



East Lancashire Health Economy
Medicines Management Board

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Guideline on Diagnosis & Management of Vitamin D Deficiency in Adults for Non-Specialists

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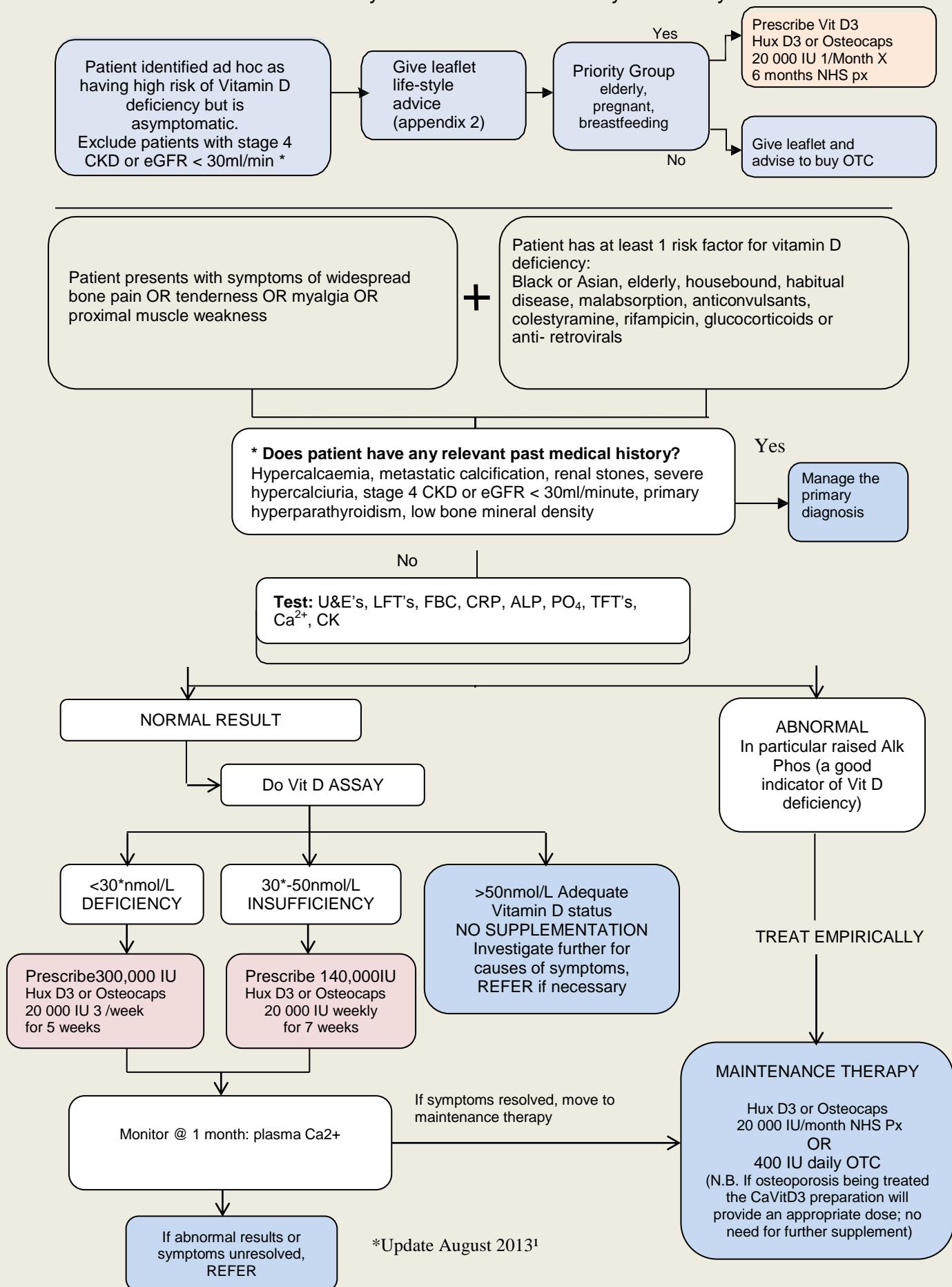
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Summary Flowchart

Adult Patient Pathway for Vitamin D Deficiency in Primary Care



Introduction

Awareness of Vitamin D deficiency in the UK population has increased substantially in recent years but developing guidance on this subject is difficult for the following reasons:

- There is a lack of consensus regarding the precise definition of Vitamin D deficiency.
- The evidence-base is not completely defined in relation to best management of different vitamin D deficiency states resulting in a wide range of treatment regimens.
- Lack of consensus regarding necessity of diagnostic tests and the monitoring following treatment.
- The availability of licensed vitamin D products is limited and unlicensed products have variable (and often substantial) costs.

Publication of the Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management by the National Osteoporosis Society provides some consensus on the definition of deficiency and appropriate dosing [update August 2013].¹

Structure and mechanism of action of vitamin D

In this guidance the term vitamin D refers to colecalciferol (D₃) and ergocalciferol (D₂) which are the precursors of the active hormone 1α, 25-dihydroxyvitamin D (1α,25(OH)₂D), also known as calcitriol. Vitamin D is hydroxylated in the liver to 1α, 25-OH-D, and further hydroxylated in the kidney through the action of parathyroid hormone (PTH) to form calcitriol.

The active form of vitamin D, calcitriol, exerts its effect by binding to the vitamin D receptors (VDRs) which are widely distributed through many body tissues.

At present, most of our knowledge and evidence base for management of Vitamin D related issues comes from effects on bone metabolism. To exert its effect on bone metabolism and calcium absorption, vitamin D is first converted to calcitriol. This is a self-regulating process, and evidence of vitamin D deficiency then being manifest through high levels of PTH.

Prevalence of deficiency

A recent UK survey among the white population showed that in the winter and spring there was a 50% prevalence of insufficiency and 16% deficiency.

In contrast the prevalence in a multi-ethnic population shows much higher rates of deficiency. Among South Asians tested in routine clinical practice more than 90 % were found to have insufficient or deficient levels².

Supplementation has been clearly defined by the national advice leaflet at:

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_132508.pdf

This guidance has been developed in response to a need for a clearly defined management pathway based on a pragmatic approach to product availability, simplicity and mindful of optimising patient compliance.

These guidelines exclude patients whose Vitamin D deficiency may be secondary to other conditions requiring specialist supervision.

Aims of Guidelines

- Advice on the diagnosis and management of Vitamin D deficiency in adults and children
- Clinical and cost effective investigation of suspected Vitamin D deficiency
- Clinical and cost effective prescribing of Vitamin D therapy and choice of supplements
- An appropriate balance between patient lifestyle, self-management and medical treatment

Vitamin D and adults

Patients with vitamin D deficiency in whom there is suspicion of mal-absorption, renal or hepatic disease, or where there is a co-existing condition leading to increased risk of toxicity with treatment, should be discussed with secondary care before initiating treatment.

For all other adult patients the following guidance is applicable:

Asymptomatic individuals – High risk groups include those with darker skin pigmentation, institutionalised or housebound patients, vegetarians, those with medical risk and low exposure to sunlight. DO NOT TEST for Vitamin D levels

Symptomatic disease: Rickets, osteomalacia or hypocalcaemia – this often presents insidiously with bone pain, proximal muscle weakness and diffuse muscular aches. It is also associated with increased fracture risk. It is important in this group to exclude other pathologies and take routine bloods. If there is no indication of abnormality, measurement of vitamin D levels will be needed to confirm diagnosis. The results will differentiate between deficiency and insufficiency and the appropriate treatment regimen can be selected.

Risk factors for Vitamin D deficiency

- Black or Asian
- Elderly
- Housebound
- Habitual skin covering
- Vegan/ vegetarian
- Liver/ renal disease
- Malabsorption
- Anticonvulsants, colestyramine, rifampicin, glucocorticoids or anti-retrovirals

Causes of deficiency

- reduced skin synthesis (sunscreen use, skin pigmentation, ageing, season, latitude, time of day, patients with skin grafts and low UVB exposure amongst the housebound)
- decreased bioavailability (mal-absorption with cystic fibrosis, coeliac disease, Crohn's, bypass surgery, medications that reduce cholesterol absorption, and obesity)
- increased catabolism with such drugs as anticonvulsants and glucocorticoids
- exclusive breast feeding for more than 6 months

- increased urinary loss through nephrotic syndrome
- impaired vitamin D hydroxylation (liver failure)
- impaired vitamin D activation (chronic kidney disease or inherited enzyme deficiency)
- acquired disorders such as primary hyperparathyroidism and granulomatous disorders (TB, sarcoidosis)

Clinical features of Vitamin D deficiency

SYMPTOM, SIGN, BIOCHEMISTRY	CHILDREN	ADULT
Seizures	✓	✓
Tetany	✓	✓
Hypocalcaemia	✓	✓
Irritability	✓	
Leg bowing	✓	
Knock knees	✓	
Impaired linear growth	✓	
Delayed walking	✓	
Limb girdle pain	✓	✓
Muscle pain	✓	✓
Proximal myopathy	✓	✓

Other Biochemical Features of Deficiency

Biochemical abnormalities include raised **alkaline phosphatase** in early vitamin D deficiency (should be considered within the differential diagnosis for unexplained raised alkaline phosphatase), almost universally in children with vitamin D deficiency rickets and also found in 80% or more of adults with osteomalacia. An additional biochemical feature pointing to a bony origin is if the serum alkaline phosphatase is relatively more elevated than the γ -glutamyl transferase.

In longstanding symptomatic vitamin D deficiency hypocalcaemia and hypophosphatemia are associated with the severity of the disease and the patient's dietary calcium intake.

Elevation of plasma parathyroid hormone caused by secondary hyperparathyroidism, is typical but may not be found in neonates and young infants or in about a quarter of adults with vitamin D insufficiency.

When to assay

Patients who have presented with symptoms and have known risk factors for Vitamin D deficiency whose biochemistry is abnormal **DO NOT NEED a Vitamin D assay**.

Empirical maintenance therapy can be started without assay in adults who present with classical symptoms/signs of vitamin D deficiency AND with known risk factors AND with abnormal biochemistry (e.g. raised Alk Phos)

Patients who have presented with symptoms and have known risk factors for Vitamin D deficiency whose biochemistry is normal will require a definitive diagnosis.

Measurement – vitamin D status is determined by measuring serum 25-hydroxyvitamin D (25-OH-D). This has a circulating half-life of one to two months with levels actively replenished from fat stores. It is an expensive assay and many patients can be advised to change their lifestyle or take supplements without measuring serum 25-OH-D.

Reference ranges – if it is appropriate to measure serum 25-OH-D the results should be interpreted as below:

25 OH D Levels	Nanograms	Status	Nanomoles
	<12ng/mL	Deficiency	<30nmol/L
	12-20ng/mL	Insufficiency	30-50nmol/L
	20-30ng/mL	Adequate	50-75nmol/L
	>40ng/mL	Optimal	>100nmol/L
	>60ng/mL	High*	>150nmol/L

[August 2013]

N.B. Serum concentrations of 25(OH)D reported in either nanograms per millilitre (ng/mL) or nanomoles per litre (nmol/L). 1ng/ml = 2.5nmol/L. Since 2010 clinical chemistry laboratories should be reporting results in nmol/L

*Emerging evidence links potential adverse effects to high concentrations.

Monitoring requirements

Important: All patients receiving treatment doses for vitamin D deficiency or insufficiency should be monitored as follows:

- 1 month after loading dose: check plasma-calcium concentration
- 3 months after loading dose: check plasma-calcium, phosphate, alkaline phosphatase and parathyroid hormone*

*Measuring PTH is difficult in the community because the sample has to reach the lab within four hours. Ensure sample taken at correct time to allow transport to lab for analysis, and sample is clearly labelled.

Important: All patients receiving calcium supplementation for hypocalcaemia, in addition to pharmacological doses of vitamin D need more frequent monitoring of plasma-calcium every 1-2 weeks in the first months of treatment to determine length of time calcium supplementation is needed and to avoid hypercalcaemia. Patients or carers should be informed about the symptoms of hypercalcaemia e.g. weight loss, sickness, vomiting, headache, abdominal pain, apathy, and polyuria.

Treatment of Deficiency and Insufficiency on the NHS

A diagnosis of either deficiency or insufficiency is confirmed by lab analysis of vitamin D status. When deficiency or insufficiency is diagnosed, treat as below and use the Read code:

C28 vitamin D deficiency

Colecalciferol (oral) is the preferred form of vitamin D for treatment. It raises levels of 25(OH)D more effectively than ergocalciferol (injected).

Choice of product should be led by patient preference taking into consideration their beliefs.

Where there is no choice in products containing gelatin there is a statement from WHO that permits Muslims to take medicines encapsulated by gelatin³.

N.B. Patients to be co-prescribed a Vitamin D supplement with an oral an anti-resorptive agent do not need a loading dose but may start maintenance therapy.¹ [August 2013]

Treatment following definitive diagnosis by assay should be given on the NHS.

Clinical state	Loading Dose	Dosing options
Deficiency	300,000IU colecalciferol taken orally over 6 – 10 weeks	Hux D3 or Osteocaps 20,000 IU x 3/week for 5 weeks OR 20,000 IU x 3 1 st week followed by 2/week for 6 weeks

Clinical state	Loading Dose	Dosing options
Insufficiency	140,000IU colecalciferol taken orally over 5 – 10 weeks	Hux D3 or Osteocaps 20,000 IU per week for 7 weeks

Patients who after loading dose require maintenance therapy or those who are treated empirically, the recommended doses are as follows:

Clinical state	Dose	Dosing options
Maintenance	400 – 800IU colecalciferol daily	Hux D3 or Osteocaps 20,000 IU x1 monthly NHS Px OR 400-800 IU daily OTC

It is suggested that apart from priority groups, maintenance therapy should be over the counter i.e. purchased by the patient, in conjunction with lifestyle advice (see Appendix 2 for Vitamin D sources).

Asymptomatic high risk patients and those who move to maintenance should be directed to purchase OTC supplements, alongside advice on lifestyle and diet

Referrals

Referral to a specialist is advised for the following groups of patients:

All children under 1 year	Atypical biochemistry	Focal bone pain
Deficiency due to malabsorption	Failure to respond to treatment after 3 months	Atypical clinical manifestations
Liver disease	Lymphoma	Metastatic cancer
Parathyroid disorders	Renal disease	Renal stones
Sarcoidosis	Short stature	Skeletal deformity
Tuberculosis	Unexplained deficiency	Unexplained weight loss

Special populations

Renal disease – in CKD there is decreased activation of vitamin D in the kidney, along with decreased gut calcium absorption and increased phosphate retention. As the eGFR declines these processes may trigger secondary hyperparathyroidism with bone reabsorption, pathological fractures and metastatic calcification. As the eGFR declines further there will be inadequate production of active vitamin D. For these patients replacement with alfacalcidol will be needed under the supervision of the renal department.

Pregnancy – There is a direct correlation between maternal vitamin D status and that of the foetus/infant on delivery. NICE CG62 Antenatal care recommends *“All women should be informed at the booking appointment about the importance for their own and their baby's health of maintaining adequate vitamin D stores during pregnancy and whilst breastfeeding. In order to achieve this, women may choose to take 10 micrograms of vitamin D per day, as found in the Healthy Start multivitamin supplement.”*

Breast feeding – The vitamin D content of breast milk is related to the mother's exposure to UV light and her dietary intake of vitamin D. While there is a concern that a daily supplement of 400IU (10mcg)/day for lactating mothers will not raise vitamin D levels to the normal range, there is evidence that these amounts will prevent neonatal hypocalcaemia and rickets.

Elderly and housebound – the elderly are at risk of vitamin D deficiency due to a combination of factors. These include lower sun exposure and decreased skin synthesis in residential home populations, poor nutrition and lower levels of renal hydroxylation. The DoH recommends a dietary intake of 400IU in the population over 65 years. SIGN guidance (2002) suggests the use of calcium with vitamin D for everyone over 65, as there is evidence for the reduction of hip fracture. It remains unclear whether vitamin D alone offers the same protection as the combination product. Calcium plus vitamin D is a cheap, safe and licensed product and presents a cost effective intervention in this group.

What about Prevention?

People at risk and those demonstrated to have suboptimal serum 25-OHD levels should be targeted for lifelong lifestyle advice, especially about sun exposure and diet. There is a leaflet (Appendix 2) which offers advice on vitamin D supplementation.

There is no clear cost effective evidence that supplementation prevents the long term sequelae in the insufficiency group. It is for this reason that a prescription is not advised.

Alfacalcidol

Alfacalcidol is not considered appropriate for community use in Vitamin D deficiency unless advised by Renal or Clinical Blood Sciences (Clinical Chemistry) Specialists due to risk of hypercalcaemia.

A recent signal alert from the National Patient Safety Alerts (NPSA) highlights the risks associated with alfacalcidol prescribing:

<http://www.nrls.npsa.nhs.uk/resources/?entryid45=132827>

Patients receiving treatment with alfacalcidol should have plasma-calcium levels checked once or twice a week as per product SPC when initiating treatment, and whenever nausea and vomiting or other symptoms of toxicity occur during treatment. Once stabilised, plasma calcium levels should be checked at intervals.

References:

1. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management; National Osteoporosis Society, April 2013
2. Hypponen E, Power, Hypovitaminosis in British adults aged 45. Am J Clin Nutr 2007; 85:860-8
3. World Health Organisation. Regional Office for the Eastern Mediterranean. July 2001.
Full document available at
http://www.ganfyd.org/images/1/11/Porcine_gelatine_medications_Islam_WHO_2003.doc

Appendix 1: Sources of Vitamin D

The major natural source of vitamin D is sunlight, with a small amount coming from the diet. For white populations 20-30 minutes of sunlight exposure to the face and forearms in the middle of the day during summer generates approximately 2,000IU vitamin D. Two or three exposures a week are estimated to generate healthy levels.

Populations with pigmented skin need 2-10 times the exposure of a fair skinned individual.

In the United Kingdom there is insufficient UVB of the necessary wavelength between October and March to generate vitamin D.

Sun exposure for vitamin D production has to be balanced against the risk of skin cancer. Sunscreens with a sun protection factor of 15 or more block 99% of dermal vitamin D synthesis.

There are few foods rich in vitamin D. The following table lists common dietary sources:

Oily fish e.g. trout, tuna, salmon, herring, mackerel, sardines, ilish/hilsa	200-400IU per 100g
<i>Farmed fish may have lower levels than wild fish</i>	
Margarine	280IU per 100g
Some breakfast cereals	120-320IU per 100g
Red meat	40IU per 100g
Egg yolk	20IU each
Cod liver oil	1360IU per 15ml
Mushrooms	Small quantities

NB. In the UK margarine, infant formula milk and some cereals are fortified with vitamin D

Vitamin Supplements

Your doctor has identified that you have risk factors for Vitamin D deficiency. You may want to consider purchasing your own supply of Vitamin D from health food shops, pharmacies or from the internet.

The strength or dose you will need is **400-800 units** of Vitamin D daily or 10-20mcg of Vitamin D.

If the doctor advises you to take a higher dose of 2,000-2,500 units of Vitamin D daily, the following are suggestions:

Holland & Barrett Sunvite vitamin D₃ 1,000 units caplets

Natures Remedy Vitamin D₃ 1,000 units tablets or capsules

Or ask your local pharmacist to advise you on a suitable product

Summary

The following points summarise the advice around what you can do to improve your health and vitamin D levels:

- Increase your exposure to sunlight to advised levels e.g. while walking to the shops or taking the children to school. If you don't want to expose your face and arms in public, try to sit outside in private for a short time each day
- Look at your diet and consider changes you can make to increase the food groups that are high in Vitamin D levels
- Purchase a Vitamin D supplement. Your Doctor recommends the following dose:

- If you begin to have symptoms of bone or muscle pain, or tenderness, make an appointment to see your doctor

Vitamin D



This leaflet explains about Vitamin D deficiency and what you can do to help yourself

What is Vitamin D?

Vitamin D is a fat-soluble vitamin. It is also known as colecalciferol. In humans Vitamin D is unique both because it is available in our diet and also when sun exposure is adequate the body can synthesize it (as Vitamin D₃). The Recommended Dietary Amount often seen on food packaging for Vitamin D assumes that no synthesis occurs and that all of a person's vitamin D is from their diet.

Vitamin D is activated by metabolism in the kidneys and its action is to regulate the concentration of calcium and phosphate in the bloodstream, promoting the healthy growth of bone. Vitamin D prevents [rickets](#) in children and [osteomalacia](#) in adults, and, together with calcium, helps to protect older adults from [osteoporosis](#).

Vitamin D also affects nerve & muscle function, inflammation, and influences the action of many genes that regulate the growth of cells.

Risks factors for Vitamin D deficiency?

The following are risk factors:

Pigmented skin

Elderly or housebound

Wearing of occlusive garments or habitual sunscreen use

Liver or kidney disease

Vegetarian or fish free diet

Multiple short interval pregnancies

Certain drug treatments (ask your pharmacist or doctor)

Are there any changes you can make to reduce any of the above risks that may apply to you?

Life style changes you can make:

Go out into the sun: 2-3 exposures of sunlight on bare skin per week from April to September should be enough to last through the year. Each episode should be 20-30 minutes to bare arms and face and should not cause sunburn.

Include foods in your diet that are rich in Vitamin D e.g.

Oily fish species, such as [Salmon](#), [Mackerel](#), [Sardines](#), [Tuna \(fresh\)](#),

Whole [egg](#)

Beef liver,

Fish liver oils, such as [cod liver oil](#),

Mushrooms and UV-irradiated yeast are the only [vegan](#) sources of vitamin D from food sources.

Some foods are artificially fortified with vitamin D such as margarine, fat spreads and some breakfast cereals—look out for the RDA (Recommended Daily Amount) of Vitamin D on food packaging.