UPDATE: VITAMIN D SUPPLEMENTATION FOR MULTIPLE SCLEROSIS

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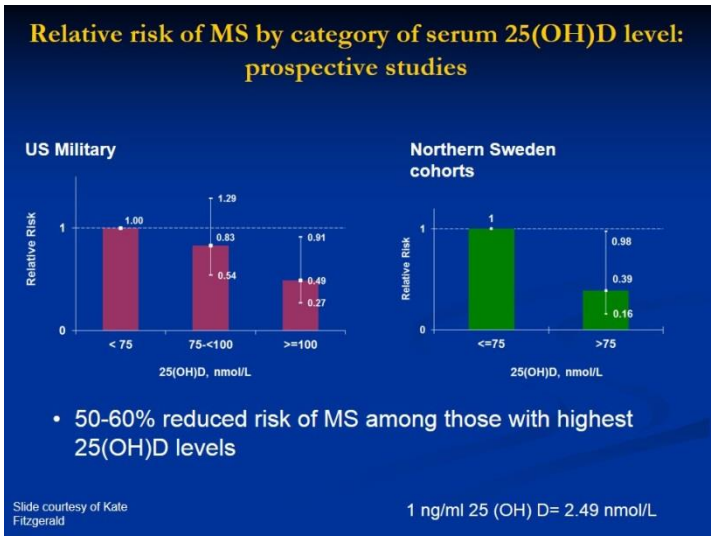
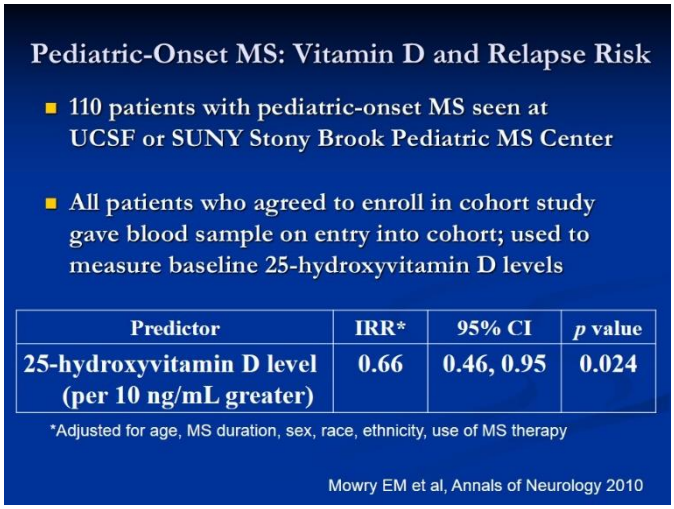
Overview:
The main source of vitamin D for humans is sun exposure. Ultraviolet light converts a cholesterol in the skin to pre-vitamin D, which is ultimately converted in the liver to 25-hydroxyvitamin D (typically what is measured in humans as a marker of vitamin D status, referred to herein as such or as "vitamin D levels"). 25-hydroxyvitamin D is converted in the kidney to the active metabolite, 1, 25 dihydroxyvitamin D, but the conversion also occurs in immune cells and in neurons. Lower levels of vitamin D are associated with greater risk of MS, which was replicated in a subsequent study from Sweden (see figure below).(1,2) There are data supporting an association between vitamin D status and disease course; these and current results of clinical trials of vitamin D supplementation in people with MS will be reviewed.



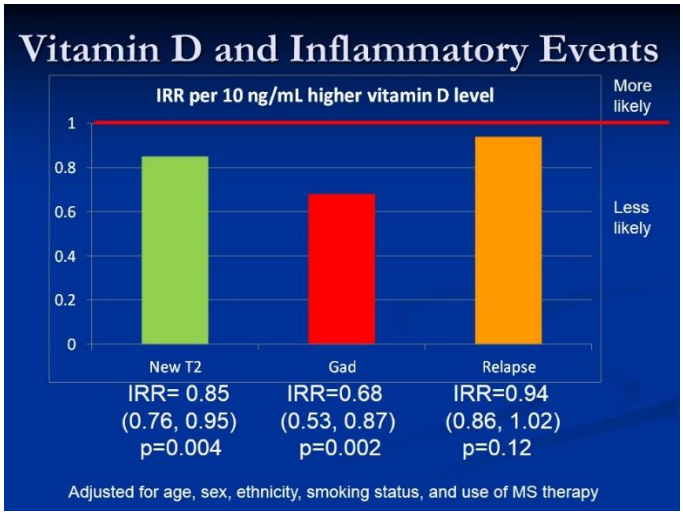
Vitamin D as a Prognostic Marker:

Several cross-sectional or retrospective studies demonstrated lower levels of vitamin D among people with MS, but such study designs raised the questions of reverse causality (perhaps those with MS spent less time in the sun due to the development of Uhthoff's with overheating and thus had lower levels of vitamin D than those without MS). However, more recent longitudinal studies have shown that among those with established MS, lower levels of vitamin D are associated with *subsequent* inflammatory disease activity.



Higher levels of vitamin D are associated with lower risk of subsequent relapses in pediatric-onset MS.(3) The same association was also reported in adult-onset MS.(4)

In terms of imaging evidence, higher levels of vitamin D also are associated with reduced subsequent risk of new T2 or gadolinium-enhancing lesions (5):



The relationship of vitamin D status with neurodegenerative outcomes is perhaps less certain but is of interest given that it is the neurodegeneration that appears to underlie long-term MS-related disability. Interestingly, in people with very early MS (clinically isolated syndrome) enrolled in a small clinical trial, we demonstrated that higher levels of vitamin D were associated with less subsequent loss of normalized gray matter volume:

Amount preserved normalized gray matter volume	Per 10 ng/mL higher vitamin D level
At ~18 months (repeated measures)	7.8 (1.0, 14.6), p=0.025
At month 12 (regression)	7.9 (-1.6, 17.3), p=0.10

Vitamin D Supplementation:

There have been several pilot trials of vitamin D supplementation in people with MS, none of which has been large enough to provide definite conclusions about the efficacy of vitamin D. The trials have largely been of short duration and have used various doses of vitamin D; there have not been any definite serious adverse events.

In one trial by Burton and colleagues, patients were treated with escalating doses of up to 40,000 IU/day of vitamin D, versus the control arm, in which participants could take up to 4,000 IU/day (at their discretion). Some of the secondary outcomes showed apparent benefits of higher-dose vitamin D.(7) A tiny pilot trial, not surprisingly,

did not show an impact of vitamin D supplementation. On the other hand, a small pilot (n=66) trial in patients treated with interferon beta randomized patients to 20,000 IU/week of vitamin D_3 versus placebo and showed reduced gadolinium-enhancing lesions in the vitamin D group (p=0.004).(9) The SOLAR trial in Europe reported a reduction in combined unique lesions; the final publication is pending.(10)

Future Directions:

The results of ongoing vitamin D supplementation trials will be critical to determining the necessity of using this as a treatment for people with MS. Additional work is needed to investigate if it is effective for all people with MS or only specific subgroups as well as to explore the mechanisms by which vitamin D may be playing a role in the disease pathogenesis so as to possibly identify new treatment targets.

References:

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