Vitamin D, UVR and three autoimmune diseases: an update

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Abstract. There is increasing experimental and epidemiological evidence that UVR exposure and/or vitamin D intake may be protective for the development of some autoimmune diseases: multiple sclerosis, type 1 diabetes and rheumatoid arthritis.

Introduction

Current sun safe messages stress sun protection to avoid the adverse health effects of excessive sun exposure – skin cancers and eye damage. However, UVR exposure also has beneficial effects, particularly through the induction of vitamin D synthesis via cutaneous irradiation. Furthermore, there may also be other, direct, beneficial effects of UVR irradiation of the skin particularly on immune function.

The Human Immune Response

The human immune response has two interacting arms. The primitive, innate immune response is mediated by white blood cells, complement, cytokines and acute phase proteins and provides a rapid but rather non-specific and poorly targeted immune response with particular effect against extracellular organisms such as bacteria. The adaptive immune response is found only in higher animals and is precise and specific but rather slow. It is mediated by specialized T and B lymphocytes and cytokines and characterized by immunological memory: each subsequent exposure to an antigen is associated with a more vigorous and rapid response. On antigenic stimulation, B lymphocytes may transform into plasma cells to secrete antigen-specific antibody. Different T cell populations can be directly cytotoxic or become T regulatory cells (responsible for controlling self-reactive T cells systemically) or "helper" T cells – assisting B cells with antibody production (Th2 cells) or assisting cytotoxic T cells (Th1 cells). Th1 and Th2 immune responses are relatively, but not completely, antagonistic.

Vitamin D

Vitamin D is formed in the skin by the action of UVB radiation on 7-dehydrocholesterol (7-DHC) incorporated in the plasma membrane of epidermal keratinocytes. 7-DHC undergoes chemical rearrangement in the skin and then is transported in the blood and further metabolized in the liver (25(OH)D) and kidney ($1,25(OH)_2D_3$). Older age, deeper skin pigmentation, sunscreen use and obesity impair the vitamin D producing potential of UVB exposure. In addition, time of day, season, cloud cover and latitude alter the number of UVB photons available for vitamin D production.

Vitamin D has well known beneficial effects for the musculo-skeletal system [1], but there is increasing evidence of other beneficial effects: vitamin D receptors are present in many body tissues, including the colon, prostate, breast, heart, β-islet cells of the pancreas and activated T and B lymphocytes; vitamin D stimulates insulin production and has effects on myocardial contractility; vitamin D regulates cell proliferation and differentiation and may thus have an anti-tumour action; vitamin D modulates T and B lymphocyte function.

UVR – induced immunosuppression

UVR exposure causes local and systemic immunosuppression both directly, and indirectly via enhanced vitamin D synthesis.

UVB irradiation of the skin causes DNA damage and oxidative stress in keratinocytes and Langerhans cells and isomerization of urocanic acid from the trans to the cis forms. These actions suppress natural killer cells of the innate immune response and impair antigen presenting function. In addition UVB irradiation is associated with increased levels of Th2 cytokines, TNF-α and IL-10 and the induction of T regulatory cells. Because Th2 and Th1 immune response are relatively antagonistic, the increase in Th2 cytokines tends to suppress Th1 (cell-mediated) pathways.

UVA irradiation probably also has important immunosuppressive effects, but these are less well-researched. The effects of UVA immunosuppression may be dose dependent, with low doses enhancing the immune memory response, medium doses (eg ½ MED) immunosuppressive due to depletion of Langerhans cells and high doses possibly protective against UVB immunosuppression and enhancing a Th1 immune response.

However, UVB irradiation also results in the production of vitamin D which has independent immunosuppressive effects. Vitamin D inhibits production of Th1 cytokines, induces T regulatory cells, suppresses activation of Th1 cells by inhibiting the maturation of antigen presenting cells and enhances phagocytosis by white blood cell lines.

UVR irradiation also stimulates the release of several neuropeptides, α-melanocyte stimulating hormone, calcitonin gene related peptide and substance P, which may have immune effects, particularly to induce IL-10 (Th2 cytokine) and inhibit the function of antigen presenting cells.

The overall effect from both direct and indirect effects of UVR exposure of the skin is both local and systemic immunosuppression, with particular suppression of cell-mediated (Th1) immune function and induction of circulating T regulatory cells.

Autoimmune Diseases

Multiple sclerosis, type 1 diabetes and rheumatoid arthritis are autoimmune diseases thought to be characterized by overactivity of the Th1 immune response and reactivity to self-antigens. The experimental evidence presented in the previous section is consistent with growing epidemiological evidence of a protective effect of UVR exposure on the onset and/or progression of these three diseases.

Multiple sclerosis (MS): MS is the leading cause of neurological disability in early to middle adulthood in Australia. It is characterized by central nervous system inflammation, demyelination and scarring with lesions disseminated in time and location. There is a striking latitudinal gradient of increasing MS prevalence with higher latitude. For example, a study from Australia demonstrated a 7 fold higher prevalence in Tasmania compared to North Queensland. In addition there is a strong association between regional UVR levels and MS prevalence in Australia ($r = -0.91$, $p = 0.01$). Season of birth studies suggest that autumn birth may be protective for the development of MS. In individual-level studies there is an inverse association between MS mortality and occupational sun exposure, lower hospital admission rates for skin cancer in those with a prior diagnosis of MS and a strong inverse correlation between population monthly serum 25(OH)D levels and active MS lesions on MRI. Interestingly, the Tasmanian case control study showed that higher sun exposure at ages 6-15 years was protective for the development of MS. A cohort study has shown that vitamin D supplementation ($\geq$ 400IU/day) after age 25 was associated with a decreased risk of MS.

In the Ausimmune Study, a multicentre case control study underway in four regions in Australia (Brisbane, Newcastle, Geelong and the Western Districts of Victoria and Tasmania) there is a strong latitudinal gradient in the incidence of first demyelinating illness (a frequent precursor to MS diagnosis), with an increase in incidence of 8.1% (95% CI 5.8 – 10.5) per degree of higher latitude across the latitude of Brisbane (27 deg S) to Tasmania (41-43 deg S).

Type 1 diabetes is caused by the autoimmune destruction of pancreatic β-islet cells. It is a disease of young people (onset usually <30 years) that is becoming increasingly common over the last two decades. There is evidence of a latitudinal gradient in type 1 diabetes prevalence in Europe and Australia and a negative correlation between annual ambient UVR and type 1 diabetes prevalence ($r = -0.80$, $p = 0.02$). Some studies have shown a seasonal pattern of birth or of diagnosis, with a spring or summer excess. Two case control studies have shown that vitamin D (or cod liver oil) supplementation in infancy or during pregnancy is protective for the development of type 1 diabetes. Similarly, one cohort study showed that regular vitamin D supplementation during infancy was associated with a marked decrease in risk of developing type 1 diabetes (OR = 0.12, 95% CI 0.03 – 0.51). Genetic studies show an association between type 1 diabetes and polymorphisms in the vitamin D receptor.

Rheumatoid arthritis is a chronic multisystem disease, characterized by persistent inflammatory synovitis. It is common, affecting 0.8% of the population, with females more commonly affected than males. In contrast to multiple sclerosis and type 1 diabetes, there is no clear latitudinal gradient in prevalence. Vitamin D insufficiency has been documented in persons with rheumatoid arthritis but it is not clear whether this is associated with the causes of rheumatoid arthritis or a result of disease-related impairment of mobility. A cohort study has shown that higher dietary vitamin D intake or use of supplements containing vitamin D is associated with a lower risk of developing rheumatoid arthritis (RR = 0.66, 95% CI 0.43 – 1.00). Intervention studies show that higher doses of 1α-vitamin D are associated with improved pain symptomatology and improvement in blood markers of inflammation.

Conclusion

There is accumulating experimental and epidemiological evidence that UVR exposure and/or vitamin D adequacy have an important protective effect on the development and possibly progression of three autoimmune diseases – multiple sclerosis, type 1 diabetes and rheumatoid arthritis. However this evidence is not yet conclusive and we require a better understanding of whether there are critical periods when adequate UVR exposure or vitamin D are important. Sun exposure advice should take into account the possible beneficial effects of UVR exposure and vitamin D adequacy on autoimmune and other diseases.

References

Ponsonby, A-L., Lucas, RM., van der Mei, I. UVR, vitamin D and three autoimmune diseases--multiple sclerosis, type 1 diabetes, rheumatoid arthritis. *Photochem Photobiol* 81(6):1267-75.