

New light on an old vitamin: The role of the sunshine vitamin D in chronic disease

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Published online: 27 May 2017

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As a child, I always enjoyed consuming milk products and more so as I grew and became active in athletics. One of my dynamic trainers, Dieter Roth, was responsible for leading me and my fellow athletes into Bavarian championships. I was fortunate to never have suffered a fracture from excessive running or weight training. Perhaps my daily vitamin D consumption helped in addition to genetics. I became interested in the science of vitamin D after encountering some patients with hypercalcemia [1]. During my tenure at the University of Mississippi, one of my mentees, Dr. M. Ullah, had expressed desire to explore the field of hypertension and I recommended that he review literature on the topic vitamin D and blood pressure regulation, resulting in several publications [2–5].

My interest grew after I met a pregnant black African American woman that presented with nausea/vomiting, hypertension, a serum calcium of 14 mg/dl (elevated), parathyroid hormone (PTH) level of 102 pg/ml (elevated), and 25-hydroxy(OH) vitamin D level of 12 ng/ml. After hydration and a declining serum calcium to 10 mg/dl, she was prescribed oral vitamin D2 50,000 IU weekly and advised to follow-up. She had a history of noncompliance and (interestingly) took the prescribed vitamin D daily instead of weekly after discharge. She did not follow up in the antenatal or endocrine clinic as scheduled until 3 months later when she presented to

the emergency room with headaches and elevated blood pressures (150–170 mm Hg systolic and 70–80 mm Hg diastolic). At this time, her serum calcium level was mildly elevated at 10.9 mg/dl, PTH was 49 pg/ml (inappropriately normal for the level of serum calcium) but the 25-OH vitamin D level was now very high (348.9 ng/ml). At 39 weeks of pregnancy, she had an elective Cesarean delivery of a healthy baby without further complications. The infant was monitored closely for 72 h for any signs of tetany, because of the mother's primary hyperparathyroidism which created a high risk for hypocalcemia. The serum calcium of the baby was normal (10.1 mg/dl) at birth and the baby remained completely asymptomatic at the time of discharge from the hospital, suggesting that at least one parathyroid gland of the baby was not suppressed in functionality, secreting PTH [6].

To my knowledge, the highest reported 25-OH vitamin D level of “vitamin D intoxication” due to food products or dietary supplements is 1482 ng/ml (3700 nmol/L). This has been treated with intravenous fluid hydration, administration of glucocorticoids, sodium phosphate, and bis phosphonates, without complications on 2 year follow-up (reviewed in Araki et al., ref. [7]). The second highest reported 25-OH vitamin D level is 1220 ng/ml (3045 nmol/L) and occurred in a 58-year old man with a concomitant serum calcium of 15 mg/dl (3.75 nmol/L). Symptoms included fatigue, excessive thirst, polyuria, and poor cognition. Utilizing liquid chromatography, tandem mass spectroscopy detected exclusively 25OHD3 and no 25OHD2. The man took multiple supplements with one labeled to contain 1600 IU (40 mcg) of vitamin D, 99% D3, however, analysis showing that each such capsule contained 186,400 IU (4660 mcg) of vitamin D3 [7]. As it turns out, the patient had taken 1,864,000 IU (46,600 mcg) of vitamin D3 daily for 2 months and was treated with normal saline, furosemide, calcitonin, and pamidronate over several weeks, considering that the half-life of 25OH vitamin

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D is 2–3 weeks. He remained normocalcemic and asymptomatic after the 25OH vitamin D level dropped below 400 ng/ml (1000 nmol/L).

Some aspects of vitamin D intoxication and approaches for prevention, diagnosis, and treatment of the vitamin D deficiency pandemic are reviewed by the “D-lightful” vitamin D expert, Professor Michael Holick, in the leading article of this guest issue edited by Professor Giovanna Muscogiuri [8]. I am delighted that Prof. Muscogiuri has recruited top experts to review various topics related to vitamin D. This guest issue will publish in two issues, Part 1, June, and Part 2, September 2017.

Professor Holick’s article is followed by an interesting review on vitamin D reducing the incidence of and increasing survival from breast, colorectal, lung, ovarian, pancreatic, and prostate cancer [9]. Since some hormones are also considered neurosteroids [10, 11] and that children with low(er) 25-OH vitamin D levels at 3 months of gestation, at birth, and at age 8 are prone to develop an autism spectrum disorder, Dr. Cannell provides an overview on autism and vitamin D [12]. We recently published a guest issue on metabolism and skin diseases including an article on adipokines in psoriasis [13, 14]. The possible bidirectional links between psoriatic disease and vitamin D is analyzed in this journal issue [15]. The same authors also provide an overview on the impact of environmental pollutants, obesity, and vitamin D status [16]. Obviously, energy balance plays an important role in the current obesity epidemic [17]. Most of this epidemic is driven by an imbalance between energy intake and consumption, likely facilitated by hedonic behavior, change in taste perception, and other factors, with nutrition playing a central role [18, 19]. The important role of nutritionists in the current obesity and vitamin D epidemic is reviewed by Savastano and colleagues in Part 1 of this guest issue [20]. Vitamin D and its implications in diabetes mellitus is analyzed by Grammatiki and colleagues [21]. Interestingly, low vitamin D levels have been found to be associated with a pro-inflammatory state, insulin resistance, glucose intolerance and obesity, which is reviewed by Garbossa and Folli [22]. Adipokines are atherothrombotic risk factors in obese subjects [23]. The last article is written by Gruebler and colleagues who conclude that vitamin D is a strong risk marker for cardiovascular risk factors and disease, similar to what has been reported in men with low testosterone levels [24–27].

Part 2 of this issue (September), will feature topics in female fertility, polycystic ovarian syndrome and endometriosis, and the relationship to vitamin D [28, 29], followed by immunology related aspects including kidney transplantation, autoimmune endocrine disorders including thyroid and adrenal disease [30–33]. After an expedition covering extraskeletal aspects of vitamin D, the concluding review focuses on musculoskeletal health [34].

Acknowledgements My thanks to Professor Muscogiuri and all the authors who contributed to this topic on vitamin D.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest related to this article.

References

- Falk S, Kratzsch J, Paschke R, Koch CA. Hypercalcemia as a result of sarcoidosis with normal serum concentrations of vitamin D. *Med Sci Monit.* 2007;13(11):CS133–6.
- Ullah MI, Uwaifo GI, Nicholas WC, Koch CA. Does vitamin D deficiency cause hypertension? Current evidence from clinical studies and potential mechanisms. *Int J Endocrinol.* 2010;2010:579640.
- Ullah MI, Koch CA, Tamanna S, Rouf S, Shamsuddin L. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. *Horm Metab Res.* 2013;45(9):682–7.
- Koch CA, Chrousos GP. Overview of endocrine hypertension. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–2016 Oct 26.
- Koch CA, Chrousos GP (eds). *Endocrine hypertension. Contemporary endocrinology series.* Springer, New York; 2013, ISBN: 978–1–60761–547–7 (Print), ISBN-10: 978–1–60761–548–4 (online).
- Ullah MI, Uwaifo GI, Koch CA. Primary hyperparathyroidism and hypercalcemia during pregnancy. *Horm Metab Res.* 2017;49: in press.
- Araki T, Holick MF, Alfonso BD, Charlap E, Romero CM, Rizk D, Newman LG. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. *J Clin Endocrinol Metab.* 2011;96(12):3603–8.
- Holick MF. The Vitamin D deficiency pandemic: approaches for diagnosis, treatment, and prevention. *Rev Endocr Metab Disord.* 2017.
- Moukayed M, Grant WB. The roles of UVB and vitamin D in reducing risk of cancer incidence and mortality: a review of the epidemiology, clinical trials, and mechanisms. *Rev Endocr Metab Disord.* 2017. doi: [10.1007/s11154-017-9415-2](https://doi.org/10.1007/s11154-017-9415-2).
- Koch CA, Bornstein SR, Pacak K, Chrousos GP. How does metyrapone decrease seizures? *Neurosurg Rev.* 1998;21(4):302–3.
- Baulieu EE, Robel P, Schumacher M. Neurosteroids: beginning of the story. *Int Rev Neurobiol.* 2001;46:1–32.
- Cannell JJ. Vitamin D and autism: what’s new? *Rev Endocr Metab Disord.* 2017. doi: [10.1007/s11154-017-9409-0](https://doi.org/10.1007/s11154-017-9409-0).
- Zouboulis CC, Stratakis CA, Chrousos GP, Koch CA. Metabolism and skin diseases. *Rev Endocr Metab Disord.* 2016;17(3):241–6.
- Wolk K, Sabat R. Adipokines in psoriasis: an important link between skin inflammation and metabolic alterations. *Rev Endocr Metab Disord.* 2016;17(3):305–17.
- Barrea L, Savanelli MC, Di Somma C, Napolitano M, Megna M, Colao A, Savastano S. Vitamin D and its role in psoriasis: an overview of the dermatologist and nutritionist. *Rev Endocr Metab Disord.* 2017. doi: [10.1007/s11154-017-9411-6](https://doi.org/10.1007/s11154-017-9411-6).
- Barrea L, Savastano S, Di Somma C, Savanelli MC, Nappi F, Albanese L, Orio F, Colao A. Low serum vitamin D-status, air pollution and obesity: a dangerous liaison. *Rev Endocr Metab Disord.* 2016. doi:[10.1007/s11154-016-9388-6](https://doi.org/10.1007/s11154-016-9388-6).

17. Turner JB, Kumar A, Koch CA. The effects of indoor and outdoor temperature on metabolic rate and adipose tissue - the Mississippi perspective on the obesity epidemic. *Rev Endocr Metab Disord*. 2016;17(1):61–71.
18. Koch CA. EDITORIAL: “The Koch’s” view on the sense of taste in endocrinology. *Rev Endocr Metab Disord*. 2016;17(2):143–7.
19. Koch CA. Introduction to the sense of taste in endocrinology. *Rev Endocr Metab Disord*. 2016;17(2):139–41.
20. Savastano S, Barrea L, Savanelli MC, Nappi F, Di Somma C, Orio F, Colao A. Low vitamin D status and obesity: role of nutritionist. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9410-7](https://doi.org/10.1007/s11154-017-9410-7).
21. Grammatiki M, Rapti E, Karras S, Ajjan RA, Kotsa K. Vitamin D and diabetes mellitus: causal or casual association? *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-016-9403-y](https://doi.org/10.1007/s11154-016-9403-y).
22. Garbossa SG, Folli F. Vitamin D, sub-inflammation and insulin resistance. A window on a potential role for the interaction between bone and glucose metabolism. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9423-2](https://doi.org/10.1007/s11154-017-9423-2).
23. Csongrádi É, Káplár M, Nagy B Jr, Koch CA, Juhász A, Bajnok L, Varga Z, Seres I, Karányi Z, Magyar MT, Oláh L, Facsó A, Kappelmayer J, Paragh G. Adipokines as atherothrombotic risk factors in obese subjects: associations with haemostatic markers and common carotid wall thickness. *Nutr Metab Cardiovasc Dis*. 2017. doi: [10.1016/j.numecd.2017.02.007](https://doi.org/10.1016/j.numecd.2017.02.007).
24. Grüber MR, März W, Pilz S, Grammer TB, Trummer C, Müllner C, Schwetz V, Pandis M, Verheyen N, Tomaschitz A, Fiordelisi A, Laudisio D, Cipolletta E, Iaccarino G. Vitamin-D concentrations, cardiovascular risk and events - a review of epidemiological evidence. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9417-0](https://doi.org/10.1007/s11154-017-9417-0).
25. Ullah MI, Washington T, Kazi M, Tamanna S, Koch CA. Testosterone deficiency as a risk factor for cardiovascular disease. *Horm Metab Res*. 2011;43(3):153–64.
26. Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. *Drug Des Devel Ther*. 2014;8:101–12.
27. Morgentaler A, Zitzmann M, Traish AM, Fox AW, Jones TH, Maggi M, Arver S, Aversa A, Chan JC, Dobs AS, Hackett GI, Hellstrom WJ, Lim P, Lunenfeld B, Mskhalaya G, Schulman CC, Torres LO. Fundamental concepts regarding testosterone deficiency and treatment: international expert consensus resolutions. *Mayo Clin Proc*. 2016;91(7):881–96.
28. Wagner CL, Hollis BW, Kotsa K, Fakhoury H, Karras SN. Vitamin D administration during pregnancy as prevention for pregnancy, neonatal and postnatal complications. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9414-3](https://doi.org/10.1007/s11154-017-9414-3).
29. Muscogiuri G, Altieri B, de Angelis C, Palomba S, Pivonello R, Colao A, Orio F. Shedding new light on female fertility: the role of vitamin D. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9407-2](https://doi.org/10.1007/s11154-017-9407-2).
30. Sarno G, Nappi R, Altieri B, Tirabassi G, Muscogiuri E, Salvio G, Paschou SA, Ferrara A, Russo E, Vicedomini D, Vincenzo C, Vryonidou A, Della Casa S, Balercia G, Orio F, De Rosa P. Current evidence on vitamin D deficiency and kidney transplant: What’s new? *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9418-z](https://doi.org/10.1007/s11154-017-9418-z).
31. Altieri B, Muscogiuri G, Barrea L, Mathieu C, Vallone CV, Mascitelli L, Bizzaro G, Altieri VM, Tirabassi G, Balercia G, Savastano S, Bizzaro N, Ronchi CL, Colao A, Pontecorvi A, Della Casa S. Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-016-9405-9](https://doi.org/10.1007/s11154-016-9405-9).
32. Nettore IC, Albano L, Ungaro P, Colao A, Macchia PE. Sunshine vitamin and thyroid. *Rev Endocr Metab Disord*. 2017. doi: [10.1007/s11154-017-9406-3](https://doi.org/10.1007/s11154-017-9406-3).
33. Tirabassi G, Salvio G, Altieri B, Ronchi CL, Della Casa S, Pontecorvi A, Balercia G. Adrenal disorders: is there any role for vitamin D? *Rev Endocr Metab Disord*. 2016.
34. Bhattoa HP, Konstantynowicz J, Laszcz N, Wojcik M, Pludowski P. Vitamin D: Musculoskeletal health. *Rev Endocr Metab Disord*. 2016. doi: [10.1007/s11154-016-9404-x](https://doi.org/10.1007/s11154-016-9404-x).



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