

ALS-UNTANGLED

ALSUntangled No. 24: Vitamin D

*The ALSUntangled Group***Introduction**

There has recently been growing interest in the role of vitamin D in neurological disorders, including ALS (1–9). Physicians on internet blogs (10) and in chat rooms (11) have even begun suggesting that PALS (PALS) take vitamin D. In this paper, on behalf of patients with ALS (PALS) who are asking about it (11), we review vitamin D in general, and its potential role in ALS.

What is vitamin D and what are its general roles in health and disease?

Vitamin D is a fat-soluble secosteroid. Vitamin D can be found in certain foods but the main source is from the sun. The skin can synthesize vitamin D₃ (cholecalciferol) through ultraviolet irradiation of 7-dehydrocholesterol. Vitamin D₃ must then be metabolized to 25-hydroxyvitamin D₃ in the liver and then to 1 α ,25-dihydroxyvitamin D₃ in the kidney before function (12). Because the human body produces its own vitamin D, the concept that it is a vitamin is incorrect. 1 α ,25-dihydroxyvitamin D₃ binds to a single vitamin D receptor (VDR), which is a nuclear receptor. Following a reaction between 1 α ,25-dihydroxyvitamin D₃ and the VDR, DNA transcription is either initiated or suppressed, depending on the gene.

The most established function of vitamin D is to increase serum calcium concentrations (12). Hence, it is essential for skeletal mineralization, preventing rickets in children and osteomalacia in adults and for prevention of hypocalcemic tetany (12,13). However, the role of vitamin D extends beyond calcium and the bone. Vitamin D receptors (VDRs) are widespread in the human body and not limited only to enterocytes, osteoblasts, and distal renal tubule cells (14). Some of the proven roles of vitamin D outside of bone and calcium include: terminal differentiation of promyelocytes to monocytes, preventing proliferation of parathyroid gland cells and influencing T-cell mediated immunity (12–16).

What are the optimal levels of serum vitamin D?

The optimal level of serum vitamin D is unknown but is usually determined according to PTH levels. Professional societies define vitamin D deficiency when the level of 25-hydroxyvitamin D₃ is below 10–20 ng/ml and insufficiency when the level of 25-hydroxyvitamin D₃ is between 10–20 and 30 ng/ml (17–19). Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D₃ are greater than 150 ng/ml.

How might vitamin D have a role in ALS?

Vitamin D can influence several distinct pathways that are potentially important in ALS pathophysiology (reviewed in (1)). Vitamin D increases the concentration of calcium binding proteins in motor neuron cells (20), which may limit damage induced by calcium influx (21,22). Vitamin D can attenuate oxidative stress (3,23), promote autophagy of misfolded proteins (8), modulate inflammation (1,8–12), increase serum VEGF levels (24) and help regulate axonal regeneration (25). Vitamin D may protect motor neuron cells from FasL-induced apoptosis and potentiate neurotrophic activity in motor neuron cells (9). All of these pathways have been manipulated in different ways in previous ALS trials, unfortunately without success.

More generally, there is evidence that higher vitamin D levels are associated with greater muscle strength in healthy adults (26). Vitamin D supplementation can reduce fall risk in the elderly (27). While very recent studies show that vitamin D is not a panacea for good health (28), increased strength and decreased fall risk would be helpful in PALS, regardless of mechanism.

What data are available on vitamin D in mouse models of ALS?

Mice bred without vitamin D receptors have impaired motor performance (29). There have been three studies of G93A-ALS mice, all performed by the

same group. In the first, the mice were fed with either an adequate (1 IU D(3)/g feed) or deficient (0.025 IU D(3)/g feed) dietary intake of vitamin D (2). Mice on the deficient diet had delayed ALS onset, but worse motor performance following onset. In a second study, G93A mice were fed with either an adequate (1 IU/g feed) or high dose (10 IU/g feed) dietary intake of vitamin D (4). Mice in the high dose group had marginally better motor performance (not meeting statistical significance since $p > 0.05$). There were no differences in ALS onset, progression rate or lifespan. In a third study, G93A mice were fed with either an adequate (1 IU D (3)/g feed) or very high dose (50 IU D(3)/g feed) dietary intake of vitamin D (5). Mice on the very high dose had improved motor performance ($p < 0.05$) but there was still no effect on ALS onset, progression or lifespan. Furthermore, female mice showed evidence of possible vitamin D(3) toxicity as evidenced by reduced food intake. These are all small studies and have not been independently replicated.

What do we know about vitamin D in PALS?

Arguing against a role for vitamin D deficiency in causing ALS are the epidemiological observations that people born in the summer are actually slightly more likely to develop ALS, and that there is no latitudinal gradient in ALS incidence (30).

One group studied the relation between vitamin D levels and ALS progression (9). This small study of 74 ALS patients concluded that vitamin D levels were generally low in PALS, and that those patients with severely low vitamin D levels had more rapid progression of their ALSFRS-R scores and shorter survival compared to patients with normal vitamin D levels. Unfortunately, this observation may be biased; patients who are sicker might tend to stay indoors longer and hence have a lower vitamin D level.

In another even smaller study, vitamin D levels were checked in 37 consecutive PALS (6). The mean vitamin D level in the ALS group was below normal at 22.3 ng/ml (normal range, 30–80 ng/ml), with 81% of the ALS group having a vitamin D level lower than 30 ng/ml, and 43% being lower than 20 ng/ml. Twenty PALS took 2000 IU of vitamin D daily. After adjustment for age and baseline vitamin D levels in a linear regression model, the ALSFRS-R score decline was smaller in patients taking vitamin D at nine months ($p = 0.02$), although not significantly different at three or six months. Median vitamin D levels rose from 18.5 to 31.0 ng/ml at six months in the group taking vitamin D. No side-effects secondary to vitamin D supplementation were reported. This study confirms that PALS may have vitamin D deficiency, which is common in many chronic illnesses. However, given the small numbers and limited follow-up, it is not clear from this whether supplementing vitamin D can slow ALS progression or prolong survival.

Table I. Comparison of patients with ALS in Pro-Act who are on or off vitamin D.

Vit D	Results	
	Type	Rate of Decline
Yes	ALSFRS	-0.8389
Yes	ALSFRS-R	-1.0956
No	ALSFRS	-0.8409
No	ALSFRS-R	-1.0977

Within the PRO-ACT database (31) there are 110 patients on vitamin D and 4728 not on vitamin D who have multiple ALSFRS or ALSFRS-R scores. There is no difference in ALSFRS or ALSFRS-R progression between these two groups (Table I). Vitamin D levels in these patients are not known. Within the PatientsLikeMe community, there are five PALS who report taking vitamin D for their ALS, and two of these have publicly available evaluations. Neither patient noted any perceived benefits or side-effects (32). A Google search of 'vitamin D for ALS' uncovered no additional reports of patients taking vitamin D for their ALS.

Costs and potential side-effects

Vitamin D is not expensive. A five-month supply costs around \$11 (33). However, there can be significant side-effects, particularly at higher doses. The Endocrine Society's Upper Limit of safe levels is 10,000 IU/day (34). Beyond that dosing range there are risks for hypocalcemia, which can be life threatening.

Conclusion

At this time, there is evidence that PALS, like those with other chronic illnesses, are at increased risk for vitamin D deficiency. It is therefore reasonable to screen PALS for this. If vitamin D deficiency is found, it seems reasonable to supplement vitamin D according to established guidelines (31) in order to avoid medical complications of vitamin D deficiency. It is not yet clear, however, that vitamin D supplementation can slow disease progression, improve muscle strength, or reduce falls in PALS. We support further studies to answer these questions.

The ALSUntangled Group currently consists of the following members: Chafic Karam, Alex Sherman, Ervin Sinani, Roger Selsov and Erick Macklin, Richard Bedlack, Lyle Ostrow, Orla Hardiman, Terry Heiman-Patterson, Laurie Gutmann, Mark Bromberg, Gregory Carter, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, L. P. Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlyne Jackson, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorens

Shoemith, Steven Nash, Nicholas Maragakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula, Gleb Levitsky, Mieko Ogino, Jeffrey Rosenfeld, Efrat Carmi, Merit Cudkowicz, Christina Fournier, Paul Barkhaus, Eric Valor, Brett Morrison.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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