Archives of Osteoporosis (2018) 13:62
https://doi.org/10.1007/s11657-018-0465-1

ORIGINAL ARTICLE

All 25-hydroxyvitamin D-deficient Indian postmenopausal women do not have secondary hyperparathyroidism

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Received: 27 March 2017 / Accepted: 27 July 2017

Abstract

Summary This study shows a high 25-hydroxyvitamin D deficiency among postmenopausal women accompanying secondary hyperparathyroidism. However, a sizable number of subjects did not have secondary hyperparathyroidism despite having low 25-hydroxyvitamin D levels. This condition arises a research question in clinical practice needed to be addressed in the future.

Purpose The present study was attempted to determine the prevalence of secondary hyperparathyroidism and also to analyze the mean value (cutoff) of 25-hydroxyvitamin D from where the PTH begins to rise in Indian postmenopausal women.

Methods A cross-sectional study including 334 postmenopausal women attending the outpatient department (MOPD) of Lok Nayak Hospital, New Delhi, between July 2008 and June 2010. Institutional ethical approval was obtained for this study. The apparently healthy postmenopausal women and attendees of the patients were included in the study. Post-thyroidectomy, thyroid illness, pregnant women, subjects taking drugs that can affect bone mineral metabolism, such as glucocorticoids, antitubercular therapy, antiepileptic, and 25-hydroxyvitamin D supplement were excluded from the study. BMD parameters such as PTH and 25(OH)D were measured by using commercial kits from DiaSorin, USA, and blood chemistry was evaluated by standard methods from the central facility of the center. Dietary calcium was analyzed by applying a food frequency questionnaire by a trained dietician.

Results Mean (SD) age of the subjects was 56.4 ± 7.7 years. The mean BMI was 24.7 ± 5.5 kg/m^2. The baseline biochemical investigations such as total bilirubin, liver function test (LFT), kidney function test (KFT), calcium, phosphorous, total protein, and serum albumin were in reference range except alkaline phosphatase (ALP). The mean values of 25(OH)D and PTH were 12.95 ± 8.08 ng/ml and 91.60 ± 75.56 pg/ml respectively. The 24-h dietary calcium intake was 487.06 ± 239.36 mg/24 h. 25-hydroxyvitamin D deficiency was found in 277 subjects (82.93%) and was inversely related to PTH. Forty-three subjects had 25-hydroxyvitamin D levels between 20 and 29 ng/ml (12.87%), and only 14 subjects (4.19%) had optimum 25-hydroxyvitamin D levels. Secondary hyperparathyroidism was found in 235 (70.35%) subjects; however, it was not found in 30%.

Conclusions Majority of postmenopausal women of India had 25-hydroxyvitamin D deficiency with raised PTH levels. The cutoff point of 25-hydroxyvitamin D at which PTH began to rise was found at 25 ng/ml which seems similar to that of the Caucasians.

Keywords Secondary hyperparathyroidism (SHPT) · Parathyroid hormone (PTH) · 25-hydroxyvitamin D deficiency (VDD)

Introduction

25-Hydroxyvitamin D deficiency is common in Indian population [1] and elsewhere [2–6]. The evidence of 25-hydroxyvitamin D inadequacy in postmenopausal women along with other population has also shown throughout worldwide studies [7–14]. Age dependency of the PTH-25-OHD relationship reflects the composite effects of age-related decline in calcium absorption and kidney function test (KFT). This unselected large population database study could guide

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Published online: 27 May 2018

clinical management of patients based on an age-dependent, PTH-25-OHD continuum (PTH) [15]. The approach to define recommended 25-hydroxyvitamin D intake has been disputed in all populations [16]. Results of various population-based studies such as LASA [17], BRAZOS [18], PIVUS [19], (WHAS)-I and II [20], and MORE [2] show high prevalence of 25-hydroxyvitamin D deficiency in postmenopausal women along with a negative correlation with PTH.

The most common factors associated with inadequate 25-hydroxyvitamin D levels comprised with limited sun exposure, lack of dietary 25-hydroxyvitamin D intake, nursing home environment, wintertime, and increasing age (over 70 years) [21]. Prevalence of osteoporosis is 25 to 30% in women older than 50 years and is a major health concern. In clinical practice, there are few subjects in whom PTH does not rise despite low to very low 25-hydroxyvitamin D levels. Such studies are inadequate; thus, we attempted to determine the relationship between 25(OH)D and PTH in postmenopausal women. Here, we hypothesized that postmenopausal women of India will have low 25-hydroxyvitamin D status further leading to an increase in serum PTH.

Methods

This was a cross-sectional study carried out in the Department of Medicine, Maulana Azad Medical College, and associated Lok Nayak Hospital, a tertiary care hospital, New Delhi, India. The sample size of this study was calculated by sigma stat 2.03 software. The power of the study was adjusted with 5%. A total of 334 postmenopausal women, who visited the medical outpatient department (MOPD) during the period from July 2008 to June 2010, were recruited. The approval of the study was obtained from the institutional ethics committee (IEC). Informed written consent was obtained from all subjects prior to inclusion. All study subjects were also given a patient information sheet for their understanding and education. All patients were subjected to clinical history and examination using a predesigned performa. Past and present history of illness, previous medications and average duration of sun exposure including surface area of the body exposed daily were also documented in the study. Exclusion criteria included post-thyroidectomy, thyroid illness, pregnant women, and drug use that can affect bone mineral metabolism. History of glucocorticoids, antitubercular therapy, antiepileptic, and 25-hydroxyvitamin D supplement were excluded. Patients having cancer or with any fractures were also excluded from the study.

Fasting venous samples of all subjects were drawn at 0800–0900 h without venostasis in calcium-free tubes. Serum was separated from refrigerated and centrifuged at 800×*g* for 15 min at 4 °C and stored in multiple aliquots at − 20 °C ultra refrigeration. Serum calcium, phosphorous ($P0_4$), alkaline phosphatase (ALP), total bilirubin (TB), total protein (TP), albumin, kidney function test (urea, creatinine), and liver function test (SGOT, SGPT) were estimated on the day of collection and were determined using standard methods and auto-analyzed in the central laboratory of the hospital.

Serum calcium was adjusted according to albumin levels. The normal levels of s. calcium, phosphorous, and alkaline phosphate were 8.7–10.2 mg/dl, 2.5–4.5 mg/dl, and 33–96 IU/L respectively. Albumin-adjusted serum calcium (mg/dl) = observed serum total calcium + (normal albumin-observed albumin concentration) × 0.8. (Normal mean serum albumin was taken as 4 g/dl.) Samples were protected from light during processing.

25(OH)D was measured by radioimmunoassay (RIA) using commercial kits (DiaSorin, USA) and serum PTH was measured by immunoradiometric assay (IRMA). The sensitivity of the method is > 1.5 ng/dl. 25-Hydroxyvitamin D deficiency was defined as serum 25(OH)D levels that were less than 20 ng/ml (50 nmol/l) [8]. The sensitivity of the method is 0.7 pg/ml. The intra assay variation ranged from 2.0 to 3.6% CV and the inter assay variation ranged from 3.4 to 4.9% CV. The reference range of PTH was taken to be 9–54 pg/ml. Twenty-four-hour calcium intake was assessed by a trained dietician.

Statistical analysis was performed by using SPSS version (17.0) (SPSS Inc., Chicago, IL). One-sample *t* test was performed for the analysis. Baseline laboratory parameters are represented as mean ± SD. *P* value < 0.05 was considered significant ($\alpha = 5\%$). Pearson correlation coefficient (*r*) analysis was performed against 25-hydroxyvitamin D.

Results

The characteristics of this study are shown in Table 1. The mean age of the subjects was 56.41 ± 7.74 years. The baseline bone mineral parameters such as calcium (mg/dl) and phosphorous (mg/dl), alkaline phosphatase (Ka/U), parathyroid hormone (pg/ml), 25(OH)D (ng/ml), and 24-h dietary calcium (mg/dl) were 9.25 ± .80 mg/dl, 3.87 ± .79 mg/dl, 168.51 ± 103.89 Ka/U, 91.60 ± 75.56 pg/ml, 12.95 ± 8.08 ng/ml, and 487.06 ± 239.36 mg/dl respectively.

Blood chemistry parameters such as LFT and KFT were in reference range in all subjects except ALP, which was higher in 82.33% (*N* = 275). The mean value of sun exposure was 37.17 ± 21.13 (min/day). Out of 334 subjects, 25-hydroxyvitamin D deficiency (< 20 ng/ml) was found in 82.93% (*N* = 277; *P* = 0.001).

25-Hydroxyvitamin D insufficiency (20–29 ng/ml) was found in 13% (*N* = 43) of subjects. Optimum levels of 25-hydroxyvitamin D (> 30 ng/ml) were found just in 4.19% (*N* = 14).

Table 1 Baseline characteristics of subjects

Parameters	Values (Mean ± SD)	*P* value
Age (years)	56.41 ± 7.74	–
Height (cm)	145.2 ± 12.21	–
Weight (kg)	51.5 ± 12.06	–
BMI (kg/m^2)	24.7 ± 5.5	–
Sun exposure (min/day)	37.17 ± 21.13	0.01
S. calcium (mg/dl)	9.25 ± .80	0.01
S. phosphorous (mg/dl)	3.87 ±. 79	0.01
S. alkaline phosphatase (Ka/U)	168.51 ± 103.89	0.01
24 dietary calcium (mg/24 h)	487.06 ± 239.36	0.01
S. parathyroid hormone (pg/ml)	91.60 ± 75.56	0.01
25(OH)D (ng/ml)	12.95 ± 8.08	0.01

P value was considered significant (< 0.05)

Secondary hyperparathyroidism (SHPT) was found in 70.35% ($N = 235$; $P = 0.001$). A negative correlation was found between 25-hydroxyvitamin D and parathyroid hormone in the entire group ($r = -0.116$). All the baseline parameters were significant ($P = 0.001$) by using one-sample *t* test (variations in the values in comparison with mean value of the parameter).

The above parameters were correlated with 25-hydroxyvitamin D and are shown in Table 2. The mean age (years), sun exposure (min/day), calcium (mg %), s. phosphorous (mg %), ALP (U/L), and 24-h dietary were 0.082, 0.057, − 0.047, 0.080, − 0.082, − 0.116, and 0.051 respectively.

Blood chemistry parameters such as serum bilirubin (mg/dl), ALT (U/L), AST (U/L), urea (mg %), and creatinine (mg %) were − 0.051, − 0.048, − 0.059, 0.012, and 0.089 respectively. Age and sun exposure were positively correlated with 25-hydroxyvitamin D ($r = 0.082$ and 0.057). However, PTH, ALP, and calcium ($r = -0.116$, $r = -0.082$, and $r = -0.047$ respectively) were negatively correlated with 25-hydroxyvitamin D (Table 2). However, no correlation was observed in urea, creatinine, and phosphorous.

Table 2 Correlation of different parameters with 25-hydroxyvitamin D

Parameters	Correlations with 25-hydroxyvitamin D (*r*)
Age (years)	0.082
Sun exposure (min/day)	0.057
S. calcium (mg/dl)	− 0.047
S. phosphorous (mg/dl)	0.080
S. alkaline phosphatase (Ka/U)	− 0.082
24 dietary calcium (mg/24 h)	0.051
S. parathyroid hormone (pg/ml)	− 0.116

P value was considered significant (< 0.05)

PTH and 25-hydroxyvitamin D were inversely related with each other in the entire group of postmenopausal women ($r = -0.116$) (Fig. 1). The majority of the subjects $N = 235$ (70.65%) had raised PTH levels characterized as SHPT.

We observed through the graph (Fig. 2) that the mean value of 25-hydroxyvitamin D was 25 ng/ml from where the PTH begins to rise.

Comparison between SHPT and Non-SHPT group

Among 98 (29.04%) of the subjects, levels of PTH did not rise (non SHPT group) despite lower levels of 25-hydroxyvitamin D (< 30 ng/ml). The mean age of the subjects from this group was 55.74 ± 7.49 years and mean 25-hydroxyvitamin D (ng/ml), PTH (pg/ml), alkaline phosphatase (Ka/U), calcium (mg/dl), phosphorous (mg/dl), and 24-h dietary calcium (mg/24 h) were 10.60 ± 4.62, 33.57 ± 16.14, 157.32 ± 99.52, 9.36 ± 0.88, 0.5 ± 0.21, and 467.47 ± 222.6 respectively. While comparing the SHPT group with the non SHPT group, the levels of 25-hydroxyvitamin D were statistically significant ($P = 0.0135$) Table 3.

Discussion

25-Hydroxyvitamin D deficiency has been widely reported in different regions of India and in postmenopausal women [22, 23]. In this study, we observed that 83% of the postmenopausal women have had 25-hydroxyvitamin D deficiency. Both 25-hydroxyvitamin D and PTH were inversely correlated with each other [24]. Seventy-one percent (two third) of the subjects had SHPT although one third of subjects did not (non SHPT).

Life expectancy in India has increased; this situation not only contributed to 25-hydroxyvitamin D deficiency but also increased the incidence of osteoporosis [13].

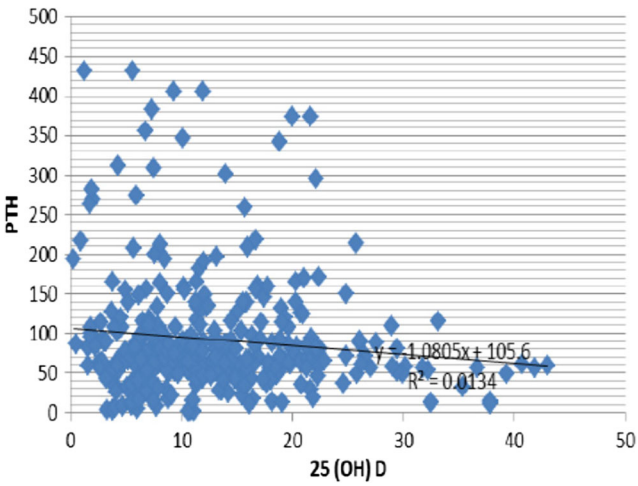

Fig. 1 Relationship between PTH and vitamin D

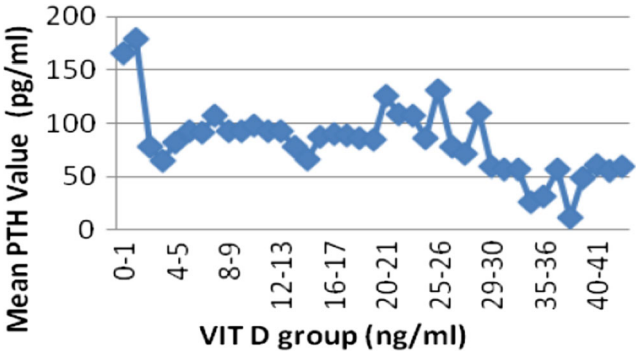

Fig. 2 Levels of PTH according to vitamin D

Studies have indicated that Indians have lower bone mineral density than North American and European counterparts [25, 26]. Additionally, osteoporotic fractures occur 10–20 years earlier in Indian compared to Caucasian population [27]. Looking at an Indian scenario, both 25-hydroxyvitamin D deficiency and osteoporosis are commonly located [28, 29]. Previous studies from New Delhi, India, have shown that ≥ 90% of 25-hydroxyvitamin D deficiency was found in healthy Asian Indians including men and women [30]. Our finding shows that higher prevalence of 25-hydroxyvitamin D deficiency (82.93%) is similar to previous studies from southern parts of India [31]. Additionally, 12.87% of the subjects had 25-hydroxyvitamin D insufficiency and just 4.19% of the subjects had 25-hydroxyvitamin D sufficiency based on the criteria used by Lips P [2]. Arya V. and colleagues have shown that 78.8% of population have 25-hydroxyvitamin D deficiency considering 20 ng/ml as cutoff value [22].

A study from northern part of India reported 66.67% of 25-hydroxyvitamin D deficiency in asymptomatic healthy postmenopausal women [32]. Overall, studies performed in various populations in India have shown a poor 25-hydroxyvitamin D status with an inverse relationship between PTH. These studies included young population with 25-hydroxyvitamin D deficiency along with SHPT condition [23, 30–32]. We observed that 235 subjects (70.35%) had secondary hyperparathyroidism (SHPT) ($r = -0.116$; $P = .001$).

Although PTH levels begin to rise followed by 25-hydroxyvitamin D deficiency, according to our study, a sizable number of the subjects ($N = 98$; 29.34%) had normal levels of PTH who did not evoke secondary hyperparathyroidism despite low 25-hydroxyvitamin D levels. This finding is often observed in clinical practice, and hence the exact cause behind this physiology is unknown. Particularly in this group, biochemical parameters were otherwise normal except alkaline phosphatase. However, excess calcium absorption and immobility may contribute to this condition though we could not find such correlations. Therefore, this research question further needs separate evaluation at clinical and molecular levels as well.

While comparing SHPT and non SHPT groups, interestingly, both 25-hydroxyvitamin D and PTH were statistically significant along with renal function (creatinine level) (Table 3) which adds an evidence to be a potential biomarker for screening of such ambiguity including with PTH.

25-Hydroxyvitamin D deficiency is an important cause of secondary hyperparathyroidism. We have also observed the pattern of PTH according to 25-hydroxyvitamin D levels. Traditionally, 25-hydroxyvitamin deficiency is defined as level of 25-hydroxyvitamin D at which PTH starts rising. We evaluated that PTH starts to increase when 25-

Table 3 Comparison between SHPT and non SHPT groups

Parameters	SHPT group ($N = 251$)	Non SHPT group ($N = 98$)	*P* value
Age (years)	56 ± 0.23	55.74 ± 7.49	–
Calcium (mg/dl)	9.22 ± 0.77	9.36 ± 0.88	0.1438
Phosphorous (mg/dl)	3.84 ± 0.68	3.90 ± 1.02	0.5241
Alkaline phosphatase (Ka/U)	171.36 ± 105.73	157.32 ± 99.52	0.2580
24 dietary calcium (mg/24 h)	486.01 ± 240.08	467.47 ± 222.6	0.5088
Parathyroid hormone (pg/ml)	115.62 ± 77.51	33.57 ± 16.14	*0.0001*
25-Hydroxyvitamin D (ng/ml)	12.72 ± 7.94	10.60 ± 4.62	*0.0135*
S. ALT (IU)	26.97 ± 20.76	25.76 ± 13.23	0.5924
S. AST (IU)	28.57 ± 14.38	26.27 ± 10.61	0.1515
S. urea (mg %)	30.23 ± 12.66	29.18 ± 17.2	0.5316
Creatinine (mg %)	0.85 ± 0.3	0.80 ± 0.91	*0.0001*

Upon Comparison between SHTP and Non SHTP groups, the *P* values (italicized entries) of parameters including Parathyroid hormone, 25 hydroxyvitamin D and S. Creatinine were found significant

Group referred as 'Non SHTP' where values of PTH did not rise despite significant vitamin D deficiency among sizable number of subjects (N=98)

P value was considered significant (< 0.05)

hydroxyvitamin D levels are lower than 25 ng/ml. 25-Hydroxyvitamin D cutoff levels in Indian postmenopausal women are in concordance with that in Caucasians and other populations. Researchers suggested that PTH does not rise if 25-hydroxyvitamin D levels are > 28 ng/ml. Other studies, on the other hand, suggested that 25-hydroxyvitamin D < 37 ng/ml causes some difference in PTH levels [33–35]. The baseline laboratory investigations such as LFT and KFT were in reference range except alkaline phosphatase. The levels of alkaline phosphatase (ALP) were higher among 275 subjects (82.33%; $P = 0.001$).

The Indian subcontinent is situated between 8.4° N and 37.6° N latitude and gets adequate sunshine throughout the year. It has been presumed that Indians get a good opportunity to have sufficient sun exposure. 25-Hydroxyvitamin D sufficiency is subjected to young skin, optimal and effective exposure to sunlight, and adequate calcium intake (ACI). A positive correlation was found between sun exposure and 25-hydroxyvitamin D levels ($r = 0.057$).

Among all the participants, majority of subjects were Muslims, 160 subjects (48%) who used to wear veil (religious clothing pattern). Several studies concluded that these Muslim women had low 25-hydroxyvitamin D levels who wear veil clothing [23]. Studies from outside of India show that a lack of adequate sunlight exposure, either due to indoor confinement or residence in regions, situated at higher latitudes, was found to be a major contributor to 25-hydroxyvitamin D deficiency. Similarly in India, due to the extreme heat of the midday sun, it is usual for people to wear dresses that cover most of their body parts, leaving the arms and face exposed. In addition, most white-collar Indian workers prefer to remain confined at their homes or offices, especially during winters [36].

25-Hydroxyvitamin D levels are lower in the winter season as compared to summer but there was no significant difference in 25-hydroxyvitamin D levels in the winter and spring seasons (Fig. 3). Studies have shown that 25-hydroxyvitamin D levels may vary according to seasons. Many studies have shown lower 25-hydroxyvitamin D levels during winter months than summer [36]. Our study shows lower 25-hydroxyvitamin D levels both in the winter and spring seasons may be due to lesser access of UVB rays in those seasons

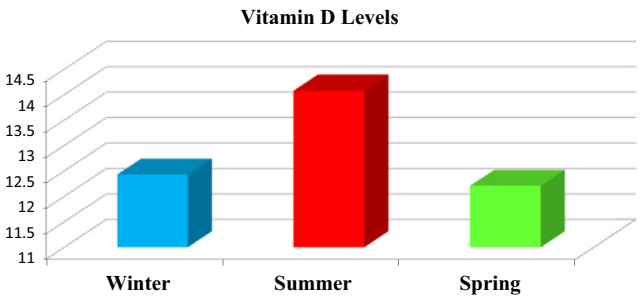

Fig. 3 Vitamin D levels in different seasons

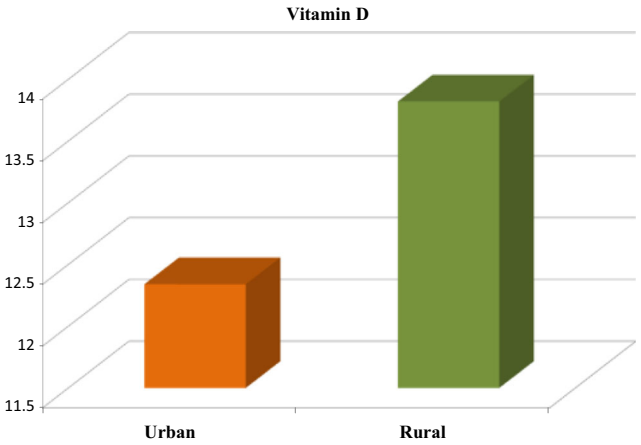

Fig. 4 Status of vitamin D between urban and rural subjects

despite spending long hours under sunlight. Although in summer's the levels of vitamin D were found elevated as compared to winter and spring season but it appears that majority of Indians do not have a sun-seeking behavior due to extreme heat during daytime for variety of reasons which constitutes in deficiency of vitamin D. Studies from south Indian parts have shown that rural dwellers have higher 25-hydroxyvitamin D levels than urban [14]. A low prevalence of 25-hydroxyvitamin D deficiency was seen in rural subjects compared with urban subjects from this study [31]. In our study, 41% of the subjects who belong to rural areas show lower 25-hydroxyvitamin D levels compared to urban dwellers (Fig. 4).

Strength of the study

The present study comprises Indian postmenopausal women as there are limited numbers of studies conducted on postmenopausal women. The study describes the burden of 25-hydroxyvitamin D deficiency in postmenopausal women and subsequently describes the status of subjects who do not have secondary hyperparathyroidism. We have shown the level of the mean 25-hydroxyvitamin D level at which PTH begins to rise.

Limitations of the study

The major limitation to this study is that we did not evaluate BMD of subjects due to non-accessibility of DEXA scan at our center.

Conclusion

Indian postmenopausal women have 25-hydroxyvitamin D deficiency with an inverse relationship found between PTH

and 25-hydroxyvitamin D. The cutoff point of 25-hydroxyvitamin D at which PTH began to rise was 25 ng/ml which is similar to that of Caucasians. Among non SHPT groups, screening of renal function may be a potential biomarker and might add new information. Further research is required at clinical and molecular levels to understand this phenomenon completely.

Acknowledgements We are also thankful to our study participants and their relatives. We are thankful to Mr. A. K. Roy, technical officer, Nuclear Medicine lab, for performing hormonal assays and Ms. Mridula Mahana, Sr. Dietitian of Lok Nayak Hospital, for dietary calcium analysis.

Funding information This study received financial support from the Indian Council of Medical Research (ICMR) New Delhi.

Compliance with ethical standards

The present study was approved from the institutional ethics committee (IEC) of the hospital. All subjects were informed in detail for the purpose of this study and recruited after obtaining their written consent.

Conflicts of interest None.

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