MedNut Mail

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

Denosumab and nutrition

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https://medicationsandnutrition.online

Commentary

Denosumab is prescribed for the treatment of bone loss in adults at high risk of bone fractures. It is a human monoclonal antibody that binds to RANKL which inhibits the RANK/RANKL pathway resulting in inhibition of osteoclast formation, function and survival. The consequent outcome is a reduction in bone resorption and therefore increase in bone mass and strength.

Tumour necrosis factor ligand superfamily includes RANKL, and seems to also be associated with the immune system, such as augmenting the ability of dendritic cells to stimulate naive T-cell proliferation, and possibly regulating both interactions between T-cells and dendritic cells, and the T-cell-dependent immune response.

Denosumab side effects include -

- hypocalcaemia, hypomagnesaemia and hypophosphataemia;
- increased risk of rebound fractures following cessation of this intervention unless there is a transition to an alternative antiresorptive intervention;
- impairment of bone growth in children with open growth plates and possible inhibited eruption of dentition;
- osteonecrosis of the jaw.

There is consistency in the recommendation for adequate calcium and vitamin D intake. Studies consistently administered 1,000 mg calcium/day and variously administered 400 IU/day (women-only trials) or 800 IU/day (men-only trials, men and women trials).

There is a recommendation that serum calcium and vitamin D levels be measured, and low levels treated, prior to commencement of denosumab intervention.

A Cancer Centre in the United States developed guidelines that include baseline and 6-monthly monitoring of magnesium and phosphate in those receiving both denosumab and cancer treatment; they did not include calcium status in their research.

There is an increasing number of case studies that identify a likely drug-drug interaction when denosumab and intravenous (IV) iron are administered within a short timeframe of each other. Proposed mechanism of action - a reduced parathyroid response to denosumab-induced hypocalcaemia

occurs after IV iron induced hypophosphataemia.
Hypophosphataemia occurs within a couple of weeks after IV iron is administered and can persist for to 6–12 weeks whilst hypocalcaemia can occur up to 6 months after denosumab administration. The authors advise the highest risk for co-administration of these drugs is within the first 2 weeks, however the risk may persist for up to 3 months, and therefore recommend a minimum gap of 3 months between administration of denosumab and IV iron.

Limited evidence indicates zinc levels steadily increase during the first 2 years of denosumab treatment, and then steadily decline.

There is contradictory evidence in relation to an interaction between denosumab and phenylalanine.

Other nutrients associated with RANKL that may or may not be associated with denosumab ie no direct evidence which is most likely due to lack of research -

- **Pantothenate** – dose dependently regulates RANKL induced osteoclastogenesis;
- **Vitamin C** – associated with inhibiting osteoclast activity and stimulating osteoblast maturation, as well as decreasing the expression of the osteoclast-specific genes including *RANK*, *RANKL*;
- **Vitamin K** – inhibits RANKL and thus reduces osteoclastogenesis;
- **Selenium** - inhibits RANKL-induced gene expression and phosphorylation of IκBα inhibitor and consequently decreases Reactive Oxygen Species production and silences the osteoclast differentiation signal;
- **CoQ10** - inhibits RANKL-induced osteoclast activation and stimulates osteoblast activity;
- **Lipids** - cholesterols are important in RANK-RANKL signal transduction during osteoclastogenesis, and both high levels of cholesterols and fats increase bone turnover; unsaturated fatty acids have been shown to inhibit osteoclastogenesis and therefore protect bone.

The possibility of denosumab interacting with various nutrients seems to be primarily researched by clinicians looking for a solution and possibly the cause of an immediate problem.

It seems likely that any prescribed medication that interferes with any of the above identified nutrients is likely to alter denosumab effectiveness, therefore it seems advisable for calcium, phosphate, magnesium and vitamin D be monitored every 6 months, and for iron, selenium, zinc,

vitamin C, vitamin K, pantothenate and CoQ10 to be monitored annually.

What actions will you initiate when you see someone whose prescribed medications include denosumab – will you recommend regular monitoring of the -

- identified nutrients that are associated with a denosumab-induced negative impact?
- broader range of nutrients associated with bone health?

Conclusions

Denosumab is a relatively recently developed prescribed intervention and is likely to be an early leader in the field of monoclonal antibodies as a treatment.

As negative impacts arise as a consequence of denosumab prescription then a broad range of nutritional possibilities as contributing factors needs to be considered – not just the most known and/or popular.

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: GORD, tremor, hyperthyroidism

Biochemistry with Pharmaconutritional Consequences

Na:	140	mmol/l	Hb:	126	g/L	Albumin:	39	g/L	BSL:		mmol/l
K:	3.8	mmol/l	Lymph:	0.7		Total Protein:	73	g/L	HbA1C:		
Urea:	6.5	mmol/l	MCV:	89	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.059	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR > 60, Ca 2.39, Ca corr 2.40, Mg 0.95, phos 1.14

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
Carbimazole	(08:00, 20:00) A, Fe, Iodine, L			NV				☑						☑
COLOXYL WITH S					D									
EFEXOR XR				NV	CD	↕	↓	☑				☑		
Mirtazapine				N	D	↑	↑					☑		
MOVICOL				N	D									
Paracetamol				NV	CD									
Propranolol		☑		NV	CD		↓							☑
Quetiapine					C	↑						☑		
SINEMET	(08:00, 12:00, 17:00) Fe			NV	CD	↕	↓	☑				☑	☑	

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

Biochemistry comments
Recent relevant biochemistry within acceptable ranges.

Glycaemic comments
Currently prescribed 3 medications that may alter glycaemia.

Bowel management comments
Regular aperient prescribed.
Oral PRN aperient prescribed.
No Nurse Initiated interventions administered.

Staff comments
Staff advise Mrs ABX had a fall and #NOF, and since return from hospital as not eaten well and is refusing and resistive with her meals.

Observations
Mrs ABX is a small, pale, frail lady with a flat demeanour and who was lying in bed when I went to speak to her - she told me she sometimes feels like vomiting.

Pharmaconutrition comments
Currently prescribed 8 medicines that alter bowel status.
Currently prescribed 7 medicines that include nausea as a side effect.
Currently prescribed 5 medicines that include vomiting as a side effect.
Currently prescribed 3 medicines that decrease appetite.

The side effects of the multiple medicines currently prescribed could be exacerbating Mrs ABX's poor appetite and could also be contributing to her sense of wanting to vomit.

Carbimazole has a function as a vitamin K antagonist therefore advisable to monitor vitamin K status.

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

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

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

Advisable for magnesium not to be administered at the same time as sinemet.

Three medications, propranolol, quetiapine, Sinemet, alter glycaemia therefore advisable to monitor status on a regular basis.

Mrs ABX's recent loss of weight increases her risk of overmedication with carbimazole therefore advisable to check the effectiveness of both the current thyroid and depression management interventions.

Mrs ABX's diagnoses include arthritis which is typically associated with

chronic pain - nutritional factors that may be useful to consider in pain management include -

- 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 carbimazole.

Summary of organs and some transporters, relevant prescribed medications, and impacted nutrients

Organ·(transporter)¤	Thiamine¤	Choline¤
Liver·(OCT1·inhibitor)¤	Quetiapine¤	Quetiapine¤
Kidneys·(OCT2·inhibitor)¤	Mirtazepine¤	Mirtazepine¤
Kidneys·(OCT2·substrate)¤	Propranolol¤	Propranolol¤

Organ uptake of 2 key nutrients is inhibited by 2 of the prescribed medicines therefore it remains in the blood.

It is likely blood test results for thiamine and choline will reveal high-normal or elevated nutrient levels; duration of inhibition is currently unknown therefore fasting results are likely to be more reliable. Except for pyridoxine (B6) we don't know how elevated blood nutrients are expressed in the body so we don't know what factors to monitor.

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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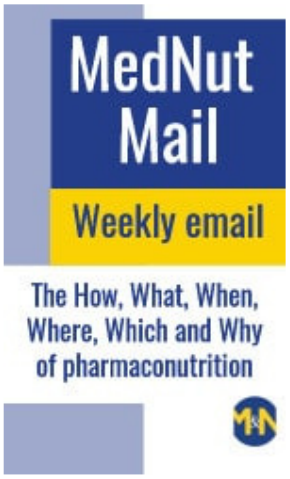

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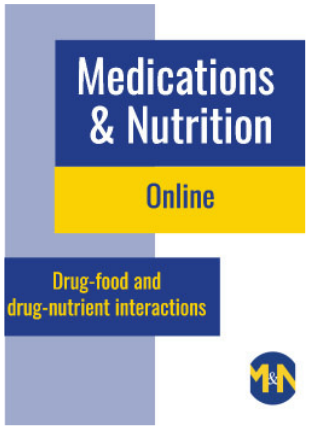

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