

# Postoperative hypoparathyroidism in patients after total thyroidectomy – retrospective analysis

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## Abstract

**OBJECTIVES:** Hypoparathyroidism is the most frequent complication of thyroidectomy. The incidence rates of temporary and permanent postoperative hypoparathyroidism vary from 7 to more than 60% and from 0 to 9%, respectively.

**DESIGN:** The aim of the study has been to evaluate the incidence of hypoparathyroidism and clinical manifestations of hypocalcaemia after total thyroidectomy, as well as assess factors that affect the frequency of the symptomatic hypocalcaemia, and benefits resulting from the measurement of parathyroid hormone (PTH) concentration on the first day after thyroidectomy.

**SETTING:** The studied group consisted of 330 patients after total thyroidectomy, while the control group consisted of 86 patients who underwent total resection of one lobe only or subtotal thyroidectomy.

**RESULTS:** Based on the measurements of serum PTH concentration on the first day after total thyroidectomy, postoperative hypoparathyroidism was diagnosed in 48% of patients. After total thyroidectomy, the frequency of clinical symptoms of hypocalcaemia was twice less than the incidence of hypoparathyroidism confirmed by biochemical testing. Total thyroidectomy occurred to be an independent factor of the increased risk of postoperative hypoparathyroidism. This risk was even higher in the cases widened by lymphadenectomy, and among patients with Graves' disease. In the group of patients with decreased serum PTH concentration the occurrence of clinical symptoms of hypocalcaemia significantly depended on serum PTH concentration – patients with lower PTH levels reported paresthesias more frequently.

**CONCLUSIONS:** Serum PTH levels below 5 pg/ml seems to be a good prognostic factor of the occurrence of hypocalcaemia symptoms. The information about low PTH concentration allows to start the pharmacotherapy faster and avoid clinical manifestation of hypocalcaemia.

## INTRODUCTION

Thyroid gland diseases account for 80% of endocrinopathies and a lot of them is cured surgically. It is estimated that about 25000 thyroidectomies are annually performed in Poland, including 1800 operations of thyroid cancer; thyroidectomy is the most frequent surgical procedure regarding endocrine glands (Brzeziński 2013).

In surgical treatment of thyroid diseases, tendencies to total thyroidectomy and to widening indications to more radical operation are currently observed. Apart from all types of thyroid cancer, the indications for total thyroidectomy are: multinodular goitre, large goitre compressing contiguous anatomical structures, Graves' disease (especially when goitre is large or tumorous or significant orbitopathy is simultaneously present), and – according to some authors – nodular variant of Hashimoto thyroiditis or amiodarone-induced thyrotoxicosis (Serpell *et al.* 2007, Qureshi *et al.* 2015).

The main complications of thyroidectomy are permanent recurrent laryngeal nerve palsy, permanent hypoparathyroidism, transient hypocalcaemia, postoperative hemorrhage and wound infection. Therefore, the objectives of surgeon during thyroidectomy is to conserve the parathyroid glands and laryngeal nerves, as well as to maintain accurate hemostasis.

Hypoparathyroidism is the most frequent complication of thyroidectomy. According to data from different centres, the incidence rates of temporary and permanent postoperative hypoparathyroidism vary from 7 to more than 60% and from 0 to 9%, respectively (Roh *et al.* 2011; Huang 2012; Baldassarre *et al.* 2012).

Postoperative hypoparathyroidism is caused by accidental parathyroidectomy (inadvertent removal of parathyroid glands, especially in the case of their variable anatomical localization, for example interstitially in the thyroid gland), impairment of blood supply (devascularization) of the parathyroid glands, mechanical damage (injury) of the parathyroid glands (crushing or using high temperature nearby gland) or by fibrotic process, which occurs within neck after surgery (Paek *et al.* 2013). Impairment or lack of parathyroid hormone (PTH) secretion takes place in these conditions.

Reduction of PTH concentration leads to decrease in calcium concentration (hypocalcaemia) and its clinical manifestations. Symptoms of postoperative hypoparathyroidism occur usually 24–48 hours after surgery, but sometimes even later. Commonly they are transient and withdraw spontaneously within 1 week to several months (usually 4–6 weeks), but sometimes as late as 1–2 years after surgery. However, numerous patients do not recover and suffer from permanent hypoparathyroidism – they require lifelong calcium and active form of vitamin D supplementation, and their life quality is severely disrupted. In 2015, guidelines on treatment of chronic hypoparathyroidism in adults were published by the European Society of Endocrinology, in which

goals of management, therapeutic recommendations and monitoring rules were presented (Bollerslev *et al.* 2015).

Hypocalcaemia leads to increase of neuromuscular excitability. Perioral numbness, peripheral paresthesias and muscles cramps are symptoms of mild hypocalcaemia. Laryngeal spasm, tetany, seizures and cardiac symptoms are serious and potentially life-threatening complications of severe hypocalcaemia. Identifying Chvostek's and Trousseau's signs during clinical examination allows to reveal latent tetany (Baldassarre *et al.* 2012; Williams *et al.* 2011).

In spite of many surgical problems, the identification of parathyroid glands and protecting them against damage constitutes the indispensable element of the safe operating treatment. In concern of better well-being and greater comfort of patients during convalescence, surgeon should not only prevent postoperative hypoparathyroidism, but also early recognize the parathyroid insufficiency and plan the pharmacotherapy properly to avoid symptomatic (very unpleasant for patients) hypocalcaemia.

The aim of this study has been to evaluate the incidence of hypoparathyroidism and clinical manifestations of hypocalcaemia after total thyroidectomy, as well as to assess factors that affect the frequency of symptomatic hypocalcaemia, and benefits resulting from the measurement of parathyroid hormone concentration on the first day after thyroidectomy. Early identification of patients with postoperative hypoparathyroidism is very important, because it allows to start the pharmacotherapy faster and to avoid clinical manifestation of hypocalcaemia.

## MATERIAL AND METHODS

Retrospective study was conducted in patients with tumors of the thyroid gland treated surgically (2009–2011) in the Department of General, Oncological and Endocrine Surgery Medical University of Lodz, located in the Department of General and Endocrine Surgery, Polish Mother's Memorial Hospital, Research Institute, of Lodz. In this period, 902 thyroid glands surgical operations were performed, including 365 total thyroidectomies.

This study covers the period of hospitalizations during which surgical procedures were performed. Therefore, in this study the postoperative hypoparathyroidism was considered only as an early complication of surgery, without investigation in how many cases that complication would be temporary or permanent in longer perspective.

The inclusion criteria for the studied group were following: total thyroidectomy, the determination of preoperative serum calcium concentration, no evidence of hypoparathyroidism in medical history and the measurement of PTH concentration within the first day after surgery. The selected group consisted of

330 patients, in age ranged from 18 to 85 years. The control group consisted of 86 patients who underwent total resection of one lobe of the thyroid (unilateral lobectomy) or partial resection of the gland (subtotal thyroidectomy). The other criteria of inclusion to the control group were the same as in the studied group. All the patients, both from studied group and from Controls were in clinical and hormonal euthyroidism.

The diagnosis of postoperative hypoparathyroidism was established on the basis of low serum calcium and PTH levels, and additionally, on the basis of clinical symptoms of hypocalcaemia. The half-life of PTH in circulation is 2–4 minutes, so PTH measurement can be used as an early diagnostic method of postoperative hypoparathyroidism (Singh *et al.* 2013).

Serum PTH concentration was measured in Centre of Medical Laboratory Diagnostics in the Polish Mother's Memorial Hospital – Research Institute, using analyzer Elecsys 1010, 2010 and E170 made by Roche Diagnostics. Assays for quantitative *in vitro* measurement of intact PTH (iPTH) in serum or plasma were used. In these assays specific monoclonal antibodies against 1–37 and 38–84 fragments of human PTH were employed; normal range of PTH concentration is 15.0–65.0 pg/ml (1.6–6.9 pmol/l) and measuring range is 1.2–5000 pg/ml (0.127–530 pmol/l).

## RESULTS

In the studied group (86% female and 14% male patients) the mean age of patients was  $52 \pm 13$  years ( $x \pm SD$ ). The demographic structure of studied group is presented in Table 1. Types of surgical procedures performed in both the studied group and Controls are demonstrated in Table 2.

The most frequent histopathological diagnosis after total thyroidectomy was non-toxic nodular goitre (57%) and the nodular goitre with morphological signs of hyperactivity (30%). Thyroid cancers were diagnosed in 13% of patients: 34 patients had papillary thyroid carcinoma (PTC), 4 – follicular thyroid carcinoma, 2 – medullary thyroid carcinoma, 1 – anaplastic thyroid carcinoma and 2 – metastases of clearcellular carcinoma of the kidney to the thyroid gland (Table 3). In 10 cases of PTC, histopathological signs of chronic thyroiditis were also observed.

In 24% of patients from the studied group additional factors that increase the risk of postoperative hypoparathyroidism have been found. That group included 43

patients who underwent total thyroidectomy, widened by lymphadenectomy (13%), 11 patients with Graves' disease (3%), 9 – with retrosternal goitre of enormous size (3%), 7 – with recurrent goitre (2%) and 10 – with intraoperative hemorrhage or with hemorrhage in early postoperative period (3%). Five (5) patients who underwent lymphadenectomy, had additional risk factors: recurrent goitre (3 patients), Graves' disease (1 patient) and intraoperative hemorrhage (1 patient).

Based on the measurements of serum PTH concentration on the first day after total thyroidectomy, postoperative hypoparathyroidism (PTH <15 pg/ml) was diagnosed in 159 patients from the studied group (159/330; 48%) and that percentage was significantly higher than in the control group (10/86; 12%) ( $p < 0.001$ ). In group of patients with postoperative hypoparathyroidism after total thyroidectomy, serum PTH concentration ranged from 1.2 to 14.66 pg/ml. Normal serum PTH concentration (15–65 pg/ml) was observed in 165 patients (50%) and increased serum PTH level (>65 pg/ml) was found in 6 persons (2%). In 76 patients (23%) symptoms of hypocalcaemia were observed, such as, e.g. mild paresthesias (tingling of facial and limbs muscles). In most of these patients decreased serum PTH concentration was found, but 4 persons with symptoms of hypocalcaemia had normal serum PTH level. The clinical symptoms of hypocalcaemia were reported in 45% of patients (72/159) with decreased serum PTH concentration. Most frequently symptoms of hypocalcaemia appeared on the first day after surgery (37/76 – 49%) (within the day “0” and on the second day after surgery they occurred in 21% and 18%, respectively).

Statistical analysis of the results revealed that probability of postoperative hypoparathyroidism occurrence was raising significantly with the increasing extension of thyroid gland surgery ( $p < 0.001$ ). The risk of postoperative hypoparathyroidism was significantly higher in the studied group than in the control group. The highest risk occurred in patients in whom total

**Tab. 1.** Age and sex distribution of patients included in the study.

	Age			Sex	
	<45 years	45–60 years	>60 years	Males	Females
Numbers	98	135	97	45	285
(%)	(30%)	(41%)	(29%)	(14%)	(86%)

**Tab. 2.** Types of surgical procedures performed in the studied group (total thyroidectomies) and in Controls.

	Studied group		Controls	
	Total thyroidectomy without lymphadenectomy	Total thyroidectomy with lymphadenectomy	Lobectomy	Subtotal thyroidectomy
Numbers (%)	287 (87%)	43 (13%)	31 (36%)	55 (64%)

thyroidectomy was widened by lymphadenectomy and the lowest in patients who underwent lobectomy (1/31; 3%). Serum PTH concentrations depending on extent of surgery are presented in Table 4.

We analyzed serum PTH concentration after division of the studied group depending on factors increasing the risk of postoperative hypoparathyroidism. Especially high frequency of postoperative hypoparathyroidism was found in patients with Graves' disease (64%), in cases of hemorrhage (60%) and in patients with concurrent lymphadenectomy (58%), but there were no statistically significant differences between decreased and normal PTH concentration in these subgroups ( $p < 0.43$ ) (Table 5). The lack of statistically significant differences most probably resulted from small number of patients in studied subgroups.

Statistical analysis did not reveal correlation between sex and serum PTH concentration after total thyroidectomy ( $p < 0.828$ ), but in the group of patients with decreased serum PTH level, differences in the frequency of clinical symptoms of hypocalcaemia between women (51%) and men (24%) were statistically significant ( $p < 0.034$ ).

**Tab. 3.** Histopathological diagnoses in the studied group (total thyroidectomies).

Histopathological diagnoses	n	%	Total	
			n	%
Papillary thyroid carcinoma	34	10		
Follicular thyroid carcinoma	4			
Thyroid cancers	Medullary thyroid carcinoma	2	43	13
	Anaplastic thyroid carcinoma	1		
	Metastasis of clarcocellular carcinoma to the thyroid gland	2		
		3		
Nodular goitre	Non-toxic nodular goitre	187		
	Nodular variant of Hashimoto disease	2	57	
	Nodular goiter with morphological features of hyperactivity	87	287	87
	Nodular variant of Graves' disease	11	30	
	<b>Total</b>	<b>330</b>	<b>100</b>	<b>330</b>

In 8% of cases, the histopathological examination of the removed tissue revealed the presence of whole parathyroid glands or their pieces. In 3 patients, 2 parathyroid glands were excised and all of them had serum PTH concentration below 14.99 pg/ml. In 17 (77%) out of 22 patients in whom 1 parathyroid gland was removed, serum PTH concentration was below 14.99 pg/ml (Table 6). Based on statistical analysis, we may assume that percentage of patients with decreased serum PTH concentration rises with the increased amount of removed parathyroid gland tissue ( $p < 0.004$ ).

We analyzed the occurrence of hypocalcaemia symptoms in the group of patients with decreased serum PTH concentration, depending on particular ranges of serum PTH levels (Table 7). Statistical analysis revealed that clinical symptoms of hypocalcaemia were related to serum PTH concentration – in the patients with of lower PTH levels paresthesias occurred more frequently ( $p < 0.002$ ). We have concluded that serum PTH levels below 5 pg/ml seem to be a good prognostic factor of the occurrence of hypocalcaemia symptoms.

In our study a decreased PTH concentration was a main criterion for recognition of postoperative hypoparathyroidism, however, serum levels of total calcium were also estimated. The total serum calcium concentration measured on the first day after thyroidectomies was lower by 16% when compared with its value before operation [ $0.39 \text{ mmol/l}$  ( $SD \pm 0.19$ )], however in the group of patients with a decreased PTH level the discrepancies were definitely higher – 21% [ $0.51 \text{ mmol/l}$  ( $SD \pm 0.15$ )] (Table 8).

## DISCUSSION

Hypoparathyroidism resulting from thyroidectomy worsens quality of patients' life because of the necessity of chronic pharmacological treatment (active vitamin D metabolite and calcium carbonate) and medical care. Most frequently, postoperative hypoparathyroidism is not a result of permanent destruction of parathyroid glands and usually it persists during 6 months (sometimes 1–2 years) after surgery. When patients treated because of persistent postoperative hypoparathyroidism were reevaluated after therapy withdrawal, it turned out that 2–5 years after surgery 50% of them did not need substitutive therapy (they had normal PTH and calcium levels) (Jurecka-Lubieniecka *et al.* 2006).

**Tab. 4.** Serum PTH concentrations depending on the extent of surgery.

	Lobectomy (Controls)	Subtotal thyroidectomy (Controls)	Total thyroidectomy without lymphadenectomy	Total thyroidectomy with lymphadenectomy
Serum PTH 0–14.99 pg/ml	1 (3%)	9 (16%)	134 (47%)	25 (58%)
Serum PTH $\geq 15.0$ pg/ml	30 (97%)	46 (84%)	153 (53%)	18 (42%)

The frequency of postoperative hypoparathyroidism varies considerably between different surgical centres. Temporary hypoparathyroidism occurs in 1.6–50% patients, while permanent one in 1.5–4.9% cases (Roh *et al.* 2011; Khairy *et al.* 2011; Radivojević *et al.* 2012). These discrepancies are probably the result of different methods and diagnostic criteria used by authors to define this complication. In the study evaluating safety of total thyroidectomy (336 surgical procedures) permanent hypoparathyroidism occurred in 1.8% cases, while significant temporary hypocalcaemia (calcium concentration <2.0 mmol/l) concerned 13.4% patients and non-significant temporary hypocalcaemia (calcium concentration 2.0–2.1 mmol/l) was observed in 23.8% (Serpell *et al.* 2007). In that series the overall rate of hypocalcaemia was 39% (PTH levels were not measured). In our study, postoperative hypoparathyroidism, based on serum PTH levels measured on the first day after total thyroidectomy, was recognized in 48% of patients and in 45% of patients with low PTH levels symptoms of hypocalcaemia were present.

Many authors postulate that PTH determination is the most effective strategy to identify postoperative hypoparathyroidism, in contrary to other clinical and laboratory (e.g. serum calcium level) parameters. Measurement of serum PTH levels has the advantage of directly assessing gland function. There is a debate whether PTH measurements should be performed intraoperatively, few hours or one day after thyroidectomy (Kovacevic *et al.* 2011; Yano *et al.* 2012). In one of the recent studies, in which 806 total thyroidectomies were analyzed, the overall incidence of hypocalcaemia was 23.6%, with the permanent hypocalcaemia in 1.61% and symptomatic hypocalcaemia in 10.91% (Nair *et al.* 2013). In the above study, the intraoperative PTH assay was done in 155 patients: hypocalcaemia developed in 21.3% of patients and permanent hypocalcaemia was noted in 2.6%; 50% of hypocalcaemic patients had intraoperative PTH level below 10 pg/ml. The conclusion was that the intraoperative intact PTH assay – which is recommended by Australian Society of Endocrine Surgeons – is a good tool to predict postoperative hypocalcaemia. The authors noted that this test has low sensitivity but high specificity (Nair *et al.* 2013). In other study, Rivere *et al.* concluded that PTH assay in the blood samples collected in the morning after total thyroidectomy was an effective strategy to detect hypoparathyroidism (Rivere *et al.* 2014). The authors recommend an assessment of PTH concentra-

tion after total thyroidectomy and supplementation of calcium and calcitriol in patients with serum PTH levels  $\leq 13$  pg/ml to avoid symptomatic hypocalcaemia and prolonged hospitalizations (Rivere *et al.* 2014). In prospective, randomized controlled study conducted by Cayo *et al.* (2012), PTH levels were also obtained in the morning after surgery and the authors concluded that it was highly specific method of prediction whether the patients were at risk of symptomatic hypocalcaemia. They have established that PTH concentration below 10 pg/ml allows to accurately identify patients with high risk of hypocalcaemia (48% had presented symptomatic hypocalcaemia), whereas all patients with a postoperative PTH  $\geq 10$  pg/ml can safely be discharged from hospital without supplementation (Cayo *et al.* 2012). In turn, Landry *et al.* (2012) demonstrated that limiting supplementation to patients with PTH level of lower than 6 pg/ml or a serum calcium level lower than 8 mg/dl on the first postoperative day may eliminate unnecessary calcium/vitamin D intake and follow-up assessments in up to 58% of patients

**Tab. 5.** Percentage of decreased or normal serum PTH concentrations, depending on factors increasing the risk of postoperative hypoparathyroidism.

	Decreased PTH level	Normal PTH level
Lymphadenectomy	58%	42%
Graves' disease	64%	36%
Recurrent goitre	57%	43%
Intraoperative hemorrhage/reoperation because of hemorrhage	60%	40%
Huge retrosternal goitre	56%	44%
Thyroidectomies without additional risk factors	45%	55%

**Tab. 6.** Serum PTH concentrations depending on the number of parathyroid glands found in histopathological preparations.

Number of parathyroid glands found in histopathological preparations	Patients with serum PTH 0–14.99 pg/ml	Patients with serum PTH $\geq 15$ pg/ml
0	139 (46%)	166 (54%)
1	17 (77%)	5 (23%)
2	3 (100%)	0

**Tab. 7.** The occurrence of clinical symptoms of hypocalcaemia in the group of patients with decreased serum PTH concentration, depending on particular ranges of serum PTH levels.

	PTH 0–4.99 pg/ml	PTH 5–9.99 pg/ml	PTH 10–14.99 pg/ml
Patients with clinical symptoms of hypocalcaemia	32 (64%)	30 (42%)	10 (26%)
Patients without clinical symptoms of hypocalcaemia	18 (36%)	41 (58%)	28 (74%)

**Tab. 8.** The average reduction of total serum calcium concentration on the first day after thyroidectomy with respect to the level before surgery.

	Number of patients (%)	The average reduction of total serum calcium concentration	
		mmol/l (x±SD)	%
PTH 0–14.99 pg/ml	33 (58%)	0.51 (± 0.15)	21
PTH ≥15.0 pg/ml	24 (42%)	0.23 (± 0.12)	9
Total	57 (100%)	0.39 (± 0.19)	16

undergoing thyroidectomy (Landry *et al.* 2012). In our study, dependence between serum PTH concentration and probability of symptomatic hypocalcaemia was confirmed. Moreover we found that serum PTH levels below 5 pg/ml seem to be a good prognostic factor for the occurrence of hypocalcaemia symptoms.

The proponents of total thyroidectomy claim that the frequency of postoperative complications is similar after total and subtotal thyroidectomy (Serpell *et al.* 2007; Wilhelm *et al.* 2010). However, many medical centres present an opinion that a risk of postoperative complications increases with extension of the surgery (Järhult *et al.* 2012). The observations made in the present study speak for the latter opinion. The patients who underwent total thyroidectomy were at significantly higher risk of postoperative hypoparathyroidism than patients from the control group. The highest risk occurred in patients in whom total thyroidectomy was widened by lymphadenectomy and the lowest in patients who underwent lobectomy.

The risk of postoperative hypoparathyroidism is believed to be increased by some additional factors, like: co-occurrence of Graves' disease, lymphadenectomy, intraoperative hemorrhage and huge, retrosternal goitre, as well as reoperation. In our study, 24% of patients who underwent total thyroidectomy were burdened with additional risk factors of postoperative hypoparathyroidism. We divided the studied group, depending on factors increasing the risk of postoperative hypoparathyroidism, but we did not notice statistically significant differences in PTH concentration between particular subgroups ( $p < 0.43$ ), what probably was the result of small number of patients in these subgroups. However, especially high frequency of postoperative hypoparathyroidism was found in the patients with concurrent lymphadenectomy, with Graves' disease and in cases complicated by intraoperative hemorrhage. Landry *et al.* (2012) observations were similar – in patients who underwent a central neck dissection, the risk of postoperative hypoparathyroidism was higher. In contrast, Cayo *et al.* (2012) demonstrated that extent of surgery did not allow to predict neither PTH concentration  $< 10$  pg/ml nor hypocalcaemic symptoms.

Thyroid diseases are definitely more frequent in women than in men. Sousa Ade *et al.* (2012) demonstrated that one of the predictors of postoperative hypocalcaemia was age over 50, whereas in other studies younger age was a prognostic factor of symptomatic hypocalcaemia (Paek *et al.* 2013; Cayo *et al.* 2012). In our study, we did not observe any influence of age on the incidence of postoperative hypoparathyroidism ( $p < 0.194$ ). It seems that in the elderly people ( $> 60$  years old) hypocalcaemic symptoms occur less frequently.

Breuer *et al.* (2013) evaluated the patients with Graves' disease after thyroidectomy and they demonstrated that postoperative hypocalcaemia was more frequent in children than in adults because of longer time of surgery in children. Sousa Ade *et al.* (2012) also recognized the duration of surgery as a predictor of postoperative hypocalcaemia. In our study the average duration of surgery was approx. 74 minutes and was shorter than in adults from Breuer *et al.* (2013) study (~99 minutes). We did not demonstrate the correlation between the duration of surgery and occurrence of postoperative hypoparathyroidism ( $p < 0.277$ ). However, it seems that the duration of surgery over 120 minutes increases risk of this complication.

In the present study no statistical significant association between gender and postoperative hypoparathyroidism was found. Similar observation was made by other authors (Paek *et al.* 2013; Cayo *et al.* 2012; Sousa *et al.* 2012). The analysis of our results showed, however, that in the group of patients with confirmed postoperative hypoparathyroidism (with decreased PTH level) symptoms of hypocalcaemia occurred more frequently among women than men ( $p < 0.034$ ).

## CONCLUSION

In conclusion, serum PTH levels below 5 pg/ml, measured within the first day after total thyroidectomy, seem to be a good prognostic factor of the occurrence of hypocalcaemia symptoms. The information about low PTH concentration allows to start the pharmacotherapy faster and, thereby, to avoid the clinical manifestation of hypocalcaemia. Thanks to such an approach to the problem of postoperative hypoparathyroidism, we can provide the greater safety for patients and comfort for medical personnel – planned medical care is always better organized and it entails a lower risk of error than emergency care.

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**Conflict of interest statement.** The authors declare no conflict interest.

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