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Ultraviolet radiation and autoimmune 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. To date, most of the information has accumulated from population studies that have studied the relationship between geography or climate and autoimmune disease prevalence. An interesting gradient of increasing prevalence with increasing latitude has been observed for at least two of the three diseases. This is most evident for multiple sclerosis, but a similar gradient has been shown for insulin-dependent diabetes mellitus in Europe and North America. 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. In particular, the possible contribution of an UVR-induced increase in serum vitamin D ($1,25(OH)_2D_3$) levels in the beneficial immunomodulation of these diseases is discussed.

Keywords: Autoimmune disease; Epidemiology; Diabetes mellitus; Multiple sclerosis; Vitamin D

1. Introduction

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 6 months should be kept out of direct sunlight and that pediatricians should incorporate sun protection advice into their health supervision practices (AAP, 1999). However, the 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

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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) in the context of recent developments in photoimmunology. 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 (Hogancamp et al., 1997) and IDDM (Eurodiab ACE Study Group, 2000) and temporal trends over time suggest environmental factors are also important disease determinants. The trend in MS incidence over time is difficult to interpret in view of changing diagnostic procedures. 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, with a higher increase among children less than 5 (Eurodiab ACE Study Group, 2000).

2. Photoimmunology and organ-specific autoimmune disease

These autoimmune diseases are characterised by a breakdown in immunological self-tolerance that may be initiated by an inducing agent such as an infectious microorganism (possibly acting via molecular mimicry) or a foreign antigen from food (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). 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 ($1,25(OH)_2D_3$), 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 (IFN γ) (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.

3. Latitude, season and these autoimmune diseases

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. For Australia, the decrease is 1 kJ m^{-2} per 10° latitudinal increase (Udelhofen et al., 1999). An increase in MS is generally found with increasing latitude in Europe and the USA, with some exceptions (Hogancamp et al., 1997). In the US, differences in ethnic ancestry by latitude may also contribute to the latitude gradient (Page et al., 1993). However, in the first Nurses' Health Survey, a gradient of increasing MS incidence with latitude was observed after adjustment for confounders, including ancestry (Hernán et al., 1999). Also, an earlier report showed that the association between MS prevalence and latitude at birth did not persist

after adjustment for winter solar radiation (Acheson et al., 1960).

In Australia, a 6-fold 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 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). The amplitude of the change in MS prevalence by latitude (a nearly 4-fold increase) (McLeod et al., 1994) between Brisbane (28°S) and Hobart (43°S) is more consistent with the UVR difference between Hobart and Brisbane mid-winter (a 4.9 fold difference in daily total effective UVR in mean erythemal doses (MEDs)) (Gies, 1994) than mid-summer (a 1.2-fold difference in daily total effective UVR (MEDs)) (Gies, 1994). A latitudinal gradient has also been reported for childhood IDDM. An examination of childhood IDDM incidence across 15 countries reported that a model based on temperature and latitude appeared to explain 40% of the variation in IDDM risk (Diabetes Epidemiology Research International Group, 1988). In Europe, an approximately 3-fold incidence increase has been observed with increasing latitude (Eurodiab ACE Study Group, 2000) and a gradient of increasing incidence with latitude has also been reported within China (Yang et al., 1998). A recent review has also noted that RA has also been reported to be more common at higher latitudes (Cantorna, 2000).

The seasonal variation of UVR, with a winter nadir, increases with increasing latitude. For example, within Australia, the mid-summer to mid-winter ratio of daily effective UVR (MEDs), in Darwin (12°S) is 1.1 while the ratio is 3.0 for Brisbane (28°S) and 12.8 in Hobart (43°S) (Gies, 1994). For childhood IDDM, a seasonal pattern of births with summer excess has been reported in several locations (Rothwell et al., 1999; Samuelsson et al., 1999; Schranz, 1998) but this has not been consistently found (Jongbloet et al., 1998; Rothwell et al., 1999). RA has not been studied to the same extent, although one report found no variation with month of birth (Buchanan et al., 1987). Variation in MS risk has also been reported, with a spring (James, 1991; Sadovnick and Yee, 1994; Templer et al., 1992) or autumn (Salemi et al., 2000) birth excess. 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. 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 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. Optic neuritis (ON) is a common presentation of MS characterised by acute disease onset with a short latent time to diagnosis (Jin et al., 1999). A seasonal pattern of monosymptomatic ON has been reported with a higher spring incidence compared to winter and a positive correlation between presentation and average monthly sunny hours ($r = 0.67$, $P = 0.02$) (Jin et al., 1999). This correlation, at first examination, may appear inconsistent with previous reports of an inverse association between UVR and MS. However, ON presentation may well reflect an underlying pathological process that may have commenced some months prior and, if this were the case, ON disease initiation, rather than presentation, may still be inversely related to UVR. Optic neuritis is likely to be affected by direct environmental exposures acting at the back

of the retina (Hutter and Laing, 1996) of which visible light is an obvious exposure with seasonal variation. 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 IFN γ 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 2 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. Low dietary omega-3 fatty acids have been implicated in MS (Hutter and Laing, 1996) and have also been shown to increase UVB-erythemal sensitivity (Rhodes et al., 1994). Infections may play a role in autoimmune disease development but UVR exposure may act as a modifier, down regulating infection-induced T helper cell overactivity (McMichael and Hall, 1997).

4. Analytical epidemiological studies on UVR and these autoimmune 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. Potential cohort studies to examine relationships between past UVR exposure and MS, IDDM or RA incidence are hampered by difficulties in serial exposure measurement during childhood, a long latent period (particularly for MS and RA) and the low incidence of these diseases at the population level. Cohort studies to examine the effect of personal UVR exposure on disease progression are more feasible, particularly for MS. Case-control studies may be hampered by poor exposure measurement of past sun exposure and recall bias. The measurement of lifetime sun exposure has been problematic in skin cancer epidemiology over time (Armstrong and Kricker, 1995). The rarity of these autoimmune diseases has generally led to prevalent rather than incident case-control studies. However, since sun exposure and dietary vitamin D intake may be affected by the presence, severity or duration of disease, the contribution of disease to the measurement of these exposures must be carefully considered.

Recent improvements in communication technology now enhances the opportunity to conduct multicentre incident case-control studies, which include the additional benefit of providing large variation in field exposures such as ambient UVR. Study measurements to assess past sun exposure are also developing. These include measurements of age-adjusted actinic damage on the dorsum of the hand (Fritschi et al., 1995) the possible use of a ratio of spectrophotometric melanin density in exposed to unexposed sites to indicate cumulative lifetime sun exposure (Lock-Andersen et al., 1998) and the possible use of mitochondria DNA deletions in the epidermis as a candidate biomarker for past UVR exposure (Birch-Machin, 2000). The use of dietary-adjusted serum 25(OH)D levels as a biomarker for UVR exposure over the past 1–2 months also requires consideration. Furthermore, the classification of skin phenotype, a possible confounder or effect modifier of UVR-induced suppression, has improved with the use of spectrophotometric skin measures at 400–420 nm which correlate ($r = 0.68$) with melanin density histologically (Dwyer et al., 1998). These recent advances, together with our growing understanding of photoimmunology, indicate that future analytical observational studies on this issue should

prove worthwhile. 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).

5. Vitamin D and these autoimmune diseases

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 1–2 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 (Eurodiab Substudy 2 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 cod liver oil, a substance rich in vitamin D and omega-3 fatty acids. The adjusted odds ratio for cod liver oil consumption in pregnancy and childhood IDDM was 0.36 (0.14, 0.90) (Stene et al., 2000). Third, a birth cohort study in Finland recently reported that children who took the recommended dose of vitamin D during the first year of life (2000 IU daily) had a lower risk of subsequent Type 1 diabetes (RR 0.22 (0.05–0.89)) (Hypponen 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 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 EpsteinBarr

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.

6. Conclusion

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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