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UV Radiation, Vitamin D and Human Health: An Unfolding Controversy

UVR, Vitamin D and Three Autoimmune Diseases—Multiple Sclerosis, Type 1 Diabetes, Rheumatoid Arthritis

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ABSTRACT

We review the evidence indicating a possible beneficial role for UVR on three Th1-mediated autoimmune diseases: multiple sclerosis, type 1 diabetes and rheumatoid arthritis in relation to recent developments in photoimmunology. Recent work suggests that UVR exposure may be one factor that can attenuate the autoimmune activity leading to these three diseases through several pathways involving UVB and UVA irradiation, UVR-derived vitamin D synthesis and other routes such as α-melanocyte-stimulating hormone, calcitonin gene related peptide and melatonin. Ecological features, particularly a gradient of increasing prevalence of multiple sclerosis and type 1 diabetes with higher latitude, provide some support for a beneficial role of UVR. Analytical studies provide additional support, particularly as low vitamin D has been prospectively associated with disease onset for all three diseases, but are not definitive. Randomized controlled trial data are required. Further, we discuss how associated genetic studies may assist the accumulation of evidence with regard to the possible causal role of low UVR exposure and/or low vitamin D status in the development of these diseases.

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Abbreviations: APC, antigen presenting cell; CD, cluster of differentiation; °S, degrees South in latitude; HLA, human leukocyte antigen; IFNγ, interferon gamma; Ig, immunoglobulin; IFNγ, interferon gamma; IL, interleukin; IU, international unit; mJ cm^{-2}, millijoule per centimeter squared; LC, Langerhans cell; MC1R, melanocortin 1 receptor; MS, multiple sclerosis; MSH, melanocyte-stimulating hormone; MRI, magnetic resonance imaging; ON, optic neuritis; RA, rheumatoid arthritis; TGF β, transforming growth factor beta; Th 1, T helper type 1; Th 2, T helper type 2; UVR, ultraviolet radiation; VDR, vitamin D receptor; 1,25OH$_2$D$_3$ 1,25, dihydroxy vitamin D3; 25OHD, 25 hydroxy vitamin D.

INTRODUCTION

Here, we review the evidence indicating a possible beneficial role for ultraviolet radiation (UVR) on three T helper type 1-mediated autoimmune diseases: multiple sclerosis, type 1 diabetes and rheumatoid arthritis, in relation to recent developments in photoimmunology. As in a previous review (1), the focus is on the photoimmunological and epidemiological findings. We also discuss how these findings indicate that public sun exposure messages need to consider the adverse effects of inappropriate UVR for a wide range of health exposures.

T lymphocyte-mediated autoimmune inflammation appears to underlie multiple sclerosis, type 1 diabetes and rheumatoid arthritis (2). These autoimmune diseases are characterized by a breakdown in immunological self-tolerance that may be initiated by an inducing agent, such as an infectious microorganism (2). In these three diseases, a cross-reactive autoimmune response may occur, attracting a Th 1 cell-mediated response that results in chronic inflammation (3) against self-antigens. T helper cells are a subgroup of T lymphocytes expressing CD4+ markers. They are subdivided by the pattern of cytokines they produce. Stimulation of Th 1 cells results in increased levels of interleukin (IL) 2, interferon γ and also IL 12 (3). The latter is not directly secreted from Th 1 cells but from IFNγ-stimulated macrophages (3). These cytokines are often termed Th 1 type cytokines. Th 2 cells produce IL4, IL5, IL6 and IL10 (3). However, it appears that the pathogenesis of these three autoimmune diseases is more complex than Th 1 overactivity alone. Recent work indicates that alterations in T regulatory cell activity may also contribute to the development of autoimmune diseases (4).

Genetic factors appear to be involved in each of these autoimmune diseases, but the low concordance among identical twins for MS (5) and type 1 diabetes (6) and trends of increasing incidence for type 1 diabetes and MS over time (7) suggest environmental factors are also important disease determinants. Recent work suggests that UVR exposure may be one factor that can attenuate the autoimmune activity leading to these three diseases through several mechanisms.

MECHANISMS INVOLVED IN IMMUNOSUPRESSION DUE TO UVR AND RELATED EXPOSURES

Photobiologists have classified solar UVR wavelength into regions as UVC (200–290 nm), UVB (290–320 nm) and UVA (320–400

nm) (8). High energy UVC is totally absorbed by atmospheric ozone, thus having minimal penetration to the Earth's surface (9) and little effect on human health. Atmospheric ozone also prevents all but a small fraction of (longer wavelength) UVB reaching the earth's surface (9). Ambient UVR experienced at ground level is a mixture of UVA and UVB with proportions variously estimated at 94% UVA, 6% UVB (8) and 97% UVA, 3% UVB (10). At any time and location the relative proportions depend on levels of atmospheric ozone, season, latitudinal position and cloud cover (11). Vitamin D is largely UVB-derived via conversion of steroid precursors in the skin and subsequent hydroxylations in the liver and kidney (12) and other tissues. Only a small amount of vitamin D derives from dietary sources (13). Serum 25OHD is often used as a marker of vitamin D status (13).

Immunosuppression Due to UVB Irradiation

Most of the research concerning UVR-induced immunosuppression has focused on the immunosuppressive effects of UVB. In human studies, the initial events following UVB exposure include DNA damage and oxidative stress in keratinocytes and Langerhans cells (the main antigen-presenting cells of the epidermis) and isomerization of urocanic acid from the *trans*- to the *cis*-form. UVR-induced DNA damage and other UVR-related changes can deplete LCs (14,15) and also impair their antigen-presenting function (14). Irradiation of the epidermis increases the levels of tumor necrosis factor alpha and IL10 (14) with the latter being a key cytokine involved in immunosuppression (16) and tolerance (17). The primary immunological function of IL10 is the modulation of antigen-presenting cell function, but IL10 release is also associated with local induction of antigen-specific T cell tolerance (16).

According to numerous laboratory models and some human data, there is increasing evidence that UVB irradiation can induce T regulatory (suppressor) cell activity (14,17). The mechanism of action of T regulatory cells is not yet well understood, but recent research evidence suggests that there are distinct populations of T regulatory cells (18), some of which are induced by UV irradiation. CD25+ CD4+ regulatory T cells expressing CTLA4 are a unique suppressive T cell line produced normally in the thymus. These regulatory T cells play an important role in removing self-reactive T cells that have escaped the process of clonal deletion (negative selection) in the thymus (19). Some T cells can provide antigen-specific immune suppression following induction by UVR (14). IL10 (produced in the epidermis following UVR irradiation [14,16]) may be important for the differentiation and activity of populations of T regulatory cells in the periphery (14,18). By suppressing self-reactive T cells, regulatory T cell populations may prevent auto-immune diseases (18,19).

Immunosuppression Due to UVA Irradiation

In the past, the deleterious effects of UVR exposure have been largely attributed to damage caused by higher energy UVB irradiation. More recently, attention has shifted to understanding the effects of UVA irradiation, in particular, in view of the wavelength composition of UVR at ground level and the greater penetration into skin structures of UVA than UVB (20). In a recent review, Halliday summarized this research and suggested that UVA has a dose-dependent effect on UVR-induced immunosuppression that may be as important as UVB-induced immunosuppression (21). At low doses (up to 840 mJ cm^{-2}), UVA appears to enhance secondary immunity (that is, strengthens the immune memory response) (21). At medium doses (1680 mJ cm^{-2}; one half a minimal erythemal dose), UVA is immunosuppressive, in part, via nitric oxide-induced depletion of LCs (22). At high doses, UVA may protect against UVB-induced immunosuppression by switching on interferon γ, IL12 (which can drive Th 1-type immune responses) and heme oxygenase production, with subsequent inhibition of UVB-induced increases in IL10 (21). Overall, Halliday concludes that UVA switches on a complex pattern of signals in a dose dependent way, but UVA is immunosuppressive in both man and mouse (21).

Immunosuppression Due to Enhancement of Vitamin D Production

Vitamin D is being increasingly recognized as an important immunomodulator (23). Some of the main immune actions of the active form of Vitamin D, 1,25(OH)$_2$D$_3$, are summarized below:

1. 1,25(OH)$_2$D$_3$ inhibits the production of Th1 type cytokines such as interferon γ, IL2 and IL12, limiting the IL12 driven expansion of dependent Th 1 cells (24).
2. 1,25(OH)$_2$D$_3$ and its analogs may suppress the activation of Th 1 cells by the direct modification of dendritic cells, inhibiting the differentiation and maturation into mature antigen-presenting cells (APCs) rendering them unable to stimulate T cells (25).
3. 1,25(OH)$_2$D$_3$ may enhance the presence and/or function of T regulatory cells (26). Studies done in animal models of MS, type 1 diabetes and transplantation support a model in which 1,25(OH)$_2$D$_3$ may augment the function of T suppressor cells to maintain self-tolerance (27).
4. 1,25(OH)$_2$D$_3$ may enhance phagocytosis by monocyte and macrophage populations (28).
5. 1,25(OH)$_2$D$_3$ may down-regulate acquired immune responses via an inhibitory effect on major histocompatibility complex class II antigen expression by professional antigen-replacing cells (28).

Immunosuppression by Other Mechanisms

Neuropeptides, released by sensory nerves, can also be involved in local and systemic immunosuppression after UV irradiation by induction of secondary mediators such as cytokines (29). A neuropeptide called α-melanocyte-stimulating hormone exhibits anti-inflammatory and immunomodulating activities by its effect on MC1R-expressing antigen-presenting cells. These cells include monocytes (30). α-MSH can down-regulate the production of proinflammatory cytokines and is a strong inducer of IL10 in monocytes and keratinocytes (30). Another neuropeptide, calcitonin gene-related peptide (CGRP), causes mast cells to degranulate and release IL10 (31). Melatonin may also play a role in immunomodulation. The sun not only emits ultraviolet electromagnetic waves but also visible light waves (400–700 nm) and infrared waves (700–3000 nm). Visible light waves, and, in particular, those with a wavelength close to the ultraviolet spectrum, suppress melatonin levels (32). Activation of melatonin receptors on T helper cells appears to enhance T lymphocyte priming and the release of Th 1 type cytokines (33, 34). Thus, Th 1 activity may also be reduced through UVR by increasing neuropeptides such as α-MSH or through associated visible light by reducing melatonin levels.

Although there are several pathways whereby UV irradiation causes immunosuppression, the clinical outcome of the combined effects of UVA and UVB irradiation, taking account of the ratios in which they occur naturally, their relative skin penetration and the production of vitamin D, remains unclear.

MULTIPLE SCLEROSIS

Multiple sclerosis is a leading cause of neurologic disability in early to middle adulthood. It is characterized by central nervous system inflammation, demyelination and scarring with lesions disseminated in time and location (35). The clinical course can be relapsing/remitting or progressive. MS is more common in women than in men, in a ratio of 2:1 and onset is typically between the ages of 20 and 40 years. Approximately 1.1 million individuals worldwide have MS, with the highest known prevalence in the Orkney Islands (250/100,000) and the lowest in Japan (2/100,000) (35).

One of the most striking epidemiological features of MS is a gradient of increasing prevalence with higher latitude. Such a gradient has been reported in Europe and the USA, with some exceptions (5). Differences in ethnic ancestry by latitude may contribute to the latitude gradient (36,37) but environmental factors may also be important. A protective effect of UVR-induced immunosuppression on MS is a possible contributing factor because ambient UVR levels decrease with increasing latitude (38). An early report showed that the association between MS prevalence and latitude at birth did not persist after adjustment for winter solar radiation (39).

For Australia, the decrease in annual averaged ambient UVR is 1 kJ m^{-2} per 10° latitudinal increase (40). Also a sixfold increase in MS prevalence exists from North Queensland (19° South in latitude) to Hobart, Tasmania (43° South in latitude) (41). The MS prevalence gradient persists even when the sample is restricted only to immigrants from the United Kingdom (42). No association between age of migration and MS risk was found in an Australian case control study (42), consistent with a strong field environmental effect operating in Australia beyond the early childhood period. We have recently reported a strong association ($r = -0.91$, $P = 0.01$) between regional UVR levels and MS prevalence in Australia (43).

Season of birth variation in MS risk has been examined in several studies. Ambient UVR varies seasonally with a winter nadir (44). A spring (45,46) birth excess has been reported for most studies (47) but not all (48), and others have reported an autumn excess (49) or bimodal pattern (50). A pooled analysis of datasets from Canada, Great Britain, Denmark and Sweden ($n = 42,045$) showed that significantly fewer (8.5%) people with MS were born in November and significantly more (9.1%) were born in May (51). This indicates the association between a seasonal factor and MS risk may not be linear; thus, a smooth sinusoidal curve by season may not occur, even if a factor that varies seasonally is associated with MS.

The winter–spring excess of births in schizophrenia has been hypothesized to reflect inadequate maternal vitamin D during a critical fetal programming period during early intrauterine life (50,52) because vitamin D has been shown to have a role in neural development (52,53). The hypothesis draws from recent advances in our understanding of the early origin of adult disease and proposes a 'critical window' during which vitamin D levels may have a persisting impact on adult health outcomes. With regard to autoimmune disease, vitamin D could also play a role in the development of central immunological tolerance, resulting in the elimination of self-reactive lymphocytes during lymphopoiesis. Such tolerance develops primarily in fetal life (2). In addition, serum 25OHD concentration from cord blood correlates positively with IL10 levels (54) and children born in summer compared with winter have a significantly higher IL10 to total IgE ratio (54). Because IL10 reduces both Th 1 and Th 2 responses to antigens (16), it is also possible that UVR and/or vitamin D may influence the likelihood that an individual shows tolerance to antigens and allergens in early life.

The onset of some forms of MS may be insidious and thus seasonal onset patterns are difficult to discern. Optic neuritis, however, is a common presentation of MS with often a clear pattern of onset. A seasonal pattern of monosymptomatic optic neuritis has been reported with a higher spring incidence than winter and a positive correlation between presentation and average monthly sunny hours ($r = 0.67$, $P = 0.02$) (55). This correlation, at first examination, may appear inconsistent with previous reports of an inverse association between UVR and MS. However, the underlying pathological process may have commenced several months previously and, if this were the case, optic neuritis disease initiation, rather than presentation, may still be inversely related to UVR levels.

The clinical course of relapsing-remitting MS has been characterized in some studies by a spring excess of relapses (56). In progressive MS, a winter peak of IFNγ and IL12 has been observed (57). A recent ecological study has shown a striking inverse correlation ($r = -0.85$) between population monthly serum 25OHD levels, which are largely UVR induced (12), and the mean monthly number of active MS lesions detectable by imaging scan two months later, among MS patients in South Germany (58). Although the distribution of active MS lesional activity in that study showed a seasonal pattern with a spring excess (58), another MRI study on 92 people with MS that examined intraindividual MS lesional activity did not report significant seasonal variation (59).

There are now several analytical epidemiological studies that have examined UVR and/or vitamin D and MS. The case control (60,61) and cohort (62) studies are outlined in Table 1. Although childhood sun exposure appeared particularly important with regard to MS onset in the Tasmanian case control study (61), occupational sun exposure has an inverse association with MS mortality in the U.S. death certificate study (60) and vitamin D supplementation after age 25 in the U.S. nurses cohort was inversely associated with MS onset (62). Thus, any beneficial action of UVR and/or vitamin D may operate in adulthood as well as childhood. Further, in the Tasmanian case control study, winter sun exposure appeared more important than summer sun exposure (61), consistent with the notion that inadequate UVR/vitamin D beneath a certain threshold may be involved. The U.S. Nurses Cohort Study was particularly important, as the reported association was prospective, using vitamin D measurements that had also been related to other vitamin D insufficiency disorders such as hip fractures (62).

The Oxford Record Linkage Study found that, in a ten year follow-up of people admitted to the hospital with MS, subsequent admission to the hospital for skin cancer was significantly less common than in a comparison cohort matched on age, sex and other factors (63). This study did not attempt to assess UVR before MS onset and thus this finding of a skin cancer deficit may partly reflect a contribution of lower postdiagnosis sun exposure among

Table 1. Case control and cohort studies reporting on the association between UVR and/or vitamin D and multiple sclerosis, type 1 diabetes or rheumatoid arthritis

Author, Year	Location	Design	Population	Control or cohort (N)	Case (N)	Outcome assessment	Exposure assessment	Adjusted covariates	Odds ratio	95% CI
Freedman et al., 2000[60]	USA (24 states)	Death certificate case control	Deaths 1984–1995 with same residence at birth and death	Controls n = 115 195	4282	Cause of death MS vs. other	1. Residential sunlight a) Low b) Med c) High 2. Occupational sunlight a) Indoor worker b) Outdoor worker	• Age • Sex • Race • Socioeconomic status	1. a) 1.00 b) 0.89 c) 0.53 2. a) 1.00 b) 0.75	(referent) 0.55, 0.63 0.48–0.57 (referent) 0.61–0.80
van der Mei et al., 2003[61]	Tasmania	Age- and sex-matched case control study	Tasmanian residents with a grandparent both in Tasmania	Controls n = 272	136	MS	1. Higher exposures at ages 6–15 (average 2–3 h or more a day during summer weekends and holidays) 2. Higher actinic damage on the dorsum of left hand (grades 4–6 vs. 3)	1. Melanin density, smoking history 2. Melanin density, smoking history, sun exposure after diagnosis	1. 0.31 2. 0.32	0.16–0.59 0.11–0.88
Munger et al., 2004[62]	USA	Prospective cohort	Nurses' Health Study I and II	(I) n = 92 253 (II) n = 95 310	173	Incident MS	Total vitamin D intake at baseline a) Highest vs. lowest quintile b) Vitamin D supplement use ≥400 IU/day vs. nil	• Age • Smoker • Latitude at birth	a) 0.69 b) 0.60	0.42–1.15 0.39–0.92
Eurodiab 2, 1999[75]	Seven European countries	Multicenter, Case control	Registry cases and population-based controls. Note control selection varied across centers, most commonly schools	Control n = 2335 (76%)	820	Type 1 diabetes by age 15 using validated registries	Report of vitamin D supplementation in infancy with partial record validation	• Breast-feeding duration >3 months • Maternal age • Birth weight • Study center	0.65	0.52–0.83
Stene et al., 2000[76]	Vest-Agder county, Norway	Case control	Birth cohort of 1982–98, resident in county during 1998	Control n = 1071 (73%)	85	Type 1 diabetes before age 15, on national register	a) Maternal report, regarding cod liver oil during pregnancy b) Maternal report regarding multivitamin use during pregnancy c) Maternal report regarding cod liver oil during first year of life d) Maternal report regarding vitamin D during first year of life	• Age • Sex • Breast-feeding • Maternal education • Other supplement use	a) 0.36 b) 1.11 c) 0.82 d) 1.27	0.14–0.90 0.69–1.77 0.47–1.42 0.70–2.31

Table 1. *Continued*

Author, Year	Location	Design	Population	Control or cohort (N)	Case (N)	Outcome assessment	Exposure assessment	Adjusted covariates	Odds ratio	95% CI
Hyponnen et al., 2001[77]	Northern Finland	Birth cohort	Live births due 1966	n = 10,366 (91% of live births to one year, 86% to 1997)	81	Type 1 diabetes by end of 1997 by registry, (type 2 diabetes checked for and excluded if age 20 or more at diagnosis)	Parental interview data at infant age 1 year 1. Vitamin D supplementation dose a) Recommended (2000 IU) vs. low (<2000 IU) b) High (>2000 IU) vs. low (<2000 IU) 2. Vitamin D supplementation frequency. a) Irregular vs. none b) Regular vs. none	• Sex • Gestational and maternal age • Parity • Maternal education • Social status • Standardized birth weight • Infant growth rate	1. a) 0.16 b) 0.12 2. a) 0.22 b) 0.14	0.04–0.74 0.03–0.51 0.05–0.89 0.02–1.01
Merlino et al., 2004[83]	Iowa, USA	Prospective cohort	Women aged 55-69 years who did not have RA in 1986, followed up in 1992 or 1997 surveys	At risk cohort n = 29 368 (follow-up = 314 181 person years)	152	Incident RA (validated)	1. Dietary vitamin D over past year at baseline by food frequency questionnaire a) <169 IU/day b) 169–289.9 IU/day c) ≥290 IU/day 2. Vitamin D supplement use at baseline by questionnaire a) Nonusers b) <400 IU c) ≥400 IU	• Age • Caloric intake • Smoking • Hormone replacement therapy • Decaffeinated coffee intake • β-cryptoxanthin intake	1. a) 1.00 b) 0.87 c) 0.72 Trend $p = 0.16$ 2. a) 1.00 b) 0.65 c) 0.66 Trend $p = 0.03$	(referent) 0.58–1.29 0.46–1.14 (referent) 0.36–1.15 0.43–1.00

people with MS. An alternative explanation is a common antecedent factor, giving rise to both a higher risk of MS and reduced risk of skin cancer. A small study of vitamin D, calcium and magnesium supplementation in MS patients showed that, after a period of 1–2 years, less than half the number of exacerbations were observed than the expected number based on case histories (64). More recently, a small ($n = 39$) randomized control trial comparing 6 months of 1000 international units of vitamin D and 800 mg calcium compared with 800 mg calcium alone reported a significant increase in transforming growth factor beta (TGF β) levels (65), an important anti-inflammatory cytokine (66). Randomized controlled trials to evaluate the effect of longer term vitamin D supplementation on clinical and MRI indicators of multiple sclerosis disease activity are required.

TYPE 1 DIABETES

Type 1 diabetes results from autoimmune destruction of pancreatic beta cells and consequent insulin deficiency. Onset may be at any age but is most common before the age of 30 years (35). The prevalence of type 1 diabetes has been increasing worldwide over the past two decades. The disease is equally common in men and women. There is considerable geographic variation in incidence of type 1 diabetes, from 35/100 000 in Finland to 3/100 000 in Japan and China (35).

A latitudinal gradient has also been reported for childhood diabetes (67,68). For example, in Europe an incidence increase has been observed with increasing latitude (6). An examination of climatic temperature and latitude appeared to explain 40% of the variation in type 1 diabetes incidence across 15 countries (67). A negative correlation between annual ambient UVR and type 1 diabetes prevalence ($r = -0.80$, $P = 0.018$) has been reported for Australia (69).

A seasonal pattern of births with a spring or summer excess has been reported in several locations (70–72) but this has not been found consistently (73). Recently, an investigation of seasonality of birth in 19 European regions found no uniform season of birth pattern (74).

Two case control studies (75,76) and one cohort study (77) have reported that vitamin D supplementation in infancy or cod liver oil (a vitamin D rich oil) supplementation is associated with a reduced risk of type 1 diabetes (Table 1). In the Finnish birth cohort, children with infant rickets, a bone disease reflecting vitamin D deficiency, had a threefold increased risk of type 1 diabetes (77). The finding that the risk of type 1 diabetes was sharply reduced at doses of vitamin D over 2000 international units/day in the Finnish cohort (77) suggests that the reason that vitamin D supplementation was not associated with type 1 diabetes in the study by Stene et al. (76) may be that vitamin D supplements in the latter study were given at a lower dose (78).

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic, multisystem inflammatory condition characterized by persistent inflammatory synovitis but having a highly variable clinical course (35). It affects approximately 0.8% of the population with a female-to-male ratio of approximately 3:1. Prevalence increases with increasing age, but sex differences decrease with age. The disease affects all races but is less common in rural sub-Saharan Africa (35).

Disease most commonly develops between the ages of 35 and 40 years and a clear latitudinal gradient has not been established to the same extent as for MS or type 1 diabetes (69). The disease is characterized by the overproduction of proinflammatory cytokines and an abnormal Th 1 type response (79). Vitamin D insufficiency or deficiency (80,81) has been documented in patients with rheumatoid arthritis.

Low $1,25(OH)_2D_3$ was associated with higher rheumatoid arthritis disease activity in cross-sectional studies (80–82). However, the finding of a positive correlation between $1,25(OH)_2D_3$ and alkaline phosphatase indicates this may in part reflect that people with higher disease activity have increased bone resorption (80).

Intervention trials of vitamin D or vitamin D analogues such as 1α-vitamin D on disease activity in patients with rheumatoid arthritis are reviewed by Zitterman (79). Intervention trials with a dosage of 1 μg 1α-vitamin D were not associated with an improved outcome. However, administration of higher amounts of 1α-D or other vitamin D forms was associated with improved pain symptomatology and a significant reduction in C reactive protein, a marker of inflammatory disease activity (79,82).

Dietary and supplemental vitamin D at cohort entry were associated with a reduced risk of incident rheumatoid arthritis in the Iowa cohort (83) (Table 1). An interesting feature of this study was that the cohort consisted of women aged 55 years and older at cohort entry, indicating that the apparent beneficial effect of vitamin D supplementation was evident in middle or older age.

ARE THESE FINDINGS CAUSAL?

The findings presented above provide some evidence of an association between low UVR and/or vitamin D and these three disorders, but these findings are not conclusive. However, many of the findings suggest that these associations may reflect an underlying causal protective role for low UVR and/or vitamin D. A high degree of biological plausibility for a beneficial effect of UVR-induced immunomodulation is suggested by photoimmunological work. Some of the pathways for this effect are independent of vitamin D. The ecological findings are generally coherent but with some exceptions. In general, the case control and cohort studies shown in Table 1 are consistent. Many of the associations in Table 1 are of high magnitude and have a dose–response gradient. Cohort studies now show that low vitamin D is prospectively associated with disease onset for all three diseases. At the time of our last review (1), only one of the three cohort studies listed in Table 1 had been published. The timing of action of any UVR/vitamin D effect is not clear. As discussed, fetal and early life may be important, but at least three analytical studies (60,62,84) indicate an effect in adult life. The current observational case control and cohort studies have not fully excluded that a confounding factor associated with sun exposure behavior or vitamin D ingestion is contributing to the apparent inverse association between these factors and disease onset. There remains a lack of human experimental studies on the effect of UVR and/or vitamin D on the onset or progression of these three diseases. A detailed consideration of the relative merits of different types of intervention studies is beyond the scope of this review. For MS, randomized controlled trials of vitamin D and/or ultraviolet irradiation would be more feasible in relation to disease progression than onset.

GENETIC STUDIES

Genetic studies can provide indirect information to strengthen the likelihood that an environmental factor, such as low UVR, is causally related to autoimmune diseases. First, if the adverse effect of a low level of exposure to an environmental factor on disease is specifically observed in individuals with a genetic vulnerability to develop disease, then this information helps to "rule in" an environmental factor as a true disease determinant. In addition, genetic studies can provide important information on the mechanisms involved in diseases associated with low UVR and/or vitamin D.

Individual variation in pigmentation could influence the response of UVR. The MC1R plays a key role in the production of the skin pigment melanin. A fair skin type or low melanin has been associated with an increased risk of both type 1 diabetes and MS (61,84). Recently, His294-encoding MC1R variants were associated with an increased risk of MS (85). MC1R is activated by MSH, which is also involved in UVR-induced immunosuppression. The hormone can modulate the function of MC1R expressing monocytes and also down-regulate the expression of MHC class I molecules on monocytes (30). In MS, for example, the HLA class I region has been associated with risk of MS (86), and thus it is possible that a gene–gene interaction might exist between gene variants related to MC1R and HLA class I.

Another genetic candidate is the vitamin D receptor (VDR) gene. VDRs are present in a number of cell types including Th 1 cells. Several polymorphisms have been identified in the VDR gene, one of which (FokI) has been associated with altered VDR gene expression or function (87). In MS, some studies (88,89) found an association between VDR gene polymorphisms and MS but not all (90). One study also found evidence for interaction between VDR polymorphisms with HLA class II alleles (89). Variation in vitamin D receptor gene status has been associated with type 1 diabetes in two populations (91,92), but no association has been found for rheumatoid arthritis (93,94).

IMPLICATIONS OF THESE FINDINGS FOR SUN EXPOSURE GUIDELINES

Photoimmunological work shows that many of the effects of UVR on immune function appear to be independent of pathways involving vitamin D. Data from human studies are currently not sufficient to allow a disentangling of the possible relative contribution of low UVR from low vitamin D. Without this information, it is difficult to be sure that use of a vitamin D supplement among sun avoidant persons would completely compensate for insufficient UVR exposure if insufficient UVR exposure was causally related to disease.

The findings summarized in this review highlight the critical importance of considering the benefits as well as adverse effects of UVR for a wide range of human health outcomes, not just skin cancer or rickets, when formulating public heath policy on UVR exposure (95). The evidence discussed in this review indicates that adverse effects related to immune overactivity could potentially be a problem for people with low personal sun exposure and vitamin D deficiency. Note that for health effects that are mediated through vitamin D, dietary vitamin D intake needs to be considered. There is a need to provide information on the minimum sun exposure required for beneficial health effects, including the maintenance of vitamin D levels, and the maximal sun exposure to avoid the adverse health effects associated with excessive sun exposure. Sun exposure advice needs to take into account not only time in the sun but also time of day, season, residential latitude, area of exposed skin, pigmentation and dietary vitamin D intake (96). Further work is required to assess the correct titration of human exposure to ambient UVR for optimal immune function and overall health.

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