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ORIGINAL ARTICLE

The role of parathyroid hormone (PTH) and vitamin D in falls and hip fracture type

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Abstract

Background Fragility fractures of the hip are associated with high morbidity and mortality, and represent a rather devastating consequence of osteoporosis. Hip fractures are traditionally investigated as a whole, although it has been recently implied that distinct pathogenic mechanisms may lead either to trochanteric or subcapital fractures.

Aims To investigate whether differences exist by hip fracture type with respect to serum 25(OH)D (vitamin D) and parathyroid hormone (PTH) levels, in addition to epidemiological and demographic data, including history of falls.

Methods The inclusion criteria were met by 116 patients [48 men and 68 women; mean age 80.8 ± 8.5 (range 62–94) years]. Patients were analyzed according to hip fracture type, history of falls, and vitamin D and PTH status.

Results Older age, recurrent falls, serum levels of PTH > 65 pg/ml, and severe vitamin D deficiency were found to be associated with trochanteric fractures. Additionally, older age, female gender, PTH > 65 pg/ml, and severe vitamin D deficiency were related to recurrent falls. Meanwhile, patients with absence of PTH response to low vitamin D levels, were not repeated fallers and suffered mostly from subcapital fractures.

Discussion and conclusion Elevated PTH levels predispose both to falls and trochanteric fractures, while vitamin D-deficient patients with normal PTH levels are mostly related to subcapital fractures. It is thereby indicated that different pathophysiological processes lie behind subcapital and trochanteric fractures. A better understanding of these mechanisms may assist in the development of prevention strategies for individuals recognized at risk for falls and either type of hip fracture.

Keywords Parathyroid hormone (PTH) · 25 (OH) vitamin D · Hip fracture type · Falls

Introduction

Osteoporosis represents the most common bone disease in humans, and as the population ages its prevalence will increase, affecting people of both sexes and all races [1, 2]. The most important complication of osteoporosis is the occurrence of a low-energy fragility fracture (vertebral, hip, distal radius, proximal humeral) that may or may not result from fall, and it has been estimated that approximately one out of two Caucasian women and one out of five men will experience an osteoporosis-related fracture at some point in their lifetime [2, 3]. In contrast to most vertebral compression fractures, which are the most common fragility fractures, hip fractures in general, result from falls and represent a rather devastating consequence of osteoporosis associated with high morbidity and mortality [3–5]. Low bone mineral density (BMD) and recurrent falls have been widely considered as significant risk factors for hip fractures [3, 6–8]. Other well-known factors include physical activity, Body Mass Index, smoking, excessive alcohol consumption, age, and glucocorticoids therapy [6, 7, 9–11]. Low serum 25-hydroxyvitamin D (25(OH)D) levels and the response of parathyroid hormone (PTH) to vitamin D deficiency have been also associated with the risk of hip fractures [6, 7, 12–19]. In the main body of literature nonetheless, hip fractures are investigated as a whole, rather than as different types of fractures, albeit the available data that distinct pathogenic mechanisms may lead either to trochanteric (extracapsular) or subcapital (intracapsular) fractures [7, 13, 14, 20, 21]. It has been suggested that sufferers from

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trochanteric fractures tend to be older, more osteoporotic, and present a positive history of frailty fractures compared to patients with subcapital fractures [20–24]. Vitamin D and PTH are directly associated with bone metabolism, therefore their role in patients with osteoporotic hip fractures has been widely investigated [6, 12, 13, 15, 16, 21, 25, 26]. Few investigators have also studied vitamin D and PTH in relation to the type of hip fracture, and it has been shown that these parameters may differ significantly between trochanteric and subcapital fracture sufferers, thus implying that variations in bone metabolism status may contribute to the hip fracture type [13, 14, 16, 25]. Nevertheless, there has been paucity in literature ever since. The purpose of this study was to investigate whether individuals sustaining osteoporotic hip fractures present differences by hip fracture type, regarding epidemiological and demographic data. It was further hypothesized that differences exist in biochemical parameters of bone and mineral metabolism, and especially in the levels of serum 25(OH)D (vitamin D) and PTH, among different types of hip fractures.

Materials and methods

We prospectively studied patients with low-energy hip fractures between December 2015 and April 2016, as well as between December 2016 and April 2017. The selection criteria for study participants were as follows: (1) individuals who were prior to their fracture ambulatory and able to walk outdoors; (2) community-dwelling / non-institutionalized older adults; (3) no history of gastrointestinal diseases causing malabsorption syndromes or previous gastrointestinal surgery; (4) estimated glomerular filtration rate (eGFR) greater than 60 ml/min 1.73 m^2; (5) no history of using estrogens, bisphosphonates, 25(OH)D and/or calcium supplementation, or drugs affecting the bone metabolism or calcium homeostasis; (6) no pathological fracture secondary to any underlying oncological process, Paget's disease or primary hyperparathyroidism; and (7) patients admitted within 24 h from the fall/fracture incident. Finally, 116 patients (48 men and 68 women) were eligible for enrollment in our study. Blood samples were obtained on admission from each patient, and along with the routine tests (full blood count, creatinine, urea nitrogen, serum electrolytes, and liver function tests), the following serum essays were additionally performed: c-reactive protein (CRP), albumin, 25(OH)D levels, PTH, calcium, phosphate, and magnesium. The history of falls of each patient was also evaluated. Patients were analyzed according to hip fracture type, and vitamin D and PTH status. Vitamin D deficiency was defined as 25(OH) D < 12 ng/ml (30 nmol/l) based on recent recommendations from the Institute of Medicine (IOM) [27, 28]. The upper limit of serum PTH was set to 65 pg/ml [29], with greater values being indicative of secondary hyperparathyroidism. The absence of PTH response to vitamin D deficiency, was defined as blunted PTH response or "functional hypoparathyroidism" [13, 16]. The methods that were used to measure PTH and 25(OH)D were the ELSA-PTH method (a solid phase two-site immuno-radiometric assay; ref. values: 15–65 pg/ml) for PTH, and the IDS OCTEIA 25-OH vitamin D kit (enzyme immuno-assay for quantitation of 25(OH)D in human serum; ref. values 48–144 nmol/l) for 25(OH)D.

Data were tabulated in a Microsoft Excel® sheet (Microsoft Corporation, Redmond, Washington, USA), and were analyzed using the SPSS v.18.0 statistical package for personal computers (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values ± SD (standard deviation), and categorical variables as percentages. The Kolmogorov–Smirnov test was utilized for normality analysis of the parameters and all data were found to be normally distributed. The comparisons between groups were performed using the independent samples *T* test for continuous variables, and the Chi square test for categorical variables. The correlation between variables was examined using the Pearson correlation. Logistic regression analysis was performed to determine the odds ratio (OR) and 95% confidence intervals (CI) for associations between type of hip fracture (dependent variable) and the variables studied; all potential confounding variables with statistical significance ≤ 0.15 on univariate analysis were included in the final multivariate analysis. Tests were two-sided, and the level of statistical significance was set to 0.05.

Results

Mean age of patients was 80.8 ± 8.5 years (range 62–94 years). Trochanteric fractures were roughly more frequent than subcapital fractures (51.7% vs 48.3%), and the mean number of falls of patients during the preceding year was 0.97 ± 1.17 falls (range 0–4) (Table 1). A significant relation was found between hip fracture type and falls, as well as between PTH-vitamin D axis, and hip fracture type and falls. More precisely, trochanteric fractures were significantly related to the number of falls (Table 2). On the same time, three out of four patients with subcapital fractures claimed not having sustained previously a fall, which was not the case in patients with trochanteric fractures; at least one fall prior to index fracture was reported by approximately 73% and 21% of patients with extracapsular and intracapsular fractures, respectively ($p < 0.001$) (Table 3a). Though gender was not related to the type of hip fracture, a significant relation between gender and falls was found; about 86% of patients that sustained at least one fall, were women, while most men (83.3%) did not report a falling

Table 1 Patients' demographics and characteristics

Gender	
Female	68
Male	48
Trochanteric	60
Subcapital	56
Falls	1 ± 1.2
Age (years)	80.8 ± 8.5
BMI (kg/m^2)	24.7 ± 3.8
ASA grade	2.9 ± 0.9
Time to surgery (days)	2.5 ± 2.2
LoS (days)	7 ± 3.1

Falls, Age, BMI (Body Mass Index), ASA (American Society of Anaesthesiologists) grade, time-to-surgery, and LOS (length of hospital stay) values in mean ± standard deviation (SD)

incident the year prior to index fracture (Table 3b). Age in our study was significantly related to both hip fracture type and falls (Table 2); trochanteric fracture sufferers and repeated fallers were older than their peers (87.1 ± 4.4 years vs 73.9 ± 6.2, $p < 0.001$, and 84.5 ± 7 vs 77.3 ± 8.4, $p = 0.001$, respectively). Regarding laboratory measurements, lower values of 25(OH)D were found in women (15.9 ± 6.6 ng/ml vs 20.6 ± 8.7 ng/ml, $p = 0.024$), and in patients with recurrent falls (13.3 ± 4.8 ng/ml vs 22.1 ± 7.7 ng/ml, $p < 0.001$). Serum PTH was found to be significantly higher in patients with trochanteric fractures (86.1 ± 17.3 pg/ml vs 70.8 ± 16.2 pg/ml, $p = 0.001$) and in patients with recurrent falls (88.4 ± 16.3 pg/ml vs 69.6 ± 15.3 pg/ml, $p = 0.001$) (Table 2). No statistically significant differences were found in the rest of the parameters studied, with respect to hip fracture type, falls, and gender.

When patients were grouped according to the value of serum 25(OH)D (less and greater than 12 ng/ml) and PTH (less and greater than 65 pg/ml) the following observations were made; 27.6% of patients were classified as vitamin D-deficient, with a mean value of 25(OH)D 8.5 ± 2.5 ng/ml, and these patients were associated with both recurrent falls ($p = 0.012$) and trochanteric fractures ($p = 0.029$); patients with elevated PTH levels were also associated

Table 3 Patients grouped by hip fracture type, falls, gender, vitamin D deficiency and hyperparathyroidism

	Hip fracture type		*p*
	Subcapital fracture (%)	Trochanteric fracture (%)	
Falls (preceding year)			
No falls	78.6	26.7	< 0.001
≥ One fall	21.4	73.3	
25(OH)D			
> 12 ng/ml	85.7	60	0.029
< 12 ng/ml	14.3	40	
PTH			
> 65 pg/ml	57.1	93.3	0.001
< 65 pg/ml	42.9	6.7	
	Falls (during preceding year)		*p*
	No falls (%)	≥ One fall (%)	
Gender			
Female	33.3	85.7	< 0.001
Male	66.7	14.3	
25(OH)D			
> 12 ng/ml	86.7	57.1	0.012
< 12 ng/ml	13.3	42.9	
PTH			
> 65 pg/ml	56.7	92.9	0.003
< 65 pg/ml	43.3	7.1	

Chi square test. Variables presented as percentages. Patients grouped by hip fracture type, falls, gender, vitamin D deficiency and hyperparathyroidism. Only statistically significant differences are shown

Table 2 Clinical and laboratory characteristics by hip fracture type, gender, and falling events

	Hip fracture type		*p*	Gender		*p*	Falls (during preceding year)		*p*
	Subcapital	Trochanteric		Female	Male		No falls	≥ One Fall	
Age[a]	73.9 ± 6.2	87.1 ± 4.4	< 0.001	82.3 ± 8.1	78.5 ± 8.7	0.09	77.3 ± 8.4	84.5 ± 7	0.001
PTH (pg/mL)[a]	70.8 ± 16.2	86.1 ± 17.3	0.001	82.2 ± 16.5	73.7 ± 19.8	0.079	69.6 ± 15.3	88.4 ± 16.3	0.001
25(OH)D (ng/mL)[b]	19.6 ± 7.7	16.2 ± 7.7	0.094	15.9 ± 6.6	20.6 ± 8.7	0.024	22.1 ± 7.7	13.3 ± 4.8	< 0.001
Ca (mg/dL)*	8.5 ± 0.6	8.8 ± 0.7	0.526	8.1 ± 0.8	8.9 ± 0.7	0.246	8.2 ± 0.9	8.8 ± 0.7	0.189
P (mg/dL)	3.1 ± 0.6	3 ± 0.9	0.782	2.9 ± 0.6	3.1 ± 0.7	0.196	3 ± 0.8	2.8 ± 0.5	0.372
Mg (mg/dL)	1.8 ± 0.4	1.9 ± 0.1	0.862	1.8 ± 0.6	2 ± 0.2	0.325	2 ± 0.3	2 ± 0.6	0.868
CRP (mg/L)	12.2 ± 3.1	12.9 ± 3.9	0.108	11.9 ± 3.3	13 ± 4.1	0.066	12.3 ± 4.4	12.7 ± 3.8	0.594
Falls (n)[c]	0.29 ± 0.6	1.6 ± 1.2	< 0.001	1.4 ± 1.2	0.3 ± 0.7	< 0.001	–	–	–

[a]Significant difference by hip fracture type and falls, [b]Significant difference by gender and falls, [c]Significant difference by hip fracture type and gender (Levene's test $p < 0.05$), *Adjusted for serum albumin

with recurrent falls ($p=0.003$) and trochanteric fractures ($p=0.001$), and a significant relation to gender was additionally observed in these patients, since 88.2% of women were found with hyperparathyroidism as compared to 58.3% of men ($p=0.009$). It was further shown that individuals with blunted PTH response to vitamin D deficiency sustained less falls ($p=0.021$), and suffered mostly from subcapital fractures ($p=0.05$), as compared to patients with normal PTH response (hyperparathyroidism) to vitamin D deficiency (Table 4). Interestingly, in patients without vitamin D deficiency, the presence or absence of elevated PTH levels was shown to be significantly related to trochanteric or subcapital fractures ($p=0.03$), respectively. Logistic regression analysis performed in backward manner revealed that only age (OR 3.42; 95% CI 1.14–10.26; $p=0.028$) and falls (OR 43.15; 95% CI 1.10–168.19; $p=0.044$) were significant independent predictors for specific hip fracture type. When age was removed from our analysis, PTH (OR 1.20; 95% CI 1.05–1.38; $p=0.010$) and vitamin D (OR 1.56; 95% CI 1.14–2.15; $p=0.006$) were also found to significantly predict the type of fracture, in addition to falls (OR 13.18; 95% CI 2.95–58.94; $p=0.001$). The rest of the parameters studied were excluded from the regression analysis, due to p values greater than 0.15.

The correlational analysis by hip fracture type (Table 5) revealed that in patients with trochanteric fractures there was a strong positive relationship between PTH and the number of falls, a strong negative relationship between 25(OH)D and the number of falls, and a weak positive relationship between PTH and age. On the other hand, in patients with intracapsular fractures, age was positively correlated with 25(OH)D, and negatively with PTH. Lastly, as expected, a significant negative correlation was noted between PTH and 25(OH)D in both types of hip fractures. However, in patients with trochanteric fractures this correlation was almost linear (-0.912, $p<0.001$), whereas in subcapital fracture sufferers the correlation was moderate ($r=-0.589$, $p<0.001$), further indicating that low vitamin D levels do not always result in PTH increase. When this is the case, a subcapital rather than a trochanteric fracture is more likely to occur.

Discussion

Until complicated by fragility fractures, which occur after minimal or no identifiable trauma, osteoporosis is a progressive and silent disease [1, 4, 5]. Fractures of the hip, a common manifestation of fragility fractures, represent the most devastating consequence of osteoporosis; 25% of these patients have to spend time in a nursing home following the fracture, and approximately half of patients will not be able to return to their pre-fracture activity levels, while the mortality rate in the first year has been reported as high as 32%, with men almost twice as likely to die as women [4, 5]. Since hip fractures place an enormous medical, personal, and financial burden, a great deal of research has been undertaken, regarding not only the management of patients in the acute phase of a fragility hip fracture, but also the development of prevention strategies that can lessen the burden on patients and societies [1, 4]. Despite that most published data do not discriminate extracapsular and intracapsular fractures, there is recent evidence that etiology and pathophysiology differ between the two main types of hip fractures [7, 13, 14, 21]. For instance, the Break Study, a multicenter Italian study, showed that a history of vertebral fractures and type II diabetes were associated with the trochanteric than the cervical localization of hip fracture [30]. Substantial differences with respect to bone composition,

Table 5 Significant correlations between clinical and laboratory characteristics in patients with trochanteric and subcapital fractures

	Hip fracture type			
	Trochanteric		Subcapital	
	r	*p*	*r*	*p*
PTH × age	0.40	0.029	−0.578	0.001
PTH × falls	0.668	< 0.001	–	–
25(OH)D × falls	−0.860	< 0.001	–	–
25(OH)D × age	–	–	0.720	< 0.001
25(OH)D × PTH	−0.912	< 0.001	−0.589	0.001

Pearson's correlation coefficients. Only significant correlations are shown

Table 4 Patients grouped by vitamin D deficiency and PTH response

	25(OH)D < 12 ng/ml		*p*	25(OH)D > 12 ng/ml		*p*
	PTH < 65 pg/ml	PTH > 65 pg/ml		PTH < 65 pg/ml	PTH > 65 pg/ml	
Hip fracture type						
Subcapital	77.8%	13%	0.05	83.3%	46.7%	0.03
Trochanteric	22.2%	87%		16.7%	53.3%	
Falls (*n*)	0.3 ± 0.6	2.3 ± 1.2	0.021	0.3 ± 0.8	0.7 ± 0.8	0.227
25(OH)D (ng/mL)	8 ± 2.3	8.6 ± 2.7	0.776	27 ± 5.4	19.2 ± 4.5	< 0.001
PTH (pg/mL)	58 ± 5.2	103.9 ± 11	< 0.001	56.7 ± 5.7	77.1 ± 7.3	< 0.001

Chi square and independent samples analysis. Only statistically significant differences are shown

structure, and geometry have been reported, in addition to variations in epidemiological, demographic, and clinical characteristics [7, 13, 14, 21, 25, 31–34].

With respect to age, patients with trochanteric fractures in this series were found to be older than patients with subcapital fractures; moreover, when the age of females and males was analyzed separately, the differences between groups remained. Nevertheless, controversy exists in literature, and our finding whilst in agreement with similar findings from other studies [14, 20, 23, 24, 35], is in disagreement with others [21, 36]. It has been demonstrated, however, that with age the incidence of trochanteric fractures increases rapidly [4, 7, 37, 38]. Therefore our results strengthen the hypothesis that age is associated with the type of hip fracture, and more precisely that older adults are more prone to trochanteric fractures than younger individuals.

The incidence of falls among the elderly is high, and it has been estimated that about one out of every three–four older individuals, who live at home, may experience at least one fall per year, a rate that may be even higher among the elderly living in a nursing home [3]. After taking into account that more than 90% of hip fractures, after the age of 65, occur by falls, it is obvious that falling events consist a significant risk factor for hip fractures [3, 7, 39]. But still, whether recurrent falls may or may not predispose to a certain type of hip fracture has not been widely investigated. An important finding of this study was that repeated fallers are associated with trochanteric fractures. This was also shown recently by Tal et al. [21], who found that trochanteric fractures were more prevalent than cervical, in patients who suffered from recurrent falls. Moreover, recurrent falls, in the present study, were found to be gender-related; about 70% of women, in contrast to 17% of men, reported at least one falling event the year prior to index hip fracture, while 47% of women and 12.5% of men reported more than two falling events. This finding is in line with observations made in the general population, where women older than 70 years tend to fall more frequently than men [40].

Vitamin D deficiency has been associated with increased falls, diffuse musculoskeletal pain, and low muscle mass and strength [6, 15, 41–45]. These effects may be due to the fact that skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function [15]. The levels of 25(OH)D in this study were found to be lower in patients with recurrent falls. Furthermore, 27.6% of patients were classified as vitamin D-deficient. In these patients the number of falls was significantly higher compared to vitamin D non-deficient patients, thus providing further evidence to the argument that low serum vitamin D levels result in falls, and consequently to hip fractures. A difference in the mean value of serum 25(OH)D between different hip fracture types could not be established in this series, which is in accordance with other studies in the literature [13, 14]. However, when patients with vitamin D deficiency were compared to non-deficient patients, a higher prevalence of trochanteric fractures was found in the former patients (Table 3a).

Another important finding was that the type of hip fracture is related to PTH levels, as well as to the response of PTH to the various ranging of vitamin D. Generally, in the setting of vitamin D deficiency, PTH increases, to mobilize calcium from the skeleton, resulting into local foci of bone weakness, decreased bone mineral density, osteopenia, and osteoporosis [6, 15, 34, 41]. However, the PTH increase may result in different levels of bone loss [12, 16] and, as it was also hereby shown, not all patients with severe vitamin D deficiency present PTH excess [12, 13, 16]. Fisher et al. [13], were the first to show that the status of vitamin D-PTH axis is significantly related to hip fracture type, and found that in the setting of vitamin D deficiency, elevated PTH levels are related to trochanteric fractures, whereas PTH levels within normal limits (blunted PTH response) are related to subcapital fractures. Similarly, in this series, trochanteric fracture sufferers presented significantly higher PTH levels compared to patients with subcapital fractures. Conversely, hip fracture type was significantly related to PTH levels, since 86% of patients with PTH < 65 ng/ml and 64% of patients with PTH > 65 ng/ml suffered from trochanteric and subcapital fractures, respectively. Moreover, it was shown that a fraction of patients with vitamin D deficiency were "functionally hypoparathyroid", and the analysis revealed that the prevalence of cervical hip fractures was significantly higher in these patients, whereas trochanteric fractures were more prevalent in patients with secondary hyperparathyroidism. An additional novel finding was that vitamin D non-deficient patients, who nonetheless exhibited elevated PTH levels, were also more susceptible to trochanteric fractures. The PTH-related findings in this study indicate that the presence of PTH excess, whether secondary to vitamin D deficiency or not, may result in trochanteric fractures, most probably due to the PTH-induced osteopenia and osteoporosis. The status of vitamin D-PTH axis with respect to falls was also investigated. It was shown that an excess in PTH levels can be related to recurrent falls, a finding that is in line with results from previous studies [12, 46, 47]. It was additionally observed that patients with elevated PTH levels and vitamin D deficiency tend to fall more often than patients with vitamin D deficiency and no PTH response.

We further investigated the relationship between PTH, 25(OH)D, age, and falls with respect to the type of hip fracture. In patients with trochanteric fractures falls were strongly associated with PTH (positively) and vitamin D (negatively), while a positive correlation was noted between age and PTH. Interestingly enough, in patients with subcapital fractures age correlated negatively with PTH and positively with vitamin D. Lastly, the correlation between PTH and 25(OH)D was negative and almost linear in trochanteric fractures, and moderate in subcapital fracture sufferers. It is

indicated thereby that a decrease in the levels of vitamin D may occur with age, and if this depletion is not well regulated, PTH decreases instead of increasing. This failure of the parathyroid gland to mount an adequate PTH response can result in subcapital fractures, whereas a well-regulated PTH response may result in trochanteric fractures.

We recognize two limitations in this study. First, data regarding hip morphology and structure, falling mechanisms, and BMD were not investigated, despite that these factors may be related to the type of hip fracture. Second, the limited sample size may weaken our results. Yet, the prospective study design, along with meticulous patient selection, according to the inclusion criteria, offered an homogeneity in our sample; diseases, medications, and other factors (seasonal variations in vitamin D levels, patients of different origins) that could alter serum PTH and 25(OH)D levels were taken into consideration, and excluded from this study, thus limiting bias and strengthening the analysis.

Summarizing the results from this study, it can be implied that different pathophysiological processes lie behind subcapital and trochanteric fractures. Older age, recurrent falls, serum levels of PTH > 65 pg/ml, and severe vitamin D deficiency are associated with trochanteric fractures. Additionally, older age, female gender, PTH > 65 pg/ml and severe vitamin D deficiency are related to recurrent falls. Patients with elevated PTH levels secondary to severe vitamin D deficiency are more prone to recurrent falls and trochanteric fractures. Meanwhile, patients with absence of PTH response to low vitamin D levels, are not repeated fallers and suffer from subcapital fractures more frequently. The etiology behind the different responses of PTH to vitamin D depletion remains unknown, whereas the mechanisms that induce recurrent falls and trochanteric fractures in this setting are yet to be investigated. Elucidation of these differences and of the varied biochemical interactions, may assist in the development of prevention strategies for individuals, who will be recognized at risk for falls and either subcapital or trochanteric fractures.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. No benefits have been or will be received from a commercial party related directly or indirectly to the subject matter of this article.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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