

Ultraviolet radiation and organ-specific auto-immune disease: insights from epidemiological research

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Abstract. This review examines the epidemiological evidence that suggests ultraviolet radiation (UVR) may play a protective role in three autoimmune diseases: - multiple sclerosis, insulin-dependent diabetes mellitus and rheumatoid arthritis. Latitudinal disease prevalence gradients, seasonal influences on both disease incidence and clinical course and, more recently, analytical studies at the individual level have provided further support for a possible protective role for UVR in some of these diseases but the data are not conclusive. Organ-specific autoimmune diseases involve Th1 cell-mediated immune processes. Recent work in photoimmunology has shown ultraviolet B (UVB) can specifically attenuate these processes through several mechanisms which we discuss

Review

Accumulating evidence that excessive exposure to solar ultraviolet radiation (UVR) can increase the risk of skin cancer has led to health promotion activities aimed at reducing human UVR exposure [Ness *et al.*, 1999]. For example, it has been recommended that infants less than six months should not be exposed to direct sunlight and that pediatricians should incorporate sun protection advice into their health supervision practices [AAP, 1999]. However, any notion that UVR is inherently an adverse exposure to be maximally avoided cannot be fully reconciled with our evolutionary heritage. After all, we must presume that levels of skin pigmentation in regional populations originally evolved over many millennia to optimise the amount of UVR absorbed by the skin in terms of the balance of biological benefits and risks. The possible benefits of UVR exposure on human health should therefore be assessed alongside the adverse effects [Ness *et al.*, 1999].

In this review, we discuss the epidemiological findings that suggest a possible beneficial role for UVR on three autoimmune diseases: multiple sclerosis (MS); insulin-dependent diabetes mellitus (IDDM); and rheumatoid arthritis (RA). Organ-specific T lymphocyte-mediated autoimmune inflammation appears to underlie these three diseases [Mackay, 2000]. Genetic factors appear to be involved but the low concordance among identical twins for MS and IDDM and temporal trends over time suggest environmental factors are also important disease determinants. A temporal increase in the annual incidence of childhood IDDM of 3.4% (2.5 – 4.4%) has been documented in Europe from 1989 to 1994. [Eurodiab ACE Study Group, 2000].

These autoimmune diseases are characterised by a breakdown in immunological self-tolerance that may be initiated by an inducing infectious or dietary agent [Mackay, 2000]. A cross-reactive autoimmune response occurs and a 'self-molecule' is no longer self-tolerated, but becomes immunogenic, attracting a T helper cell type 1 (Th1)- mediated response that results in chronic inflammation [Mackay, 2000]. Recent work suggests that UVR exposure may be one factor that can attenuate Th1-mediated immune responses through several mechanisms. Firstly, UVR can cause local immunosuppression [Kripke, 1994] and a reduction in contact hypersensitivity and delayed type hypersensitivity [Duthie *et al.*, 1999; Kripke, 1994]. Sub-epidermal cytokine signalling alterations can also induce soluble mediators which can exert systemic immunosuppression [Goettsch *et al.*, 1993; Kripke, 1994]. Secondly, the active form of vitamin D (1,25(OH)₂D₃), derived from UVR-supported biosynthesis, has immunomodulatory effects [Hayes *et al.*, 1997; Lemire, 1992]. Peripheral monocytes and activated T helper cells have vitamin D receptors and vitamin D or its analogues can down-regulate T helper cell activity [Lemire, 1992]. Thirdly, sunlight suppresses melatonin secretion [Liebmann *et al.*, 1997]. Activation of melatonin receptors on T helper cells appears to enhance T lymphocyte priming and the release of Th1 type cytokines such as interferon gamma [Liebmann *et al.* 1997]; [Maestroni, 2001]. A role for UVR in promoting the secretion of melanocyte stimulating hormone (MSH), which may suppress Th1 cell activity, has also been proposed [Constantinescu, 1995]. Overall, these findings indicate that UVR can suppress Th1-mediated immune activity.

One of the most striking epidemiological features of MS is a gradient of increasing prevalence with latitude. This is consistent with the hypothesis of a protective effect for UVR-induced immunosuppression on MS [McMichael and Hall, 1997] because annual averaged UVR levels decrease with increasing latitude. In Australia, a sixfold increase in MS prevalence from North Queensland (latitude 19°S) to Hobart, Tasmania (43°S) exists [McLeod *et al.*, 1994]. The gradient persists even among immigrants from the United Kingdom and Ireland, a subgroup of similar ancestry [Hammond SR *et al.* 2000]. We have recently reported a strong association between regional UVR levels and MS prevalence in Australia ($r = -0.91$, $p = 0.01$) [van der Mei *et al.*, 2001]. A latitudinal gradient has also been reported for childhood IDDM. An examination of childhood IDDM incidence across fifteen countries reported that a model based on temperature and latitude appeared to explain 40% of the variation in IDDM risk

(Diabetes Epidemiology Research Interest Group 1988). A recent review has also noted that RA has also been reported to be more common at higher latitudes [*Cantorna, 2000*].

For childhood IDDM, a seasonal pattern of births with summer excess has been reported in several but not all locations. The season of birth results have been less consistent for MS and RA. In view of the increasingly seasonal distribution of ambient UVR with increasing latitude, a formal assessment of how seasonal birth risk varies by latitude is required to assess the contribution of latitude of birth to these conflicting findings. The winter-spring excess of births in schizophrenia has been suggested to possibly reflect inadequate maternal vitamin D during a critical foetal programming period during early uterine life [*McGrath, 1999*] because vitamin D has been shown to have a role in neural [*Musiol and Feldman, 1997*] and immunological [*Bouillon et al., 1995*] development. An analogous situation is possible with autoimmune disease because central immunological tolerance, resulting in the elimination of self-reactive lymphocytes during lymphopoiesis, develops primarily in fetal life [*Mackay, 2000*].

Seasonality of disease onset is a well described feature of childhood IDDM with most [*Karvonen et al., 1998; Neu et al., 1997; Toth et al., 1997*], not all [*Ramachandran et al., 1996*], studies reporting seasonality in IDDM incidence. Again, a formal examination of how the seasonal pattern of disease onset varies by latitude could be informative. The onset of RA or MS may be more insidious than IDDM and thus temporal onset patterns are more difficult to examine. The clinical course of relapsing-remitting MS has been characterised in some studies by a spring excess of relapses [*Sandyk and Awerbuch, 1993*]. In progressive MS, a winter peak of interferon-gamma and interferon 12 has been observed [*Balashov, 1998*]. A recent ecological study has shown a striking inverse correlation ($r = -0.85$) between population monthly serum 25(OH) D levels, which are largely UVR-induced [*Holick, 1994*], and the mean monthly number of active MS lesions detectable by imaging scan two months later among MS patients in South Germany [*Embry et al., 2000*].

Overall, these ecological studies have some epidemiological features that are consistent with the hypothesis that UVR-induced immune suppression is beneficial for these diseases. However, the evidence is far from conclusive. These studies lack individual exposure level data and within populations there is a wide log normal distribution of personal sun exposure [*Gies et al., 1999*]. Furthermore, these studies cannot control for the confounding effect of other possible causal factors in the aetiology of these diseases that may also vary by latitude or season, such as infection or diet. In addition, because of the lack of data on joint exposures at the individual level, possible interactions between environmental exposures can not be studied for these complex diseases.

There has been a lack of observational analytical epidemiological studies on the association between UVR exposure and the incidence or clinical course of these diseases. A recent analytical case-control study on MS mortality recently reported that among outdoor workers,

the adjusted odds ratios for low, medium and high regional sunlight were 0.89(0.64, 1.22), 0.52(0.38, 0.71) and 0.24(0.15, 0.38) for MS compared to indoor workers with low ambient sunlight ([*Freedman et al., 2000*]).

We now consider vitamin D in relation to these diseases. Vitamin D deficiency has been noted among patient groups with RA and MS for many years but earlier reports highlighted that this may reflect disease-related alterations to either dietary or solar determinants of vitamin D or changes in vitamin D metabolism [*Als et al., 1987; Nieves et al., 1994*]. In rheumatoid arthritis, intervention with vitamin D or its analogues has been linked to lower levels of disease activity [*Andjelkovic et al., 1999; Oelzner et al., 1999*]. A small study of vitamin D and mineral intervention in MS patients showed that, after a period of one to two years, less than half the number of exacerbations were observed compared to the expected number based on patient case histories [*Goldberg et al., 1986*]. Although the ecological report of an inverse association between 25(OH) D level and MS disease activity [*Embry et al., 2000*] could possibly reflect that 25(OH) D was a good marker for other UVR-induced processes that independently suppressed disease activation, other findings indicate that vitamin D, itself, may be the pertinent UVR-related exposure. First, in 1999 the Eurodiab Group reported that vitamin D supplementation in infancy was inversely associated with childhood IDDM (AOR 0.65(0.52, 0.83)) in a multicentre case-control study [*Group, 1999*]. Second, a population-based case control study in Norway found mothers of children with IDDM were less likely to report antenatal supplementation with Vitamin D-rich cod liver oil [*Stene et al., 2000*]. Third, a birth cohort study in Finland reported that children who took Vitamin D supplements in early life were less likely to develop IDDM (RR 0.22(0.05-0.89)) [*Hyponnen et al. (2001)*]. Fourth, molecular epidemiological work has shown that individuals with vitamin D receptor gene allelic variants [*Zmuda et al., 2000*] are at increased risk of MS in a Japanese population [*Fukazawa et al., 1999*]. Variation in VDRG status has also been associated with IDDM [*Chang et al., 2000; McDermott et al., 1997*].

These several studies indicate that any beneficial effect of UVR on these diseases may be mediated through photosynthesised vitamin D. However, among darkly pigmented and lightly pigmented people, differences in disease incidence, particularly for MS, show some discrepancy with regard to this hypothesis. For a given level of UVR exposure, individuals with darkly pigmented skin are more prone to developing vitamin D deficiency [*Holick, 1994*]. Dark skin immigrants to higher latitudes have been shown to have an increased rate of vitamin D deficiency and this has been associated with a higher prevalence of several non-autoimmune diseases that are related to vitamin D deficiency. However, in general, host Caucasian populations have higher rates of MS. In the US, the MS prevalence rates in African-Americans are half those for white Americans [*Hogancamp et al., 1997*].

This apparent anomaly could reflect one or more of the following four explanations:

- (i) autoimmune disease prevalence is under-reported in vitamin D deficient populations;

- (ii) vitamin D deficiency during early life may be more important (in the United Kingdom, whereas MS was uncommon among adult immigrants from India, Asia and Africa, the children of these immigrants had a higher MS prevalence similar to the general English population [Elian *et al.*, 1990];
- (iii) people with darker skin may have other immunological changes related to skin pigmentation, not mediated by vitamin D, that can counter any effect of vitamin D deficiency on autoimmune up-regulation [Rees and Flanagan, 1999];
- (iv) protective factors operating outside the pathway of UVR-induced suppression are more common in dark-skinned populations (e.g. earlier age of childhood infections with Epstein-Barr virus).

Even if the apparent beneficial effect of UVR-induced immunosuppression was mediated through vitamin D, we argue that, because sunlight is a naturally occurring exposure, there is still a need to understand fully the spectrum of related health effects so that appropriate advice can be given with regard to personal UVR exposure.

In conclusion, the epidemiological features of these autoimmune diseases are, in part, consistent with recent photoimmunological work showing UVR-mediated immune suppression through several mechanisms. Some studies suggest that higher vitamin D levels may mediate any beneficial effect of UVR. However, the data are not conclusive and further analytical epidemiological and biomolecular work is required to assess the health risks and benefits and, hence, the correct titration of this important natural exposure for optimal human health.

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