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RESEARCH ARTICLE

Are Vitamin D Supplements an Adequate Substitute for Sun Exposure?

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ABSTRACT

It is becoming well understood that low blood levels of 25-hydroxyvitamin D (25(OH)D) are a risk factor for many diseases and other adverse health effects including hypertension, cardiovascular disease, stroke, breast cancer, colorectal cancer, metabolic syndrome, type 2 diabetes, obesity, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, Alzheimer's disease, autism, schizophrenia, asthma, preterm birth, maternal mortality, myopia and COVID-19. Levels of serum 25(OH)D are at the same time a measure of vitamin D status and, since 70-90% of this biomolecule is produced by sun exposure, a measure of sun exposure. There is some disagreement among scientists as to whether vitamin D supplements are an effective substitute for sun exposure for attenuation of these diseases and adverse health effects. In this paper we review the current state of the science on this subject and conclude that vitamin D supplements are not an adequate substitute for sun exposure for attenuation of most of these diseases and adverse health effects, particularly hypertension and cardiovascular disease, and should not be recommended in lieu of sun exposure to patients presenting with low levels of serum 25(OH)D. Vitamin D supplementation for such patients could even be harmful, because it will raise patients' serum 25(OH)D levels, thereby giving patients a false sense of security and obscuring the best available metric for insufficient sun exposure.

Background

Humans evolved under the sun, and the human body's complex chemistry at the cellular and molecular levels needs a certain amount of sun exposure to function correctly[1]. Beginning with the industrial revolution when people began working indoors and living in crowded cities, large numbers of people began for the first time to get less sun exposure than is needed for good health[1,2]. The first sun-deprivation disease to appear was rickets, and in 1921 the mediator was discovered to be vitamin D. For the following 80 years, vitamin D was thought to be the only health benefit of sun exposure[1,2].

A laboratory test deemed to be the best metric for vitamin D measures the concentration in the blood of 25-hydroxyvitamin D (25(OH)D)[3], a precursor of the active form of vitamin D. This test is still in use today[3]. Since 70-90% of 25(OH)D is produced by sun exposure[4-6], this test also became the best metric for sun exposure.

The movement indoors continued throughout the 20th century. By 2001, with the migration of work from outdoors to indoors and the attractions of indoor life such as air conditioning, television, video games and the internet causing people to spend much of their leisure time indoors, average Americans were spending more than 93% of their time indoors[7]. The movement indoors has been exacerbated by public health authorities advising the public to minimize sun exposure because of an exaggerated fear of skin cancer[8].

Starting at the beginning of the 21st century, scientists around the world began discovering correlations between increased risks of a wide variety of diseases and low levels of 25(OH)D[1,2]. They also began discovering a diversity of mediators produced in the body by sun exposure, indicating that some of the health benefits of sun exposure may not be attributable to vitamin D[1,2,9].

Numerous scientific studies over the past 20 years have correlated low levels of 25(OH)D with dramatically increased risk of premature death and a large number of diseases and adverse conditions including hypertension, cardiovascular disease, stroke, breast cancer, colorectal cancer, metabolic syndrome, type 2 diabetes, obesity, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, Alzheimer's disease, autism, schizophrenia, asthma, preterm birth, maternal mortality, myopia and COVID-19[1,2,9,11]. The adverse health effects of insufficient sun exposure have grown to the point that insufficient sun exposure has become a significant public health problem[1]. Studies in the last decade indicate that low levels of 25(OH)D may be responsible for 340,000 preventable deaths per year in the United States[1], making low levels of 25(OH)D the nation's second largest public health problem after tobacco with its 480,000 preventable deaths per year[10]. This enormous burden of disease and death falls disproportionately on Black Americans because the larger amount of melanin in their skins, which developed by evolution of their African ancestors under the powerful equatorial sun, is not suited for the weaker sun of America and absorbs more of the sun's rays than the lesser amount of melanin in the skins of White Americans[9,11].

Despite all the scientific discoveries of the past 20 years, there is still some disagreement among scientists as to whether low levels of serum 25(OH)D should be treated with vitamin D supplements or with more sun exposure, which comes down to the question of whether sun exposure has health benefits beyond the production of vitamin D which cannot be replicated with vitamin D supplements. It is important to resolve this issue since the time has come for medical professionals to recommend either vitamin D supplements or sun exposure, or a combination of both, to the American public to address this public health problem. In this review we examine the current state of the scientific evidence on this subject.

Mediators Produced by Sun Exposure

Vitamin D. It has been known for almost a century that photons from the sun react with 7-dehydrocholesterol in the skin to form vitamin D3 which is then metabolized in the liver to form serum 25(OH)D and subsequently in the kidneys to form the active form of vitamin D, 1-25-dihydoxyvitamin D[1,5]. For many years, vitamin D has been commonly assumed to be the only health benefit of sun exposure. More recently, there has been greater awareness of the diversity of other mediators released in response to sun exposure, suggesting that the beneficial effects of sun exposure may be mediated by multiple sun-induced molecules in addition to vitamin D[1,2,9,12].

Nitric Oxide. The 1998 Nobel Prize in Medicine was awarded for the discovery of nitric oxide as an important signaling molecule in the cardiovascular system that protects the heart, stimulates the brain and kills bacteria[9]. In 2009, it was discovered that sun exposure converts nitrogen derivates stored in the skin to nitric oxide which is mobilized to the circulatory system and causes a significant decrease in blood pressure [1,2,9,13-17].

Dopamine. Sun exposure has been found to stimulate release of dopamine in the retina[18].

Other Sun-Generated Mediators. In addition to nitric oxide and dopamine, sun exposure generates other bioactive molecules which exert systemic effects that cannot be replicated by vitamin D

supplements. Other sun-induced mediators include cytokines, corticotropin- releasing hormone, urocortins, proopiomelanocortin-peptides and enkephalins that are released into circulation to produce systemic effects independent of vitamin D synthesis [1,9,19,20]. Sun exposure also can convert *trans*-urocanic acid to *cis*-urocanic acid which is an immunosuppressant[21,22] and affects the skin transcriptome and the blood transcriptome including genes for immunity[12,21,23].

Randomized Controlled Trials and Mendelian Randomization Analyses

Randomized Controlled Trials (RCTs). The reference standard of evidence for determining whether the health risk associated with low levels of 25(OH)D can be effectively addressed by vitamin D supplementation is the randomized, placebo-controlled trial. The vitamin D and Omega-3 TriaL (VITAL) is a recent 5-year randomized clinical trial in 25,871 U.S. men and women investigating the health effects of taking vitamin D supplements. It is the largest and most definitive RCT of vitamin D supplementation to date, and found that vitamin D supplementation did not reduce the risk of cancer or cardiovascular disease or improve cognitive function[24-26], although a prespecified secondary analyses indicated that cancer risk (but not CVD risk) was reduced by vitamin D supplementation in subjects with a body mass index (BMI) of less than 25 but not in subjects with BMI of 25 or higher[27,28]. Prior RCTs have shown mixed results[29]. Some authors have criticized negative results of vitamin D supplementation trials for their inclusion of subjects who initially were not vitamin D deficient and for the trials' relatively short durations[11]. These aspects of many RCTs may stem from ethical considerations of administering placebos to vitamin D deficient participants over long periods of time[11].

Mendelian Randomization Analyses. Mendelian Randomization analyses are genetic studies which can overcome the problems of both reverse causation and confounding when assessing the causal relationship between an exposure and an outcome[30,31].

Specific Diseases

All-Cause Mortality. High levels of serum 25(OH)D and high sun exposure have been found to be associated with reduced all-cause mortality[1,2,32-34]. However, a Mendelian randomization study showed that genotypes associated with low serum 25(OH)D were associated with all-cause mortality but not cardiovascular disease mortality, suggesting that a mediator other than vitamin D contributes to the reduction in cardiovascular mortality[31].

Hypertension and Cardiovascular Disease (CVD). Sun exposure significantly reduces hypertension[17,35], and the mediator has been shown to be nitric oxide, not vitamin D[13-17]. RCTs have shown no significant reduction in systolic or diastolic blood pressure from vitamin D supplementation[36,37]. CVD is inversely associated with levels of serum 25(OH)D[38,39], but no association with vitamin D has been found in Mendelian randomization analyses[31]. Vitamin D supplementation RCTs [40,41], including the recent large VITAL trial [24-26], have shown no association between vitamin D supplementation and reduced CVD risk or mortality, including in participants with low levels of serum 25(OH)D[11]. Nitric oxide is a ubiquitous signaling molecule and an important endogenous vasodilator produced by the vascular endothelium[1,42]. This has changed the understanding of hypertension because it shows that high blood pressure can develop not only as a result of an overproduction of vasoconstrictor substances, but also as a consequence of impaired synthesis production of a continuously produced vasodilator such as nitric oxide[1]. Studies in healthy humans[1,15] show that sun exposure relaxes arterial resistance in association with nitric oxide release and lowers blood pressure independently of temperature. These findings are important because hypertension is the leading cause of non-communicable diseases despite current pharmacotherapy[1,43]. A recent observational study in a large cohort of chronic hemodialysis patients confirmed that environmental UVR exposure is inversely associated with blood pressure independently of ambient temperature[1,44]. These results are in line with the Mendelian randomization findings that genotypes associated with low serum 25(OH)D are associated with increased all-cause mortality but not with increased cardiovascular mortality[31]. This supports the view that a mediator other than vitamin D contributes to the observed reduction in cardiovascular mortality[1,31]. In line with the above hypothesis is the finding that those with habitual low sun exposure are at twice the risk of cardiovascular mortality compared with those with greatest sun exposure[1,33] and that daytime myocardial infarctions reduce with increased sunlight in summer[1,45].

Colorectal Cancer. Colorectal cancer is inversely associated with levels of serum 25(OH)D[1,2,9,11]. There appear to be no RCTs or MR analyses to affirm or deny association with vitamin D. However, one murine study showed reduced colorectal cancer load in animals supplemented with vitamin D or exposed to ultraviolet radiation (UVR), but only UVR reduced progression to malignancy[46], indicating that some mediator from sun exposure other than vitamin D may be involved in reducing the risk of colorectal cancer.

Breast Cancer. Breast cancer is inversely associated with levels of 25(OH)D[1,47,48], but a recent MR analysis found no evidence to support an association with vitamin D[49].

Metabolic Syndrome, Obesity and Type 2 Diabetes. Metabolic syndrome and type 2 diabetes are inversely associated with levels of 25(OH)D[1,50,51]. A murine study[1,52] found that UVR suppressed obesity and type 2 diabetes, but these benefits were not reproduced by vitamin D supplementation. UVR suppression of metabolic syndrome development was blocked by application of a nitric oxide scavenger to the skin and reproduced by application of a topical nitric oxide donor cream[1,52]. These results complement experimental evidence for the involvement of nitric oxide in metabolic syndrome obtained with genetic models[1,53] and suggest that sun exposure may be an effective means of suppressing the development of obesity and metabolic syndrome through vitamin D-independent mechanisms. RCTs of vitamin D supplements and type 2 diabetes show mixed results, but on balance indicate some effect for supplementation, and an MR analysis showed an effect of vitamin D on type 2 diabetes[11,54].

Alzheimer's Disease and Other Cognitive Decline. MR analyses[11,55] have found an association with vitamin D, providing evidence that vitamin D supplementation may reduce risk of dementia[11], although VITAL found no effect of vitamin D supplements for these diseases[24-26].

Multiple Sclerosis (MS). MS is inversely associated with sun exposure[1,11,56-60] and with levels of 25(OH)D[1,11,61-65], and there is some evidence that sun exposure and vitamin D may be independent risk factors for MS[1,60,66], suggesting that sun exposure may reduce MS risk through vitamin D and non-vitamin D pathways [1,67,68]. A 2014 murine study found that UVR suppressed autoimmune encephalomyelitis (EAE – an animal model of MS), independent of vitamin D production[2,69]. In a Mendelian randomization analysis, a genetic risk score comprised of three alleles known to be associated with higher predicted 25(OH)D levels was associated with lower risk of MS[11,30]. RCTs for vitamin D supplementation have mixed results[1,30,70]. In a recent study, the preeminent vitamin D and MS scientist Hector DeLuca and co-author L. A. Plum concluded that it appears unlikely vitamin D supplements can be used to suppress MS and discussed several other sun-induced molecules that may be the mediators for sun exposure's favorable effects on MS[71].

Myopia. Children who spend more time outdoors are less likely to become myopic, irrespective of how much near work they do or whether their parents are myopic. The likely mechanism for this protective effect is light-stimulating release of dopamine from the retina, which inhibits axial elongation, the structural basis of myopia[18]. The prevalence of myopia in the United States in persons aged 12 to 54 years increased from 25% in 1971 to 41% in 2001[72]. Also on the rise is high myopia, a condition that increases the risk of retinal detachment, glaucoma, and the early development of cataracts. While simple myopia is correctable, these pathological consequences make high myopia one of the leading causes of visual impairment and blindness[73].

Acute Respiratory Tract Infection (ARTI) and COVID-19. ARTI and COVID-19 are inversely associated with levels of 25(OH)D [11,74,75]. RCTs of vitamin D supplementation and ARTI and COVID-19 have shown positive results [11,76,77].

Asthma. Asthma is inversely associated with levels of 25(OH)D[1,74,75,79,80]. RCTs of vitamin D supplementation and asthma have shown positive results[11,78,81,82].

Discussion

Vitamin D was discovered one hundred years ago and within a decade thereafter it was known that sun exposure on 7-dehydrocholesterol in human skin caused a chemical reaction in which vitamin D was produced[85]. For the remainder of the 20th century, most scientists believed that vitamin D was the only beneficial molecule produced in the human body by sun exposure. Since the beginning of the 21st century, however, scientists have discovered many other sun-produced bioactive molecules which have beneficial effects that cannot be replicated by vitamin D supplements[1]. Nonetheless, as discoveries have been made over the past 20 years of inverse relationships between levels of serum 25(OH)D and risks of various diseases, many medical professionals have continued to believe that the mediator in all cases is vitamin D, leading them to recommend vitamin D supplements rather than sun exposure for mitigation of these risks. This practice is still widely followed even though randomized controlled trials have failed to show positive effects of vitamin D supplements for many of these diseases.

The 2010 Institute of Medicine vitamin D study concluded that vitamin D supplements were effective only for bone health[86], and the VITAL trials found that vitamin D supplements were not effective to reduce the risk of cancer, cardiovascular disease or cognitive decline[24-26]. A recent article in the New England Journal of Medicine went so far as to state that people should stop taking vitamin D supplements to prevent major diseases or extend life[24]. Some scientists have criticized the RCTs for including subjects with low baseline levels of

25(OH)D and for following subjects for inadequate time periods[11] while noting that ethical considerations may inhibit change of these two variables in future trials[11].

There is substantial evidence that sufficient sun exposure significantly reduces the risk of hypertension, CVD and stroke, and that the mediator is nitric oxide[1]. Since nitric oxide is the mediator, it is not surprising that no association with vitamin D is seen in MR studies or RCTs of vitamin D supplements. CVD is the leading cause of death in the United States[83]. Hypertension is the leading cause of lost disability adjusted life years worldwide and underlies 18% of all deaths[84]. There is substantial evidence that sufficient sun exposure significantly reduces the risk of myopia and that the mediator is dopamine[1].

Our review indicates that while there is some evidence that vitamin D supplements may be effective in treating a few specific diseases such as COVID-19, they are clearly not effective in preventing or treating hypertension, CVD, stroke or myopia, and the weight of opinion appears to be that they are not effective with respect to cancer, cognitive decline or MS. The fact that other sun-induced mediators such as nitric oxide have been shown to exist in the human body and to exert systemic effects that cannot be replicated by vitamin D supplements strongly indicates that vitamin D supplements are not an adequate substitute for sun exposure for persons suffering from the long-term effects of low levels of serum 25(OH)D.

Conclusion

Patients presenting with low levels of serum 25(OH)D should be advised to get more suberythemal sun exposure to raise their levels of serum 25(OH)D to healthy levels. Vitamin D supplementation should not be advised, since it has been shown to be ineffective for hypertension, CVD, stroke and myopia and cannot provide the favorable effects of other sun-induced mediators. Vitamin D supplementation for such patients could even be harmful because it will raise patients' serum 25(OH)D levels, thereby creating a false sense of security and obscuring the best available metric for insufficient sun exposure.

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Conflicts of Interest

David G. Hoel has done consulting for the American Suntanning Association

Allen Miller is founder and president of the Sunshine Health Foundation www.sunshinehealthfoundation.org.

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