Original Article

TIBIAL TENDERNESS IDENTIFIES SECONDARY HYPERPARATHYROIDISM RESPONDING TO HIGH-DOSE VITAMIN D IN PAKISTANI WOMEN

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ABSTRACT

Objective: To assess the utility of anterior tibial tenderness (ATT) measured by visual analogue scoring (VAS) as a clinical diagnostic tool for vitamin D deficiency in a high-risk population of Pakistani women.

Methods: ATT was measured by VAS in 75 premenopausal women age 17 to 56 years (mean, 41.3 years) with generalized aches and pains and calcium <11 mg/dL (normal, 8 to 11 mg/dL) who were seen at a tertiary care center in Lahore, Pakistan. This was followed by administration of 1.8 million units of vitamin D3 in divided doses. ATT, vitamin D, and parathyroid hormone (PTH) levels were checked before and after the injections. Correlation between ATT, vitamin D, and PTH, as well as changes in ATT, vitamin D, and PTH following supplementation were determined.

Results: Pre-intervention average calcium and vitamin D were 9.3 mg/dL (range, 8 to 10.3 mg/dL) and 12.1 ng/mL (range, 1.5 to 32.6 ng/mL), respectively. Seventy-four percent of the participants (53/75) had vitamin D deficiency and elevated PTH (>60 pg/mL). Mean PTH was 81.6 pg/mL (range, 29.1 to 370 pg/mL). Changes in ATT correlated strongly ($r = 0.422$; $P = .013$) with changes in PTH. Following supplementation, there was significant improvement in ATT ($P<.01$) and vitamin D level ($P<.01$), with a decrease in PTH level ($P<.01$).

Conclusion: ATT is a valid clinical diagnostic measure of vitamin D deficiency in South Asian women. **(Endocr Pract. 2013;19:596-601)**

Abbreviations:
ATT = anterior tibial tenderness; **BMI** = body mass index; **IM** = intramuscular; **PTH** = parathyroid hormone; **VAS** = visual analogue scoring

INTRODUCTION

Vitamin D is critical for calcium homeostasis and optimal bone health. Vitamin D deficiency is linked with colorectal cancer, depression, diabetes, hypertension, and multiple sclerosis (1). Vitamin D is synthesized in human skin upon exposure to ultraviolet B (UVB) light or obtained from the diet, and vitamin D insufficiency results in parathyroid hormone (PTH) secretion, which increases bone resorption and can lead to osteomalacia. Although advanced osteomalacia is now uncommon, vitamin D deficiency is highly prevalent worldwide and disproportionately affects Muslim women of the Indo-Pak subcontinent due to following factors (2,3):

- Females of childbearing age traditionally remain indoors and dress modestly in head-to-toe clothing when they do go out.
- The use of sunscreen is ubiquitous among urban women.
- Urbanization is on the rise in South Asia. Urban women have less sun exposure than rural women who regularly work outdoors, and thus urban women have a higher incidence of vitamin D deficiency (4,5).

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- Year-round extreme temperatures necessitate limiting sun exposure.
- Dark pigmentation hampers effective production of vitamin D in the skin.
- Dietary sources of vitamin D are limited, and fortified food is not readily available. Excess phytates and fiber in the staple diet impede absorption of vitamin D from the gut (6).

Despite the fact that vitamin D deficiency is a common cause of aches and pains among Pakistani women (7,8), the nonspecificity of this complaint limits its usefulness in diagnosis. Depression is highly prevalent (9) and often presents as "aches and pains" to the general practitioner because societal norms constrain pursuit of psychiatric care. The known association between vitamin D deficiency and depression (10) adds to the complexity of diagnosis.

Pressure-induced tenderness of the tibia has been linked with osteomalacia (11,12). It is rational, therefore, to presume that this sign would also be present in cases of milder vitamin D deficiency. Quantification of bone tenderness using a visual analogue scoring (VAS) system (13) could lead to clinical diagnosis of vitamin D insufficiency at an earlier stage. Biochemical confirmation of the deficiency requires detection of secondary hyperparathyroidism (14) due to the lack of a standard reference value for vitamin D in Pakistani women. Adequate correction of deficiency status lowers the secondarily increased PTH level, and this criterion is useful in assessing the effectiveness of replacement.

Biochemical testing for each patient who presents with aches and pains that may be associated with vitamin D deficiency is economically unfeasible; at present measurement of the vitamin D level costs $25 (2,000 Pakistani Rupees [PKR]), and determination of PTH level costs about $50 (4,000 PKR) and is only available in a few laboratories in Pakistan. Annual per capita expenditure on healthcare in Pakistan was $22.5 in 2007 (15), a factor which underscores the need for an affordable vitamin D deficiency screening tool.

METHODS

Objectives

The objective of this longitudinal, interventional study was to identify a reproducible clinical sign for vitamin D deficiency.

Study Population

We recruited 75 women who presented at an outpatient clinic at the Services Institute of Medical Sciences in Lahore, Pakistan with generalized aches and pains, regular menstrual cycles, and normal general physical exam. Lahore lies between latitude 31.15° and 31.45° north and longitude 74.01° and 74.39° east. The study lasted from November to April. Inclusion criteria included local ethnicity, birth, and upbringing in Pakistan, as well as residence in Lahore for at least 10 years.

Exclusion criteria included serum calcium of >11 mg/dL, serum phosphate >5 mg/dL, alkaline phosphatase more than twice the upper normal limit, intake of vitamin D or calcium supplements in the past 3 months, liver enzymes greater than three times the upper normal limit, blood urea greater than twice the upper normal limit, taking or requiring anticonvulsants or glucocorticoids, more than 6 months' history of diarrhea, abnormal prothrombin time, and platelet count <250,000. We also excluded patients with any local or systemic pathology (including neuropathy), psychiatric condition, or visual handicap that would make VAS unreliable, as well as patients unable to give written informed consent.

After approval for the study was received from the institutional ethics committee, the purpose and methodology of the trial were explained to each participant, and written informed consent was obtained. A detailed history was then taken, with particular emphasis on dietary habits and degree of sun exposure.

Biochemical Testing

Overnight (8 hours) fasting blood samples were collected for determination of vitamin D, PTH, serum calcium, serum phosphate, urea, and liver enzyme levels. Vitamin D was measured using an immunosorbent radioimmunoassay on 3.5 mL of clotted blood (reference kit no.: 68100E; Diasorin, Stillwater, MN). Assay precision was evaluated at Diasorin by testing four control levels. The total imprecision ranged from 9.4 to 11.1%.

PTH was determined from 3.5 mL of blood treated with ethylaminediaminetetraacetic acid by the immulite technique using a DPC chemiluminescent enzyme-labeled immunometric assay (Diagnostic Product Corporation, Los Angeles, CA). The interassay precision (pg/mL) ranged from 8.6 to 9.0%.

Measurement of Anterior Tibial Tenderness (ATT) via Visual Analogue Scoring

A visual analogue scoring (VAS) system for pain was shown to each participant along with a detailed explanation of the scoring procedure. VAS has been used successfully in the assessment of subjective nonquantifiable phenomena such as pain (13). All of the participants graded their tibial tenderness using VAS before and 3 months after vitamin D injections.

Moderate pain was defined as that which necessitated medication. Severe pain was explained to all subjects as that which was unbearable and was not relieved by medication. A point on the anteromedial flat surface of the tibia was marked on the skin 10 cm superior to the most

prominent point of medial malleolus. With the participant lying comfortably in bed, the lower leg was externally rotated so that the flat anteromedial tibia faced upwards. The point marked on the shin was subjected to stress for 10 seconds using the instrument shown in Figure 1.

The apparatus was designed to apply a deforming stress of 1 kg/cm^2. The patient was asked to grade their discomfort on the visual analogue scale from 1 to 10. This procedure was repeated on the contralateral side. The average of the two readings was taken as the patient's "VAS Pain Score."

Choice of 1.8 Million Units of Vitamin D as Treatment

We chose to treat vitamin D deficiency with intramuscular injections of 1.8 million international units (IU) of vitamin D3. Intramuscular injection (IM) of 150,000 to 300,000 IU of vitamin D was shown to be effective in treating vitamin D deficiency in elderly Finnish patients (16). Currently, the Institute of Medicine recommends a maximum of 600 IU of vitamin D per day (17), whereas the dose in the present study would roughly equate to 5,000 IU/day if administered annually and 10,000 IU/day if dosing was repeated at 6-month intervals. The unconventionally high dose used was based on reports indicating the safety and efficacy of equivalent or higher (albeit daily) vitamin D therapy in deficient individuals (18), as well as two pilot studies by the same author involving treatment first with 600,000 IU and then 1.2 million IU of the vitamin; no significant improvement in clinical/laboratory parameters was observed with this regimen.

Choice of the IM Route for Administration of Vitamin D

We chose the IM route for vitamin D replacement for the following reasons:

- Patients are more likely to be compliant with 3 injections given on alternate days than with oral vitamin D pills for a minimum of 30 weeks (at 60,000 IU per week) for an equivalent dose.
- Malabsorption syndromes, parasitic infestation, and chronic diarrhea are common in our population. Data suggest suboptimal enteral absorption of vitamin D in such patients (19).
- Disposable needles and syringes from reliable brands are now available in most urban areas for less than $0.05 (cost at the time of this study) per syringe.
- Injections are perceived as more effective and are thus better adhered to by the public (20). The long half-life (1 to 2 months) of vitamin D makes it possible to administer in yearly or six monthly bolus doses (stoss therapy) (16,21). Vitamin D administered via the IM route takes about 2 to 3 months for symptomatic effect (7). This is the reason why VAS was repeated after 3 months.

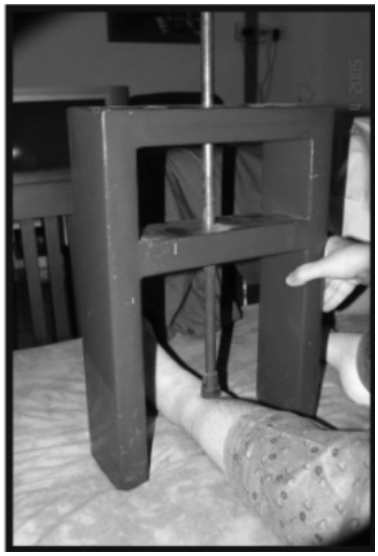

Fig. 1. Apparatus used for tibial tenderness measurement. This metal instrument with a rubber head was designed to apply 1 kg of weight to a 1-cm^2 area.

Intervention

At the following visit, we ascertained inclusion in the study based on laboratory results. All participants were prescribed intragluteal injection of 1.8 million IU of vitamin D3 to be taken in three divided doses (600,000 IU on alternate days). Calcium carbonate (1,200 mg) was also prescribed in twice daily dosage. All participants were advised to maintain the same dietary habits and degree of sun exposure as before the study.

One month after the vitamin D injections, participants were reviewed for compliance, symptoms, and any side effects of therapy. Blood samples were collected for determination of serum PTH and vitamin D levels. A final assessment was made at 3 months from the time of the replacement injections, when ATT was measured by VAS and any differences from the initial readings were noted.

Statistical Analyses

All data were examined descriptively and analytically. Quantitative variables such as body mass index (BMI), vitamin D, PTH, VAS values, etc., are reported as the mean and SD. The Wilcoxon signed rank test was applied for comparison of pre- and posttreatment vitamin D and PTH levels and VAS values. Correlation analysis was performed between different combinations of parameters using Spearman's rank correlation test. The level of significance for each test was set at 5%.

RESULTS

A total of 75 premenopausal women were recruited for the study. A total of 53 participants completed the study.

Patient characteristics and vitamin D-related laboratory data are summarized in Table 1.

The ages of the women recruited for the study ranged from 17 to 56 years, with a majority (>70%) in the range of 37 to 47 years. The mean BMI of the study population was 28.5 and showed no significant relationship with levels of vitamin D (P = .13), calcium (P = .65), or intact PTH (P = .128). The distributions of vitamin D and PTH levels in study participants are summarized in Table 2. The initial mean vitamin D and PTH levels were 12.1 ng/mL and 81.6 pg/mL, respectively. The mean ATT VAS value was 6.3 at the outset of the study and dropped to a mean value of 4.0 at 3 months after vitamin D administration. The mean vitamin D level rose from 12.1 to 51.9 ng/mL following vitamin D supplementation, whereas the mean intact PTH level dropped from 81.6 to 40.24 pg/mL (Table 3). Postintervention, 47 of the 53 participants reached a vitamin D level of >30 ng/mL, and 49 women experienced normalization of PTH level.

There was no significant correlation between the change in ATT following therapy and vitamin D level (P = .157). However, the ATT VAS value varied directly with the change in PTH level (Table 3 and Fig. 2; r = 0.422; P = .013). The change in PTH level following supplementation correlated negatively with the preintervention vitamin D level (Table 4; P = .02). No significant correlation was observed between BMI and the change in PTH level with therapy (P = .265).

DISCUSSION

This was a pilot study to identify a reliable and easy to elicit clinical sign of vitamin D deficiency in a high-prevalence population. Our study showed that changes in ATT as measured by VAS strongly correlate with significant decreases in PTH level (P = .001). Predictably, the maximum PTH response was observed in the group with the lowest vitamin D levels, and vice versa. PTH level may be a better indicator of vitamin D sufficiency than serum vitamin D level, particularly when no definitive normal range has been established (22). A vitamin D concentration of about 30 ng/mL is considered the desirable lower limit because this is the level of vitamin D at which PTH is suppressed (23). An elevated PTH level is perhaps the best indicator of insufficient vitamin D in our population.

Table 1
Patient Characteristics and Vitamin D-Related Biochemistry Data

	n	Min	Max	Mean	SD
Age (years)	53	17	56	41.3	8.2
BMI	53	16.5	42.4	28.9	5.4
Calcium (mg/dL)	53	8	10.3	9.3	0.5
Vitamin D (ng/mL)	53	1.5	32.6	12.1	17.5
PTH (pg/mL)	53	29.1	370	81.6	47.8
Visual Analogue Score	53	2	10	6.3	2

Abbreviations: BMI = body mass index; PTH = parathyroid hormone.

Table 2
Pre-intervention Vitamin D and PTH Levels

Vitamin D level (ng/mL)	n	Percent	Min	Max	Mean	SD
<20	43	81	1.5	18.1	9.09	4.1
20-30	8	15.1	20	26.8	23.5	2.4
>30	2	3.8	30.1	32.6	31.37	1.7
PTH level (pg/mL)	**n**	**Percent**	**Min**	**Max**	**Mean**	**SD**
<10	—	0	—	—	—	—
10-60	14	26	29.1	59.8	48.9	9.6
>60	39	74	60.4	370	93.3	50.6
Total	53	100	29.1	370	81.9	47.8

Abbreviation: PTH = parathyroid hormone.

Table 3
Change in Mean Vitamin D Level, Parathyroid Hormone Level, and Tibial Tenderness Visual Analogue Score Postintervention

	Initial value	Final value	Change (delta)	*P* value
Vitamin D (ng/mL)	12.1	51.87	39.77	.01
PTH (pg/mL)	81.6	41.36	40.24	.01
ATT[a]	6.3	4.0	2.3	.01

Abbreviations: ATT = anterior tibial tenderness; PTH = parathyroid hormone.
[a] Change in ATT (ΔATT) correlates with change in PTH (ΔPTH) ($r = 0.422$; $P = .013$) but not with change in vitamin D (Δvit D) ($P = .157$).

Although our study subjects served as their own controls, improvement in VAS value due to a placebo effect cannot be ruled out. However, the fact that changes in the VAS correlate significantly with changes in PTH level after vitamin D replacement (Fig. 2) suggests that it is more likely that the observed improvements were related to the treatment. A larger study involving a control group with a normal level of vitamin D and a group treated with placebo is needed to determine if the preliminary results obtained in this study are applicable to the general population. Calcium supplements without vitamin D can lower PTH. While passive calcium absorption in the ileum and jejunum is not vitamin D dependent, it is much less reliable. It is possible but unlikely that the improvement noted in our population was due to calcium and not vitamin D.

Despite the high dose of vitamin D given in this study, postintervention mean vitamin D levels did not rise above 52 ng/mL, nor did the mean PTH fall below 40 pg/mL. Toxicity is only of concern if the vitamin D level exceeds 100 ng/mL (24). Though efficacy of the dose used is apparent from the results, the length of sustained response needs to be determined. Studies with longer follow-up periods are needed to answer this question. Some authorities believe the IM route to be associated with variable bioavailability, and it might be interesting to observe and compare the results of this study with oral administration of vitamin D.

CONCLUSION

In summary, our data suggest that measurement of ATT using VAS is a useful clinical tool for diagnosing vitamin D insufficiency in Pakistani women. A larger study is warranted to assess the validity and reliability of the ATT/VAS approach as a potential screening test at the population level.

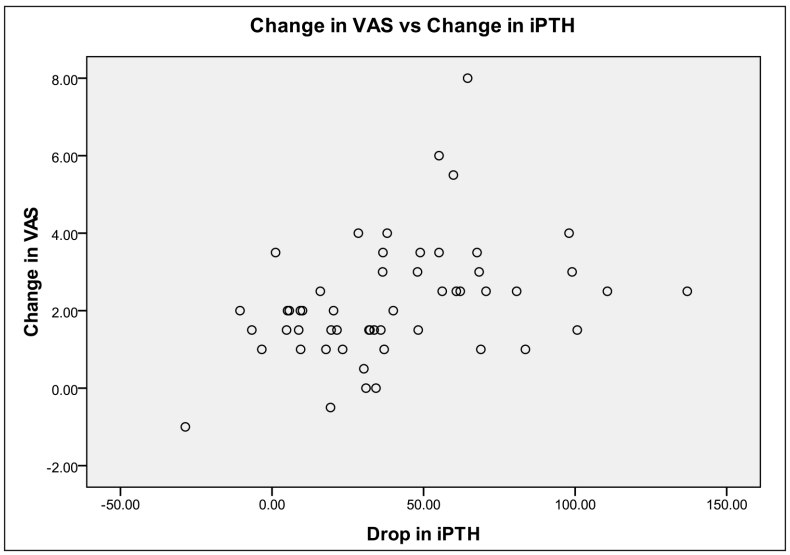

Fig. 2. Change in tibial tenderness measured by VAS versus change in iPTH. *iPTH* = intact parathyroid hormone; *VAS* = visual analogue scoring.

Table 4
PTH Response According to Initial Vitamin D Level

Groups by vitamin D level	Initial vitamin D level (ng/mL)	Mean vitamin D	n	Drop in mean PTH postintervention (pg/mL)	SD
1	0-7	2.2	8	51.7	37.01
2	7-14	10.1	32	42.2	34.83
3	14-21	18.1	5	36.3	33.33
4	21-28	24.6	6	24.4	24.24
5	28-35	20.5	2	20.5	14.81
Total	0-35	12.11	53	40.24	33.50

Abbreviation: PTH = parathyroid hormone.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Bischoff-Ferrari H, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B.** Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr.* 2006;84:18-28.
2. **Islam MZ, Lamberg-Allardt C, Kärkkäinen M, Outila T, Salamatullah Q, Shamim AA.** Vitamin D deficiency: a concern in premenopausal Bangladeshi women of two socio-economic groups in rural and urban region. *Eur J Clin Nutr.* 2002;56:51-56.
3. **Mehboob F.** Prevalence of osteomalacia in females from old city of Lahore. *Ann King Edward Med Uni*. 2002;8: 175-176.
4. **Puri S, Marwaha RK, Agarwal N, et al.** Vitamin D status of apparently healthy schoolgirls from two different socio-economic strata in Delhi: relation to nutrition and lifestyle. *Br J Nutr.* 2008;99:876-882.
5. **Harinarayan CV, Ramalakshmi T, Prasad UV, et al.** High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians. *Am J Clin Nutr.* 2007;85:1062-1067.
6. **Batchelor AJ, Compston JE.** Reduced plasma half-life of radio-labelled 25-hydroxyvitamin D3 in subjects receiving a high-fibre diet. *Br J Nutr.* 1983;49:213-216.
7. **de Torrenté de la Jara G, Pécoud A, Favrat B.** Musculoskeletal pain in female asylum seekers and hypovitaminosis D3. *BMJ*. 2004;329:156-157.
8. **Masud F.** Vitamin D levels for optimum bone health. *Singapore Med J*. 2007;48:207-212.
9. **Muhammad Gadit AA, Mugford G.** Prevalence of depression among households in three capital cities of Pakistan: need to revise the mental health policy. *PLoS One*. 2007;2:e209.
10. **Murphy PK, Wagner CL.** Vitamin D and mood disorders among women: an integrative review. *J Midwifery Womens Health*. 2008;53:440-446.
11. **Birtane M, Tuna H, Ekuklu G, Demirbağ D, Tuna F, Kokino S.** Pressure-induced pain on the tibia: an indicator of low bone mineral density? *J Bone Miner Metab*. 2004; 22:456-461.
12. **Jane de Beur SM, Langman CB.** Bedside evaluation of bone and mineral disorders. Primer on Bone Diseases and Disorders of Mineral Metabolism. 2006;6:120-122.
13. **Wewers ME, Lowe NK.** A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health*. 1990;13:227-236.
14. **Levis S, Gomez A, Jimenez C, et al.** Vitamin D deficiency and seasonal variation in an adult South Florida population. *J Clin Endocrinol Metab*. 2005;90:1557-1562.
15. World Health Statistics 2012. WHO Library Cataloguing-in-Publication Data. WHO Press, Geneva, Switzerland; 2012. Available at: http://www.who.int/gho/publications/world_health_statistics/EN_WHS2012_Full.pdf.
16. **Heikinheimo RJ, Inkovaara JA, Harju EJ, et al.** Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int*. 1992;51:105-110.
17. **Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Institute of Medicine.** Dietary Reference Intakes: calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press, 1997.
18. **Vieth R.** Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr.* 1999;69: 842-856.
19. **Low CW, Paris PW, Clemens TL, Nolan J, Holick MF.** Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. *Am J Clin Nutr.* 1985;42:644-649.
20. **Janjua NZ, Hutin YJ, Akhtar S, Ahmad K**. Population beliefs about the efficacy of injections in Pakistan's Sindh province. *Public Health*. 2006;120:824-833.
21. **Souberbielle JC, Cormier C, Kindermans C, et al.** Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. *J Clin Endocrinol Metab*. 2001;86:3086-3090.
22. **Veith R, Chan PCR, MacFarlane GD.** Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr.* 2001;73:288-294.
23. **Malabanan A, Veronikis IE, Holick MF.** Redefining vitamin D insufficiency. *Lancet*. 1998;351:805-806.
24. **Jones G.** Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr.* 2008;88:582S-586S.