Cortés Berdonces M, Jódar Gimeno E

Departamento de Endocrinología y Nutrición Clínica - Hospital Universitario Ruber Juan Bravo - Quirón Salud Pozuelo - Universidad Europea de Madrid (España)

Vitamin D and endocrinal diseases

DOI: http://dx.doi.org/10.4321/S1889-836X2017000200006

Correspondence: Esteban Jódar Gimeno - Hospital Universitario Ruber Juan Bravo - C/Juan Bravo 49 - 28006 Madrid (Spain)
e-mail: esteban.jodar@quironsalud.es

Diabetes mellitus type 2

In the 1970s the link between vitamin D and diabetes (DM) began to be studied with research suggesting resistence to insulin and insulin secretion[1]. Several studies suggest that vitamin D stimulates insulin secretion and decreases insulin resistance[2-5] and correlates with impaired glucose tolerance, fasting hyperglycemia, and type 2 diabetes mellitus (DM2)[6].

In the case of DM2, numerous case-control and cohort studies have been published which analyze the relationship between vitamin D deficiency and the incidence of DM2 with conflicting results. In 2013, Song et al. carried out a meta-analysis to assess the strength and form of the association between the levels of 25-hydroxycholecalciferol (25HCC) and the incidence of DM2[7]. This meta-analysis includes a total of 21 prospective studies with a population of 76,220 subjects and an incidence of DM2 of 4,996 cases.

Comparing the highest to the lowest levels, the relative risk of developing DM2 was 0.62 (95% CI 0.54-0.70). The highest levels of 25HCC were related to a lower risk of diabetes, regardless of sex, follow-up time in the study, sample size, diagnostic criteria for diabetes or method of vitamin D analysis. This inverse relationship was maintained, although it was diminished when adjusted for adiposity and other metabolic parameters related to obesity. This decreased risk was most evident from levels of 25 HCC greater than 20 ng/ml. In the same meta-analysis, each 4 ng/ml increase in 25 HCC levels was associated with a 4% decrease in DM2 risk.

Subsequently, in January 2017, a systematic review was published that includes the studies of the meta-analysis of Song and other later studies[8]. The relative risk for DM2 was 0.77 (95% CI 0.72-0.82) when subjects with levels of 20-30 ng/ml of 25 HCC were compared to the lowest levels of vitamin D. Association between vitamin D and risk of DM2 presented a U-curve, with nadir at 65 ng/ml, a concentration that was associated with the lowest relative risk.

In agreement with these results, other meta-analyzes such as Parker et al.[9] or Forouhi et al.[10], find the same correlation. In the latter, the relative risk of DM2 comparing the highest and lowest quartiles of 25HCC was 0.59 (0.52-0.67), with a low heterogeneity [I (2)=2.7%, p=0.42] among the 11 included studies through 2012.

Nowadays, it is vital to know if this increased risk of diabetes can be reversed using vitamin D supplements. It is important to know the benefit in the general population as well as in subgroups of age, gender and ethnicity and evaluate the effect of different dose supplements. To date, there are no large-scale, long-term intervention trials that meet these criteria and thus provide definitive results.

The RECORD study is a randomized clinical trial where patients received 800 IU / day of vitamin D, 1,000 mg of calcium, both drugs or placebo. In this paper, we evaluated the incidence of diabetes among the different groups, but this was a secondary objective (the primary aim was the rate of fractures). A relative risk reduction of DM of 33% was found in the supplemented patients but it was not statistically significant[11]. In WHI (Women's Health Initiative Calcium/Vitamin D Trial) study 33,951 women were randomized to 400 IU of vitamin D or placebo for 7 years, monitoring the onset of diabetes. There were no statistically significant benefits[12]. The possible explanation for the lack of beneficial effects in this large trial is the low dose of vitamin D administered (which is also suggested by the lack of effect on fractures and difficulties in adherence).

Other studies include a limited number of patients and have not been shown to reduce the incidence of DM2. Mitri et al. carried out a meta-analysis with 11 randomized clinical trials and another with 8 observational studies. The research carried out with observational studies concluded that individuals with a vitamin D intake greater than 500 IU/day had a 13% reduction in the risk of DM2 compared with an intake of less than 200 IU/day. In the meta-analysis of randomized clini-

cal trials, they found that vitamin D supplementation does not show any beneficial effect on blood glucose measurements among people with normal glucose tolerance but does have a benefit in people with glucose or insulin intolerance basal resistance[13].

In conclusion, there is enough scientific evidence that associates an increased risk of diabetes in people with vitamin D deficiency and there is sufficient biological plausibility. However, the effect of vitamin D supplementation on diabetes prevention has so far not been proven.

Diabetes mellitus type 1

There is evidence to suggest a link between vitamin D and autoimmune diseases. We know that there are vitamin D receptors in both the beta cell and the immune system. Studies in animal models have shown that severe vitamin D deficiency increases the risk of developing DM1[14].

In vivo, a study in 8 healthy adults conducted by the Holick group, showed that vitamin D supplements regulate the expression of 291 genes in leukocytes that interfere with more than 160 pathways linked to cancer, cardiovascular disease and autoimmune diseases. This study demonstrates that vitamin D is an important immunomodulator of both the innate and adaptive response[15]. Multiple observational studies have linked vitamin D levels and autoimmune diseases such as diabetes mellitus type 1[16-22] but so far clinical trials for prevention of DM1 using vitamin D or 1,25-DHCC are inconsistent.

A meta-analysis published in 2008 of 5 observational studies found a significantly lower risk of DM1 in children who had been supplemented with vitamin D compared to those who did not take supplements (odds ratio 0.71, 95% CI 0.60-0.84)[23]. However, studies published involving patients with recent onset DM 1 or LADA (latent autoimmune diabetes of the adult) have shown no improvement in C-peptide levels or in the preservation of the beta-cell[24,25].

As with type 2 diabetes mellitus, there is a paucity of well-designed randomized controlled trials that answer the question of whether vitamin D supplementation plays a therapeutic role in the prevention or treatment of type 1 diabetes mellitus.

Autoimmune thyroid disease

With less scientific evidence, some observational studies have linked vitamin D deficiency with autoimmune thyroid disease, both Graves-Basedow's disease and Hashimoto's thyroiditis. A meta-analysis based on these studies has shown that vitamin D levels were lower in people with autoimmune thyroid disease than in healthy controls[26]. As for intervention studies, the results again do not show a clear effect, in some cases there has been a reduction in antibody levels in patients supplemented with 1000 IU / day of vitamin D3, but without changes in thyroid function with respect to controls[27]. We are still far from obtaining definitive studies that evaluate the role of vitamin D supplementation in people with autoimmune thyroid disease.

Primary hyperparathyroidism

Vitamin D deficiency is common in patients with primary hyperparathyroidism (PPH) and there is evidence that the clinical presentation of PPH is more severe in patients with low vitamin D[28] levels. This vitamin D deficiency has been associated with higher levels of PTH that fall after administering supplements without risk of worsening hypercalcemia or hypercalciuria[29,30]. It has also been associated with higher levels of calcium and alkaline phosphatase, lower levels of plasma phosphate, lower bone density in the hip and distal third of the radius, more severe bone disease and therefore an increased risk of hungry bone syndrome after parathyroidectomy[31]. It is therefore important in these patients to correct this deficit to maintain sufficiency.

Obesity

There is an inverse association of serum OH levels and body mass index (BMI), which associates obesity with vitamin D deficiency[32]. In Spain, this negative correlation has also been demonstrated in children younger than 15 years, where the prevalence of hypovitaminosis D was significantly higher in the severe obesity groups (81.1%) and obesity (68.2%) than in overweight children (55%) or normal weight (58.1%)[33].

Doubts arise as to how this association is established, whether it is obesity that produces a vitamin D deficit, whether it is the deficit that influences the development of obesity or both. Considering that vitamin D is lipo-soluble, it is possible that the adipose tissue will take vitamin D and decrease its bioavailability[32,34]. Vitamin D deficiency, on the other hand, may lead to adipose tissue dysfunction, with a negative correlation between the levels of 25HCC and leptin levels, as well as those of insulin[35]. The biological substrate is the existence of vitamin D and 1α hydrolase receptors in human adipose tissue. In addition, preadipocytes and differentiated adipocytes respond to calcitriol or active D hormone and this vitamin D has been shown to increase adipogenesis and regulate the growth and remodeling of adipose tissue[36].

Conflict of interest: The authors declare they have no conflict of interest regarding this work.

Bibliography

1. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science. 1980;(209):823-5.
2. Chiu KC, Chu A, Go VL, Saad F. Hypovitaminosis D is associated with insulin resistance and β cell dysfuction. Am J Clin Nutr. 2004;79(5):820-5.
3. Lind L, Heanni A, Lithell H, Hvarfner A, Seorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men.

Am J Hypertens. 1995;8:894-901.
4. Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ. Glucose intolerance and impairment of insulin secretion in relation to vitamin D eficiency in east London Asians. Diabetologia. 1995;38:1239-45.
5. Boucher BJ, John WG, Noonan K. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004;(80):1666.
6. Wimalawansa SJ. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J. Steroid Biochem. Mol. Biol. J Steroid Biochem Mol Biol. 2016 Sep 20. pii: S0960-0760(16)30253-9. doi: 10.1016/j.jsbmb.2016.09.017.
7. Song Y, Wang L, Pittas AGea. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A meta-analysis of prospective studies. Diabetes Care. 2013;36:1422-28.
8. Ekmekcioglu C, Haluza D, Kundi M. 25-Hydroxyvitamin D Status and Risk for Colorectal Cancer and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Epidemiological Studies. Int. J. Environ. Res. Public Health. 2017 Jan 28;14(2). pii: E127. doi: 10.3390/ijerph14020127.
9. Parker J, Hashmia O, Dutton , Mavrodaris , Stranges , Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis. Maturitas. 2010;65(3):225-36.
10. Forouhi NG, Ye Z, Rickard AP, Khaw KT, Luben R, Langenberg C, et al. Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies. Diabetologia. 2012;55:2173-82.
11. Avenell A, Cook JA, MacLennan GS, McPherson GC. Vitamin d upplementation and type 2 diabetes: a substudy of a randomised placebo-ontrolled trial in older people (RECORD trial, ISRCTN51647438). Age Ageing. 2009;38:606-9.
12. de Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, Kestenbaum B, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. Diabetes Care. 2008;31:701-7.
13. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr. 2011; 65(9):1005-15.
14. Giulietti A, Gysemans C, Stoffels D, Van Etten E, Decallone B, Overbergh L, et al. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice. Diabetologia. 2004;47:451-62.
15. Hossein-nezhad A, Spira A, Holick MF. Influence of Vitamin D Status and Vitamin D3 Supplementation on Genome Wide Expression of White Blood Cells: A Randomized Double-Blind Clinical Trial. PLoS ONE. 2013;8(3):e58725.
16. EURODIAB Study Group. Vitamin D supplement in early childhood and risk for type I (insulin-dependent) diabetes mellitus. Diabetologia. 1999;42:51-4.
17. Borkar VV, Devidayal V, Verma S, Bhalla AK. Low level of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatric Diabetes. 2010; 11:345-50.
18. Pozzilli P, Manfrini S, Crinò A, Picardi A, Leomanni C, Cherubini V, et al. Low levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 in patients with newly diagnosed type 1 diabetes. Hormone and Metabolic Research. 2005;37:680-3.
19. Littorin B, Blom P, Schölin A, Arnqvist HJ, Blohmè G, Bolinder J, et al. Lower levels of plasma 25-Hydroxyvitamin D among oung adults at diagnosis of autoinmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologia. 2006; 49:2847-52.
20. Cooper JD, Smyth DJ, Walker NM, Stevens H, Burren OS, Wallace C, et al. Inherited variation in vitamin D genes is associated with predisposition to autoinmune disease type 1 diabetes. Diabetes. 2011;60:1624-31.
21. Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes mellitus. J Pediatrics. 2009;154:132-4.
22. Frederiksen BN, Kroehl M, Fingerlin TE, Wong R, Steck AK, Rewers M, et al. Association between vitamin D metabolism gene polymorphisms and risks of islet autoinmunity and progression to type 1 diabetes: the diabetes autoimmunity study in the young (DAISY). J Clin Endocrinol Metab. 2013;98:1845-51.
23. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch Dis Child. 2008; 93(6):512-7.
24. Pitocco D, Crino A, di Stasio E, Manfrini S, Guglielmi C, Spera S. The effects of calcitriol and nicotinamide on residual pancreatic beta-cell function in patients with recent-onset Type 1 diabetes. Diabetes Med. 2006; 23(8):920-3.
25. Walter M, Kaupper T, Adler K, Foersch J, Bonifacio E, Ziegler AG. No efect of the 1 alpha- hydroxymitamin D3 on beta-cell residual function and insulin requirement in adults with new onset type 1 diabetes. Diabetes Care. 2010;33(7):1443-8.
26. Wang J, Lv S, Chen G, Gao C, He J, Zhong H. Meta-analysis of the association between vitamin D and autoinmune thyroid disease. Nutrients. 2015; 7(4):2485-98.
27. Simsek Y, Cakır I, Yetmis M, Dizdar OS, Baspinar O, Gokay F. Effects of Vitamin D treatment on thyroid autoimmunity. J Res Med Sci. 2016;18(21):85.
28. Silverberg SJ. Vitamin D deficiency and primary hyperparathyroidism. J Bone Miner Res. 2007 Dec;22 Suppl 2:V100-4. doi: 10.1359/jbmr.07s202.
29. Grey A, Lucas J, Horne A, Gamble G, Davidson JS. Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. J Clin Endocrinol Metab. 2005;90:2122-6.
30. Holick MF, Binkley NC, ischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 201;96(7):1911-30.
31. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young J, Rejnmark L, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2011;28:1-19.
32. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72:690-3.
33. Durá-Travé T T, Gallinas-Victoriano F, Chueca-Guindulain MJ, Berrade-Zubiri S. Prevalence of hypovitaminosis D and associated factors in obese Spanish children. Nutr Diabetes. 2017 Mar 13;7(3):e248. doi: 10.1038/nutd.2016.50.
34. Parikh SJ, Edelman M, Uwaifo GI. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metabol. 2004;89:1196-9.
35. Stokic E, Kupusinac A, Tomic-Naglic D. Vitamin D and dysfunctional adipose tissue in obesity. Angiology. 2014; 66:613-8.
36. Nimitphong H, Holick MF, Fried SK, Lee MJ. 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 promote the differentiation of human subcutaneous preadipocytes. Plos One. 2012;7(12).