

Sun exposure, vitamin D and immune function - where to now?

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Abstract. Exposure of the skin to UV radiation causes local and systemic immunosuppression through vitamin D and non-vitamin D pathways. This has implication for skin cancer development, autoimmune diseases and vaccination. New studies are exploring the clinical and public health importance of UV-induced immune suppression.

Introduction

Animal and human studies show that exposure of the skin to UV radiation causes both local and systemic immune suppression (reviewed in (Norval & Halliday 2011)). This is important to the development of skin cancers, where suppression of the immune system “permits” growth of abnormal cells. Immune suppression following high dose UV irradiation also allows reactivation of viral infections, e.g. cold sores on the lips.

Latitudinal variation in the incidence, prevalence and/or mortality of some autoimmune diseases suggests a possible role of (low) sun exposure in their etiology. That is, UV radiation suppresses the over-reactivity of the immune system that underlies these autoimmune diseases. For example, there was an almost 7-fold increase in the prevalence of multiple sclerosis (MS) in Australia in 1981 comparing Townsville to Tasmania. Interestingly, in the USA, a latitude gradient in prevalence of MS in the first Nurses’ Health Study (participants born before 1946) had disappeared in the second Nurses’ Health Study (born after 1946) (Ascherio & Munger 2007).

These geographic patterns of disease occurrence have been attributed to a protective effect of higher vitamin D levels. Observational studies have also shown that higher levels of sun exposure, or vitamin D status, are associated with decreased incidence of MS, although the evidence for other autoimmune diseases has been less convincing.

Most recently, animal and human studies have suggested that higher levels of exposure to UV radiation may have beneficial effects for MS through both vitamin D and non-vitamin D pathways (Becklund et al. 2010, Lucas et al. 2011). Notably, although lower latitude and higher sun exposure are commonly used as proxies of higher vitamin D status, so too is higher vitamin D status a proxy for higher sun exposure. Thus in observational studies, beneficial effects of higher vitamin D status could reflect the importance of higher levels of sun exposure itself. Unravelling the independent contributions of vitamin D and sun exposure in the risk of autoimmune diseases is now a field of active research (Hart et al. 2011)

The immune system can be separated into innate and adaptive components, with considerable cross-communication between them. Innate immunity is the primitive immunity also found in lower order animals. Trafficking of immune cells to the site of the threat and the ensuing inflammatory response contains the threat, with subsequent destruction of the pathogen by immune cells and the chemicals they produce. In the innate system, a

similar response occurs even when the same threat is encountered again. In the adaptive immune system, found only in primates and humans, the first encounter with a pathogenic threat “trains” the immune system; “memory” of that threat is retained life long, and a second encounter, the immune response is faster and more efficient. This adaptive memory response is the basis for vaccination.

Vitamin D is thought to up-regulate innate immunity, but down-regulate some of the adaptive immune pathways. UV irradiation also down-regulates parts of the adaptive immune system, including through non-vitamin D pathways, possibly involving cis-urocanic acid, nitric oxide or other mediators. While suppression of adaptive immunity could protect against autoimmune diseases, there is some limited evidence that it may also impair the immune response to vaccination.

Where to now?

In a suite of studies in the last five years we have further investigated the association between sun exposure, vitamin D and immune function.

In the Ausimmune Study, we examined the risk of having a first attack of central nervous system (CNS) demyelination (FDE) that is a common precursor of MS, in four regions of Australia: Brisbane (27°S), Newcastle (33°S), Geelong (37°S) and Tasmania (43°S). We showed that, in Australia, the latitude gradient in CNS demyelination observed in 1981 was still present in 2006, and of similar magnitude (Fig 1).

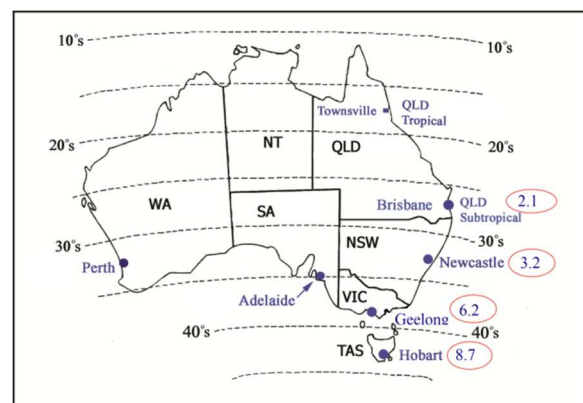


Figure 1. Incidence of FDE in Australia (per 100,000 per year), 2003-6 (data from (Taylor et al. 2010))

Higher vitamin D status was associated with decreased FDE risk – as were higher levels of sun, including when both factors were included in the same statistical model. This suggests that sun exposure is affecting FDE risk independently of vitamin D status. This finding is now being taken forward in two trials aiming to prevent the progression from FDE to clinically definite MS: the PrevANZ Study, a clinical trial of vitamin D

supplementation; and the PhoCIS Study, a clinical trial of UV-B phototherapy. The study protocols are aligned and data will be comparable. These studies will elucidate whether exposure to UV-B radiation and/or vitamin D status affect the risk of developing MS.

We have also examined geographic variation in type 1 diabetes in Australia. Here there was an inverse latitude gradient – increasing incidence with decreasing latitude and ambient UV radiation. However, the gradient reversed in areas of high population density (Elliott et al. 2010). This is consistent with lower sun exposure reported in urban, compared to rural, regions.

Additional work is now being undertaken in type 1 diabetes to further explore geographical patterns but also to look at individual-level associations between vitamin D metabolites and type 1 diabetes risk. Clinical trials to-date to prevent type 1 diabetes in children at high risk have not shown a convincing protective effect.

We have also explored the immune response to vaccination. In the AusUVI Study, 210 volunteers living in Canberra or Townsville were vaccinated with a novel antigen and their sun exposure (using electronic dosimeters), vitamin D status, and immune responses monitored. Higher levels of exposure to UV radiation on the day before, and the day of, vaccination resulted in an impaired cellular adaptive immune response. There was no association with vitamin D status. We now aim to test the relevance of this level of immune suppression in populations receiving vaccinations in locations with high ambient UV radiation levels or where there is a risk of high sun exposure around the time of vaccination.

Recent work has suggested that levels of free or bioavailable vitamin D may be of most importance to some health outcomes (Powe et al. 2013). The vitamin D metabolites circulating in the blood are largely tightly bound to a vitamin D binding protein. There are different genetic forms of this protein, with different affinities for vitamin D metabolites. A small proportion of the circulating vitamin D metabolites are free in blood or loosely bound to albumin. Studying bioavailable vitamin D in relation to autoimmune diseases may provide more insights into the biological risk pathways.

Conclusion

Sun exposure (Lucas et al. 2013) and vitamin D levels (Salzer et al. 2012) have both been decreasing over the past 30 years. Along with these decreases, the incidence of a range of autoimmune diseases has been increasing (Bach 2002). Such co-occurrences may be coincidental, but deserve full exploration. Sun exposure is the main risk factor for cutaneous malignant melanoma. Over the last ten years there has been a slowing and then a decrease in annual melanoma incidence in younger age groups in Australia. This is likely to be the beneficial result of decreasing levels of sun exposure, particularly high dose intermittent sun exposure.

Understanding whether there are beneficial effects of sun exposure other than the synthesis of vitamin D is important in determining whether moderated sun exposure, rather than sun avoidance with vitamin D supplementation is the required for optimal health.

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