Original Article

Treatment with Vitamin D3 in Vitamin D Deficient Adolescents: A Pilot Study

Global Pediatric Health
Volume 7: 1–5

DOI: 10.1177/2333794X20976240
journals.sagepub.com/home/gph
SAGE

Mohan Kumaratne, MD, FAAP[1], Franck Vigneron, PhD[2], and Jasmine Cisneros, BS, RN[3]

Abstract

Multiple epidemiological studies have shown that vitamin D deficiency is highly prevalent amongst adolescents in the USA. However, recommendations regarding the treatment of vitamin D deficiency in healthy adolescents are not well defined. We carried out a prospective pilot study, to determine whether treatment with 2000 international units of vitamin D3 daily for 3 months, would normalize the vitamin D levels in vitamin D deficient adolescents. Following treatment there was a 56.02% increase in the vitamin D levels from the mean baseline values and 80.39% of the subjects normalized their vitamin D levels. There were no adverse effects associated with this intervention. This study offers complementary guidelines to the existing recommendations from the American Academy of Pediatrics on the optimal dose and duration of vitamin D3 therapy in vitamin D deficient, but otherwise healthy adolescents. Further prospective, large scale, case control studies are indicated to validate our results.

Keywords

vitamin D, vitamin D deficiency, treatment of vitamin D deficiency, vitamin D deficiency in adolescents

Received February 24, 2020. Received revised October 15, 2020. Accepted for publication November 4, 2020.

Introduction

The primary role of vitamin D is the mineralization of bone by regulating osteoblast activity and facilitating the absorption of calcium and phosphorus from the intestines and calcium from the kidneys via its active metabolite 1,25 dihydroxy vitamin D.[1,2] Therefore vitamin D deficiency results in rickets in growing children and adolescents and osteomalacia in adults.[3] Additionally, recent epidemiological studies have linked vitamin D deficiency to cardiovascular disease,[4,5] dyslipidemias,[6-8] diabetes mellitus,[9,10] cancers,[5,11,12] and auto immune diseases,[3,13,14] although causality has not yet been established. Thus, vitamin D deficiency effects not only musculoskeletal health, but potentially a wide range of acute and chronic medical conditions. It is therefore important to recognize and treat vitamin D deficiency promptly and effectively.

The American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM), defines vitamin D deficiency, as a serum 25 -hydroxyvitamin D level of < 20 ng/ml.[3,15] By this definition, the prevalence of vitamin D deficiency amongst healthy US adolescents varies from 21% to a high of 42%, depending on the geographical location, ethnicity, sex, sun exposure, BMI and the diet of the population studied.[16-19] In a previous study we reported that 27.8% of healthy Hispanic adolescents presenting to our community clinic for routine physical examinations were vitamin D deficient.[20] Guidelines from the AAP and the IOM, regarding vitamin D supplementation for infants, children, adolescents and adults are well established.[3,22] Whilst there are evidence based guidelines for treating vitamin D deficiency states such as rickets[3,21,22] and those associated with chronic medical conditions such as chronic kidney disease[23,24] and cystic fibrosis,[25-27] there are no recommendations from the AAP or the IOM, regarding the treatment of vitamin D deficiency in otherwise healthy adolescents. We conducted a prospective pilot study to determine whether treatment with 2000 international units (IU) of vitamin D3 (Cholecalciferol) daily for 3 months, would normalize the vitamin D levels in vitamin D deficient, but

[1]Fountain Valley Regional Hospital, Fountain Valley, CA, USA
[2]California State University Northridge, Northridge, CA, USA
[3]Azusa Pacific University, Azusa, CA, USA

Corresponding Author:
Mohan Kumaratne, 17692 Beach Blvd Ste 200, Huntington Beach, CA 92647, USA.
Email: mohankum@msn.com

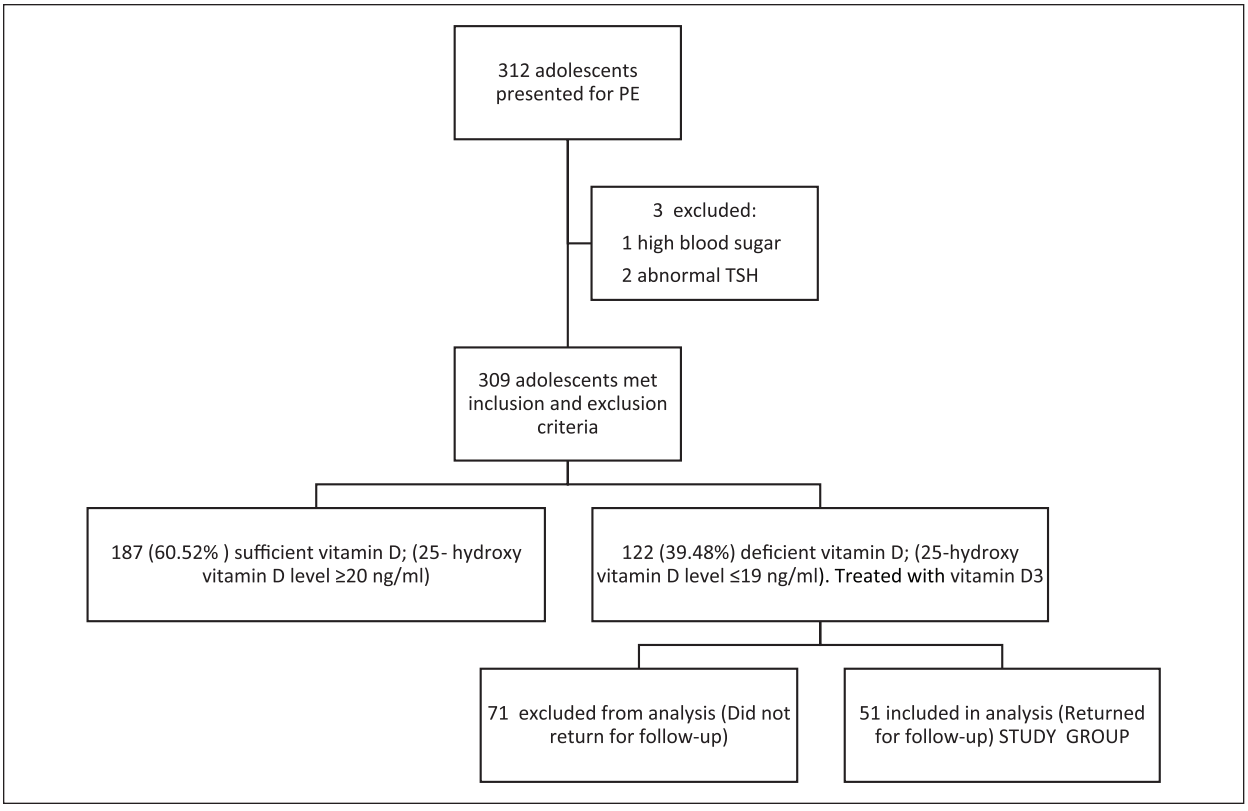

Figure 1. Flow Chart of patients assigned for treatment with vitamin D3.

otherwise healthy adolescents, who were not taking vitamin D supplements.

Design

Prospective interventional study, with each patient acting as a retrospective control.

Subjects and Methods

The study was conducted between December 1st 2017 and July 31st 2019, in a community based pediatric and adolescent medicine practice in Huntington Beach, CA. Healthy adolescents 13 to 19 years of age presenting for routine physical examinations were eligible for the study. Adolescents with acute or chronic medical problems, dietary restrictions, abnormal labs, and those taking vitamin D supplements were excluded. At time of presentation detailed history, complete physical examination and standard labs to include complete blood count (CBC), comprehensive metabolic panel (CMP), blood sugar, thyroid stimulating hormone (TSH), 25-hydroxyvitamin D level, and urinalysis were done. According to AAP parameters, those adolescents with a serum 25-hydydroxyvitamin D level below 20 ng/ml were considered to be vitamin D deficient and were empirically treated with 2000 IU of vitamin D3 (cholecalciferol) daily for 3 months and advised to return in 3 months for a follow up examination and measurement of their CMP, serum 25-hydroxyvitamin D level, and for a urinalysis. All participants were counselled about a vitamin D adequate diet, exercise and sun exposure. Written informed consent was obtained from all the adolescents and their parents, prior to recruitment for the study. Formal ethics approval was deemed not necessary by the pediatric peer review committee at Fountain Valley Regional Hospital, since the study involved treatment with vitamin D, a vitamin supplement freely available over the counter to the public.

Results

During the study period, 312 consecutive adolescents with no acute or chronic medical problems, who were not taking vitamin D supplements, presented for annual physical examinations (PE) and consented for the study. The flow chart for patients eligible for vitamin D3 treatment are in Figure 1 below.

Table 1. Baseline Characteristics of Study Group.

Variable	
Mean age in years (SD)	15 (±2)
Female sex (%)	34 (66.67)
Male sex (%)	17 (33.33)
BMI percentile (SD percentile)	80.49% (±25.96%)
Ethnicity: Hispanic (%)	50 (98)
Mean blood pressure (SD)	110/70 (±11/8)
Mean serum 25-hydroxyvitamin D ng/ml (SD)	16.01 (±2.58)
Mean serum calcium mg/dl (SD)	9.68 (±0.23)
Mean serum glucose mg/dl (SD)	81.93 (±8.11)
Urinalysis	Within normal limits

N = 51.

Table 2. Laboratory Values Following Treatment.

Mean serum 25-hydroxy vitamin D ng/ml (SD)	24.98 (±7.1)
Mean blood pressure (SD)	111/67 (±5/7)
Mean serum calcium mg/dl (SD)	9.63 gm (±0.34)
Mean serum glucose mg/dl (SD)	80.78 (±10.26)
Urinalysis	Within normal limits

N = 51.

The baseline characteristics of the study group are in Table 1 and the laboratory data following treatment are in Table 2.

There was a 56.02% increase in the mean serum 25-hydroxyvitamin D level from the mean baseline value following treatment Tables 1 and 2. 41 patients (80.39%) in the study group had normalized their serum 25-hydroxyvitamin D level to ≥ 20 ng/ml and in 10 patients (19.61%) it was yet deficient (≤19.9 ng/ml).

The follow up serum calcium, blood sugar, and urinalysis were within the normal range. There was no evidence of hypercalcemia, nephrolithiasis, or any other adverse symptoms associated with the vitamin D3 therapy.

Discussion

The dose for vitamin D supplementation in healthy adolescents is well defined by the AAP[3] and the IOM.[22] However there are no guidelines from the AAP or the IOM, regarding the optimal dose and duration of vitamin D3 therapy, in the treatment of vitamin D deficiency in otherwise healthy adolescents. Talib et al has reported that treatment with 5000 IU of vitamin D3 daily for 8 weeks corrected the vitamin D deficiency in a cohort of predominantly hispanic and black adolescents.[28] Following a placebo controlled, double blind, pilot study, Wu et al have reported that both 50,000 IU vitamin D3 monthly or 150 000 IU 3 monthly for 1 year safely and effectively corrected vitamin D deficiency in a population of adolescents from Tasmania, Australia.[29] The Indian Academy of Pediatrics recommends 60 000 IU/week of vitamin D for 6 weeks in the treatment of vitamin D deficiency in adolescents.[30]

In adolescents, in order to avoid toxicity, as well as for cost and logistical reasons, it is important to treat vitamin D deficiency, with the least concentrated dose for the shortest duration that normalizes the vitamin D levels. Treatment with 2000 to 5000 IU of vitamin D3 daily has not been associated with vitamin D toxicity,[31,32] whilst super high doses for prolonged periods have been reported to cause hypercalcemia and nephrolithiasis.[33-35] In our population of healthy vitamin D deficient adolescents, we empirically treated the vitamin D deficient subjects with 2000 IU of vitamin D3 daily for 3 months. Following treatment with vitamin D3, there was a 56.02% increase of the mean vitamin D levels from the mean pretreatment values and the levels normalized in 80.39% of the subjects. There was no hypercalcemia, nephrolithiasis, or any adverse symptoms associated with this intervention.

The AAP does not recommend routine screening for vitamin D deficiency in healthy adolescents presenting for annual physical examinations. However epidemiological data shows that vitamin D deficiency is highly prevalent across the US, and in our community the prevalence was 27.8%. This warrants screening for vitamin D deficiency during annual physical examinations and prompt and effective treatment, in order to avoid skeletal and extra skeletal morbidities, in those who are vitamin D deficient.

We conclude that in a cohort of otherwise healthy, vitamin D deficient adolescents, who were not taking vitamin D supplements, treatment with 2000 IU of vitamin D3 daily for 3 months, increased the 25-hydroxyvitamin D level by 56.02% from the mean baseline values and normalized the vitamin D levels in 80.39% of the subjects. This was a pilot study, where the study sample was small, 98% of the subjects were of Hispanic ethnicity, there was no control population and the study were limited to the community in Huntington Beach, California. In order to test the hypotheses further, prospective, large scale case control studies, from across the USA is indicated.

Acknowledgments

The authors wish to thank Vicenta Cisneros and Meguen Salazar for secretarial help, and Shanti Gunawardena, MD for reviewing the manuscript.

Author Contributions

All authors contributed equally to the paper.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Mohan Kumaratne https://orcid.org/0000-0003-1307-2962

References

1. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266-281.
2. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc*. 2010;85:752-758.
3. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008;122:398-417.
4. Al Mheid I, Quyyumi AA. Vitamin D and cardiovascular disease: controversy unresolved. *J Am Coll Cardiol*. 2017;70:89-100.
5. Manson JE, Cook NR, Lee I-M, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380:33-44.
6. Faridi KF, Zhao D, Martin SS, et al. Serum vitamin D and change in lipid levels over 5 years: the atherosclerosis risk in communities study. *Nutrition*. 2017;38:85-93.
7. Birken CS, Lebovic G, Anderson LN, et al. Association between vitamin D and circulating lipids in early childhood. *PLoS One*. 2015;10:e0131938.
8. Sriram S, Croghan I, Lteif A, Donelan-Dunlap B, Li Z, Kumar S. Relationship between 25(OH)D levels and circulating lipids in African American adolescents. *J Pediatr Endocrinol Metab*. 2016;29:1165-1172.
9. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Vianen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*. 2001;358:1500-1503.
10. Pittas AG, Dawson-Hughes B, Sheehan P, et al. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med*. 2019;381:520-530.
11. Tangpricha V, Flanagan JN, Whitlatch LW, et al. 25 – Hydroxyvitamin D-1alpha-hydroxylase in normal and malignant colon tissue. *Lancet*. 2001;357:1673-1674.
12. Cross HS, Bareis P, Hofer H, et al. 25-Hydroxyvitamin D (3) – 1alpha-hydroxylase and vitamin D receptor gene expression in human colonic mucosa is elevated during early cancero-genesis. *Steroids*. 2001;66:287-292.
13. Tsoukas CD, Provvedini DM, Manolagas SC. 1,25-dihydroxyvitamin D_3: a novel immunoregulatory hormone. *Science*. 1984;224:1438-1440.
14. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D_3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. *J Clin Endocrinol Metab*. 1983;57:1308-1310.
15. Rosen CJ, Abrams SA, Aloia JF, et al. IOM committee members respond to endocrine society vitamin D guideline. *J Clin Endocrinol Metab*. 2012;97:1146-1152.
16. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med*. 2004;158:531-537.
17. Kumar J, Munter P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. *Pediatrics*. 2009;124:e362-e370.
18. Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. *Pediatrics*. 2013;131:e152-e161.
19. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: a review of the current evidence. *Arch Pediatr Adolesc Med*. 2008;162:513-519.
20. Kumaratne M, Gayle E, Cisneros J. Vitamin D deficiency and association with body mass index and lipid levels in hispanic american adolescents. *Glob Pediatr Health*. 2017;4:2333794X17744141.
21. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930.
22. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Institute of Medicine of the National Academies. Washington, DC: The National Academies Press; 2013.
23. Al-Aly Z, Qazi RA, Gonzalez EA, et al. Changes in serum 25-hydroxyvitamin D and plasma intact PTH levels following treatment with ergocalciferol in patients with CKD. *Am J Kidney Dis*. 2007;50(1):59-68.
24. Langman CB, Mazur AT, Baron R, et al. 25-hydroxyvitamin D3 (calcidiol) therapy of juvenile renal osteodystrophy: beneficial effect on linear growth velocity. *J Pediatr*. 1982;100:815-820.
25. Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab*. 2005;90:1888-1896.
26. Green DM, Leonard AR, Paranjape SM, et al. Transient effectiveness of vitamin D2 therapy in pediatric cystic fibrosis patients. *J Cyst Fibros*. 2010;9:143-149.
27. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155(suppl 6):S73-S93.
28. Talib HJ, Ponnapakkam T, Gensure R, Cohen HW, Coupey SM. Treatment of vitamin D deficiency in predominantly Hispanic and Black adolescents: a randomized clinical trial. *J Pediatr*. 2016;170:266-272.
29. Wu F, Xiao C, Aitken D, Jones G, Winzenberg T. The optimal dosage regimen of vitamin D supplementation for

correcting deficiency in adolescents: a pilot randomized controlled trial. *Eur J Clin Nutr*. 2018;72:534-540.
30. Khadilkar A, Khadilkar V, Chinnappa J, et al. Prevention and treatment of vitamin D and calcium deficiency in children and adolescents: Indian Academy of Pediatrics (IAP) guidelines. *Indian Pediatr*. 2017;54: 567-573.
31. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD, Drugs, and Therapeutics Committee of The Pediatric Endocrine Society. Vitamin D supplementation and risk of toxicity in pediatrics: A review of current literature. *J Clin Endocrinol Metab*. 99:1132-1141.
32. Heaney RP. Vitamin D: criteria for safety and efficacy. *J Nutrition Reviews*. 2008;66:S178-S181.
33. Taylor PN, Davies JS. A review of the growing risk of vitamin D toxicity from inappropriate practice. *Br J Clin Pharmacol*. 2018;84:1121–1127.
34. Misgar RA, Sahu D, Bhat MH, Wani AI, Bashir MI. Vitamin D toxicity: a prospective study from a tertiary care center in Kashmir Valley. *Indian J Endocrinol Metab*. 2019;23:363-366.
35. Kaur P, Mishra SK, Mithal A. Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency. *Clin Endocrinol*. 2015;83:327-331.