Environmental determinants of previtamin D synthesis in the United Arab Emirates

Adam J. Buckley a, Zara Hannoun a, Nader Lessan a, Michael F. Holick b, and Maha T. Barakat a

aImperial College London Diabetes Centre, Research Department, Abu Dhabi, United Arab Emirates; bBoston University Medical Center, Section of Endocrinology, Diabetes, and Nutrition, Department of Medicine, Boston, MA, USA

ABSTRACT
Despite abundant sunshine throughout the year, vitamin D deficiency is endemic in the UAE. Solar radiation within the UVB range of the spectrum is required for the photosynthesis of previtamin D3 in the skin. Atmospheric transmission of UVB is strongly influenced by atmospheric conditions and solar zenith angle. We investigated the effects of diurnal and seasonal variation on the availability of sufficient UVB radiation for adequate previtamin D3 synthesis using an established in vitro model. Borosilicate ampoules of 7-dehydrocholesterol, the precursor of previtamin D3, in ethanol (50 μg/mL) were exposed to direct sunlight in an urban area of Abu Dhabi, at one hourly intervals between 0800 and 1700, on one day of each month over a period of one year. Conversion to previtamin D3, vitamin D3 and metabolically inactive photoisomers was analyzed using high performance liquid chromatography. The efficiency of 7-dehydrocholesterol conversion to previtamin D3 varied estimated UVB intensity. At the latitude of Abu Dhabi (24.2 N) previtamin D3 synthesis can occur throughout the year. However very little if any previtamin D3 was produced before 0900 hrs. and after 1600 hrs. Local conditions in Abu Dhabi are likely sufficient to maintain vitamin D levels throughout the year given adequate sun exposure.

KEYWORDS
7-dehydrocholesterol; atmospheric modeling; lumisterol; previtamin D3; tachysterol; UVB; vitamin D3

Introduction
Despite the increasing public awareness of the potential health benefits of adequate vitamin D intake, vitamin D deficiency remains endemic worldwide. The active form, 1,25-dihydroxyvitamin D (1,25(OH)2D), plays a crucial role in metabolic processes ranging from calcium and phosphorous metabolism to cell maturation and growth.

Given sufficient sunlight containing UVB radiation the 7-dehydrocholesterol in the skin is converted to previtamin D3. 7-dehydrocholesterol is isomerised to previtamin D3 by photons at wavelengths of 290-315nm, corresponding to the ultraviolet B (UVB) range of the electromagnetic spectrum. A heat-dependent process converts previtamin D3 (which is thermodynamically unstable) to vitamin D3, while further exposure to UVB radiation photoisomerises previtamin D3 into lumisterol3, tachysterol3 or 7-dehydrocholesterol. Consequently, even brief exposure to sunlight allows for the synthesis of vitamin D3, while protracted sunlight exposure leads to production of the biologically inert isomers, avverting vitamin D toxicity. Vitamin D3 is itself degraded by solar irradiation to the metabolically inactive suprasterol 1 and 2, providing an additional safeguard against toxicity in conditions of high sunlight exposure. Vitamin D3, together with vitamin D2 acquired from dietary sources, undergoes 25-hydroxylation in the liver by Cyp2R1 to 25-hydroxyvitamin D (25(OH)D). 25(OH)D is the major circulatory form of vitamin D and correlates with total body stores, and hence is used as the substrate for most commercially available vitamin D assays. The metabolically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D), is synthesized from 25(OH)D by further hydroxylation in the kidney.

Dietary vitamin D intake is usually insufficient to meet requirements and therefore most humans remain dependent on photosynthesis. UVB intensity at ground level is determined predominantly by solar zenith angle and atmospheric ozone. In general, terrain has a low albedo...
to UV and hence reflected rays do not contribute significantly to local UVB intensity.\(^7\) While shade from trees permits sufficient transmission of UVB for vitamin D synthesis, shade from buildings and glass windows significantly attenuates biologically significant wavelengths.\(^8\) Cultural differences in clothing, and consequently the area of skin exposed to sunlight, affect vitamin D production when overall UVB exposure is low, although the effect of clothing is greatly reduced when there is an excess of available UVB.\(^9\) Melanin absorbs electromagnetic radiation at wavelengths of 280–400 nm, and hence darker skin pigmentation can diminish the potential for vitamin D synthesis.\(^10\) Assessment of individual vitamin D status is complicated by polymorphisms of the vitamin D binding protein,\(^11,12\) and by sequestration of the fat-soluble vitamin D in adipose tissue.\(^13\)

Vitamin D deficiency is highly prevalent in the UAE population. A limited number of studies have investigated the prevalence of, and local factors associated with, vitamin D deficiency. A study conducted in Al Ain demonstrated hypovitaminosis D in 65.1% of a population of 143 adolescents, with vitamin D deficiency ≤ 50 nmol/l in 10% of boys and 28% of girls.\(^14\) Vitamin D status was found to be paradoxically lower in summer than in winter in a population of 138 female university students in Abu Dhabi, in whom sun avoidance behavior was common and independently negatively correlated with vitamin D status.\(^15\) Of children aged 8–14 attending an ambulatory clinic at Sheikh Khalifa Medical City in Abu Dhabi, 31.2% had evidence of severe vitamin D deficiency with serum 25(OH)D < 25 nmol/l.\(^16\)

We hypothesized that local environmental and atmospheric factors such as dust and ground level ozone might contribute to the high local prevalence of vitamin D deficiency; we explored this hypothesis by examining seasonal and diurnal variation in photosynthesis of vitamin D in an established in vitro model, and compared the results with predicted conversion of 7-dehydrocholesterol to previtamin D3 based on atmospheric modeling and the action spectrum of UVB for photoisomerisation of 7-dehydrocholesterol to previtamin D3.

**Materials and methods**

**In vitro conversion of 7-dehydrocholesterol**

Borosilicate glass ampoules of 7-dehydrocholesterol dissolved in ethanol (50 μg/mL) were sealed under argon as previously described,\(^17\) and stored in a cool dark location prior to use. Each ampoule was placed outside in direct sunlight, for a period of one hour, at hourly intervals between 8:00 to 16:00 on the last Wednesday of each month of 2012. Once exposed, ampoules were stored in darkness at −4°C pending analysis. The proportions of 7-dehydrocholesterol, previtamin D and vitamin D, tachysterol and lumisterol in each sample were assayed using high performance liquid chromatography (Boston University Hospital, Boston, USA) as previously described.\(^18\)

**Atmospheric model and predicted 7-dehydrocholesterol conversion**

We developed a model to predict the potential for incident UVB to convert 7-dehydrocholesterol into previtamin D3 at each of the time points sampled. Sufficiently detailed meteorological data during the period of study were not available, and it was therefore necessary to estimate UVB intensity. A simplified model of clear-sky spectral irradiance at the earth’s surface, SPCTRL2,\(^19\) as implemented in the C programming language by M. Rimes (NREL, 1998),\(^20\) was used to estimate irradiance of a horizontal surface at the latitude and longitude of Abu Dhabi (24.4667° N, 54.3667° E). Total precipitable water content was estimated at 1.5 cm. The SPCTRL2 default setting for atmospheric ozone was used. Surface albedo was estimated at 0.1. Spectral irradiance was modeled between 290 and 310 nm; at wavelengths shorter than 300 nm very little UV penetrates to ground level due to absorption by atmospheric ozone,\(^21\) while wavelengths longer than 310 nm convert 7-dehydrocholesterol to vitamin D3 with very low efficiency.\(^22,23\) SPCTRL2 estimates of combined direct and diffuse incident energy at wavelengths of 290, 295, 300, 305 and 310 nm were obtained for each studied time period, expressed in Js⁻¹m⁻²nm⁻¹, and linearly interpolated to determine the number of joules of energy delivered at each 1 nm interval of wavelength over one hour. These estimates were weighted by the action spectrum of UVB on 7-dehydrocholesterol,\(^24\) and interpolated with the assumption of a quadratic relationship between required incident energy and conversion at wavelengths between 300 and 310 nm. The results were summed, integrating the potential for photoisomerisation of 7-dehydrocholesterol by the 290–310 nm spectrum and providing an estimate of total percentage conversion to previtamin D during each time interval studied.
Results

Diurnal variation

The conversion of 7-dehydrocholesterol to previtamin D varied with time of day on each individual day studied. Over the 12 sampled days, conversion was negligible during the 0800–0900 (mean 0.53%, range 0.0–0.94%) and 1600–1700 (mean 0.33%, range 0.0–1.0%) time periods, and peaked during the 1200–1300 time period (mean 4.8%, range 4.7–11.0%). Rates of conversion to tachysterol and lumisterol followed a similar pattern, although absolute values were smaller. The conversion followed a sinusoidal pattern on each day studied, indicating that zenith angle was the most important determinant (see Fig. 1).

By extrapolation we predicted that very little conversion of 7-dehydrocholesterol would occur outside the studied time periods. Variation in the proportion of 7-dehydrocholesterol converted during each month can therefore be expressed in terms of the area under the curve of the graphs of diurnal variation in rate of conversion. Total daily conversion to previtamin D and 25(OH)D, expressed as the area under the curve of conversion at each time point studied, was 2.92 times higher in July than in January (see Fig. 2).

Observed vs. predicted conversion of 7-dehydrocholesterol to previtamin D3

Linear regression of predicted against actual conversion rates showed a strong and highly significant association (r² = 0.82, p < 0.0001, see Fig. 3). On average the model underestimated conversion, (predicted = 0.79 x observed + 0.12). This may be explained by the assumption of low surface albedo, excluding the contribution of reflected light, which, while true for a natural environment, may not apply equally to urban conditions. Linear regression of predicted against actual conversion for each time period indicated that the model tended to underestimate conversion during

---

Figure 1. Diurnal variation in 7-dehydrocholesterol conversion in vitro to previtamin D3 or vitamin D3, lumisterol or tachysterol (%) following 1 hour exposure to sunlight, during each month of the year.
the morning and overestimate conversion during the evening. Incident UVB at a point on the Earth’s surface varies with time of day according to a sinusoidal, rather than linear pattern and hence this model would tend to underestimate while incident UVB was increasing and overestimate while incident UVB was decreasing. This model made a number of simplifying assumptions, including a quadratic relationship between UVB intensity and rate of conversion and linear interpolation of UV intensities, and therefore while the significant correlation between the predicted and observed values indicates that incident UV is likely to be the most important factor influencing conversion, the remarkable numerical similarity of the predicted and observed values is likely to be coincidental.

**Discussion**

The conversion of 7-dehydrocholesterol to previtamin D3 and its photoproducts in vitro seen in Abu Dhabi are comparable with similar ampoule studies performed in the Middle East and around the world, in locations including Boston, Johannesburg, Riyadh, South India and Argentina (see Fig. 4). It has previously been established that the results of the ampoule model correlate with those observed in human skin samples exposed under the same conditions. Conversion of 7-dehydrocholesterol to previtamin D in vitro was well correlated with local availability of radiation in the UVB spectrum, and the percentage of previtamin D produced in each ampoule was equal to or exceeded that predicted by our model for each corresponding time period. Although atmospheric ozone was estimated, it would be expected that significant ground level ozone would cause measured conversion to be less, rather than greater than, predicted values. This pattern of variation suggests that local environmental factors, such as dust and ground ozone, do not attenuate incident UVB to an extent sufficient to limit previtamin D synthesis. In addition, the conversion of 7-dehydrocholesterol to previtamin D3 seen in Abu Dhabi are comparable with other sunny locations around the world, where vitamin D deficiency is
considerably rarer. Other explanations for the high prevalence of vitamin D deficiency seen in the UAE therefore need to be considered.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

Funding
The study was funded by Mubadala Healthcare.

Author contributions
AB wrote the first draft of the manuscript and analyzed the data. ZH performed the in vitro study and contributed to the manuscript. NL reviewed and revised the manuscript. MH supplied the study ampoules and performed the assays, and read and revised the manuscript. MB reviewed and commented on the manuscript. AB had full access to study data and as such is guarantor of the work.

ORCID
Adam J. Buckley http://orcid.org/0000-0001-7471-0273
Michael F. Holick http://orcid.org/0000-0001-6023-9062

References
[1] Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutri 2008; 87:1080S; PMID:18400738
[2] Glossmann HH. Origin of 7-Dehydrocholesterol (Provitamin D) in the Skin. J Invest Dermatol 2010; 130:2139-41; PMID:20445550; https://doi.org/10.1038/jid.2010.118
[3] Holick MF. The cutaneous photosynthesis of previtamin D3: a unique photoendocrine system. J Investigative Dermatol 1981; 77:51-8; PMID:6265564; https://doi.org/10.1111/1523-1747.ep12479237
[4] Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J Clin Endocrinol Metab 1989; 68:882-7; PMID:2541158; https://doi.org/10.1210/jcem-68-5-882
[5] Carter GD. Accuracy of 25-hydroxyvitamin D assays: confronting the issues. Curr Drug Targets 2011; 12:19-28; PMID:22870351; https://doi.org/10.2174/138945011793591608
[6] Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutri 2005; 135:317-22; PMID:15671234
[7] Allaart M, van Weele M, Fortuin P, Kelder H. An empirical model to predict the UV-index based on solar zenith angles and total ozone. Meteorological Applications 2004; 11:59-65; https://doi.org/10.1017/S1350482703001130
[8] Turnbull DJ, Parisi AV, Kimlin MG. Vitamin D effective ultraviolet wavelengths due to scattering in shade. J Steroid Biochem Mol Biol 2005; 96:431-6; PMID:16005208; https://doi.org/10.1016/j.jsbmb.2005.04.039
[9] Bogh MKB, Schmedes AV, Philipsen PA, Thieden E, Wulf HC. Interdependence between body surface area and ultraviolet B dose in vitamin D production: a randomized controlled trial. Br J of Dermatol 2010; 164:163-9; https://doi.org/10.1111/j.1365-2133.2010.10082.x
[10] Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. Am J Clin Nutri 2008; 88:537-40
[11] Perna L, Felix JF, Breitling LP, Haug U, Raum E, Burwinkel B, Schöttker B, Brenner H. Genetic variations in the vitamin D binding protein and season-specific levels of vitamin D among older adults. Epidemiol (Cambridge, Mass) 2013; 24:104-9; PMID:23191998; https://doi.org/10.1097/EDE.0b013e318276c4b0
[12] Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, Tamez H, Zhang D, Bhan I, Karumanchi SA, et al. Vitamin D-Binding Protein and Vitamin D Status of Black Americans and White Americans. N Eng J Med 2013; 369:1991-2000; PMID:24256378; https://doi.org/10.1056/NEJMoai1306357
[13] Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutri 2004; 79:362-71; PMID:14985208
[14] Muhairi SJ, Mehairi AE, Khouri AA, Naqbi MM, Maskari FA, Al Kaabi J, Al Daheeri AS, Nagelkerke N, Shah SM. Vitamin D deficiency among healthy adolescents in Al Ain, United Arab Emirates. BMC Public Health 2013; 13:33; PMID:23311702; https://doi.org/10.1186/1471-2458-13-33
[15] Anouti F Al, Thomas J, Abdel-Wareth L, Rajah J, Grant WB, Haq A. Vitamin D deficiency and sun avoidance among university students at Abu Dhabi, United Arab Emirates. Dermato-Endocrinol 2011; 3:235-9; PMID:22259650; https://doi.org/10.4161/derm.3.4.16881
[16] Rajah J, Haq A, Pettifor JM. Vitamin D and calcium status in urban children attending an ambulatory clinic service in the United Arab Emirates. Dermato-Endocrinol 2012; 4:39-43; PMID:22870351; https://doi.org/10.4161/derm.18250
[17] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988; 67:373-8; PMID:2839537; https://doi.org/10.1210/jcem-67-2-373
[18] Holick M, MacLaughlin J, Clark M, Holick SA, Potts JT, Jr, Anderson RR, Blank IH, Parrish JA, Elias P. Photosynthesis of previtamin D3 in human skin and the physiologic consequences. Science 1980; 210:203-5; PMID:6251551; https://doi.org/10.1126/science.6251551
[19] Bird RE, Riordan C. Simple solar spectral model for direct and diffuse irradiance on horizontal and tilted planes at the earth’s surface for cloudless atmospheres. J Climate Applied Meteo 1986; 25(1):87-97.
[20] Rymes M, Wilcox S, Anderberg M. SPCTRL2. 1998; Golden (CO): National Renewable Energy Laboratory. Available from: http://rredc.nrel.gov/solar/models/spectral/spectrl2/

[21] Leckner B. The spectral distribution of solar radiation at the earth’s surface—elements of a model. Solar Energy 1978; 20(2):143-50.

[22] Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermato-Endocrinology 2013; 5:51-108; PMID:24494042; https://doi.org/10.4161/derm.24494

[23] Bolsée D, Webb AR, Gillotay D, Dörschel B, Knuschke P, Krins A, Terenetskaya I. Laboratory facilities and recommendations for the characterization of biological ultraviolet dosimeters. Applied Optics 2000; 39:2813-22; https://doi.org/10.1364/AO.39.002813

[24] Harinarayan CV, Holick MF, Prasad UV, Vani PS, Himabindu G. Vitamin D status and sun exposure in India. Dermato-Endocrinology 2013; 5:130-41; PMID:24494046; https://doi.org/10.4161/derm.23873

[25] Pettifor JM, Moodley GP, Hough FS, Koch H, Chen T, Lu Z, Holick MF. The effect of season and latitude on in vitro vitamin D formation by sunlight in South Africa. South African Medical J = Suid-Afrikaanse tydskrif vir geneeskunde 1996; 86:1270-2; PMID:8955733

[26] Ladizesky M, Lu Z, Oliveri B, San Roman N, Diaz S, Holick MF, Mautalen C. Solar ultraviolet B radiation and photoproduction of vitamin D3 in central and southern areas of argentina. J Bone Mineral Res 1995; 10:545-9; PMID:7610924; https://doi.org/10.1002/jbmr.5650100406

[27] Alshahrani FM, Almalki MH, Aljohani N, Alzahrani A, Alsaleh Y, Holick MF. Vitamin D: Light side and best time of sunshine in Riyadh, Saudi Arabia. Dermato-Endocrinology 2013; 5:177-80; PMID:24494051; https://doi.org/10.4161/derm.23351

[28] Chen TC, Lu Z, Holick MF. Photobiology of Vitamin D. Vitamin D 2010:35-60; https://doi.org/10.1007/978-1-60327-303-9_2

[29] Levis S, Gomez A, Jimenez C, Veras L, Ma F, Lai S, Hollis B, Roos BA. Vitamin D Deficiency and Seasonal Variation in an Adult South Florida Population. J Clin Endocrinol Metab 2005; 90:1557-62; PMID:15634725; https://doi.org/10.1210/jc.2004-0746

[30] Poopedi MA, Norris SA, Pettifor JM. Factors influencing the vitamin D status of 10-year-old urban South African children. Public Health Nutrition 2011; 14:334-9; PMID:20804632; https://doi.org/10.1017/S136898001000234X

[31] Fradinger EE, Zanchetta JR. Vitamin D and bone mineral density in ambulatory women living in Buenos Aires, Argentina. Osteoporosis Int 2001; 12:24-7; PMID:11305079; https://doi.org/10.1007/s001980170153