ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Pediatric Hypercalcemia: Insights into Clinical Features and Etiologies From a Tertiary Center

Pediatrik Hiperkalsemi: Üçüncü Basamak Bir Merkezden Klinik Özellikler ve Etyolojilere Dair Bulgular

Emel Hatun Aytaç Kaplan (0000-0002-8385-4049), Zümrüt Kocabey Sütçü (0000-0001-7335-1272)

University of Health Sciences Türkiye, Başaksehir Çam ve Sakura City Hospital, Clinic of Pediatric Endocrinology, İstanbul, Türkiye

Cite this article as: Aytaç Kaplan EH, Kocabey Sütçü Z. Pediatric hypercalcemia: insights into clinical features and etiologies from a tertiary center. J Curr Pediatr. 2025;23(3):188-194

Abstract

Introduction: Hypercalcemia is rarer in children than in adults, but it is clinically significant.

Materials and Methods: This retrospective study evaluated 21 patients aged 0-18 years with hypercalcemia. Clinical characteristics, laboratory findings, and clinically indicated imaging and genetic analyses were reviewed. Patients were classified according to hypercalcemia severity and PTH status, and treatment outcomes were recorded.

Results: Of these, 33.3% were asymptomatic, and vomiting was the most common presenting complaint (19%). 66.7% of the patients had parathyroid hormone (PTH)-independent hypercalcemia, while 33.3% had PTH-dependent hypercalcemia. The etiologies included parathyroid adenoma in five patients, adrenal insufficiency in four patients, vitamin D intoxication in three patients, malignancy in three patients, osteomyelitis in one patient, pseudohypoaldosteronism in one patient, a CaSR variant in one patient, and hypophosphatasia in one patient. Four of the seven patients with PTH-dependent hypercalcemia underwent surgical treatment.

Conclusion: This study demonstrates that childhood hypercalcemia can result from a variety of factors. Measurement of serum calcium levels is essential in children with vague or nonspecific clinical symptoms. Diagnosis of malignancies may be delayed in the absence of additional findings. Early diagnosis and appropriate intervention can prevent significant complications.

Keywords
Etiology, hypercalcemia, malignancy, parathyroid hormone, pediatric

Öz

Giriş: Hiperkalsemi çocuklarda yetişkinlere kıyasla daha nadir görülmekle birlikte, klinik olarak önemli bir durumdur.

Gereç ve Yöntem: Bu retrospektif çalışmada hiperkalsemi saptanan 0–18 yaş arası 21 hasta değerlendirildi. Klinik özellikler, laboratuvar bulguları ile klinik gerekliliğe göre yapılan görüntüleme ve genetik analizler incelendi. Hastalar hiperkalsemi şiddeti ve PTH durumuna göre sınıflandırılarak tedavi sonuçları kaydedildi.

Bulgular: Hastaların %33,3'ü asemptomatikti ve en sık başvuru şikâyeti kusmaydı (%19). Hastaların %66,7'sinde paratiroid hormonuna (PTH) bağımsız hiperkalsemi saptanırken, %33,3'ünde PTH'ye bağlı hiperkalsemi mevcuttu. Saptanan etiyolojiler arasında beş hastada paratiroid adenom, dört hastada adrenal yetmezlik, üç hastada D vitamini intoksikasyonu, üç hastada malignite, birer hastada osteomiyelit, psödohipoaldosteronizm, CaSR varyantı ve hipofosfatazya yer almaktadır. PTH'ye bağlı hiperkalsemisi olan yedi hastadan dördü cerrahi tedavi almıştır.

Sonuç: Bu çalışma, çocukluk çağı hiperkalsemisinin çok çeşitli nedenlere bağlı olarak gelişebileceğini ortaya koymaktadır. Belirsiz veya spesifik olmayan klinik bulgularla başvuran çocuklarda serum kalsiyum düzeylerinin ölçülmesi büyük önem taşımaktadır. Ek bulguların yokluğunda malignite tanısı gecikebilir. Erken tanı ve uygun müdahale, ciddi komplikasyonların önlenmesine katkı sağlayabilir.

Anahtar kelimeler
Etiyoloji, hiperkalsemi, malignite, paratiroid hormon, pediatrik

Received/Geliş Tarihi : 02.05.2025
Accepted/Kabul Tarihi : 09.08.2025
Published Date/ Yayınlanma Tarihi : 29.12.2025

DOI:10.4274/jcp.2025.24571

Address for Correspondence/Yazışma Adresi: Emel Hatun Aytaç Kaplan, University of Health Sciences Türkiye, Başaksehir Çam ve Sakura City Hospital, Clinic of Pediatric Endocrinology, İstanbul, Türkiye
E-mail: emel_ctf@hotmail.com

Introduction

Hypercalcemia is rarer in children than in adults, yet it is clinically significant (1). Ionized and total calcium levels vary according to age and gender (2). The etiology of hypercalcemia varies across different age groups. Congenital causes are more common in the neonatal period, while neoplasms are more frequently encountered in adolescents (1). A classification based on the presence or absence of hyperparathyroidism can facilitate the differential diagnosis. In the absence of hyperparathyroidism, potential causes of hypercalcemia include excessive intake or impaired breakdown of vitamin D, renal phosphate loss, dietary phosphorus deficiency, malignancies, immobilization, various syndromes, and rhabdomyolysis. When hyperparathyroidism is present, the causes of hypercalcemia may include neonatal acquired hyperparathyroidism, sporadic parathyroid gland tumors, multiple endocrine neoplasms (MEN), familial hypocalciuric hypercalcemia, and familial isolated hyperparathyroidism (3).

The calcium-sensing receptor (CaSR), which is expressed in the parathyroid glands and kidneys, plays a significant role in maintaining plasma calcium levels. Increased ionized calcium levels activate CaSR, leading to the inhibition of parathyroid hormone (PTH) secretion (4). PTH reduces renal phosphate reabsorption in the distal renal tubule while stimulating calcium reabsorption and promoting the conversion of 25-hydroxyvitamin D3 to calcitriol. Calcitriol, in turn, enhances calcium and phosphate absorption in the intestines, promotes bone mineralization, and increases renal calcium reabsorption (5).

Patients with hypercalcemia may present with a range of symptoms, including hypotonia, poor feeding, vomiting, constipation, abdominal pain, numbness, polyuria, dehydration, and seizures (6). Severe cases can lead to renal failure and pancreatitis (7). A detailed dietary history, medication review, family history, assessment for dysmorphic features, and evaluation of bone abnormalities are essential for differential diagnosis (8).

The severity of clinical symptoms is often correlated with plasma calcium concentrations and is classified as mild (<12 mg/dL), moderate (12-14 mg/dL), and severe (>14 mg/dL) (9). In cases of hypercalcemia, the diagnostic workup should include cessation of medications that may be contributing to hypercalcemia, a calcium-restricted diet, and ensuring adequate hydration (5). Treatment options for hypercalcemia include furosemide, calcitonin, prednisolone, bisphosphonates, and hemodialysis (10).

This study aims to raise awareness about pediatric hypercalcemia, a rare condition with diverse etiologies, which can lead to severe complications if not addressed promptly. Through the presentation of our patients with hypercalcemia, we aim to underscore the variety of underlying diagnoses in childhood.

Materials and Methods

Our study was retrospective in design, and the study protocol was approved by the University of Health Sciences Türkiye, Başaksehir Cam ve Sakura City Hospital Ethics Committee (approval code: KAEK 2023.06.276). Between 01.06.2021 and 01.03.2023, 21 patients aged 0-18 years who presented with at least two high calcium measurements were included in the study. Patient data, including age at presentation, symptoms, and physical examination findings, were recorded. Pre-treatment fasting morning samples were analyzed for serum calcium, phosphate, alkaline phosphatase, PTH, electrolytes, renal function tests, 25-hydroxyvitamin D (25-OHD), and urine calcium/creatinine ratio.

Thyroid-stimulating hormone (TSH), free thyroxine (fT4), neck ultrasonography, parathyroid gland scintigraphy with Tc-99m sestamibi, and genetic analysis were performed as necessary based on clinical indications.

Hypercalcemia was defined according to corrected total serum calcium levels. Total serum calcium levels between 11-12 mg/dL were classified as mild, levels greater than 12 mg/dL and up to 14 mg/dL were classified as moderate, and levels exceeding 14 mg/dL were classified as severe hypercalcemia (9).

Patients were categorized into two groups based on PTH levels. Despite elevated calcium levels, PTH levels that remain within the normal range or are increased indicate PTH elevation. Classification was performed based on this criterion. Group 1 included patients with unsuppressed PTH levels, known as the PTH-dependent group, while Group 2 comprised patients with suppressed PTH levels, referred to as the PTH-independent group. The level of suppression of PTH was determined based on our hospital's age-specific reference range.

The treatment modalities used for hypercalcemia in each patient, the time required for serum calcium levels to return to normal, and the long-term course of hypercalcemia were recorded for all patients.

Statistical Analysis

Statistical analysis was conducted using the SPSS statistical software (v.21.0). Categorical variables were expressed as frequencies and percentages, while continuous variables

were presented as median values and ranges. Due to the small sample size, non-parametric methods were used for comparisons. Probability tables (2x2) were analyzed using Fisher's exact test, while the chi-square test was used for higher-dimensional tables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 21 pediatric patients were included in the study, with 10 girls (47.6%) and 11 boys (52.4%). The mean age at presentation was 6.82±6.8 years (range: 0.01-17.1). The median body weight SDS was -0.35 (range: -3.80-1.24), the median height SDS was -0.91 range: -3.20-1.49), and the median BMI SDS was -0,09 (range: -3.48 - 3.50). A wide variation was observed in the anthropometric parameters. 33.3% of the patients were asymptomatic, and vomiting was the most common presenting complaint, occurring in 19% of the cases. The details of presenting complaints are listed in Table 1.

66.7% of the patients (n=14) had PTH-independent hypercalcemia, while 33.3% (n=7) had PTH-dependent hypercalcemia. The gender ratio was similar in both groups (p=0.534). The mean age at presentation in the PTH-dependent group was 14.8 years (min=8.2, max=17.1), while in the PTH-independent group, it was 0.34 years (min=0.01, max=14.2). The age at presentation was significantly higher in the PTH-dependent group (p=0.01). Calcium levels were not significantly different between the two groups.

When other laboratory findings were examined, the PTH-dependent group showed lower phosphorus, higher albumin, higher PTH, and a lower urine calcium/creatinine ratio (Table 2).

Neck ultrasonography was performed when the PTH level was not suppressed. Parathyroid adenomas were detected in four patients (19%) with PTH-dependent hypercalcemia. Adenoma localization was as follows: one patient had it in the upper right, two patients in the lower right, and one patient in the upper left. Patients with adenomas detected

Table 1. Chief complaints at presentation

Complaint	Frequency	Percent	Valid percent	Cumulative percent
None	7	33.3	33.3	33.3
Vomiting	4	19.0	19.0	81.0
Abdominal pain	2	9.5	9.5	90.5
Muscle pain	1	4.8	4.8	38.1
Short stature	1	4.8	4.8	42.9
Seizure	1	4.8	4.8	47.6
Itching	1	4.8	4.8	52.4
Joint pain	1	4.8	4.8	57.1
Decreased urination	1	4.8	4.8	61.9
Genital suspicion	1	4.8	4.8	95.2
Sweating	1	4.8	4.8	100.0
Total	21	100.0	100.0	

Chief complaints of 21 patients, ages range from 0-18 years, presented in this table with hypercalcemia between 2021-2023 years

Table 2. Laboratory findings in the patients

Variable	Calcium (mg/dL) PTH-I/PTH-D	Phosphorus (mg/dL) PTH-I/PTH-D	Albumin (mg/dL) PTH-I/PTH-D	Urine Ca/Cr PTH-I/PTH-D	PTH (pg/mL) PTH-I/PTH-D
N	14/7	14/7	13/7	9/7	14/7
Median	12.1/12.1	4.95/2.9	4/4.9	0.92/0.2	5.1/120
Minimum	10.2/10.78	3.00/1.6	3.2/4.6	0.05/0.01	1/78
Maximum	14.4/13.7	7.60/3.9	5.2/5.1	4.50/0.6	13/640
p	0.07	0.03	0.041	<0.01	<0.01

Laboratory findings of 21 patients are presented in this table.
PTH-I: Parathyroid hormone-independent, PTH-D: Parathyroid hormone-dependent

on ultrasound showed uptake activity suggestive of adenoma on parathyroid gland scintigraphy. In one patient with a normal ultrasound, scintigraphy suggested the presence of an adenoma. The size of the adenomas ranged from 3 to 25 mm.

When all investigations were completed and etiological classification was made, five patients (23.8%) were diagnosed with parathyroid adenoma, four patients (19%) had adrenal insufficiency, three patients (14.3%) had vitamin D intoxication, three patients (14.3%) had malignancy, one patient (4.8%) had osteomyelitis, one patient (4.8%) had pseudohypoaldosteronism, and one patient (4.8%) had hypophosphatasia. One patient (4.8%) was diagnosed with a CaSR. In two patients (9.5%), the etiology could not be determined, and spontaneous resolution was observed during follow-up. The mean age of patients with parathyroid adenoma was 14.36±3.21 years (range=8.2-17.1).

Among the patients with malignancy, two had acute lymphoblastic leukemia, and one had osteosarcoma. One patient was diagnosed with multiple endocrine neoplasia type 1.

Six patients did not require any treatment. Hydration was administered to 15 patients (71.4%), bisphosphonates to 7 patients (33.3%), furosemide to 10 patients (47.6%), and hydrocortisone to 4 patients (19%). Patients who received bisphosphonate therapy had calcium levels between 10.78 and 14.4 mg/dL. Four of these patients had parathyroid adenomas, and bisphosphonate therapy was used to normalize calcium levels before surgery. Other patients who received bisphosphonates were diagnosed with osteosarcoma, acute lymphoblastic leukemia, and pseudohypoaldosteronism. Pamidronate was administered at a dose of 0.5–1 mg/kg, with a maximum of two doses. This regimen was sufficient to normalize calcium levels within 48 hours.

Four of the seven patients with PTH-dependent hypercalcemia (those with adenomas) underwent surgical treatment. The patient with MEN1 syndrome was a 15-year-old female who presented with mild hypercalcemia and was found to have a parathyroid adenoma on both ultrasonography and scintigraphy. However, during follow-up, the adenoma showed regression, and surgical intervention was not required. The patient remained asymptomatic, and calcium levels remained stable without the need for medical treatment.

In addition, two cases with spontaneously resolved mild hypercalcemia were identified. The first was a 14.3-year-old male with PTH-dependent hypercalcemia and hypocalciuria; both neck ultrasonography and scintigraphy were unremarkable. The second was a 0.2-year-old female with PTH-independent mild hypercalcemia. Neither patient required treatment, and calcium levels normalized spontaneously during follow-up.

Genetic analysis was performed on four patients with parathyroid adenoma, and no variants were detected.

Renal ultrasonography was performed in all patients. Fourteen patients (66.7%) had normal findings, while nephrocalcinosis was detected in three patients (14.3%), renal stones in two patients (9.5%), and pelvicalyceal ectasia in two patients (9.5%). The diagnoses of patients who developed complications and their calcium levels are provided in Table 3. All patients are being followed with normal calcium levels.

Discussion

Hypercalcemia is rare in children and can manifest with either asymptomatic or nonspecific symptoms. When there are no complaints, hypercalcemia may not be detected until complications arise. In the study conducted by Çullas İlarslan et al. (11), 30% of the patients were asymptomatic, with gastrointestinal symptoms being the most common (nausea, vomiting, abdominal pain, constipation). Similarly, in our study, 33.3% of patients were asymptomatic, with vomiting being the most frequent symptom.

Table 3. Complications in patients

Diagnosis	Calcium (mg/dL)	Complication
Osteosarcoma	12.2	Nephrocalcinosis
Parathyroid adenoma	13.3	Renal stones
Excessive vitamin D intake	13.8	Nephrocalcinosis
Pseudoaldosteronism	13.0	Pelvicaliectasis
Adrenal insufficiency	11.1	Pelvicaliectasis
Hypophosphatasia	12.6	Nephrocalcinosis

In this table, calcium levels of cases with complications and the complications that developed are presented

The level of PTH in hypercalcemia cases provides a practical approach to diagnosis. Primary hyperparathyroidism accounts for 1% of hypercalcemia cases in children (12,13). In the study by Çullas İlarslan et al. (11), this rate was 35%, attributed to the study being conducted in a tertiary care center. In our study, the rate of PTH-dependent hypercalcemia was 33.3%. The lack of referral for mild hypercalcemia cases could be a contributing factor. The age at presentation was more advanced in the PTH-dependent group, consistent with findings in the literatüre (13).

In a review by Markowitz et al. (14), despite high calcium levels in hypercalcemia due to primary hyperparathyroidism, unrepressed or normal PTH levels were commonly observed. Several studies have reported that patients with primary hyperparathyroidism can have normal PTH levels at diagnosis (11,13). In our study, one patient in the PTH-dependent group had an average PTH level. All patients in the PTH-independent group had low PTH levels. Since normal PTH levels do not exclude primary hyperparathyroidism, investigations targeting the parathyroid gland should be pursued in the etiology workup.

Ultrasound and technetium thyroid scintigraphy are highly effective in identifying parathyroid gland pathology (4). In cases where scintigraphy and ultrasound fail to clarify the pathology, SPECT/CT can be used. Shafiei et al. (15) reported that the sensitivity of SPECT/CT in detecting parathyroid adenoma localization was 78%, with a specificity of 97%. Li et al. (16) found this method particularly useful in detecting ectopic parathyroid adenomas. In our study, parathyroid pathology was identified by ultrasound in four out of five cases, while one case with normal ultrasound had a positive finding on scintigraphy. The combined use of both imaging techniques enhances diagnostic success. SPECT/CT examination was not needed in our cases.

In childhood cancers, bone complications are common. Mostoufi-Moab et al. (17) reported osteonecrosis in 2-10% of cases of acute lymphoblastic leukemia. Studies have shown that the frequency of hypercalcemia associated with malignant tumors ranges from 0.4% to 1.3%, with Ewing sarcoma, ALL, lymphoma, neuroblastoma, and Wilms tumor being malignancies associated with hypercalcemia (18,19). In our study, there were two patients diagnosed with ALL and one with osteosarcoma. Malignancy needs to be excluded, particularly in cases of PTH-independent hypercalcemia. In our study, calcium levels were similar in both groups, and mild or malignant calcium levels were not helpful in the diagnostic algorithm. Simultaneous measurement of PTH levels was the most essential diagnostic tool in our study.

Limited research exists on the relationship between primary hyperparathyroidism and hypophosphatemia. Two studies have emphasized the clinical significance of hypophosphatemia in this context. Additionally, simultaneous measurement of calcium and phosphorus levels is suggested to be more significant in diagnosing and treating primary hyperparathyroidism (20,21). In our study, phosphorus levels were lower in the PTH-dependent group, supporting our diagnosis. Knowing phosphorus levels can be helpful both in determining the etiology of hypercalcemia and in guiding treatment decisions.

Urolithiasis is a growing concern worldwide, with hypercalcemia being a significant cause of kidney stones. Işik et al. (22) reported hypervitaminosis D in 2% of 197 pediatric patients with urolithiasis and hypercalcemia in 27%. They emphasized that vitamin D intake greater than 400 IU/day could increase the risk of stone formation. In our study, vitamin D intoxication was found in 14.3% of patients, nephrocalcinosis in 14.3%, stones in 9.5%, and pelvicalyceal ectasia in 9.5%. The complications of hypercalcemia are significant, and its management requires careful consideration.

Primary hyperparathyroidism and parathyroid adenoma should be considered primarily in cases of advanced childhood hypercalcemia. Studies have shown an increased frequency of parathyroid adenomas in adolescents (23,24). Rampp et al. (25) reported that the most common pathology in adolescents with primary hyperparathyroidism was a single parathyroid adenoma (71%). Similarly, Hsu and Levine (26) found parathyroid adenoma in 12 out of 17 patients. Genetic and syndromic causes are rarer. Kollars et al. (12) found parathyroid adenoma in 34 out of 52 patients, with 16 having parathyroid hyperplasia, and 57% of hyperplasias were diagnosed with MEN-1. When encountering hypercalcemia in adolescents, adenoma should be considered, and further investigations should be performed. Consistent with the literature, we had five cases of parathyroid adenoma in our study, with a higher average age. Four of our cases had a single parathyroid adenoma, and one patient was diagnosed with MEN-1.

The parathyroid glands are initially visualized using ultrasound. In addition to ultrasonography, 99m Tc sestamibi scintigraphy is highly useful in detecting pathology (4). In a study by Kızılcan Çetin et al. (24), adenomas were detected with at least one of these methods. In our study, diagnosis was made with ultrasonography in four out of five cases and with scintigraphy in one case.

Adrenal insufficiency is a rare cause of hypercalcemia, and the mechanism is not fully understood. Sakao et al. reported that improvement occurs with steroid replacement (27). Schoelwer et al. (28) found elevated calcium levels in 82.5% of patients with congenital adrenal hyperplasia and hypercalcemia. Madihi et al. (29) found nephrocalcinosis in 3.3% of 120 patients with congenital adrenal hyperplasia, emphasizing the need for careful evaluation. In our study, 19% of our cases had hypercalcemia due to adrenal insufficiency, representing a considerable proportion.

Pseudohypoaldosteronism is another rare cause of hypercalcemia. While we had one case in our study, Babar and Tariq (30) reported a similar case. Aldosterone may stimulate PTH secretion indirectly by promoting hypercalciuria through its effects on the nephron, leading to secondary hyperparathyroidism. This mechanism has been proposed as a potential pathophysiological pathway explaining elevated PTH levels, particularly in cases of chronic aldosterone excess (31). Hypophosphatasia presents with hypercalcemia, hypercalciuria, and increased bone resorption. Demirbilek et al. (32) reported a case with hypophosphatasia and hypercalcemia. In our case, hypercalciuria, nephrocalcinosis, and hypercalcemia were present. Osteomyelitis is also a disease that causes hypercalcemia due to increased bone resorption. One patient in our study had osteomyelitis.

Calcium-sensing receptor mutations are an important genetic cause of hypercalcemia, often accompanied by hypophosphatemia, hypocalciuria, and hyperparathyroidism (33). Urgent treatment is required for malignant hypercalcemia, with successful use of cinacalcet in some cases (34). In our study, there was mild hypercalcemia, and no treatment other than hydration was needed. Close monitoring continues for any potential malignant elevation.

Treatment of hypercalcemia aims to prevent complications and correct the underlying cause. Mild cases do not require urgent treatment, while severe or persistent hypercalcemia requires hydration and may benefit from treatments such as furosemide, calcitonin, prednisolone, bisphosphonates, or hemodialysis (5,10). Bisphosphonates are often required in severe or persistent cases until the underlying condition is controlled. Surgical treatment is indicated for parathyroid adenomas after calcium levels stabilize. Early excision is crucial for malignant hypercalcemia. Phitayakorn and McHenry (35) found that bisphosphonates serve as a bridge before excision. In our study, four patients with parathyroid adenomas underwent surgery, with bisphosphonate treatment administered prior to surgery to normalize calcium levels. Pamidronate is the most commonly used bisphosphonate in childhood (5). Alagaratnam and Kurzawinski (36) reported parathyroidectomy as the treatment for parathyroid tumors. In a study by Çullas İlarslan et al. (11), four cases of malignancy-related hypercalcemia showed resistance to treatment and recurrent courses. In our study, 33.3% of cases required bisphosphonate therapy, and four out of five cases with adenoma underwent surgical treatment with no recurrence. We did not observe any cases of resistant or recurrent hypercalcemia.

Study Limitations

This study has several limitations, the most significant of which is the small sample size, making it difficult to compare different groups. Longer follow-up and a better understanding of the natural course of hypercalcemia and hypercalciuria could provide more detailed information on complications such as nephrolithiasis.

Conclusion

This study demonstrates that childhood hypercalcemia can be caused by various factors. The presence of complicated cases suggests that diagnosis may be delayed due to the asymptomatic progression of the condition. Mild cases are challenging to identify, and malignancies may go undiagnosed if no additional symptoms are present. Early diagnosis and emergency intervention are critical to preventing significant complications. Measurement of serum calcium levels is essential for children presenting with vague clinical findings, particularly when gastrointestinal symptoms are present. Early diagnosis and intervention are crucial to preventing severe complications.

Ethics

Ethical Approval: Our study was retrospective in design, and the study protocol was approved by the University of Health Sciences Türkiye, Başaksehir Cam ve Sakura City Hospital Ethics Committee (approval code: KAEK 2023.06.276). Between 01.06.2021 and 01.03.2023, 21 patients aged 0-18 years who presented with at least two high calcium measurements were included in the study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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