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Vitamin D and muscle☆

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ABSTRACT

Vitamin D is increasingly recognised to play an important role in normal muscle function. Low vitamin D status is associated with an increased risk of falls and proximal weakness. Since vitamin D deficiency is very common, and the signs are non-specific, it is important to maintain a high index of suspicion of vitamin D deficiency in patients with muscle pain and weakness, and it is simple to measure serum 25(OH) vitamin D. Therapy is cheap, safe and effective, but sometimes a larger dose may be needed, and, as shown in our case report, willingness of people to pay for an over the counter medication can be an issue. Following a striking case report that demonstrates muscle defects in severe vitamin D deficiency, we discuss clinical studies examining specific effects of vitamin D on physical performance, muscle strength and falls. Finally, we present an overview of molecular mechanisms that explain vitamin D's biological effects on muscle.

1. Case report

Mrs. H was a 51 year old woman who presented for management of her type 2 diabetes. She complained of muscle pain in all large muscle groups. She noted difficulty hanging out the washing and on 'bad days' difficulty brushing her hair. She complained of calf pain with walking one block which improved with rest.

Her other past medical history included a fractured leg after falling down a flight of stairs, gastro-oesophageal reflux and hypercholesterolemia.

She had no known allergies, but had one past episode of anaphylaxis for which a trigger was not identified. Mrs. H did not smoke or drink alcohol.

Her medications were metformin 1 g bd and gliclazide 80 mg, 2 tablets bd but these were not taken regularly. Her HbA1c was poorly controlled at 9.5%. She had no known retinopathy, nephropathy or neuropathy or macrovascular complications of diabetes. She was born in Turkey and had been resident in Australia for many years. Mrs. H did not wear *hajib* (veil) but did cover her arms and legs, and wore a headscarf. She did report low sun exposure.

On examination her weight was 103.5 kg and her height 155.5 cm, giving her a BMI of 42.8 kg/m^2. Blood pressure was 128/79 mmHg and her after-lunch blood glucose level was 12.6 mmol/l. Her foot architecture, pedal pulses and capillary refill were normal.

There was no muscle tenderness to palpation but power was 4/5 in all proximal muscle groups. Distal power was normal (5/5). Reflexes were present and brisk, with down-going plantar responses. There was no loss of sensation present, and pedal blood supply was normal.

On being asked to stand, she had to use her hands to help her to stand from an office chair. The timed up and go test was administered, and the time was 14 s to stand, walk across the room (3 m), turn and walk back and sit down. Although reference values for TUAG in subjects < 65 yrs have not been reported, a time of 14 s in this subject (age 51 yrs) is very abnormal. In older subjects, 10 s or less to perform timed up and go test is considered normal (Podsiadlo and Richardson, 1991).

She was requested to have serum vitamin D measured, with other blood tests and to commence vitamin D supplementation at 2000–3000 IU per day. Serum 25(OH) vitamin D was 12 nmol/l. Serum corrected calcium and phosphate were normal (2.28 mmol/l and 1.39 mmol/l respectively). Magnesium was low at 0.61 mmol/L.

She returned to clinic for her next visit, and again complained of muscle pains and weakness. On questioning, she said she had not commenced vitamin D treatment. The advice to do so was repeated, and the reasons were explained again.

At her next follow-up visit (7 months after her first visit), she again complained of muscle pains and weakness. A detailed discussion of the

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likelihood of these symptoms persisting indefinitely without commencement of vitamin D was held and she agreed to commence therapy. At her next visit she had commenced cholecalciferol 1000 IU per day, and her symptoms of weakness and muscle pain had completely resolved. She could stand, walk across the room and return to her chair in approximately 7 s.

At this time, her 25(OHD) was 65 nmol/l, accompanied by normal serum calcium, phosphate and magnesium (2.27 mmol/l, 1.10 mmol/l and 0.66 mmol/l respectively). Interestingly, her HbA1c improved from 11.1% at the visit before commencing vitamin D replacement to 8.5%.

This case illustrates some of the muscle effects of vitamin D deficiency, and also issues with patient's willingness to commence therapy.

1.1. Vitamin D and muscle function

Osteomalacia is classically considered a disease of bone resulting from impaired skeletal mineralisation due to lack of vitamin D and/or necessary substrate for hydroxyapatite formation (calcium and phosphate). However, muscle weakness, pain and hypotonia are associated clinical features of this syndrome, especially in children. Proximal myopathy, a waddling gait and in severe cases, the need for a wheelchair are seen in adults with severe, chronic vitamin D deficiency (< 20 nmol/l). Muscle defects in subjects with vitamin D deficiency have been long recognised. In fact, in the initial description of rickets in 1645, Whistler reported the combination of “flexible, waxy” bones and “flabby, toneless” muscles in young children (Whistler, n.d.).

More subtle changes in muscle function may be seen in subjects with lesser severe and perhaps less chronic vitamin D deficiency: a greater risk of falls, gradual muscle atrophy over time and reduced physical performance in athletes. In this chapter, we will discuss the spectrum of vitamin D's effects on skeletal muscle from clinical studies and emerging concepts in vitamin D's molecular effects on muscle.

2. Vitamin D and muscle

2.1. Physical performance

There is a body of literature dating back over 80 years which suggests improvements in physical performance in individuals exposed to UV radiation. These studies do not directly mention vitamin D but UV-induced alterations in vitamin D levels may have played a role in muscle function. In 1944, a German study of medical students reported 13% improvement in performance on a bicycle ergometer after 6 weeks of UV exposure (Lehmann, 1944). A Russian study in 1938 demonstrated marked improvements in sprint times amongst students exposed to UV radiation (7.4% vs. 1.7% improvement in controls) (Gorkin and Teslenko, 1938). An American study of 11 male students reported a 19% increase in cardiovascular endurance following a course of UV radiation (Allen, 1945).

Modern-day studies have reported surprisingly high rates of vitamin D deficiency in groups of athletes from Australia (33% deficient) (Lovell, 2008), the Middle East (58%) (Hamilton et al., 2010), UK (57%) (Close et al., 2013a) and USA (13.3%) (Fishman et al., 2016). Studies examining effects of vitamin D supplementation in athletes are few. In 30 British athletes randomized to vitamin D3 20,000 IU, 40000 IU or placebo for 12 weeks, significant increases in vitamin D levels at 6 and 12 weeks were not associated with any changes in physical performance (Close et al., 2013a). In a larger study of 61 male athletes and 30 healthy male non-athletes, vitamin D3 (5000 IU per day) resulted in significant improvements in 10-metre sprint times and vertical jump over the 8-weeks (Close et al., 2013b). Baseline 25OHD levels were lower in this study than in the previous one (mean ~40 vs. ~50 nmol/l) and higher 25OHD levels were achieved (mean 103 vs. ~85–91 nmol/l). However, a recent meta-analysis of 13 RCTs involving 532 athletes (vitamin D 311, placebo 221) found no improvement in measures of physical performance despite the inclusion of vitamin D deficient athletes at baseline and improvements in vitamin D levels over mean 12 weeks of follow-up (Farrokhyar et al., 2017). However, measures of physical performance were not standardised across study groups and there was heterogeneity in the types of sport and ethnicities examined.

Effects of vitamin D on muscle recovery following exercise have been examined. Baseline vitamin D levels predicted muscle recovery following an intensive exercise session in 14 recreationally active subjects (Barker et al., 2013). Interestingly, vitamin D levels initially increased (by ~5 nmol/l) and then decreased following exercise. The authors hypothesised this was due to exercise-related shifts in cytokine and protein levels.

Effects of vitamin D on muscle function were reviewed recently (Girgis et al., 2013). A well-known case-control study of 55 veiled Arabic women with severe vitamin D deficiency (mean 25OHD 7 nmol/l) reported weakness on all tested parameters of muscle function compared to a control group of 22 Danish women with higher levels (47 nmol/l) (Glerup et al., 2000). Following vitamin D repletion (IM vitamin D2: 100,000 IU per week for 1 month then monthly for 5 months and 400–600 IU orally daily), significant improvements in muscle function and pain at 3 and 6 months were reported in the Arabic women.

Supplementation studies examining physical performance in non-athletes have reported mixed results. Amongst 69 adolescent females, those who received 150,000 IU vitamin D2 orally every 3 months for 1 year demonstrated significant improvements in movement efficiency, a combination of jump height and velocity measured by mechanography, compared to baseline (Ward et al., 2010). In addition, baseline vitamin D levels correlated positively with jumping velocity.

In a Lebanese study of 179 vitamin D deficient adolescent females, randomisation to vitamin D3 (at doses of 1400 IU or 14,000 IU weekly) did not demonstrate improved grip strength (El-Hajj Fuleihan et al., 2006). Adequate vitamin D levels were achieved in the high-dose (95 nmol/L) but not in the low dose-group (42 nmol/L), suggesting that increases in lean mass and bone mineral content seen in both groups versus placebo at 1 yr were not directly due to serum vitamin D levels.

Older adults with sarcopenia showed a significant increase in muscle mass and better lower limb function following a course of vitamin D and leucine-enriched whey protein supplementation (Bauer et al., 2015). In 300 older women with a baseline 25OHD level under 60 nmol/l, significant improvements in physical performance, specifically timed up-and-go testing, were reported with 2000 IU vitamin D daily (Zhu et al., 2010).

Other randomized studies have not shown similar effects of vitamin D on muscle function. Two recent trials in which older women were given 800 IU vitamin D daily showed no change in muscle performance, and other trials have included subjects without vitamin D deficiency or have employed lower vitamin D supplemental doses, perhaps explaining their negative findings (Hansen et al., 2015; Uusi-Rasi et al., 2015).

A meta-analysis of 17 RCTs found that the effect of vitamin D supplementation on muscle strength was contingent on significant baseline vitamin D deficiency with baseline levels < 25 nmol/l (Stockton et al., 2011). We note our patient in the case report fell into this group.

Another meta-analysis showed beneficial effect of daily vitamin D (with doses ranging from 800 to 1000 IU) in older subjects with improvements in balance and muscle function, but not with walking speed (Muir and Montero-Odasso, 2011). In another meta-analysis, vitamin D's effects on muscle strength was mainly seen in older individuals (age > 65 yrs) and related to lower baseline 25OHD levels (< 30 nmol/l) (Beaudart et al., 2014).

2.1.1. Summary

Anecdotally, as seen in our case study above, vitamin D deficiency results in poor muscle function, weakness and myalgia that are

reversible upon achieving a vitamin D replete state. However, clinical studies examining effects of vitamin D on muscle function are mixed, discrepant in their vitamin D supplementation regimens, measures of physical performance and study population (athletes, adolescents, older individuals). It is therefore difficult to make concrete conclusions on vitamin D's clinical effects on muscle or optimal vitamin D levels for muscle health. The evidence drawn these studies however suggests that:

- Vulnerable, older individuals with vitamin D deficiency, particularly those living in institutions (implying reduced sun exposure and frailty) benefit from vitamin D supplementation
- Despite unexpectedly high rates of vitamin D deficiency in athletes, vitamin D supplementation has equivocal effects on athletic performance and muscle recovery
- At this stage (and with paucity of evidence in this area), vitamin D supplementation of adolescents without rickets does not have clear effects on peak muscle or bone mass or physical performance measures

2.2. Falls

Age-related decline in muscle mass and function is known as sarcopenia. It is associated with an increased risk of falls, disability and mortality in older people (Bunout et al., 2011). Vitamin D deficiency is prevalent in institutionalised, older subjects and may contribute to development of sarcopaenia (Visser et al., 2003). Subject to ageing, skin becomes less effective in UV-mediated vitamin D synthesis and renal activation of 25OHD and muscle levels of vitamin D receptor (VDR) decline (Bischoff-Ferrari et al., 2004). This may render muscles of older individuals more vulnerable to the effects of vitamin D deficiency. In addition, obesity impairs the increase in vitamin D with UV exposure (Wortsman et al., 2000), and BMI gradually increases with age in many people.

Falls are particularly troubling events in the lives of older individuals, increasing the risk of fracture, hospitalisation and chronic frailty. Falls are multifactorial and relate to sarcopenia, poor motor function and postural instability, visual impairment and a range of chronic diseases which lead to debility and deconditioning.

Observational studies have reported an association between low vitamin D status and subsequent falls risk in older people. A longitudinal study of 1600 institutionalised, older women demonstrated 20% reduction in falls risk in association with a doubling of 25OHD levels over an approximate 5-month period (Flicker et al., 2003). Conversely, other studies have shown significant increases in the prospective risk of recurrent falls, decline in physical performance and sarcopaenia in older individuals with vitamin D deficiency at baseline < 25 nmol/l (Snijder et al., 2006) (Wicherts et al., 2007) (Visser et al., 2003). An increased PTH (> 4.0 pmol/l), a secondary feature of chronic vitamin D deficiency, is also associated with sarcopenia (Visser et al., 2003).

However, such observational data are limited by a range of potential confounders. Vitamin D deficiency may be a surrogate for frailty and frail older people are less likely to spend time outdoors exposed to sunlight, and are more likely to be malnourished. Factors not considered or difficult to quantify in multivariate analyses may exist, thus highlighting the importance of randomized interventional trials.

An RCT of 625 older residents of assisted-living facilities reported significantly fewer falls in subjects on calcium (600 mg daily) and vitamin D2 (initially 10,000 IU weekly, then 1000 IU daily) for 2 years versus calcium alone (Flicker et al., 2005). Similarly, calcium (1200 mg/d) and vitamin D3 (800 IU/d) halved the incidence of falls during the 12-week treatment period versus the preceding 6-weeks, versus calcium alone (Bischoff et al., 2003). Studies have suggested that older individuals who benefit most from vitamin D supplementation are those living in institutions, recurrent fallers (Bischoff et al., 2003), less active older women (Bischoff-Ferrari et al., 2006) and stroke sufferers (Sato et al., 2005).

Other studies have not shown benefit (Porthouse et al., 2005; Grant et al., 2005). Amongst 5292 subjects over the age of 70 years, vitamin D3 (800 IU daily) had no effect on falls over 26–62 months (Grant et al., 2005). However in these negative studies (Porthouse et al., 2005; Grant et al., 2005), patients had recently suffered low-energy fracture or were at risk of fracture, indicating a greater baseline risk of falls and impaired mobility and falls per se were not the primary outcome measure of these studies.

Infrequent 'mega-doses' of vitamin D may adversely affect falls risk. An annual oral dose of 500,000 IU of vitamin D3 increased the incidence of falls in over 2000 community-dwelling older women and there was a temporal relationship with falls occurring particularly in the 3 months following the dose (Sanders et al., 2010).

In a well-cited meta-analysis, a dose-dependent effect of vitamin D in reducing falls risk was reported with a threshold dose of at least 700 IU daily (Bischoff-Ferrari et al., 2009; Ross et al., 2011). Subjects with 25OHD concentrations ≥60 nmol/l had 23% lower falls risk. However, this meta-analysis has been criticised for its reliance on 2 studies to produce the positive effect, one of which was reportedly not adequately-powered (Ross et al., 2011).

A large meta-analysis including > 45,000 people demonstrated reduced falls risk amongst those randomized to vitamin D (OR 0.86 for ≥1 fall) but this effect was not dose-dependent and not different between community-dwellers and institutionalised subjects (Murad et al., 2011). Reduction in falls risk was however greatest in those with baseline vitamin D deficiency and calcium co-administration (500 to 1200 mg daily elemental calcium).

A meta-analysis of the US Preventive Services Task Force demonstrated 17% reduction in falls in response to vitamin D and its analogues (calcitriol and alfacalcidol) (Michael et al., 2010) whilst a recent meta-analysis of 20 trials reported a non-significant 5% decrease in falls risk in older individuals (Bolland et al., 2014).

2.2.1. Summary

Although vitamin D supplementation generally reduces the risk of falls in frail, older individuals (at doses > 700 IU d), dose-dependent effects have not been clearly established with the exception of a significantly ***higher*** risk of falls in subjects receiving single mega-doses.

2.3. Molecular mechanisms

The active form of vitamin D, $1,25(OH)_2D_3$ is a transcription factor that relies on the presence of vitamin D receptors (VDR) to exert genomic effects at target sites. VDR is a nuclear receptor that is widely expressed and when bound to $1,25(OH)_2D_3$, regulates a broad array of genes.

The presence of VDR in skeletal muscle has been the subject of recent debate and is an important question in understanding the clinical effects of vitamin D deficiency on muscle function. VDR's expression in skeletal muscle implies that vitamin D may directly target this tissue. Alternatively, VDR's absence in muscle implies that vitamin D's effects on this tissue would be indirect, and occur via systemic changes in calcium and phosphate levels. Interestingly, in our case patient above, severe muscle symptoms including myalgia and weakness were associated with vitamin D deficiency but in the absence of hypocalcaemia or hypophosphatemia. This patient's clinical improvement in muscle function occurred in association with vitamin D repletion whilst her calcium and phosphate levels had not improved significantly over this time. This itself suggests direct vitamin D effects on skeletal muscle.

In the laboratory, however, this question of VDR's presence in skeletal muscle has been confounded by several factors, including changes in in VDR during muscle differentiation and development, technical factors such as non-specific VDR antibodies, highly variable muscle models and protein extraction methods (Wang et al., 2010). Most importantly, perhaps, muscle is a multi-cellular tissue with synctitia of

multinucleated, post-mitotic fibers, myofibroblasts, endothelial cells and satellite cells (muscle stem cells) with myogenic potential. Therefore, unequivocally establishing the presence of VDR in muscle or in any one of these specific muscle components has been challenging. The prevailing concept, however, is that VDR *is* expressed in skeletal muscle but at very low levels, predominates at early stages of muscle development and during muscle repair (a recapitulation of the myogenic process) and finally, modulates the uptake of its own ligand precursor, vitamin D, into skeletal muscle fibers (Girgis et al., 2014a; Girgis et al., 2014b; Srikuea et al., 2012; Abboud et al., 2013; Makanae et al., 2015; Abboud et al., 2018).

We have also learnt a great deal about vitamin D's effects on muscle through the study of transgenic mouse models. Mice with global knockout of VDR (VDRKO) have a very disordered phenotype (e.g. defects in bone, skin, metabolism and immune function) and abnormal serum calcium and phosphate levels due to impaired gut absorption. These mice have lighter muscles, smaller type I and II muscle fibers and fiber hypernuclearity that persists despite dietary supplementation with calcium and phosphate (Endo et al., 2003; Girgis et al., 2015). However, this mouse has a variety of defects which confounds direct vitamin D-muscle assessment. To circumvent this, skeletal muscle-specific VDR knockout mice were recently generated (Chen et al., 2016). Significant reductions in type II muscle fiber diameter were described in these mice, suggesting a vitamin D-specific effect on muscle fiber size. This provides biological evidence for a direct role of vitamin D deficiency in sarcopenia, which is also supported by other rodent and human studies, and possibility that vitamin D modulates myostatin, a negative regulator of muscle mass (Girgis et al., 2014a; Ceglia et al., 2013).

Functional effects of vitamin D on muscle strength have been assessed in vitamin D deficient mice tested by grip strength and using various physical performance measures in VDRKO mice (Burne et al., 2006; Minasyan et al., 2009). Vitamin D may influence muscle function by intracellular effects on calcium handling. A recent study in vitamin D deficient mice demonstrated an association between their reduced grip strength and altered expression of mRNAs encoding calcium-handling and sarco-endoplasmic reticulum calcium transport ATPase (Serca) channels (Girgis et al., 2015). Reduction in calcium within the mitochondria and sarcoplasmic reticulum of muscle fibers has been described in vitamin D deficient animals (Pleasure et al., 1979; Curry et al., 1974). Rapid effects of vitamin D on calcium signaling have also been reported in a large body of in vitro studies (Boland, 2011; Capiati et al., 2001; de Boland and Boland, 1987). Together, these findings suggest that calcium handling is a mediator of effects of low vitamin D on muscle. For an in-depth discussion of molecular mechanisms linking vitamin D and muscle, we refer readers to our comprehensive review on this topic (Girgis et al., 2013).

2.3.1. Summary

Potential molecular effects resulting in our case patient's muscle weakness may be alterations in calcium signaling and disordered muscle repair (an accumulation of damaged muscle fibers), and muscle atrophy in the context of her severe vitamin D deficiency.

3. Conclusions

This article has discussed vitamin D's effects in skeletal muscle, commencing with a striking case report describing severe yet reversible muscle weakness in a veiled female with severe vitamin D deficiency, and including an assessment of clinical trials and biological mechanisms on vitamin D and muscle. As reflected in our case report, marked deficiency of vitamin D is clearly detrimental for muscle function, independent of alterations in calcium and phosphate levels. Observational studies also associate muscle weakness, falls and reduced muscle mass with vitamin D deficiency. However interventional trials and meta-analyses in subjects with less severe forms of vitamin D deficiency have yielded contradictory findings. The validation of physical performance measures and the definition of sarcopenia remain open questions making it difficult to standardize outcome measures of these studies (Girgis, 2015) (Girgis et al., 2014c). Regarding falls, vitamin D supplementation is effective in more vulnerable elderly people, such as the institutionalised or those who are prone to falls but not excessive, single mega-doses which appear harmful in this population (Girgis, 2014). Biological mechanisms suggests the presence of VDR in muscle, a role in intramuscular calcium handling and the modulation of muscle fiber size. Further research will help to clarify optimal vitamin D supplemental regimens for muscle health independent of its effects on calcium and phosphate levels is needed. In the meantime, people with severe vitamin D deficiency (< 25 nmol/l (10 ng/ml)) are at risk of muscle pathology and would benefit from supplementation.

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