nutrients to be monitored on a regular basis ie at least annually.

Nutrients that are affected by Mr ADM's prescribed medications include -

- substrates – thiamine, riboflavin, niacin, pantothenate, pyridoxine, biotin, folate, B12, vitamin C, vitamin D, vitamin K3, retinoids, choline, carnitine;
- inhibitors – thiamine, vitamin A, vitamin D, choline.

The duration of drug inhibition of transporters currently remains unknown.

Bowel management

- regular aperient prescribed;
- oral PRN aperient prescribed;
- no Nurse Initiated interventions administered.

Staff comments

Care Staff advise poor appetite whilst Kitchen staff advise Mr ADM eats a good breakfast and that if he doesn't midday main course then he eats a larger serve of dessert.

Observations

Mr ADM is a small, pale, frail man who was sitting in an alcove watching a John Wayne western when we went to speak to him - he told us the food does not have much taste and that he would like to be able to add extra sauces such as tomato sauce to the food - does not want chilli sauce.

Mr ADM seemingly gained weight 6 months ago, and then lost weight. This data appears unreliable as several weights were recorded shortly after meals, and the last weight was not satisfactorily rechecked therefore current weight status is indeterminate.

Pharmaconutrition comments

Mr ADM's weight status is currently indeterminate, and currently prescribed thyroxine. Advisable to clarify thyroid function and ensure well-controlled as the initial intervention.

Wound healing

Nutritional interventions that support wound healing include -

- albumin within acceptable range – currently prescribed paracetamol which includes hypoalbuminaemia as a side effect;
- adequate vitamin D status - evidence indicates low vitamin D status is associated with delayed wound healing. Currently prescribed rosuvastatin and colecalciferol therefore advisable to monitor status on a regular basis;
- adequate vitamin C - important in collagen formation and the strength of the collagen. Currently prescribed esomeprazole which reduces availability of active vitamin C. It is likely wound healing will be delayed, and of poor quality whilst there is reduced availability of active vitamin C. It is also likely vitamin C interventions are

unlikely to be effective whilst a proton pump inhibitor is prescribed.

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).

Chronic pain

Mr ADM's diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include -

- vitamin D - evidence indicates increasingly brittle pain control with decreasing/low vitamin D levels. Advisable to monitor vitamin D levels on a regular basis;

- 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. Whilst not considered part of the pain management armament, Vitamin C won't cause harm and evidence suggests it may confer benefit. Currently prescribed esomeprazole 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. Currently prescribed esomeprazole and trajentamet therefore B12 intervention recommended;

- 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. Prescribed esomeprazole, thyroxine and trajentamet which decrease magnesium availability and current status is low. Magnesium is also important in the activation of thiamine, vitamin C, vitamin D, and iodide.

Falls

Mr ADM's diagnoses include falls. Nutritional factors that may be useful to ensure within acceptable ranges include –

- potassium - important in muscle function. Currently prescribed fludrocortisone therefore advisable to monitor status on a regular basis;
- calcium - important in muscle function. Currently prescribed esomeprazole, fludrocortisone and thyroxine therefore advisable to monitor status;
- vitamin D – increasing vitamin D intake increases muscle strength and decreases falls. Currently prescribed colecalciferol therefore advisable to monitor vitamin D status and ensure intervention is effective;
- B12 - is important in the righting reflex when a person stumbles. Currently prescribed esomeprazole and trajentamet therefore advisable to monitor status;
- iron – low status and currently prescribed caltrate, esomeprazole, paracetamol and thyroxine. Advisable to commence a short term intervention (preferably one that includes copper with the iron). It is highly likely that oral iron interventions will be unsuccessful and ineffective in current scenario therefore advisable to consider a non-oral iron intervention;
- zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass. Currently prescribed esomeprazole and trajentamet, and current status marginal therefore advisable to monitor status very regularly. It is highly likely that an oral intervention will be unsuccessful and ineffective in current scenario;
- magnesium - magnesium is important in vitamin D activation, de novo carnitine production, and muscle function, amongst other functions. Currently prescribed esomeprazole, thyroxine and trajentamet which significantly decrease magnesium availability and current levels are low. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to commence a short term (90-120 days) intervention and monitor its effectiveness. It is highly likely that an oral intervention will be unsuccessful and ineffective in the current scenario;
- thiamine –is important in balance and position sense. Currently prescribed esomeprazole and trajentamet therefore status is at risk both directly and indirectly (via decreased availability of magnesium). Thiamine status also at risk due to inhibition of many of its transporters.
- carnitine - carnitine is both absorbed and produced de novo, and is important in a range of muscle functions. Magnesium is important in de novo carnitine production. Currently prescribed several drugs that decrease magnesium availability and current status is low. Advisable to commence a short term (90-120 days) intervention and monitor its effectiveness. It is highly likely that an oral intervention will be unsuccessful and ineffective in the current scenario.

Insulin resistance

There are a number of nutritional interventions to improve insulin sensitivity or reduce insulin resistance including -

- 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 esomeprazole, thyroxine and trajentamet which significantly decrease magnesium availability, and current status is low. Advisable to review current management strategy;

- chromium - evidence indicates chromium both increases the number of insulin receptor cells on cell walls, and improves intracellular response to insulin. Currently prescribed fludrocortisone which impairs chromium availability therefore a short term (90-120 days) intervention of elemental chromium is likely to confer longterm benefit and is not associated with harm;

- thiamine - people with diabetes have a significantly increased urinary excretion of thiamine; thiamine is important in glycaemic control. Currently also prescribed esomeprazole and trajentamet which further decrease thiamine availability;

- biotin – evidence indicates biotin is important in a number of steps in carbohydrate metabolism. Currently prescribed several drugs that displace biotin from its absorption transporters and therefore compromises biotin availability;

- TNF-α – evidence indicates TNF- α has systemic effects that result in insulin resistance and NIDDM; low B12 status exacerbates elevated TNF- α. Currently prescribed esomeprazole and trajentamet, and currently low B12 status and no intervention. Advisable to review current B12 management strategy;

- 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). Currently prescribed esomeprazole and trajentamet therefore advisable to monitor status on a regular basis;

- potassium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways.

Currently prescribed esomeprazole therefore advisable to monitor status on a regular basis;

- calcium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways. Currently prescribed esomeprazole, fludrocortisone and thyroxine which all compromise calcium availability. Also prescribed calcium carbonate which requires gastric acidity for absorption and as esomeprazole prescribed, the intervention is not conferring benefit. Advisable to review current management strategy and consider a calcium citrate intervention that does not require gastric acidity for its absorption.

What else would you include?

Please read this as it is important …

The information in this article is provided to support Health Professionals. It is not an exhaustive protocol and Health Professionals are advised that adequate professional supervision is accessed to ensure that Duty of Care obligations with respect to safe administration of medicines is met for each consumer.

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