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ORIGINAL ARTICLE

Can preoperative vitamin D deficiency predict postoperative hypoparathyroidism following thyroid surgery?

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Abstract

Importance Postoperative hypoparathyroidism remains a relevant problem after thyroid surgery. Although the roles of vitamin D deficiency and other risk factors have been discussed in previous studies, variable results have been reported.

Objective Predicting the risk of postoperative hypocalcemia could be helpful for individual prognoses and medical treatment.

Patients and methods Documentation and analysis of bilateral thyroid operations performed between July 2011 and May 2014 were studied. Results involving age, gender, diagnosis, surgical techniques, pre- and postoperative calcium and parathyroid hormone (PTH) levels, and especially, the role of preoperative vitamin D levels were assessed in uni- and multivariate analyses.

Results Bilateral thyroid surgery was performed in 361 patients with multinodular goiters ($n = 224$), Graves' disease ($n = 40$), or thyroid carcinoma ($n = 97$). In total, 124 patients (34%) with postoperative hypoparathyroidism, defined as having a PTH level ≤ 10 pg/mL, were treated with calcium and vitamin D regardless of their symptoms. The rate of permanent hypoparathyroidism was 3.6% and correlated with the extent of surgery; the highest risks were shown for total thyroidectomy and central lymph node dissection. In univariate analysis, the extent of surgery, parathyroid autotransplantation, and histopathology were the strongest predictors of hypoparathyroidism. Even severe vitamin D deficiency (< 10 ng/mL) showed a trend only towards a higher transient hypoparathyroidism risk ($p = 0.0514$) but failed to predict permanent hypoparathyroidism.

Conclusion Postoperative PTH levels accurately identified patients at risk for hypoparathyroidism. Decreased preoperative vitamin D levels could not predict hypocalcemia, and high vitamin D levels could not prevent permanent hypoparathyroidism.

Keywords Thyroid surgery · Thyroidectomy · Postoperative hypoparathyroidism · Hypocalcemia · Vitamin D deficiency

Introduction

Hypoparathyroidism is a relevant clinical problem after thyroidectomy. It is mostly caused by intraoperative injury to the parathyroid glands and is not always preventable, even by meticulous dissection. The main reasons underlying impaired parathyroid function resulting in hypocalcemia are incidental removal of parathyroid glands or disturbance of the parathyroid gland blood supply. Autotransplantation of parathyroid tissue has been described to restore parathyroid function and prevent permanent hypoparathyroidism [1, 2].

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Parathyroid hormone (PTH) measurement on the first postoperative day allows accurate prediction of postoperative parathyroid function. If PTH levels are < 10 pg/mL, supplementation of calcium and vitamin D is recommended to prevent typical symptoms of postoperative hypoparathyroidism, such as tingling, numbness, and tetany [3]. Long-term disadvantages of hypocalcemia include calcification of the basal ganglia and renal impairment.

Several risk factors for postoperative hypoparathyroidism, such as female gender, thyroid malignancy or autoimmune thyroiditis, extent of surgery (thyroidectomy, central lymph node dissection), and parathyroid autotransplantation, have been discussed in the literature [4, 5]. 25-Hydroxyvitamin D deficiency is another potential risk factor of postoperative hypoparathyroidism, but its reliability as an indicator remains controversial among researchers. While some studies have found a significant influence of low vitamin D levels on postoperative hypocalcemia [6–8], others did not observe a

significant correlation between the two parameters [9–19]. Moreover, until now, no study has demonstrated an impact of vitamin D levels on permanent hypocalcemia.

Because preoperative low vitamin D levels could be simply improved by vitamin D medication, the interaction between both parameters, preoperative vitamin D levels and postoperative hypoparathyroidism, should be thoroughly analyzed.

This prospective study aimed to evaluate the potential influence of preoperative vitamin D levels on transient and permanent postoperative hypoparathyroidism in a large series of consecutive patients who underwent bilateral thyroid surgery at a tertiary referral center.

Patients and methods

From July 2011 to May 2014, patients who underwent bilateral thyroid surgery for benign and malignant thyroid disease were documented prospectively to evaluate postoperative hypoparathyroidism and define potential risk factors. Exclusion criteria were primary or renal hyperparathyroidism. Preoperative vitamin D levels and their potential influence on postoperative hypocalcemia were considered. All of the operations were performed at a tertiary referral center and university hospital.

Postoperative hypoparathyroidism was defined as a total calcium level < 2.1 mmol/L (8.4 mg/dL), a PTH level < 10 pg/mL or typical clinical symptoms despite normal PTH or calcium levels. Permanent hypoparathyroidism was defined as an ongoing necessity of calcium or vitamin D supplementation due to decreased PTH or calcium levels at 6 months after parathyroid surgery.

Surgical technique

Bilateral surgery on the thyroid gland was performed for benign multinodular goiter, Graves' disease, and thyroid cancer by specialized endocrine surgeons or surgeons in training under supervision. A Hartley-Dunhill operation (lobectomy and subtotal resection of the other thyroid lobe) was performed only for multinodular goiters. In all cases of Graves' disease and thyroid carcinoma (> 1 cm or with multifocal growth), a thyroidectomy was carried out. Prophylactic central lymph node dissection was performed routinely in cases of papillary thyroid carcinoma (> 1 cm, multifocal growth or proven lymph node metastases) or medullary thyroid carcinoma. The number of visualized parathyroid glands was recorded. Accidentally removed or devascularized parathyroid glands were autotransplanted into the sternocleidomastoid muscle or the strap muscles.

Biochemical evaluation and postoperative calcium and vitamin D supplementation

Routine laboratory tests for TSH, FT3, FT4, and TPO antibodies as well as for TRAK, calcitonin, serum calcium, parathyroid hormone (PTH), and 25-hydroxyvitamin D were performed preoperatively. Vitamin D levels were categorized into three groups: ≤ 10 ng/mL (severe vitamin D deficiency), 11–20 ng/mL (medium vitamin D deficiency), and > 21 ng/mL (mild or no vitamin D deficiency). On the first postoperative day, calcium and PTH measurements were performed routinely. When PTH levels were < 10 pg/mL (normal range, 15–65 pg/mL), a medication with 3 × 600 mg of calcium and 3 × 0.5 μg of calcitriol (1α,25$(OH)_2$-cholecalciferol) was started regardless of whether the patient showed typical symptoms of hypoparathyroidism. If PTH levels were between 10 and 15 pg/mL, measurements of calcium and PTH were repeated on postoperative day 2. Symptomatic patients in this group were also treated with calcium and calcitriol; asymptomatic patients were only followed. Patients with PTH levels > 15 pg/mL were not routinely treated with calcium and vitamin D medication.

At 2 weeks postoperatively, calcium and PTH levels were measured again. If PTH levels were still decreased, calcium and calcitriol medication was continued and controlled continuously for up to 1 year postoperatively.

Statistical analysis

Uni- and multivariate logistic regression analyses were performed with the binary outcome of postoperative hypoparathyroidism (yes or no) and the following variables: age, gender, diagnosis, Hashimoto's thyroiditis, thyroid gland weight, completion thyroidectomy, extent of the operation, parathyroid autotransplantation, and preoperative vitamin D level. To select the variable included in the multivariate analysis, we used a backward elimination procedure. Values are presented as the mean (± standard deviation) and median (range) for continuous variables. A two-sided p value < 0.05 was considered statistically significant. Missing values were < 5% in the data set, and no imputation strategies were used. All calculations were conducted using R Project for Statistical Computing (The R Foundation, Version 3.1.0, Vienna, Austria).

Results

A total of 361 consecutive patients (67% female, 33% male, 6–88 years) who underwent bilateral thyroid surgery were included in this analysis (Table 1). Two hundred twenty-six patients (62.6%) were treated for multinodular goiters, 38 patients (10.5%) were treated for Graves' disease, and 97 patients (26.9%) were treated for thyroid carcinoma. Mean

Table 1 Pre- and postoperative characteristics of 361 patients with bilateral thyroid surgery

Female/male	241 (66.8)/120 (33.2)
Age (years)	51.0 (6–88)
Preoperative laboratory values	
Serum calcium (range, 2.10–2.60 mmol/L)	2.39 (2.0–2.70)
25-Hydroxyvitamin D (range, 30–60 ng/mL)	20.2 (0–61)
Vitamin D < 10 ng/mL	84 (23.3)
Vitamin D 11–20 ng/mL	115 (31.9)
Vitamin D > 21 ng/mL	162 (44.8)
Diagnosis	
Multiglandular goiter	226 (62.6)
Graves' disease	38 (10.5)
Thyroid carcinoma	97 (26.9)
Surgical technique	
Hartley-Dunhill operation	71 (19.7)
Total thyroidectomy (TT)	214 (59.3)
Central lymph node dissection (CLND)	76 (21.0)
Completion thyroidectomy	19 (5.3)
Parathyroid autotransplantation, yes	162 (44.9)
Postoperative hypoparathyroidism, 124 (34.3)	
Transient	111 (30.7)
Permanent	13 (3.6)

Data are presented as *n* (%) or mean values

preoperative serum calcium levels were 2.39 mmol/L (normal range, 2.10–2.60 mmol/L). Severe vitamin D deficiency with vitamin D levels below 10 ng/mL was found preoperatively in 84/361 (23.3%) patients. The mean preoperative vitamin D levels were 20.2 ng/mL (normal range, 30–60 ng/mL). Only 21% of the patients had preoperative vitamin D levels within the normal range (> 30 ng/mL). As expected, a seasonal difference in vitamin D levels was observed, with the lowest average level of 15.2 ng/mL occurring in February, and the highest average level of 28.2 ng/mL occurring in September; this difference did not influence the postoperative PTH levels.

A total thyroidectomy (TT) was performed in 79.8% of the patients, while a Hartley-Dunhill operation was performed in 19.7% of the patients. Central neck dissection was carried out in 76 patients (21.1%) with thyroid carcinoma; an additional lateral neck dissection was performed in 7.2% of these patients. Because of the postoperative diagnosis of thyroid cancer, a completion thyroidectomy or central lymph node dissection was performed in 19 patients (5.3%). The mean weight of the resected thyroid gland specimen was 75.6 g (3.7–1262.0 g).

At least three parathyroid glands were identified intraoperatively in 248 patients (68.7%). The number of intraoperatively identified parathyroid glands did not affect postoperative hypoparathyroidism. Early postoperative hypoparathyroidism was observed in 34.3% of the subjects when two parathyroid glands were identified, in 34.5% of the subjects when three glands were identified, and in 36.7% when four glands were identified. Parathyroid autotransplantation was performed in 162 of 361 patients (44.9%). Histopathology detected small parathyroid glands in 60 patients (16.6%), most of them below 3 mm in diameter. Twenty-five of these 60 patients were diagnosed with thyroid cancer, which made the detection of the parathyroids more challenging.

On the first postoperative day, early postoperative hypoparathyroidism with PTH levels < 10 pg/mL) was found in 112 of 361 patients. Thirty-six patients had PTH levels between 10 and 15 pg/mL and were subjected to another lab test on the second postoperative day. In 26 of these patients, the PTH level increased or remained stable, and the patients remained asymptomatic and required no calcium and calcitriol supplementation. The remaining 10 patients with PTH levels between 10 and 15 pg/mL and 2 symptomatic patients with PTH levels of 15.3 pg/mL and 24.3 pg/mL were treated with calcium and calcitriol. Overall, the rate of early postoperative hypoparathyroidism was 34.3%. Permanent hypoparathyroidism, lasting longer than 6 months, persisted in 13 patients (3.6%).

Compared to males, females had a higher risk of developing early postoperative hypoparathyroidism (39.8% versus 23.3%, $p = 0.002$). However, permanent hypoparathyroidism rates were comparable between females (3.7%) and males (3.4%) (Table 2). Patient age was not associated with a higher risk of hypoparathyroidism.

Only preoperative vitamin D levels < 10 ng/mL showed a trend towards a higher risk of early postoperative hypoparathyroidism, but statistical significance was not reached ($p = 0.0514$). Overall, 39.3% of patients with vitamin D levels < 10 ng/mL developed transient hypoparathyroidism, compared to 32.7% of patients with vitamin D levels > 21 ng/mL.

The lowest rate of permanent hypoparathyroidism was observed in 2 of 115 (1.7%) patients with vitamin D levels between 11 and 20 ng/mL (Table 3). Permanent hypoparathyroidism was found in 4.8% of the patients with vitamin D levels < 10 ng/mL and in 4.3% of the patients with vitamin D levels > 21 ng/mL (n.s.).

The extent of thyroid resection was shown to significantly influence postoperative hypoparathyroidism. After Hartley-Dunhill procedures, 12.7% of early postoperative hypoparathyroidism was observed compared to 35.5% after total thyroidectomies ($p = 0.00052$) and 51.3% after total thyroidectomy and central lymph node dissection ($p < 0.0001$).

Comparable results were observed for permanent hypoparathyroidism, with the lowest rates being observed after Hartley-Dunhill operations (1.4%), followed by total thyroidectomy (2.8%) and additional central node dissection (7.9%).

Permanent hypoparathyroidism was detected more frequently in thyroid cancer patients with advanced tumor stages (2.2% pT1, 4.5% pT2, 8.0% pT3, and 33.3% pT4) and was seen more frequently in lymph node-positive patients (13.9%) compared to node-negative patients (2.6%).

Table 2 Univariate regression analysis of risk factors for early postoperative hypoparathyroidism (24 h postoperatively)

Variable	Postoperative hypoparathyroidism (24 h)	*p* value
Female gender	96/241 (39.8)	0.002*
Multinodular goiter	67/226 (29.6)	0.48
Graves' disease	13/38 (36.8)	0.06
Thyroid carcinoma	43/97 (44.3)	0.266
Total thyroidectomy vs. Hartley-Dunhill operation	76/214 (35.5) vs. 12/71 (12.7)	0.00052*
Total thyroidectomy and central lymph node dissection vs. Hartley-Dunhill operation	39/76 (51.3) vs. 12/71 (12.7)	< 0.0001*
Completion thyroidectomy	7/19 (36.8)	0.814
Parathyroid autotransplantation	81/162 (50.0)	< 0.0001*
Weight of the resected thyroid > 100 g	24/76 (31.6)	0.596
Preoperative vitamin D < 10 ng/mL	33/84 (39.3)	0.0514
Preoperative vitamin D 11–20 ng/mL	38/115 (33.0)	0.365
Preoperative vitamin D > 21 ng/mL	53/162 (32.7)	0.322

Data are presented as *n* (%) or mean values

*< 0.05 means significant results

Among patients with Hashimoto's thyroiditis, defined as chronic lymphoid inflammation in the histopathological specimen, transient/permanent postoperative hypoparathyroidism was observed in 33.7% and 4.0%, respectively. Furthermore, transient/permanent postoperative hypoparathyroidism seemed to occur more frequently in Hashimoto's thyroiditis patients than in those without this diagnosis (29.6% transient hypoparathyroidism, 3.5% permanent hypoparathyroidism). However, these results did not reach statistical significance ($p = 0.414$).

One of the strongest risk factors predicting permanent hypoparathyroidism was postoperative PTH level. Twelve of 85 patients (14.1%) with no detectable PTH levels at 24 h postoperatively developed permanent hypoparathyroidism. Among the subjects with early postoperative PTH levels of at least ≥ 1 pg/mL, only 0.4% developed permanent hypoparathyroidism.

In multivariate analysis of transient hypoparathyroidism, female gender ($p = 0.0155$), parathyroid autotransplantation ($p = 0.027$), and postoperative PTH values ($p < 0.0001$) showed prognostic significance (Table 3).

Table 3 Multivariate regression analysis of risk factors for early postoperative hypoparathyroidism (24 h postoperatively)

Variable	*p* value
Female gender	0.0006*
Multinodular goiter vs. Graves' disease	0.798
Thyroid carcinoma vs. Graves' disease	0.150
Total thyroidectomy vs. Hartley-Dunhill operation	0.475
Total thyroidectomy and central lymph node dissection vs. Hartley-Dunhill operation	0.688
Completion thyroidectomy	0.419
Parathyroid autotransplantation	< 0.0001*
Weight of the resected thyroid > 100 g vs. < 100 g	0.592
Preoperative vitamin D > 21 ng/mL vs. < 10 ng/mL	0.824
Preoperative vitamin D 11–20 ng/mL vs. < 10 ng/mL	0.640
Postoperative PTH < 10 pg/mL	< 0.0001*

Data are presented as *n* (%) or mean values

*< 0.05 means significant results

Discussion

In 2015, the AACE/ACE (American Association of Clinical Endocrinologists/American College of Endocrinology) [5] defined postoperative hypoparathyroidism as temporary (transient) when lasting up to 12 months in duration following cervical surgery and permanent when lasting longer than 12 months after cervical surgery. Clinical hypoparathyroidism includes symptoms of hyperesthesia of the hands and feet, perioral numbness, nocturnal leg cramps, and positive Chvostek/Trousseau signs. Hypoparathyroidism is biochemically indicated by a total calcium below 8.5 mg/dL (2.12 mmol/L) or a PTH level lower than 12 pg/mL (below the specific test rates of the assay).

After bilateral thyroid procedures, postoperative PTH monitoring is recommended within the first 24 h following surgery. Because of the short half-life of PTH of only 3 to 5 min, PTH levels start declining immediately after surgery. Postoperative serum calcium testing provides the lowest calcium levels not before 24 to 48 h.

When PTH levels are < 10 pg/mL [3], serum calcium levels are < 2.0 mmol/L or typical symptoms of hypoparathyroidism are recognized, calcium (3 × 500–600 mg/day) and vitamin D supplementation (2–3 × 0.5 μg of calciferol/day) are

recommended. Patients with untreated hypoparathyroidism are at risk for developing severe muscle cramps, seizures, basal ganglia calcification, cataract, cardiomyopathy, and depression.

For more than 100 years [20], hypoparathyroidism resulting from thyroid surgery has remained a relevant clinical problem. In view of postthyroidectomy rates for transient hypoparathyroidism of 18.0 to 37.1% [6, 7, 12, 14, 18, 21, 22], surgeons are continuously attempting to improve their surgical skills to preserve the parathyroid blood supply with microdissection techniques and use of magnifying glasses. Permanent hypoparathyroidism reportedly occurs in 0.6 to 2.7% of all patients undergoing thyroid surgery [1, 7, 15, 21].

In addition to the surgical techniques themselves, several other risk factors exist for developing postoperative hypoparathyroidism. In a meta-analysis of 115 observational studies published between 1990 and 2012, Edafe et al. [4] described female gender, Graves' disease, parathyroid autotransplantation, and the excision of parathyroid glands as clinical predictors of postoperative hypoparathyroidism. Lower preoperative vitamin D levels have been associated with transient hypocalcemia in some publications (Table 4).

The role of parathyroid autotransplantation in the development of permanent hypoparathyroidism remains doubtful. Almquist et al. [1] reported performing parathyroid autotransplantation in 17.3% of their total thyroidectomy cases and found that none of the 90 patients subjected to this procedure developed permanent hypoparathyroidism. In our own series between 2011 and June 2014, we followed a liberal indication for parathyroid autotransplantation (44.9% of total thyroidectomies) and found transient/permanent hypoparathyroidism in 30.7% and 3.6%, respectively. According to the initial results of this study, we restricted the number of autotransplantations from July 2014 to June 2017 (448 total thyroidectomies, 52 central lymph node dissections) to 22.0% and achieved better results for permanent hypoparathyroidism (1.0%).

Erbil et al. [6] were among the first to address the question if low preoperative vitamin D levels could increase the rate of postoperative hypoparathyroidism in 200 patients subjected to near-total or total thyroidectomy. In all 33 patients (100%) with preoperative vitamin D levels ≤ 15 ng/mL, transient hypoparathyroidism was observed postoperatively, in contrast to 9.5% of patients with vitamin D levels > 15 ng/mL exhibiting transient hypoparathyroidism. A possible limitation of this study, however, was that the rate of TT for hypocalcemic patients was 87.7%, and this rate was only 5.9% for normocalcemic patients. A significant difference between preoperative vitamin D levels < 10 ng/mL and > 20 ng/mL was also confirmed by Kirkby-Bott et al. [7], who described transient hypoparathyroidism in 35.5% of the patients with vitamin D levels < 10 ng/mL, compared to 15% in patients with vitamin D levels > 20 ng/mL.

Kim et al. [8] analyzed pre- and postoperative lab tests of 267 patients who underwent TT and central compartment neck dissection for thyroid cancer. In patients with preoperative vitamin D levels < 10 ng/mL, the rate of postoperative symptomatic hypocalcemia was significantly higher (43.8% versus 30.4%).

Other studies [10–16, 19] detected no correlation between preoperative vitamin D levels and postoperative hypoparathyroidism. Lang et al. [13] evaluated 281 patients with TT and found an inverse correlation between preoperative vitamin D levels and PTH on the first postoperative day. In 83 patients with vitamin D levels < 10 pg/mL, the median PTH level on postoperative day 1 was 2.8 pmol/L (normal range 1.2–5.7 pmol/L), compared to 45 patients with a vitamin D level > 20 ng/mL having a median PTH value of 2.2 pmol/L.

Cherian et al. [17] followed 150 patients from India who underwent TT or TT + CLND, and 53.3% had a vitamin D

Table 4 Association between preoperative vitamin D levels and early postoperative hypoparathyroidism—an excerpt of the literature between 2009 and 2017

Author	Year	*n*	Surgery	Risk of early postoperative hypoparathyroidism
Erbil [6]	2009	200	NTT + TT	Vitamin D ≤ 15 ng/mL, 100%
Kirkby-Bott [7]	2011	165	TT	Vitamin D ≤ 10 ng/mL, 35.5% Vitamin D > 20 ng/mL, 15.0%
Lin [10]	2012	152	NTT + CLND	No correlation with calcium levels
Nhan [11]	2012	139	TT	No correlation with calcium or PTH levels
Lang [13]	2013	281	TT	No correlation with calcium or PTH levels
Griffin [14]	2014	121	TT	No correlation with calcium levels
Falcone [16]	2015	264	TT	No correlation with calcium levels
Kim [8]	2015	267	TT + CLND	Vitamin D < 10 ng/mL, 43.8% Vitamin D ≥ 10 ng/mL, 30.4%
Cherian [17]	2016	150	TT + CLND	No correlation with calcium or PTH levels
Erlem [18]	2017	246	TT	No correlation with calcium or PTH levels

NTT near-total thyroidectomy, *TT* total thyroidectomy, *CLND* central lymph node dissection, *PTH* parathyroid hormone

deficiency < 20 ng/mL. Postoperatively, no correlation was observed between vitamin D deficiency and serum calcium or PTH levels (mean 19.7 mg/L versus 19.0 mg/L in patients with vitamin D > 20 ng/mL). Similar results were presented for 19 patients with severe vitamin deficiency (< 10 ng/mL).

In our series of 361 patients, we observed only a mild, non-significant correlation ($p = 0.0514$) between preoperative vitamin D levels ≤ 10 ng/mL and early postoperative hypoparathyroidism (39.3%), compared to 32.7% of patients with hypoparathyroidism having vitamin D levels > 21 ng/mL. The strongest predictors of early postoperative hypoparathyroidism were female gender, total versus near-total thyroidectomy, and parathyroid autotransplantation. In patients with thyroid carcinoma, advanced tumor categories and extensive lymph node involvement may complicate intraoperative preservation of the parathyroids as a result of tumor infiltration. In pT4 carcinomas, 33.3% of patients with permanent hypoparathyroidism required at least a low-dose medication of calcium and/or vitamin D, in contrast to 2.2% of patients with pT1 carcinomas requiring this supplementation. In total, 13.9% of patients with metastatic lymph nodes were treated for permanent hypoparathyroidism, compared to 2.6% of patients without lymph node metastases.

The strengths of our study were the large number of patients, high percentage (55.2%) of patients with vitamin D deficiency (≤ 20 ng/mL) and a correlation with not only postoperative serum calcium but also with PTH levels, which are more directly related to parathyroid function. A possible limitation of our data was that patients with different surgical procedures, such as Hartley-Dunhill operations, TT, and TT + CLND, were included; all of the patients were divided into subgroups.

Conclusions

According to our own data and recent publications, the hypothesis that preoperative vitamin D deficiency leads to a higher percentage of patients with postthyroidectomy hypoparathyroidism remains contradictory. Based on these data, the idea of eliminating postoperative hypoparathyroidism with preoperative vitamin D supplementation will not likely be successful. The best way to preserve parathyroid function continues to be a meticulous surgical technique that more strictly indicates parathyroid autotransplantation.

Compliance with ethical standards

Conflict of interest Theresia Weber has received a speaker honorarium from Sanofi-Aventis, Germany.

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

This article does not depict any studies involving animals that were performed by any of the authors.

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