Endocrinology case

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15th may 2024

Case one – Mr DS

- 31y NZ European male
- No significant PMH
- Had a blood test in Aug 2023, noted raised ALP of 145 (ref: 40-110). GGT & ALT normal
- Ca/P – normal (2.36 & 1.22 respectively; ref: 2.10-2.55 for Ca; 0.75-1.50 for P)
- PTH raised 17.6 (ref: 1.7-7.3)
- P1NP also up 139 (ref: 20-85)
- Testosterone/FSHLH/Prolactin – not checked
- Vitamin D low 29 (ref: 50-100)
- Last labs July23 – normal B12, CBC, ferritin, HbA1c & renal; TSH 2.0, CRP<1
- Negative Coeliac screen

History & Examination of Mr DS

- Never had fracture
- No symptoms of hypogonadism – has a 4mo old baby girl, wife conceived naturally; DS reports no impotence or erectile dysfunction
- No bone pain, muscle weakness or hearing loss
- Non smoker, very rarely drinks alcohol
- Enjoys indoor rock climbing
- Hardly goes outside for sun exposure – accountant
- No family history of bone diseases
- No chronic glucocorticoid use
- Diet – doesn't eat much dairy products, almost vegetarian (eats fish & chicken)
- Has been taking Finasteride 1mg daily for male pattern hair loss

- Weight 79kg, height 174cm (BMI 26 kg/m2); lots of facial hair

Progress – Mr DS

- Already started on colecalciferol 1.25mg monthly since diagnosis (Aug23)
- By Nov 23, vitamin D normalised to 109; ALP ↓ to 118 (was 145); P1NP ↑went up further to 165 (was 139); PTH normalised to 6.5
- He continued to take monthly vitamin D
- On 3/1/24: ALP ↑ again to 139; PTH/Ca/P were still normal
- On 4/5/24: ALP ↔ at 139; vitamin D 105 (normal); P1NP ↓ to 128

Test / Date	4 May 24	3 Jan 24	25 Nov 23	10 Aug 23
ALP (40-110)	139 ↑/↔	139 ↑	118 ↑	145 ↑
P1NP (20-85)	128 ↑	-	165 ↑	139 ↑
25 (OH) D	105	-	109	29 ↓
PTH (1.7-7.3)	-	7.0	6.5	17.6 ↑
Adj Calcium	2.38	2.46		2.36
Phosphate	1.29	1.29		1.22

Assessment – Mr DS

- Mildly raised ALP, raised P1NP are due to vitamin D deficiency; raised PTH was secondary hyperparathyroidism due to vitamin D deficiency
- Improvement in ALP & P1NP are slow. PTH normalized as soon as vitamin D is replaced

- For DS, there is no risk factors of having osteoporosis
- Does he need a bone density scan now?

- Paget disease of the bone? Less likely in view of his young age

- What are the other causes of raised ALP?
- When will P1NP return to normal range?
- How long should he stay on colecalciferol?

Vitamin D deficiency - Evaluation

- Defining vitamin D sufficiency: to maintain 25 (OH)D between 50-100 nmol/L
- **Causes** of vitamin D deficiency: reduced sun exposure; reduced intake or absorption; increased liver catabolism; reduced endogenous synthesis either in liver or kidney, end organ resistance
- Groups at **high risk**: hospitalised, institutionalised, home bound; pigmented skin; obesity; use o protective clothing & sunscreen; osteoporosis, hyperPTH, malabsorption (IBD & Coeliac)
- **Clinical manifestation**: majority of those with 25(OH)D 35-50 nmol/L are asymptomatic. With prolonged low 25(OH)D, there'll be ↓ intestinal Ca absorption causing hypocalcaemia, then secondary hyperparathyroidism, phosphaturia, bone demineralisation, finally osteomalacia/rickets
- Ca, P and ALP are typically normal. PTH ↑ in 40-50% of patients with 25(OH)D <50-25 nmol/L
- Those with low D & secondary hyperPTH can have accelarated bone loss (**osteoporosis) & fractures**

Vitamin D supplementation

- Vitamin D deficiency <30 nmol/L
- Vitamin D insufficiency 30-50 nmol/L
- ➔ Both groups should receive D supplement

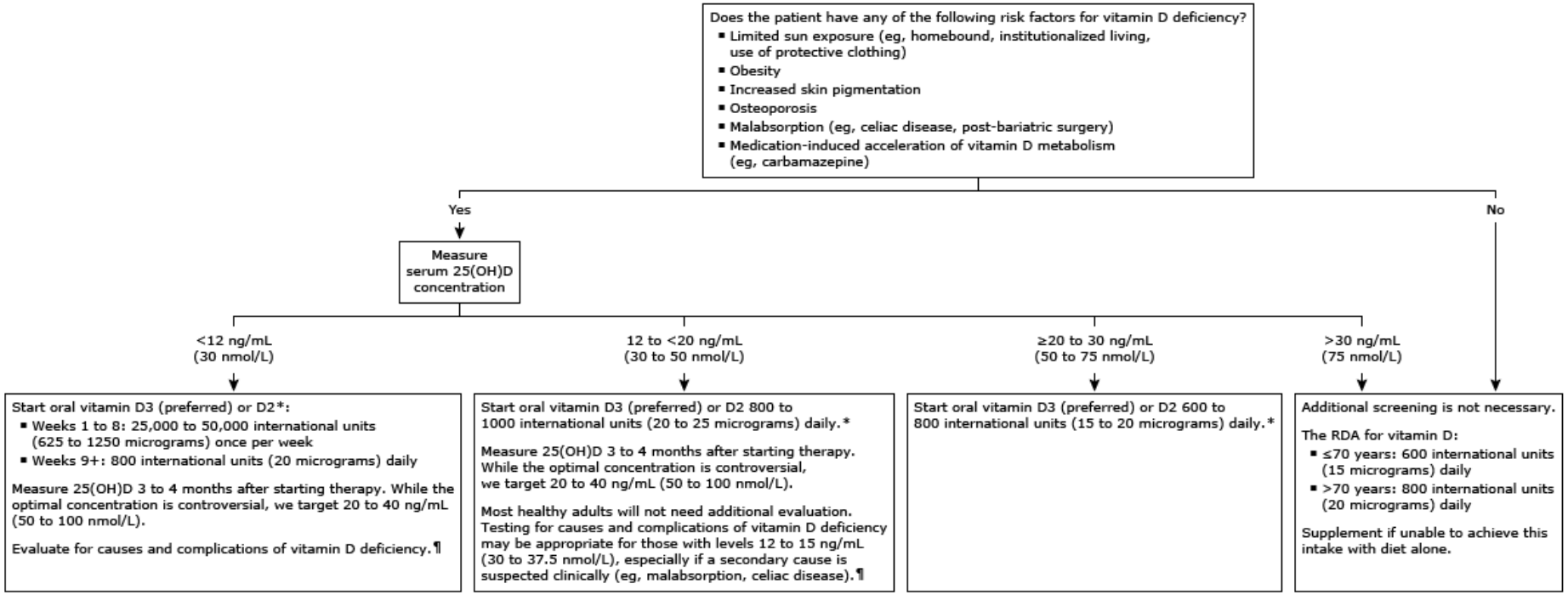
- D preparations: cholecalciferol (D3), ergocalciferol (D2);
- D3 increases serum 25(OH)D more efficiently than does vitamin D2

- 25(OH)D deficiency could cause relative hypocalcaemia and secondary hyperparathyroidism then accelerated bone loss, contributing to osteoporosis, fracture and ↑ falls risk
- D replacement will attenuate secondary hyperPTH

Vitamin D supplementation

- Adults should consume ≥600 to 800 international units (15 to 20 micrograms) vitamin D3 (cholecalciferol) daily.
- Sunlight exposure also increases vitamin D. However, sunscreens effectively block vitamin D synthesis and older skin is less efficient at converting vitamin D.
- In NZ, 1.25mg of colecalciferol = 50,000 U
- Safe upper limit of dose is 4,000 U/day
- Important to check if patient taking other supplement that contains D, to avoid excessive D (hypercalcaemia, hypercalciuria, kidney stones, pancreatic cancer)

Screening for and management of vitamin D deficiency in nonpregnant adults



This algorithm illustrates our approach to screening for and managing vitamin D deficiency in adults. Practice varies, and other experts may reasonably use a different approach.

25(OH)D: 25-hydroxyvitamin D; RDA: Recommended Dietary Allowance.

* When available, we prefer cholecalciferol (vitamin D3) rather than ergocalciferol (vitamin D2). Trial data suggest faster normalization of vitamin D levels with vitamin D3 over that seen with vitamin D2; however, the magnitude of this effect is likely not clinically significant for most patients.

¶ Patients with severe vitamin D deficiency are at risk for developing osteomalacia. In such patients, we measure:

- Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH)
- Electrolytes, blood urea nitrogen (BUN), creatinine
- Tissue transglutaminase antibodies (to assess for celiac disease)

Vitamin D deficiency

- Bone densitometry is not routinely done in patients whose only risk factor is low 25(OH)D
- Patients with low 25(OH)D need D replacement, regardless of their bone density findings
- In patients with severely low 25(OH)D, particularly with raised PTH, need for osteoporosis treatment should be reevaluated after D repletion
- Treatment of osteomalacia with calcium & D will lead to marked increase in bone mineral density, such that treatment for osteoporosis isn't needed
- Gluten free diet in Coeliac could also increase bone density
- Calcitriol is the most active vitamin D metabolite, but should not be used in osteoporosis (it is a therapy of secondary hyperparathyroidism in CKD)

Selected food sources of vitamin D[1]

Food	Amount per serving	
	In international units (IU)	In micrograms (mcg)
Cod liver oil, 1 tablespoon (15 mL)	1360	34
Salmon (sockeye), cooked, 3 ounces (85 g)	380 to 570*	9.5 to 14*
Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3 ounces (85 g) (not yet commonly available)	889	22.3
Mackerel, cooked, 3 ounces (85 g)	388	9.7
Tuna fish, canned in water, drained, 3 ounces (85 g)	40 to 68	1 to 2
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 8 ounces (240 mL)	100	2.5
Orange juice fortified with vitamin D, 8 ounces (240 mL) (check product labels, as amount of added vitamin D varies)	100	2.5
Yogurt, fortified with vitamin D, 6 ounces (180 mL) (more heavily fortified yogurts provide more of the DV)	80	2
Margarine, fortified, 1 tablespoon (15 g)	60	1.5
Sardines, canned in oil, drained, 2 sardines	46	1
Liver, beef, cooked, 3.5 ounces (100 g)	46	1
Ready-to-eat cereal, fortified with vitamin D, 6 to 8 ounces (227 g) (more heavily fortified cereals might provide more of the DV)	40	1
Egg, 1 whole (vitamin D is found in yolk)	25	0.6
Cheese, Swiss, 1 ounce (29 g)	6	0

In the United States, commercially fortified milk is one of the largest sources of dietary vitamin D

Skeletal benefits of vitamin D

- Maintain calcium & phosphate homeostasis, and to maintain bone health & muscle function
- 1,25 $(OH)_2D$ will ↑ intestinal calcium absorption, to offset obligatory calcium loss in kidneys, guts & skin.
- If dietary calcium is inadequate, PTH will ↑ bone resorption
- Optimal mineral metabolism, bone health & muscle function is achieved with D level of 50-60 nmol/L
- 25-OHD levels < 60– 75 nmol/L have been associated with lower-extremity muscle weakness and impaired balance, and accelerated losses in muscle mass, strength and physical function.
- Most Level I evidence indicates that vitamin D (at daily doses of > 800 IU [20 ug]) needs to be combined with adequate calcium (> 1000 mg per day), rather than vitamin D alone, to reduce the risk of falls and fractures; although there may be benefits with single therapies. Therefore, older people would be recommended to consume adequate (1000–1300 mg per day) but not excessive dietary intakes of calcium, together with maintaining adequate vitamin D status (within the 25-OHD range 50–60 nmol/L, allowing for seasonal variation), to reduce risk of falls and fracture

Extraskeletal benefits of vitamin D

- CANCER
- Risk of colorectal ca in D<30 nmol/L
- Risk of breast cancer in postmenopausal women reduce if D 67-87 nmol/L
- The current evidence is insufficient to support large-dose vitamin D supplementation for the purpose of cancer prevention or treatment

- Although a large number of epidemiologic studies indicate that the risks of cancer, infectious, autoimmune, and cardiovascular diseases are higher when 25-hydroxyvitamin D levels are <20 ng/mL (50 nmol/L), and that risks decrease with higher 25(OH)D concentrations, a causal association between poor vitamin D status and nearly all major diseases (cancer, infections, autoimmune diseases, and cardiovascular and metabolic diseases) has **not** been established.

Extraskeletal benefits of vitamin D

- Epidemiologic studies in predominantly White populations in North America and Europe suggest that low (especially <25 to 50 nmol/L]) compared with normal serum 25(OH)D levels are associated with higher mortality.

- In some meta-analyses, vitamin D3 supplementation in older, vitamin D-deficient patients modestly reduced risk of overall mortality.

Back to Mr DS (31y M with ↑ ALP, ↑ P1NP, ↑ PTH, (n) Ca/P, and ↓25(OH)D of 29)

- Monthly D3 had normalised his PTH & 25(OH)D within 3 months
- ALP is still mildly raised – is there another cause of this?
- Low (almost no) other risk factors to develop osteomalacia or osteoporosis
- No need for bone density scan
- Aim for dietary calcium 1000mg daily
- Skull Xray to exclude early phase of Paget disease of the bone
- Minimal exposure to sun, so will keep him on monthly colecalciferol (D3), especially with winter coming up!

Calcium Content of Common Foods

IOF International Osteoporosis Foundation

Below is a list of the calcium content of different foods.
Serving sizes are based on average portions, and calcium content is approximate.*

MILK & MILK DRINKS

Food (200ml)	Calcium (mg)
Milk, semi-skimmed	240
Milk, skimmed	244
Milk, whole	236
Milkshake	360
Sheep Milk	380
Coco Milk	54
Soy Drink (non-enriched)	26
Soy Drink (calcium-enriched*)	240
Rice Drink	22
Oat Milk	16
Almond Milk	90

YOGHURT

Food (150g)	Calcium (mg)
Yoghurt, flavoured	197
Yoghurt, with fruit pieces	169
Yoghurt, natural	207

CHEESE

Food	Serving (g)	Calcium (mg)
Hard Cheese (e.g. Cheddar, Parmesan, Emmental, Gruyère)	30	240
Fresh Cheese (e.g. Cottage Cheese, Riccotta, Mascaspone)	200	138
Soft Cheese (e.g. Brie, Camembert)	60	240
Feta	60	270
Mozzarella	60	242
Cream Cheese	60	180

CREAM & DESSERTS

Food	Serving	Calcium (mg)
Cream, double, whipped	30ml	21
Cream full	30ml	21
Custard made with milk, vanilla	120g	111
Ice Cream, vanilla	100g	124
Pudding, vanilla	120g	120
Rice Pudding	200g	210
Pancake	80g	62
Cheese Cake	200g	130
Waffle	80g	47

MEAT, FISH AND EGGS

Food	Serving (g)	Calcium (mg)
Egg	50	27
Red Meat	120	7
Chicken	120	17
Fish (e.g. Cod, Trout, Herring, Whitebait)	120	20
Tuna, canned	120	34
Sardines in Oil, canned	60	240
Smoked Salmon	60	9
Shrimp	150	45

BEANS & LENTILS

Food	Serving (g)	Calcium (mg)
Lentils	80 raw 200 cooked	40
Chick Peas	80 raw 200 cooked	99
White Beans	80 raw 200 cooked	132
Red Beans	80 raw 200 cooked	93
Green/French Beans	900 Cooked	50

STARCHY FOODS

Food	Serving (g)	Calcium (mg)
Pasta (cooked)	180	26
Rice, White (boiled)	180	4
Potatoes (boiled)	240	14
White Bread	40 (slice)	6
Wholemeal Bread	40 (slice)	12
Muesli (cereals)	50	21
Naan	60	48

FRUITS

Food	Serving (g)	Calcium (mg)
Orange	150	60
Apple	120	6
Banana	150	12
Apricot	120 (3 pieces)	19
Currant (dried gooseberry)	120	72
Figs, dried	60	96
Raisins (dried grapes)	40	31

VEGETABLES

Food	Serving (g)	Calcium (mg)
Lettuce	50	19
Kale, Collard Greens	50 (raw)	32
Bok Choy/Pak Choi	50 (raw)	20
Gombo/Okra	120 (raw)	77
Cress	120 (raw)	188
Rhubarb	120 (raw)	103
Carrots	120 (raw)	36
Tomatoes	120 (raw)	11
Broccoli	120 (raw)	112

NUTS & SEEDS

Food	Serving (g)	Calcium (mg)
Almonds	30	75
Walnuts	30	28
Hazelnuts	30	56
Brazil Nuts	30	28
Sesame Seeds	30	22
Tahini Paste	30	42

PROCESSED FOODS

Food	Serving (g)	Calcium (mg)
Quiche (cheese, eggs)	200	212
Omelet with Cheese	120	235
Pasta with Cheese	330	445
Pizza	300	378
Lasagna	300	228
Cheeseburger	200	183

OTHERS

Food	Serving (g)	Calcium (mg)
Tofu	120	126
Seaweed	100	70
Wakame	100	150

Thyroid Case - VC

- 42y Chinese female
- H/O Graves' disease, first diagnosed in Nov2015. Completed a course of Carbimazole (CBZ).
- First relapse in Aug 2020, Used PTU as she reported severe muscle & joint pain while taking CBZ, completed full course of PTU.
- Second relapse in Feb 23, so PTU was restarted.
- For her second relapse, T4 was 37, TSH<0.01. She was started on PTU 100mg (2 tabs) daily. Became euthyroid by May 23, PTU reduced to 50mg daily. Remained euthyroid until 9/5/23. No TRAb checked in between. LFT remained normal.

Thyroid case - VC

- Second relapse of Graves' disease in Feb 23, since initial diagnosis in Nov 2015.
- Had been adherent to anti thyroid drug (ATD)
- No obvious exophthalmos or lid lag; no enlarged goitre
- Non smoker, rarely drinks alcohol
- No plans of having babies (nulliparous)
- Has good understanding of Graves' disease

- She was referred to me to discuss about radioactive iodine (RAI)
- Discussion about RAI initiated

RAI – basic patient information (1)

- Iodine is extracted by thyroid from blood to use as raw material to synthesize thyroid hormone.
- Iodine is found in many foodstuff.
- Radioiodine is a short-lived form of iodine, chemically same as dietary iodine, therefore it is extracted in the same way, with up to 80% of the radioiodine is concentrated in thyroid gland within a few hours.
- Radiation from radioiodine will reduce thyroid hormone production by preventing normal cell function. It is a permanent fix (like surgery), but much safer & cheaper.

RAI – basic patient information (2)

- It is quick, painless, and usually requires only a single clinic visit. It is administered as a capsule or, less commonly, an oral solution of sodium iodine-131 (I-131)

- RAI is not an instant cure; the process will take many weeks so you should see a slow but steady improvement

- There is % risk of permanent hypothyroidism

RAI – basic patient information (3)

- The risks of using radioiodine are similar to the risks for ordinary x-rays.
- Risk of radiation escapes the thyroid is very small, but patient should also take some precautions after the RAI treatment
- Need to avoid exposing young children or anyone who is pregnant.
- Need somewhere between three and six days off work
- You should sleep apart from partners (e.g. sleep in a spare room or on a temporary bed) to minimize the amount of radiation they receive. This can be from 2 to 7 days after treatment, depending on the amount of radioiodine that has been prescribed
- You should not be attending any public meetings, going to movies or shows or taking long (more than five hours) trips on public transport for a few days after treatment (short trip & shopping without close contact is fine)
- There are no risks to pets from the radioiodine
- Need to drink a little more fluid than usual for the first two days after treatment. This helps to clear any excess radioiodine from your body.
- Make sure no-one else uses your towels. Wash your towels, sheets, underclothes and handkerchiefs separately from other laundry
- After using the toilet, flush at least twice. If there are urine spills, clean up with toilet paper and dispose of this in the toilet, then wash your hands
- Do not handle food that other people may be eating
- Do not share cutlery and dishes with other

Examples of precaution requirements after treatments with 131-I: Hyperthyroidism*

	mCi (MBq) administered			
	10 (370)	15 (555)	20 (740)	30 (1110)
Restricted periods				
Nighttime restrictions				
Sleep in a separate (6-feet separation) bed from adults for days¶ shown.	3	6	8	11
Sleep in a separate bed from pregnant partners, infant, or child for days shown.	15	18	20	23
Daytime restrictions				
You may return to work after days shown.	1	1	2	5
Maximize your distance (6 feet) from children and pregnant women for days shown.	1	1	2	5
Avoid extended time in public places for days shown.	1	1	1	3
Duration of safe travel by public transportation (bus, air, etc)Δ				
Travel time (hours) without exceeding regulatory dose limit				
Day¶ 0 (beginning with treatment)	5.9	3.9	2.9	2
Day 1	9.2	6.1	4.6	3.1
Day 2	13	8.7	6.5	4.3
Day 3	-	10.6	8	5.3

Examples should be modified to meet local and specific patient needs. These examples are based on dose rate of 0.17 mrem h^{-1} mCi^{-1} at 1 m, 500 mrem per year for family member and caregiver, 100 mrem for pregnant women, children, and the public, and occupancy factors for adults of 0.25 except for sleeping 0.33. Resumption of sleeping with a partner assumes a distance of 0.3 m.

131-I: sodium iodide.

* Assumes 50 percent uptake by thyroid, with effective $T_{1/2}$ of approximately 5 days.

¶ Day = 24-hour cycle.

Δ Assumes 100 mrem limit and 0.3 m distance.

RAI for health professional – Approach to treatment (1)

- Preferred definitive treatment of hyperthyroidism for non pregnant patients
- A negative pregnancy within 48h of treatment

- Pre treatment with Carbimazole 4-6 weeks before RAI
- There may be a transient exacerbation of hyperthyroidism after radioiodine, which is eliminated by pretreatment
- Carbimazole returns thyroid function to normal more rapidly than radioiodine
- Hyperthyroidism is controlled by 12 weeks in 97 percent of patients taking carbimazole, while 10-20% of patients receiving a single dose of radioiodine fail treatment altogether
- Older patients (>60 to 65 years) and others with comorbidities, such as coronary artery disease, atrial fibrillation, heart failure, or pulmonary hypertension.
- Patients with severe thyrotoxicosis (eg, free T4 2-3x ULN) who are not tolerating the symptoms of hyperthyroidism

RAI for health professional – Approach to treatment(2)

- To stop carbimazole 3 days before RAI.
- Controversy remains as to whether pretreatment with propylthiouracil (PTU) is more likely to result in treatment failure than pretreatment with carbimazole.
- To restart carbimazole 3 days after radioiodine to allow better control of thyroid function post-radioiodine administration, and to avoid rebound hyperthyroidism post RAI
- Allergy to carbimazole - super saturated potassium iodide (SSKI) given daily, beginning one week after radioiodine

IT IS ADVISABLE TO AVOID EXCESSIVE AMOUNTS OF IODINE AND IODIDES IN YOUR DIET FOR 3 WEEKS BEFORE YOUR TREATMENT AND SOME MEDICATIONS FOR LONGER.

- **Kelp/seaweed preparations**
- **Multivitamins with iodine**
- **Cough medicine with iodine**
- **Soy products**
- **Food supplements – Complan, Ensure**
- **Seafood**
- **Corned beef / ham**
- **Iodized salt / sea salt**
- **Iodine solution**
- **Amiodarone (medication rich in iodine)**

RAI for health professional – Approach to treatment (3)

- RAI is associated with a twofold increase in the development or worsening of thyroid eye disease , more so in smoker
- **Moderate to severe thyroid eye disease -** patients who refuse surgery and who have had adverse reactions to thionamides may need to be offered RAI with glucocorticoid coverage
- In patients with mild eye disease but risk factors for progression, concurrent administration of glucocorticoids should be administered (in the absence of major contraindications) to prevent deterioration of the eye disease
- European Group on Graves' Orbitopathy (EUGOGO) recommends a six-month course of selenium (100mcg BD) for patients with mild and active orbitopathy of relatively short duration
- Teprotumumab, an insulin-like growth factor 1 receptor inhibitor, is a relatively new, effective treatment for moderate-to-severe thyroid eye disease.
- Other secondary medical therapies include Rituximab, Tocilizumab, Mycophenolate

Summary of treatment modalities for Graves' hyperthyroidism

Treatment of Graves' hyperthyroidism

Therapy	Advantages	Disadvantages
Thionamides	Chance of permanent remission Some patients avoid permanent hypothyroidism Lower initial cost	Minor side effects – Rash, hives, arthralgias, transient granulocytopenia, gastrointestinal symptoms Major side effects – Agranulocytosis, vasculitis (lupus-like syndrome), hepatitis Risk of fetal goiter, hypothyroidism, and congenital anomalies if pregnant Requires more frequent monitoring
Radioiodine	Permanent resolution of hyperthyroidism	Permanent hypothyroidism Patient must take radiation precautions for several days after treatment, avoiding contact with young children and pregnant women Development or worsening of Graves' ophthalmopathy Rare radiation thyroiditis Patient concerns about long-term oncogenic effects of radiation
Surgery	Rapid, permanent cure of hyperthyroidism	Permanent hypothyroidism Risks for iatrogenic hypoparathyroidism and recurrent laryngeal nerve damage Risks associated with general anesthesia High cost

Summary of the advantages and disadvantages of the 3 major therapeutic modalities used in the treatment of Graves' hyperthyroidism.

Thank you for your attention

- Questions?