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Vitamin D and muscle☆

Jenny E. Gunton[a,b,c,d,*], Christian M. Girgis[a,b,c,e]

[a] Centre for Diabetes, Obesity and Endocrinology Research, The Westmead Institute of Medical Research, Westmead, Sydney, Australia
[b] The Faculty of Medicine, The University of Sydney, Australia
[c] Department of Diabetes and Endocrinology, Westmead Hospital, Sydney, Australia
[d] Division of Immunology, Garvan Institute of Medical Research, Sydney, Australia
[e] Department of Diabetes and Endocrinology, Royal North Shore Hospital, Sydney, Australia

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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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* Corresponding author at: Room 2040, Level 2, Westmead Hospital, NSW 2145, Australia.
E-mail address: Jenny.gunton@sydney.edu.au (J.E. Gunton).

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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