

Laparoscopic Sleeve Gastrectomy-Induced Decreases in FT3 and TSH are Related to Fasting C-Peptide in Euthyroid Patients with Obesity

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Objective: Laparoscopic sleeve gastrectomy (LSG) is one of the most effective therapies to treat obesity. However, whether LSG affects thyroid function remains elusive. Due to a lack of longitudinal research, we explored changes in thyroid function in euthyroid patients with obesity before and after LSG.

Methods: In total, 109 participants (59 obese patients, 30 normal controls and 20 overweight subjects) were recruited from the Second Xiangya Hospital of Central South University (CSU). All patients underwent LSG, and metabolic indicators and free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were evaluated at baseline, 6 and 12 months postoperatively.

Results: Compared to the normal control group, the concentrations of FT4 were decreased and TSH were increased in the obese group at baseline. Thyroid hormone levels in all participants were within the normal range during the 12 months after LSG. The concentrations of FT3 (4.83 ± 0.06 vs 5.03 ± 0.08 , $P = 0.023$) and TSH (1.67 ± 0.11 vs 2.25 ± 0.18 , $P = 0.000$) significantly decreased from baseline to 12 months postoperatively, while the concentrations of FT4 significantly increased (17.40 ± 0.52 vs 15.80 ± 0.32 , $P = 0.004$). The decrease in fasting C-peptide (FCP) was related to the decline in FT3 and TSH during 12 months after LSG.

Conclusion: Obesity is closely related to thyroid function. LSG promoted a significant decrease in FT3 and TSH and a significant increase in FT4 in euthyroid patients with obesity after LSG. The decline in FCP may be involved in the decrease in FT3 and TSH after LSG.

Keywords: laparoscopic sleeve gastrectomy, obesity, thyroid function

Introduction

Obesity is an important public health concern worldwide, and the global prevalence of obesity in adults has been increasing over recent decades.¹ Moderate (5%) weight loss improves metabolic function in multiple organs simultaneously, and progressive weight loss causes dose-dependent alterations in key adipose tissue biological pathways.² Metabolic surgeries, including laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB), are effective interventions that can lead to marked weight loss and improved glucose control³ and have been considered one of the treatments for obesity.⁴ It is worth mentioning that the LSG procedure has gained popularity in the past decade because it is easy to perform and is associated with a low incidence of serious complications.⁵

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The hypothalamic-pituitary-thyroid axis consists of the hypothalamus, the pituitary gland, and the adrenal glands, all of which can produce and secrete their own hormone cascade including thyrotropin-releasing hormone (TRH), thyroid stimulating hormone (TSH) and subsequent thyroid hormones. It is well established that thyroid hormone status correlates with body weight and energy expenditure.^{6,7} Hyperthyroidism promotes a hypermetabolic state characterized by increased resting energy expenditure, weight loss and gluconeogenesis, while hypothyroidism is associated with hypometabolism characterized by reduced resting energy expenditure, weight gain and reduced gluconeogenesis.⁸ The relationship between thyroid hormones and obesity are closely.^{9–13} A low free triiodothyronine (FT3) level predicts weight gain in euthyroid persons,⁹ and low free thyroxine (FT4) or slightly elevated serum TSH levels are associated with an increase in the occurrence of obesity.^{10,11} On the other hand, obesity has also been associated with significant alterations in thyroid function,^{12,13} as previous studies have shown that the concentrations of serum TSH are increased in obese patients.^{12,13}

Previous studies have generated inconsistent results and involved mainly RYGB.^{14–17} The results showed that the concentrations of TSH decreased^{14,15} or remained steady^{16,17} after RYGB, while the concentrations of FT4 increased,¹⁷ decreased^{15,16} or remained steady.¹⁴ In addition, the mechanism and clinical implications of this hormonal alteration remain unknown. Recently, the impact of LSG on thyroid function has caused great interest, but related evidence is limited. Therefore, our aim was to evaluate the effect of LSG on thyroid function in patients with obesity and normal thyroid function.

Materials and Methods

Participants

In this observational cohort study, 109 participants, including 59 obese patients (body mass index [BMI] ≥ 27.5 kg/m²), 30 normal controls ($24.0 > \text{BMI} \geq 18.5$ kg/m²) and 20 overweight participants ($27.5 > \text{BMI} \geq 24.0$ kg/m²), were recruited from the Second Xiangya Hospital of Central South University (CSU) (Changsha, Hunan, China). LSG was performed on all obese patients who met the surgical criteria.⁴ The exclusion criteria for all the participants were a prior history of thyroid disease, abnormal thyroid hormone levels, a previous diagnosis of pituitary correlation disease such as pituitary tumor or hypopituitarism, therapy

with drugs that might affect the serum thyroid hormone levels in the past 3 months, type 1 diabetes mellitus, secondary diabetes, inflammation, infectious diseases, or other autoimmune disorders, pregnancy, and malignant diseases. None of the normal controls or overweight participants had diabetes mellitus or other medical problems, nor were they taking any drugs. This study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Second Xiangya Hospital of CSU. All participants provided informed consent for the study programme.

Study Design and Laboratory Analysis

Obese subjects underwent assessments (after 10 h of fasting overnight) within 1 week before and 6 and 12 months after surgery. Study physicians recorded the body height, weight and waist circumference before and 6 and 12 months after the therapy. BMI was calculated as the body weight (kg)/height (m)². Fasting venous blood samples were tested for fasting plasma glucose (FPG), fasting C-peptide (FCP), haemoglobin A_{1c} (HbA_{1c}), FT3, FT4 and TSH.

Assays

HbA_{1c} was measured using automated liquid chromatography (VARIANT II Hemoglobin Testing System; Bio-Rad Laboratories, Hercules, CA). FCP was measured by the chemiluminescence method (ADVIA Centaur; Siemens, Munich, Germany). FT3, FT4 and TSH were determined using a direct chemiluminescent immunoassay (Siemens Healthcare Diagnostics Inc., Berlin, Germany). The intra-assay coefficients of variation for FT3, FT4 and TSH were 2.6, 3.8, and 6.5%, respectively.

Surgical Procedure

All LSG surgeries were performed in the Department of Metabolic Surgery at the Second Xiangya Hospital of CSU.

Statistical Analysis

For the statistical analysis, SPSS version 20.0 (IBM Corporation, Chicago, IL) and GraphPad Prism 5 (GraphPad Software, San Diego, CA) were used. Data with Gaussian distribution are presented as the mean $\pm$ SEM, and data with skewed distribution are presented as the median (interquartile range), as determined using the Shapiro–Wilk test. To compare the changes from baseline to the postsurgical time points within groups, repeated

measures ANOVA with the Bonferroni post hoc test was performed. The relationship between the changes in thyroid function and other parameters was estimated by Pearson correlations. A multiple stepwise regression analysis was performed to identify the clinical factors associated with changes in thyroid function. Two-tailed $P < 0.05$ was considered statistically significant.

Results

The Concentrations of FT4 Were Decreased While Those of TSH Were Increased in Obese Patients

As shown in Table 1, a total of 109 participants were recruited for this study: 59 obese patients (23 females), with a mean age of 30.7 ± 1.3 years, and age- and sex-matched normal controls ($n=30$) and overweight participants ($n=20$). BMI, waist circumference, hip circumference, FPG, FCP and HbA_{1c} were significantly higher in the obese group than in the normal control group and in the overweight group (all $P = 0.000$). Thyroid hormone levels in all the participants were within the normal range at baseline. Compared to the normal control group, the concentrations of FT4 were decreased (15.08 ± 0.32 vs 17.71 ± 0.35 , $P = 0.000$) and those

of TSH were increased (2.25 ± 0.18 vs 1.72 ± 0.13 , $P = 0.033$) in the obese group, while the concentrations of FT3, FT4 and TSH were not different in the overweight group ($P > 0.05$). Compared to the overweight group, the concentrations of FT4 were also decreased (15.08 ± 0.32 vs 17.39 ± 0.43 , $P = 0.006$) in the obese group.

At baseline, as shown in Table 2, Pearson's analysis showed that BMI, waist circumference, hip circumference, FCP and HbA_{1c} had significant negative relationships with the concentrations of FT4 (all $P < 0.05$), while BMI, waist circumference and hip circumference were significantly positively related to the concentrations of TSH (all $P < 0.05$). As shown in Table 3, the multiple stepwise regression analysis indicated that BMI correlated with the concentrations of FT4 ($\beta = -0.373$, $P = 0.022$), while waist circumference was related to TSH ($\beta = 0.191$, $P = 0.047$).

The Concentrations of FT3 and TSH Decreased While Those of FT4 Increased in Obese Patients at 12 Months After LSG

As shown in Table 1, BMI, waist circumference, hip circumference, FPG, FCP and HbA_{1c} were all significantly decreased in the obese patients from baseline to 12 months

Table 1 Clinical Characteristics of Patients with Obesity at Baseline and 6 and 12 Months After LSG

	At Baseline			6 Months After LSG	12 Months After LSG
	Normal Control (n=30)	Overweight (n=20)	Obesity (n=59)	Obesity (n=59)	Obesity (n=59)
Age (years)	29.3±0.5	28.3±0.6	30.7±1.3	\	\
Gender (female/male)	16/14	10/10	23/36	\	\
T2DM (with/without)	\	\	38/21	\	\
Duration of T2DM (months)	\	\	3 (1–22.5)	\	\
BMI (kg/m ²)	21.0±0.3	25.2±0.2 ***	40.2±0.9 ***####	29.2±0.5 \$\$\$	27.3±0.4 \$\$\$
Waist (cm)	75.4±1.1	84.5±1.3 ***	123.0±1.9 ***####	97.7±1.3 \$\$\$	93.5±1.02 \$\$\$
Hip (cm)	91.2±0.8	98.6±1.1 ***	122.6±1.8 ***####	105.1±1.2 \$\$\$	101.3±0.9 \$\$\$
FPG (mmol/L)	4.5±0.1	4.7±0.1	7.1±0.4 ***####	4.6±0.1 \$\$\$	4.6±0.1 \$\$\$
FCP (pmol/L)	284.3±16.3	489.9±46.4 **	1140.6±68.6 ***####	602.7±27.9 \$\$\$	526.5±28.2 \$\$\$
HbA _{1c} (%)	5.2±0.1	5.3±0.2	7.3±0.3 ***####	5.3±0.1 \$\$\$	5.3±0.1 \$\$\$
FT3 (pmol/L)	5.05±0.11	5.23±0.10	5.03±0.08	4.66±0.10 \$	4.83±0.06 \$
FT4 (pmol/L)	17.71±0.35	17.39±0.43	15.80±0.32 ***##	16.54±0.28 \$	17.40±0.52 \$
TSH (mIU/L)	1.72±0.13	1.95±0.15	2.25±0.18 *	1.55±0.10 \$\$\$	1.67±0.11 \$\$\$

Notes: Data are presented as the mean ± SEM and the median (25th–75th percentile); * $P < 0.05$ compared with the normal control group; ** $P < 0.01$ compared with the normal control group; *** $P < 0.001$ compared with the normal control group; ## $P < 0.01$ compared with the overweight group; #### $P < 0.001$ compared with the overweight group; \$ $P < 0.05$ compared with obesity at baseline; \$\$\$ $P < 0.01$ compared with obesity at baseline; \$\$\$\$ $P < 0.001$ compared with obesity at baseline.

Abbreviations: BMI, body mass index; FCP, fasting C-peptide; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA_{1c}, haemoglobin A_{1c}; LSG, laparoscopic sleeve gastrectomy; TSH, thyroid stimulating hormone.

Table 2 Correlation Between Thyroid Function and the Clinical Data of All Subjects at Baseline

	FT4		TSH	
	r	p	r	p
BMI	-0.373	0.000	0.177	0.048
Waist	-0.342	0.000	0.191	0.047
Hip	-0.362	0.000	0.189	0.049
FPG	-0.012	0.904	0.000	0.996
FCP	-0.274	0.004	0.135	0.161
HbA _{1c}	-0.266	0.005	0.033	0.731

Note: Boldface text indicates a significant linear relationship.

Abbreviations: BMI, body mass index; FCP, fasting C-peptide; FPG, fasting plasma glucose; FT4, free thyroxine; HbA_{1c}, haemoglobin A_{1c}; TSH, thyroid stimulating hormone.

Table 3 Multiple Stepwise Regression Analysis of Thyroid Function and the Clinical Data of All Subjects at Baseline

Dependent Variables	Independent Variables	β	t	P
FT4	BMI	-0.373	2.398	0.022
TSH	Waist	0.191	2.008	0.047

Note: Boldface text indicates a significant linear relationship.

Abbreviations: FT4, free thyroxine; TSH, thyroid stimulating hormone.

after LSG (all $P = 0.000$). Thyroid hormone levels in all the obese patients were within the normal range at baseline and 12 months after LSG. As shown in [Figure 1A](#), the concentrations of FT3 were decreased significantly at 6 months and 12 months after LSG compared to those at baseline (4.66 ± 0.10 , 4.83 ± 0.06 vs 5.03 ± 0.08 ; $P = 0.001$, $P = 0.023$, respectively). As shown in [Figure 1B](#), the concentrations of FT4 were increased significantly at 6 months and 12 months after LSG compared to those at baseline (16.54 ± 0.28 , 17.40 ± 0.52 vs 15.80 ± 0.32 ; $P = 0.034$, $P = 0.004$, respectively). As shown in [Figure 1C](#), the concentrations of TSH were

decreased significantly at 6 months and 12 months after LSG compared to those at baseline (1.55 ± 0.10 , 1.67 ± 0.11 vs 2.25 ± 0.18 ; $P = 0.000$, $P = 0.000$, respectively).

The Decrease in FCP Was Related to the Decline in FT3 and TSH During the 12 Months After LSG

As shown in [Table 4](#), Pearson's analysis showed that the declines in FPG and HbA_{1c} had significant negative relationships with the decrease in FT3 during the 12 months after LSG ($P = 0.018$, $P = 0.005$, respectively), while the decrease in FCP had a positive relationship with the decrease in FT3 ($P = 0.000$). The decline in hip circumference had a significant negative relationship with the increase in FT4 during the 12 months after LSG ($P = 0.18$), and the decline in FCP had a significant positive relationship with the decrease in TSH ($P = 0.041$). As shown in [Table 5](#), the multiple stepwise regression analysis indicated that the decrease in FCP was related to the decline in FT3 ($\beta = 0.365$, $P = 0.006$) and TSH ($\beta = 0.272$, $P = 0.045$) during the 12 months after LSG.

Discussion

In a population of patients with obesity and normal thyroid function, we found that the concentrations of FT4 were decreased while those of TSH were increased compared to normal controls. Moreover, the concentrations of FT3 and TSH decreased while those of FT4 increased in obese patients at 12 months after LSG. The decrease in FCP was related to the decline in FT3 and TSH during the 12 months after LSG. Previous studies have reported mainly RYGB.^{14–17} Since all the subjects underwent LSG, our research adds evidence of the effect of LSG on thyroid function in obese patients.

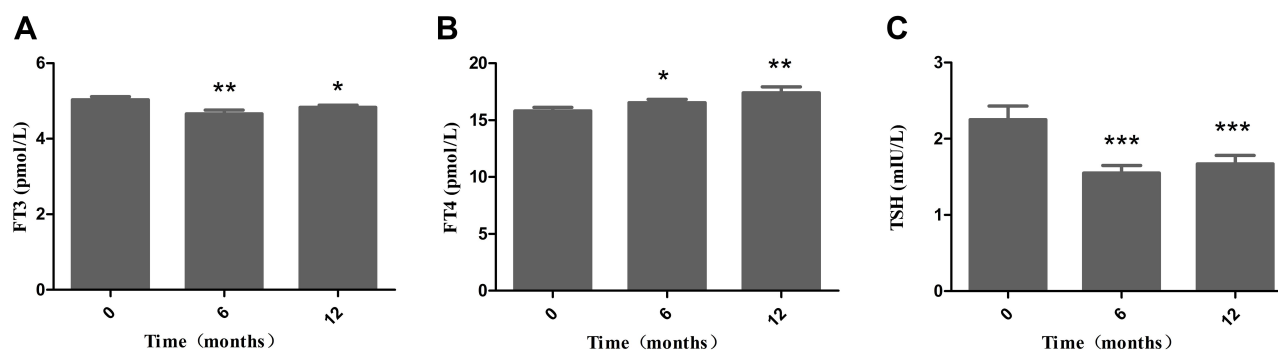


Figure 1 Alterations ($\pm$ SEM) in the levels of FT3 (A) FT4 (B) and TSH (C) in obese patients during the 12 months after LSG. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with those at baseline.

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; LSG, laparoscopic sleeve gastrectomy; TSH, thyroid stimulating hormone.

Table 4 Correlation Between Changes in Thyroid Function and the Clinical Data of Obese Subjects During the 12 Months After LSG

	Δ FT3		Δ FT4		Δ TSH	
	r	p	r	p	r	p
Δ BMI	0.191	0.148	-0.161	0.222	-0.131	0.324
Δ Waist	0.197	0.135	-0.085	0.522	-0.134	0.311
Δ Hip	0.125	0.345	-0.213	0.018	-0.180	0.174
Δ FPG	-0.308	0.018	0.208	0.115	-0.135	0.309
Δ FCP	0.463	0.000	0.091	0.495	0.269	0.041
Δ HbA _{1c}	-0.374	0.005	0.048	0.724	-0.192	0.157

Note: Boldface text indicates a significant linear relationship.

Abbreviations: BMI, body mass index; FCP, fasting C-peptide; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA_{1c}, haemoglobin A_{1c}; LSG, laparoscopic sleeve gastrectomy; TSH, thyroid stimulating hormone.

Table 5 Multiple Stepwise Regression Analysis of Thyroid Function and Clinical Data During the 12 Months After LSG

Dependent Variables	Independent Variables	β	t	P
Δ FT3	Δ FCP	0.365	2.850	0.006
Δ TSH	Δ FCP	0.272	2.056	0.045

Note: Boldface text indicates a significant linear relationship.

Abbreviations: FCP, fasting C-peptide; FT3, free triiodothyronine; LSG, laparoscopic sleeve gastrectomy; TSH, thyroid stimulating hormone.

In our study, the concentrations of FT4 were decreased and those of TSH were increased in obese individuals compared to normal controls (Table 1). Moreover, the concentrations of FT4 were also decreased in the obese group compared to the overweight group (Table 1). Correlation analysis suggested that indicators of obesity, including BMI and waist and hip circumferences, were all closely related to FT4 and TSH (Tables 2 and 3). The mechanism and the clinical implications of TSH elevation in obesity remain unknown. As a cause of elevated TSH concentrations in obesity, the adipocyte-derived hormone leptin has been demonstrated to alter the hypothalamic pituitary axis compensatory activation.^{18,19} TSH receptors are less expressed on the white adipose tissue of obese individuals.²⁰ Moreover, TSH receptors in brown adipose tissue play a direct role in the regulation of thermogenesis.²¹ This reduction in TSH receptor expression may induce the downregulation of thyroid hormone receptors and thyroid hormone action, thereby further increasing TSH concentrations and constituting a condition of peripheral thyroid hormone resistance.²⁰ Although thyroid function in obese patients is different from that in normal controls, it has been suggested that

reference values for TSH may be inadequate to define hypothyroidism in persons with morbid obesity.²²

Altered thyroid function and the effect of metabolic surgery on postoperative thyroid function evolution are still not fully understood. Our data show that the concentrations of FT3 and TSH decreased while those of FT4 increased in obese patients at 12 months after LSG (Table 1 and Figure 1). Most,^{15,23,24} but not all,^{16,25} studies evaluating the evolution of TSH after metabolic surgery have also found a decrease in circulating TSH concentrations after intervention. Similarly, the changes in FT3 and FT4 were also inconsistent after metabolic surgery. Most studies evaluating the effect of metabolic surgery on thyroid hormones showed a significant decrease in FT3.^{14,25,26} Thyronine is mainly produced in peripheral tissues by outer-ring deiodination of thyroxine by the action of iodothyronine deiodinases.²⁷ The gene for type I iodothyronine 5'-deiodinase (D1) is upregulated and its activated is stimulated in adipose tissue of obese humans.²⁸ Evidence shows the decline in FT3 concentration after metabolic surgery is related to the decrease in D1 activity,²⁹ which could also explain the reduced level of FT3 instead of increase when TSH was decreased after metabolic surgery in our research. On the other hand, the impact of bariatric surgery on FT4 levels is more controversial, with different studies reporting decreasing,²⁶ stable,^{14,23,30} or increasing^{17,25} levels after metabolic surgery. In the above studies, we found that the operations performed on obese patients covered RYGB,^{14,26} SG²³ or gastric banding,²⁵ and one study even included two or more surgical procedures.^{17,30} Furthermore, the differences between the above studies could be due not only to the types of metabolic surgery performed but also to the characteristics of the control group and the studied patients or to the different statistical powers of the studies. Our study could supplement the effects of LSG on thyroid function in euthyroid patients with obesity.

Moreover, our correlation analysis suggested that the decline in FCP was related to the decrease in FT3 and TSH (Tables 4 and 5), which has never been found before. The level of C-peptide could reflect the level of endogenous insulin.³¹ A positive correlation between the concentrations of insulin and TSH has been observed in obese patients.³² Additionally, increased FCP could predict the presence of insulin resistance,³³ and LSG can relieve insulin resistance.³⁴ Evidence shows that thyroid function may be influenced by insulin resistance in euthyroid obese subjects.³⁵ Combined with our data, these results suggest

that the decrease in FT3 and TSH in thyroid hormones after LSG may be related to the change in FCP or insulin resistance.

Although an association between metabolic surgery and changes in thyroid hormones has been found, the underlying reasons responsible for this association are not yet well understood and may be explained by several mechanisms. First, the change in thyroid hormones is probably mediated by weight loss, while appears to be not an intrinsic effect of LSG. Decreased circulating TSH has been found to be independently associated with massive body weight loss after surgery.²⁴ Weight loss is accompanied by a significant reduction in total energy expenditure due to a decrease in both resting and non-resting energy expenditure, and losses in both fat mass and fat-free mass induced by metabolic surgery may influence the thyroid function.³⁶ It was worth noting that the thyroid function of obese patients had been changed at 12 months after lifestyle treatment to weight loss,³⁷ while not changed at 3 months.³⁸ Second, as the key component of obesity, adipose tissue can secrete a mass of leptin, which has been proposed to have a stimulatory impact on thyroid activity and thereby increase TSH and FT3 secretion.³⁹ As leptin levels declined after metabolic surgery,⁴⁰ weight loss induced by surgery could cause a decline in the concentration of TSH and FT3. Third, there may also be an added impact of metabolic surgery in addition to weight reduction. This standpoint was supported by evidence that a reduction in TSH concentrations did not correlate with the percentage of excess weight loss in some studies.^{14,23} This phenomenon is similar to other effects of bariatric surgery, such as T2DM remission, which is connected not only to weight loss but also to the surgery itself through other mechanisms, including the mediation of gastrointestinal hormones. With regard to this aspect, ghrelin modulates pituitary TSH cells and decreases the level of serum TSH, consequently changing thyroid morphology and function by reducing the T4 hormone level in the serum.⁴¹ Therefore, a reduction in ghrelin succeeding LSG⁴² would contribute to a decrease in TSH. Finally, organochlorine compounds released into the serum during lipid mobilization subsequent to weight loss play a role in T3 and FT3 reduction.⁴³

In summary, our study showed that obesity was closely related to thyroid function. LSG promoted a significant decrease in FT3 and TSH and a significant increase in FT4 in euthyroid patients with obesity after the procedure. The decline in FCP was related to the decrease in FT3 and TSH.

Abbreviations

BMI, body mass index; CSU, Central South University; D1, type I iodothyronine 5'-deiodinase; FCP, fasting C-peptide; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA_{1c}, haemoglobin A_{1c}; LSG, laparoscopic sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone.

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Disclosure

The authors report no conflicts of interest for this work.

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