Ultraviolet light, vitamin D and type 1 diabetes

Original article:

Summary and Comment:
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Summary
Mohr et al. describe the first analysis of the relationship between ultraviolet B (UVB) exposure and age-standardized incidence rates of type 1 diabetes in children. The study comprised the authors’ published data on UVB exposure worldwide (corrected for cloud cover) [1] and the Diabetes Mondiale (DiaMond) 2000 data on the incidence of type 1 diabetes in 51 regions of the world [2]. The authors observed a higher rate of type 1 diabetes in areas of the world with lower UVB exposure (p < 0.05 in multiple regression analysis) (Fig. 1).

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As UVB light is the main source of skin-produced vitamin D (285–310 nm UVB light is essential for the photochemical conversion of 7-dehydrocholesterol into previtamin D3 and vitamin D3), the authors suggest that the link between UVB exposure and the incidence of type 1 diabetes is mediated by vitamin D.

Comment
This report makes three different observations in relation to the incidence rate of type 1 diabetes: 1. (negative association) latitude (R² = 0.25; p < 0.0001), 2. (negative association) UVB exposure (R² = 0.30; p < 0.05), 3. (positive association) per capita health expenditure (R² = 0.42; p < 0.004).

Using the parameters of UVB exposure and per capita health expenditure in a multiple regression analysis, the model could explain an impressive 42% of the variation in incidence rate of type 1 diabetes (p < 0.0001).

But are these results such a surprise? The greater incidence of type 1 diabetes in countries at a higher latitude and the general north-south gradient have been repeatedly described. As UVB exposure and latitude are physically also strongly linked, it may be predicted that UVB and type 1 diabetes are also likely to be linked. The authors did not describe a model that included both latitude and UVB exposure in order to establish the most dominant factor. The association of health care expenditure (or per capita income) and type 1 diabetes is also well known and shows an even stronger link than latitude, yet no one believes it to be a causal link.

How likely is this impressive association between UVB and type 1 diabetes mediated by differences in vitamin D status? The answer depends on two additional questions:
1. How strong is the relationship between UVB exposure and vitamin D status?
2. How strong is the impact of vitamin D status on diabetes in general or on type 1 diabetes?

The correlation between the vitamin D status of different populations and their potential exposure to UVB is rather poor. Indeed, in European countries a positive relation between latitude and 25-hydroxyvitamin D status has repeatedly been found: the best 25-hydroxyvitamin D status is found in Scandinavia, in contrast to the Mediterranean countries, where the status is lower [3]. An overview of vitamin D status, as reported for healthy subjects in some 500 publications, revealed a mean 25-hydroxyvitamin D level worldwide of about 21 ng/ml, with surprisingly very little difference according to a tropical or northern climate [4]. Most likely, the skin pigmentation, clothing and sun-seeking behaviour (or lack of it) largely compensate for the different potential UVB exposure. More specifically, the high incidence of type 1 diabetes in Scandinavia is in sharp contrast to the low incidence in China, whereas it seems that vitamin D status in...
the northern part of China is substantially lower than in Scandinavia. Another striking discordance is the very poor vitamin D status in many Muslim countries but very low incidence rates of type 1 diabetes [5]. Of course it may well be that UVB or vitamin D status is a modifying factor depending on the genetic background. Also the US National Health and Nutrition Examination Survey (NHANES) data on prevailing 25-hydroxyvitamin D levels [6] are only poorly related to UVB exposure. However, the lack of essential data on vitamin D status early in life (during pregnancy, in cord serum or during the first year of life) means that the association with later occurrence of type 1 diabetes has not been properly addressed.

How strong is the link between vitamin D status and diabetes? There is a strong association between (poor) vitamin D status (as revealed by serum 25-hydroxyvitamin D) and all aspects of the metabolic syndrome (obesity, type 2 diabetes, hypertension, cardiovascular risks and events) [5, 7]. With regard to vitamin D and autoimmune diseases, there are numerous data

**Fig. 1:** Age-standardized incidence rates of type 1 diabetes per 100,000 boys <14 years of age, by latitude, in 51 regions worldwide in 2002 [3]. Data points are shown by dots. Where space allows, names shown adjacent to dots denote location (Lux, Luxembourg). Where space is limited, the following numerical codes designate the location: Beja, Tunisia; 3. Gafsa, Tunisia; 4. Kairoan, Tunisia; 5. Monastir, Tunisia; 7. Mauritius; 8. Yinchuan, China; 9. Sichuan, China; 10. Huhhot, China; 16. Nanjing, China; 17. Tianjin, China; 21. Harbin, China; 23. Changsha, China; 25. Hainan, China; 29. Hong Kong, China; 31. Israel; 32. Chiba, Japan; 33. Hokkaido, Japan; 34. Okinawa, Japan; 36. Novosibirsk, Russia; 38. Antwerp, Belgium; 39. Varna, Bulgaria; 40. Denmark; 43. France; 44. Baden Baden, Germany; 45. Attica, Greece; 48. Sicily, Italy; 49. Pavia, Italy; 50. Marche, Italy; 52. Lazio, Italy; 59. Krakow, Poland; 61. Algave, Portugal; 62. Coimbra, Portugal; 63. Madeira, Portugal; 64. Portalegre, Portugal; 65. Bucharest, Romania; 67. Slovakia; 68. Catalonia, Spain; 71. Leicestershire, UK; 72. Northern Ireland, UK; 77. Allergehny, PA, USA; 80. Avellaneda, Argentina; 82. Corrientes, Argentina; 87. Paraguay; 88. Lima, Peru; 90. Caracas, Venezuela; 97. Auckland, New Zealand. Data points not labelled because of space constrains (latitude in degrees, rate per 100,000): 11. Dalian, China (39, 0.6); 13. Beijing, China (40, 0.6); 18. Jilin, China (43, 0.4); 19. Shenyang, China (42, 0.4); 20. Lanzhou, China (36, 0.5); 22. Nanjing, China (23, 0.3); 24. Zhengzhou, China (35, 0.2); 26. Tieling, China (42, 0.2); 27. Zunyi, China (28, 0.1); 28. Wulumuqi, China (44, 0.9); 35. Karachi, Pakistan (25, 0.5); 37. Austria (48, 9.8); 45. Hungary (47, 8.7); 51. Turin, Italy (45, 11.9); 53. Lombardia, Italy (46, 7.6); 66. Slovenia (46, 6.8); 79. Chicago, IL, USA (42, 10.2). $R^2 = 0.25, p < 0.001.$
that leave no doubt that 1,25-hydroxyvitamin D is a potent immune agent, activating the innate immune system. It also downregulates the acquired immune system by a coherent action on all cell types involved (antigen presenting cells, all T cells, B cells and some natural killer cells), as well as by direct regulation of gene transcription of at least 10 different key genes involved in the immune response (e.g. interleukin [IL]-1, IL-2, IL-4, IL-12, interferon-γ).

Vitamin D supplementation early in life can reduce the subsequent risk of type 1 diabetes by about 30% according to a critical analysis of five retrospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Parameter</th>
<th>Subjects</th>
<th>Odds ratio</th>
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<tbody>
<tr>
<td>EURODIAB [9]</td>
<td>Vitamin D supplementation during first year of life</td>
<td>&lt;5 years</td>
<td>0.83</td>
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<td></td>
<td></td>
<td>5–9 years</td>
<td>0.81</td>
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<td>10–14 years</td>
<td>0.47</td>
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<td>Stene et al. [10]</td>
<td>Vitamin D supplementation with 10 μg cod liver oil &gt;5 times/week during first year of life</td>
<td>&lt;15 years</td>
<td>0.74</td>
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<td>Hypponen et al. [11]</td>
<td>Vitamin D supplementation of 2000 IU/day during first year of life</td>
<td>1–31 years</td>
<td>0.12</td>
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<tr>
<td></td>
<td>Rickets during first year of life</td>
<td>1–31 years</td>
<td>2.60</td>
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<tr>
<td>Fronczak et al. [12]</td>
<td>Vitamin D via variable food intake during pregnancy</td>
<td>5 years</td>
<td>0.49</td>
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<tr>
<td>Tenconi et al. [13]</td>
<td>Vitamin D intake during lactation</td>
<td>14 years</td>
<td>0.31</td>
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Finally, Mohr et al. argue for active interventions to bring 25-hydroxyvitamin D levels into the 50–60 ng/ml (125–150 nmol/l) range through either higher sun exposure or vitamin doses higher than the upper limit currently set by US and EU authorities. However, this is premature given that vitamin D supplementation, beyond what is known to be needed for normal calcium and bone homeostasis, has yet to be proven safe and efficient for non-calcemic endpoints such as the immune system (including type 1 diabetes), cancer and cardiovascular or metabolic risk factors.

Mohr et al. describe a strong association between latitude or UVB exposure and incidence of type 1 diabetes around the world. They also confirm strong links between vitamin D status and diabetes, especially type 1 diabetes, based on molecular, genetic, cellular and preclinical studies as well as on association studies in children and adults. The causal link between UVB exposure, vitamin D status and type 1 diabetes, however, still needs to be formally proven by randomized controlled trials.

These and other data have generated a strong hypothesis that is in need of good clinical prospective trials to guide future clinical practice.

References


