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Vitamin D in Obesity

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Abstract

Purpose of review: Vitamin D is essential for bone health, and may also have important functions in immunity and other systems. Vitamin D deficiency is common, and testing and supplementation is increasing. Serum vitamin D is lower in obese people; it is important to understand the mechanism of this effect and whether it indicates clinically significant deficiency.

Recent findings: Vitamin D is fat soluble, and distributed into fat, muscle, liver and serum. All of these compartments are increased in volume in obesity, so the lower vitamin D likely reflects a volumetric dilution effect and whole body stores of vitamin D may be adequate. Despite lower serum vitamin D, obese adults do not have higher bone turnover or lower bone mineral density (BMD). Patients undergoing bariatric surgery do have bone loss, and ensuring vitamin D sufficiency in these patients may help to attenuate bone loss.

Summary: Lower vitamin D in obese people is a consistent finding across age, ethnicity and geography. This may not always reflect a clinical problem. Obese people need higher loading doses of vitamin D to achieve the same serum 25OHD as normal weight.

Keywords vitamin D, obesity, bone,

Introduction

The main source of vitamin D in humans is production from the action of UVB light on cholesterol in skin. There is a small contribution from dietary sources such as oily fish and fortified foods. There are some geographical variations, for example in Scandinavia, dietary fish is a major source, and in the USA there is more food fortification. Vitamin D deficiency is very prevalent in the northern hemisphere; most of the UK population are vitamin D deficient in winter ¹.

There is ongoing debate about the fundamental principles of defining vitamin D deficiency. The most commonly used measure of vitamin D status is total 25-hydroxyvitamin D (25OHD) which captures 25OHD₃ and 25OHD₂. 25OHD has a long serum half-life and is a technically easy measurement, but it has been proposed that free (non-protein-bound) 25OHD is a better measurement because it more closely reflects biologically available 25OHD status. There are variations in the sufficiency threshold recommended by different advisory bodies, with recommendations generally between 50 and 75 nmol/l ^{2,3}.

Vitamin D is a pre-hormone. It is converted to the active hormone 1,25 dihydroxyvitamin D (1,25(OH)₂D) by 25-hydroxylation in the liver and 1-hydroxylation in the kidney. The final step of 1-hydroxylation is tightly regulated to prevent hypercalcaemia.

The main form circulating form of vitamin D is 25OHD. It is protein-bound in circulation (about 85% to vitamin D binding protein (VDBP), and about 15% to albumin). 25OHD is fat soluble, and distributed into fat, muscle and liver, with smaller amounts into other tissues. 25OHD is cleared by 24-hydroxylation to 24,25(OH)₂D or other inactive metabolites.

Active vitamin D, 1,25(OH)₂D is required for gut absorption of dietary calcium. Severe vitamin D deficiency causes osteomalacia in adults and in children. Less severe insufficiency causes increased bone turnover and is associated with increased fracture risk. Vitamin D deficiency has been associated with a wide range of other disorders, particularly auto-immune disorders and cancers, but a causative role in these conditions is not yet well established.

Obesity is inversely correlated with serum 25OHD. This is a consistent finding in adults and children of different ethnicities in a range of geographic locations. This observation raises several questions: Is the low serum 25OHD a consequence or cause of obesity? What is the cause of low serum 25OHD in obesity? Does the low serum 25OHD in obesity have clinical consequences for bone or other systems? Do obese people need higher doses of vitamin D supplements? Does vitamin D supplementation in obesity ameliorate any of the metabolic consequences of obesity? What happens to vitamin D status when weight changes rapidly after weight loss surgery?

Relationship between body weight and vitamin D

Obese people have lower serum 25OHD than normal weight people, and serum 25OHD is inversely correlated with body weight, BMI and fat mass. This has been shown in adults and children in northern and southern Europe, Australia and New Zealand, Saudi Arabia, Latin America and in White, Black and Hispanic groups in the USA ⁴⁻¹². Serum 25OHD is about 20% lower in obese people than normal weight ^{4,5,13}, and the prevalence of 25OHD is greater in obese people, reported at between 40-80% ^{4,9,12}.

Other measures of vitamin D status (free 25OHD and 1,25(OH)₂D) are also lower in obesity ^{4,14}.

It is likely that low serum 25OHD is a consequence of obesity, rather than the cause of obesity. A large genetic study found that high BMI and genes that predispose to obesity decrease serum 25OHD, while low 25OHD and genes associated with low 25OHD have very little effect on obesity¹⁵. In meta-analysis, vitamin D supplementation has no effect on body weight or fat mass¹⁶.

Causes of low 25OHD in obesity

There are a number of possible mechanisms that could cause low 25OHD in obesity. There could be lower input due to lower dietary intake, lower sunlight exposure or impaired skin synthesis of vitamin D. Alterations in protein binding or faster metabolic clearance in obesity could lead to lower serum 25OHD. Or the lower serum 25OHD could be due to distribution of 25OHD into a larger whole body tissue volume, particularly if 25OHD were actively sequestered in other tissues.

Dietary vitamin D intake did not differ between obese and normal weight adults in a UK population⁴. Obese people may have less sunlight exposure than normal weight people¹⁷ in some geographic regions, although in two UK studies, sunlight exposure did not vary with BMI^{4,18}. When exposed to UVB, normal-weight and obese people have a similar cutaneous synthesis of vitamin D¹⁹. Clearly, diet and sunlight behaviours will vary between different geographic and cultural groups, and may be a contributory factor to lower vitamin D in some groups.

Serum VDBP and albumin concentrations affect the total 25OHD measurement, and there are genetic variations in VDBP which cause variation in the binding affinity of DBP. However, DBP and albumin do not differ between obese and normal weight people, and the distribution of DBP genotypes is similar in obese and normal weight groups^{4,20}.

If metabolic clearance rate of 25OHD were faster in obesity, the half-life of 25OHD would be shorter and circulating 25OHD would be lower. Measurements using a stable isotope 25OHD tracer show that metabolic clearance is similar in obese and normal weight adults⁴, so this is unlikely to be the explanation for lower serum 25OHD.

The most important mechanism is probably volumetric dilution of 25OHD into greater tissue volume in obese people. 25OHD is distributed into serum, fat, muscle, liver and a small amount into other tissues²¹, and all of these compartments are increased in obesity. The difference in serum 25OHD between obese and normal weight groups is greater in summer than in winter because the summer rise in serum 25OHD is less in obese people^{4,22,23}. Obese people get similar sunlight exposure to normal weight people, and produce the same amount of vitamin D in response to sunlight exposure, but the synthesised vitamin is distributed into a larger volume, so the amount distributed into serum is less. There is a similar difference between obese and normal weight people in response to oral vitamin D dosing, with a smaller serum 25OHD rise in obesity²⁴. The dose-response relationship of vitamin D supplementation in obese adults is BMI-dependent and curvilinear, consistent with volumetric dilution²⁵ (**Figure 1**). It has been proposed that vitamin D is actively retained (sequestered) in fat but the modelling of the dose-response doesn't seem consistent with that hypothesis. There is experimental evidence that vitamin D concentration in abdominal subcutaneous fat increases with vitamin D supplementation^{26,27}, and one in vitro study suggests that adipocytes from insulin-resistant obese people might have impaired release of vitamin D²⁸. However the distribution and concentration of vitamin D and 25OHD in subcutaneous and omental fat does not differ between obese and normal weight people, and the correlation between 25OHD in subcutaneous fat and serum is similar in obese and normal weight²⁹.

Does lower 25OHD have clinical consequences in obesity?

Usually, low total 25OHD, free 25OHD and 1,25(OH)₂D would lead to lower dietary calcium absorption, and increased bone turnover with lower bone mineral density (BMD). However, obese adults have lower bone turnover than normal weight, and higher BMD with thicker, denser cortices and greater trabecular number³⁰. It is important to note that in contrast, obesity in children has adverse effects on bone strength³¹.

This lack of adverse effects on bone may indicate that obese people are not truly vitamin D deficient; although serum 25OHD is lower due to volumetric dilution, their whole body vitamin D stores are greater due to the reservoir in their fat tissue, which maintains an equilibrium with serum 25OHD and a sufficient supply.

An alternative explanation is that obese people are vitamin D deficient but that other effects of obesity compensate for the effects of vitamin D deficiency. For example, greater skeletal loading or the action of hormones such as leptin, adiponectin or oestrogen are known to have positive effects on bone mass.

If obese people are truly vitamin D deficient, there may be implications for systems other than bone. Vitamin D deficiency has been associated with a large number of disorders, such as auto-immunity, cancer, neurodegenerative disease and metabolic syndrome. However, there is not yet clear evidence for a causative role of vitamin D deficiency in many of these conditions³². Obesity does increase the risk for several of these disorders but there are other possible mechanisms than low vitamin D for these associations, and the interaction of vitamin D and obesity in causation has not yet been clearly characterised³³.

In the US NHANES population study, low serum 25OHD was associated with higher all-cause mortality in postmenopausal women with normal waist circumference; the hazard ratio for the lowest versus the highest serum vitamin D quartile (< 36.5 nmol/l vs > 65.4 nmol/l) was 1.85 (95% CI 1.00 to 3.44). In women with abdominal obesity there was no association between serum 25OHD quartile and all-cause mortality (HR 0.96, 95% CI 0.52 to 1.76)³⁴. This result suggests that obesity does modulate the relationship between serum vitamin D and health outcomes.

Does vitamin D supplementation improve the adverse metabolic profile in obesity?

A recent meta-analysis found only four or five good quality intervention studies for each of the metabolic parameters they considered (fat mass, blood pressure, lipids and glucose tolerance). There were some positive effects of vitamin D supplementation on fat mass, triglycerides, HDL cholesterol and oral glucose tolerance, but adverse effects on LDL cholesterol and blood pressure. However, due to the small numbers of studies and significant heterogeneity of methodology, the current evidence is insufficient to draw conclusions³⁵.

Inflammatory markers do not seem to be higher in vitamin D deficient obese people than in vitamin D replete obese people³⁶ and vitamin D supplementation has little effect on circulating inflammatory markers in overweight or obese people³⁷⁻³⁹.

Vitamin D with weight loss surgery

Obesity surgery leads to substantial weight loss in most patients, often about 30% of their body weight. The two main types of surgery are gastric volume reduction (eg sleeve gastrectomy) or malabsorptive (most commonly Roux-en-Y gastric bypass (RYGB), and less commonly biliopancreatic diversion with gastric switch). As expected, obese people have low serum 25OHD pre-operatively. Most studies find that serum 25OHD increases in the first month after surgery⁴⁰, which may reflect the smaller volume of dilution with weight loss. One study tried to determine whether the vitamin D stored in fat was mobilised into serum during weight loss, but found no association between vitamin D concentration in fat at time of surgery and subsequent change in serum 25OHD⁴¹. With biliopancreatic diversion, serum 25OHD tends to decline immediately after surgery, which is probably due to the greater bile and fat malabsorption with this procedure⁴².

In the longer term, vitamin D decreases. Five years after RYGB, with calcium and vitamin D supplementation in most patients, they are just vitamin D sufficient at about 50 nmol/l, but have parathyroid hormone above the reference range⁴³. Bone density and microarchitecture deteriorates for at least two years after RYGB, beyond stabilisation of body weight, despite vitamin D supplementation which maintained serum 25OHD well into the replete range⁴⁴. The bone loss is likely to be multifactorial, with decreased loading, changes in adipokines, gut hormones, insulin and sex hormones as well as other nutritional factors. Maintaining vitamin D deficiency after bariatric surgery may require higher doses than standard supplementation, but in combination with calcium and protein supplements and physical activity may attenuate bone loss⁴⁵.

Optimum vitamin D dosing for BMI

As explained above, the observed serum 25OHD of about 20% below the normal weight population in obese people may not indicate true deficiency or a clinical problem. However, despite higher total body stores, obese people can become vitamin D deficient for the same reasons as any other group. If obese people are treated to the same serum 25OHD repletion threshold as normal weight, higher loading doses will be required due the greater volume of distribution. Obese people may need repeated loading courses to achieve repletion. (Conversely, people with below-normal BMI may need lower doses, but more frequently). Drincic²⁵ describes the formula to calculate the required vitamin D dose based in BMI and the required increment in serum 25OHD. Because there are no alterations in protein binding or metabolic clearance rate in obesity, maintenance dose requirements should be similar to normal weight (although as above higher doses may be need after bariatric surgery).

Summary

Obesity is associated with lower serum vitamin D, assessed as total 25OHD, free 25OHD or 1.25(OH)₂D. This is likely due to volumetric dilution into the greater volumes of serum, fat, muscle and liver. The observed lower vitamin D in obesity doesn't seem to have adverse consequences for bone health. There is less available information about consequences for other systems, but no clear evidence of adverse effects. Vitamin D supplementation has not yet been clearly shown to benefit the adverse metabolic profile in obesity. Vitamin D does decrease after bariatric surgery, and careful attention to vitamin D repletion might help to prevent bone loss in these patients. Obese people will

need greater loading doses of vitamin D to achieve the same serum 25OHD threshold as normal weight.

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Key points

Serum vitamin D is low in obese people across age, ethnicity and geography.

The low vitamin D is due to greater volumetric dilution, and may not necessarily indicate vitamin D deficiency.

Despite lower serum vitamin D, obese people have lower bone turnover and higher bone density than normal weight people.

Bariatric surgery does cause bone loss, and vitamin D supplementation may be important in this group of patients.

Obese people need higher loading doses of vitamin D than normal weight people to achieve a similar increment in serum vitamin D.

Figure legend

Figure 1 Serum response to oral vitamin D supplementation is BMI- and dose-dependent.

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