

Association Between Serum Testosterone Levels and Cutibacterium Skin Load in Patients Undergoing Elective Shoulder Arthroplasty

A Cohort Study

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Background: Cutibacterium periprosthetic joint infections are important complications of shoulder arthroplasty. Although it is known that these infections are more common among men and that they are more common in patients with high levels of Cutibacterium on the skin, the possible relationship between serum testosterone levels and skin Cutibacterium levels has not been investigated.

Methods: In 51 patients undergoing shoulder arthroplasties, total serum testosterone, free testosterone, and sex hormone binding globulin levels obtained in the clinic before the surgical procedure were compared with the levels of Cutibacterium on the skin in clinic, on the skin in the operating room prior to the surgical procedure, and on the dermal wound edge of the incised skin during the surgical procedure.

Results: Clinic skin Cutibacterium loads were strongly associated with both clinic free testosterone levels (τ , 0.569; $p < 0.001$) and total serum testosterone levels (τ , 0.591; $p < 0.001$). The prepreparation skin and wound Cutibacterium levels at the time of the surgical procedure were also significantly associated with both the clinic total serum testosterone levels ($p < 0.001$) and the clinic free testosterone levels ($p < 0.03$). A multivariate analysis demonstrated that serum testosterone was an independent predictor of high skin Cutibacterium loads, even when age and sex were taken into account. Patients taking supplemental testosterone had higher free testosterone levels and tended to have higher skin Cutibacterium loads. Patients who underwent the ream-and-run procedure had higher total and free testosterone levels and higher skin Cutibacterium loads.

Conclusions: Testosterone levels are predictive of skin Cutibacterium levels in patients undergoing shoulder arthroplasty. This relationship deserves further investigation both as a risk stratification tool and as a potential area for intervention in reducing shoulder periprosthetic joint infection.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Periprosthetic joint infection (PJI) of the shoulder is a devastating complication for the patient and is costly for the health-care system¹⁻³. It is most often caused by commensal organisms found in healthy skin, particularly *Cutibacterium acnes*³⁻⁶. Cutibacterium are slow-growing, gram-positive rods that colonize pilosebaceous units and sebaceous glands of the skin⁷⁻¹¹. Cases of Cutibacterium PJI are difficult to anticipate before revision arthroplasty because they are not associated with the clinical or inflammatory laboratory findings typical of infections from other organisms⁹.

Because Cutibacterium is commonly found in large amounts on the surface and in the dermis of the skin overlying the shoulder, this bacterium can inoculate the shoulder arthroplasty field after the skin is surgically incised¹² and put the patient at risk for PJI. Over 70% of culture specimens of the unprepared skin surface in patients undergoing elective shoulder arthroplasty are positive for Cutibacterium^{13,14}. There is a strong association between Cutibacterium loads on the skin surface and the positivity of deep-tissue cultures. Preoperative cultures of the unprepared skin surface are

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (<http://links.lww.com/JBJSOA/A341>).

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TABLE I Demographic Characteristics, Testosterone Levels, SHBG Levels, and Culture Results for 51 Patients Undergoing Elective Arthroplasty*

Subject No.	Age (yr)	Sex	BMI (kg/m ²)	Race	ASA Class	Type of Surgery	Serum Testosterone† (ng/mL)	SHBG‡ (nmol/L)	Free Testosterone § (pg/mL)	Clinic Values				Cutibacterium Values	
										Cutibacterium	Coagulase-Negative Staphylococcus	Other Bacteria	Percentage Cutibacterium	Prepreparation	Wound
1	48.2	M	29	Asian	2	Other	2.9	16	75	1	0	3	25%	0.1	0
2	67.7	F	49	White	2	TSA	0.4	13#	10**	1	0	2	33%	1	0
3	63.8	F	22	White	3	TSA	0.1	143**	0	0	0	1	0%	0	0
4	56.1	F	44	Black	3	RSA	0.1	54	0	0	0	2	0%	0	0
5	50.0	M	31	White	3	TSA	2.6	22	59	2	0	3	40%	2	0
6	66.1	F	38	White	2	TSA	0.1	28	0	0	0	1	0%	0.1	0
7	67.4	F	19	White	2	RSA	0.1	118	0	1	1	0	50%	0	0
8	81.3	M	27	White	3	RSA	2.4	35	45	1	0	1	50%	2	0
9	65.6	F	33	White	2	TSA	0.1	28	0	0	2	1	0%	0	0
10	69.9	F	42	White	3	TSA	0.1	109	0	0.1	1	1	5%	0.1	0
11	49.0	M	24	White	2	Ream-and-run	2.9	48	42	2	0	1	67%	2	0
12	60.2	F	36	White	3	RSA	0.1	23	0	0	0	3	0%	0	0
13	59.4	F	28	White	3	TSA	0.3	34	5	0.1	0.1	0	50%	0	0
14	74.8	F	27	White	3	TSA	0.1	159**	0	0	1	0	0%	0	0
15††	69.6	M	43	White	2	Ream-and-run	4.5	16	135	1	0	3	25%	2	0
16	53.1	M	30	White	2	Ream-and-run	2.2#	22	48	1	0	1	50%	2	1
17	58.9	M	42	White	2	TSA	2#	30	41	0	0	1	0%	0	0
18	58.8	F	35	White	2	RSA	0.1	79	0	0.1	0	4	2%	0	0
19	45.3	M	29	White	1	Ream-and-run	2.5	28	55	2	1	0	67%	2	2
20	74.9	M	36	White	3	TSA	2.6	36	48	2	1	0	67%	0	0
21	71.1	M	43	Native American	3	RSA	4.4	35	85	2	0	3	40%	2	0
22	68.7	M	30	Asian	2	TSA	1.4#	21	32#	0.1	0	1	9%	0.1	0
23	60.9	F	35	White	3	RSA	0.1	72	0	0.1	2	0	5%	0	0
24	58.7	F	37	White	2	RSA	0.1	54	0	0.1	0	1	9%	0	0
25	32.2	M	23	Black	2	Ream-and-run	5.1	36	103	4	0	0	100%	2	0
26	73.1	M	26	White	2	RSA	3.8	63	50	2	0	1	67%	1	0
27	68.7	M	29	White	3	RSA	0.7#	19	17#	1	0	1	50%	0.1	0
28	71.4	F	23	White	3	TSA	0.3	97	0	0.1	0	1	9%	0	0
29	83.8	M	32	White	3	TSA	0.5#	23	11#	0	0	1	0%	0	0
30	55.8	M	27	White	2	Ream-and-run	3.1	48	48	2	0	1	67%	1	2
31	45.8	M	30	White	2	Other	5.4	53	81	1	0.2	1	45%	1	1
32	63.2	F	31	White	3	Other	0.3	72	3	1	0	3	25%	0	0
33	65.1	M	26	White	1	TSA	4.1	53	59	2	0	3	40%	1	0
34	79.4	M	30	White	2	RSA	3.7	73	41	3	0	3	50%	1	0
35	74.6	M	23	White	2	RSA	3.1	70	35	1	0	1	50%	0	0
36	77.9	M	31	White	4	RSA	3.3	43	55	3	0	1	75%	2	2
37	70.0	M	31	White	2	Other	2.1#	37	39	2	0	1	67%	4	0
38††	32.4	M	31	White	2	Ream-and-run	8.8	12	296**	3	0	3	50%	4	2
39	62.7	M	26	White	2	Other	3.5	48	56	4	0.2	0	95%	2	1
40††	60.1	M	30	White	3	Ream-and-run	6.9	27	168**	2	0	1	67%	2	0
41	61.1	F	21	White	3	RSA	0.1	25	0	0	0	1	0%	0	0
42	62.9	F	29	White	3	TSA	0.1	53	0	1	0	2	33%	0	0
43	37.5	F	21	White	1	Ream-and-run	0.4	73	4	1	0	1	50%	2	2
44	63.2	M	29	White	2	Ream-and-run	2.5	22	61	2	2	0	50%	2	2

continued

TABLE I (continued)

Subject No.	Age (yr)	Sex	BMI (kg/m ²)	Race	ASA Class	Type of Surgery	Serum Testosterone† (ng/mL)	SHBG‡ (nmol/L)	Free Testosterone § (pg/mL)	Clinic Values				Cutibacterium Values	
										Cutibacterium	Coagulase-Negative Staphylococcus	Other Bacteria	Percentage Cutibacterium	Prepreparation	Wound
45	62.0	M	30	White	2	Ream-and-run	5.6	43	98	1	0	1	50%	2	0
46††	59.0	M	32	White	2	Ream-and-run	4.4	10	141	2	0	1	67%	1	0
47	78.5	M	29	White	2	RSA	2.8	39	50	3	0	3	50%	2	3
48	56.9	M	24	White	2	Other	3.9	33	80	2	0	0	100%	4	0
49	73.9	F	27	White	2	Ream-and-run	0.3	60	4	0.1	0	0	100%	1	0
50	80.1	M	37	White	3	RSA	1.6#	21	39	2	4	0	33%	2	0
51††	59.3	M	37	White	3	Other	4.8	23	118	1	0	1	50%	1	2
Mean†††	62.9 ± 11.8 (32.2 to 83.8)	60% male (19 to 49)	31 ± 6 (19 to 49)		2.4 ± 0.6 (1.0 to 4.0)		2.2 ± 2.1 (0.1 to 8.8)	47.0 ± 32.5 (10.0 to 159.0)	45.8 ± 55.1 (0.0 to 296.0)	1.2 ± 1.1 (0.0 to 4.0)	0.3 ± 0.8 (0.0 to 4.0)	1.3 ± 1.1 (0.0 to 4.0)	0.4 ± 0.3 (0.0 to 1.0)	1.0 ± 1.1 (0.0 to 4.0)	0.4 ± 0.8 (0.0 to 3.0)

*TSA = anatomic total shoulder arthroplasty, and RSA = reverse shoulder arthroplasty. †The normal range is 2.4 to 9.2 ng/dL for men and 0.1 to 0.6 ng/dL for women. ‡The normal range is 13 to 90 nmol/L for men and 17 to 136 nmol/L for women. §The normal range is 38.7 to 147 pg/mL for men and 0.6 to 8.7 pg/mL for women. #Below normal range for sex. **Above normal range for sex. ††Patients 15, 38, 40, 46, and 51 reported receiving supplemental testosterone. †††The values are given as the mean and the standard deviation, with the range in parentheses.

predictive of whether the freshly incised dermal edge is likely to be positive for Cutibacterium¹⁵. The preoperative load of Cutibacterium on skin surface cultures obtained in the clinic is predictive of a culture-positive PJI^{16,17}.

Male sex is a strong risk factor for Cutibacterium PJI^{5,6,18-22}. Male sex is also strongly associated with the load of Cutibacterium on the unprepared skin surface in the area where an anterior deltopectoral incision is usually made for shoulder arthroplasty¹⁴; thus, there is reason to believe that sex hormone levels—specifically those of testosterone—may be predictive of the load of Cutibacterium on the skin in the area of the arthroplasty incision. Testosterone may exist free in the serum or may be bound to sex hormone binding globulin (SHBG), a glycoprotein primarily produced in the liver. The sum of bound and free testosterone is referred to as total testosterone.

To our knowledge, the relationship between testosterone levels and the load of Cutibacterium on the skin surface of the anterior shoulder has not been previously investigated in patients undergoing shoulder arthroplasty. Because of the clinical importance of Cutibacterium PJI and the well-established relationship between Cutibacterium PJI and the skin load of Cutibacterium, we tested the hypothesis that serum testosterone levels are strongly related to the loads of Cutibacterium in concurrently collected culture specimens from the unprepared skin surface obtained in the clinic from patients undergoing an elective shoulder joint replacement. Because of prior reports suggesting that patients electing the ream-and-run procedure may be at increased risk for Cutibacterium PJI^{14,17}, we also tested the hypothesis that testosterone levels and skin Cutibacterium loads are higher in patients undergoing ream-and-run procedures than in patients undergoing other types of shoulder arthroplasties. Finally, we tested the hypothesis that patients taking supplemental testosterone would have higher testosterone levels and higher loads of Cutibacterium on the unprepared skin surface than patients not taking supplemental testosterone.

Materials and Methods

Between April 1 and November 30, 2020, 51 patients undergoing elective shoulder arthroplasty were offered the opportunity to participate, provided consent, and were enrolled in this prospective clinical cohort study performed in the outpatient clinic associated with our medical center. Patients were excluded if they had a history of shoulder septic arthritis, antibiotic use within 3 months prior to the surgical procedure, or recent treatment for acne or lacked fluency in English. Sixty-three patients were screened and approached. Seven patients were ineligible due to recent antibiotic use. Fifty-six patients provided consent and 5 patients withdrew, leaving 51 patients for the study. Patient

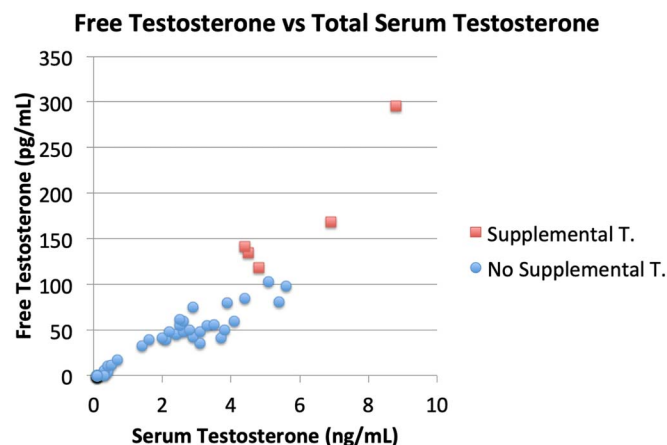


Fig. 1
Clinic free testosterone compared with total serum testosterone for 51 patients undergoing an elective shoulder arthroplasty. Patients acknowledging taking supplemental testosterone are indicated by red squares. Patients not acknowledging taking supplemental testosterone are indicated by blue circles.

TABLE II Association Between Testosterone Levels and Cutibacterium Levels on the Skin and Wound Edge*

	Clinic Skin Cutibacterium Levels		Operating Room Cutibacterium Levels			
			Prepreparation Skin		Wound Edge	
	Tau	P Value	Tau	P Value	Tau	P Value
Free testosterone	0.569	<0.001	0.581	<0.001	0.304	0.010
Total serum testosterone	0.591	<0.001	0.537	<0.001	0.269	0.022
SHBG	-0.125	0.242	-0.282	0.009	-0.090	0.439

*Kendall tau rank correlation.

ream-and-run procedure were compared with the results for the 38 patients undergoing other types of arthroplasties.

Finally, the serum testosterone levels and skin loads of Cutibacterium of patients who acknowledged taking supplemental testosterone were compared with those who did not acknowledge taking supplemental testosterone.

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Results

Fifty-one patients participated in this study (Table I). Sixty percent were male and the mean age (and standard deviation) was 63 ± 12 years (range, 32 to 84 years). The mean body mass index (BMI) was 31 ± 6 kg/m² (range, 19 to 49 kg/m²); the mean American Society of Anesthesiologists (ASA) class was 2 ± 1 (range, 1 to 4). The preponderant race was White. Thirteen patients underwent a ream-and-run procedure, 15 patients underwent anatomic total shoulder arthroplasty, 16 patients underwent reverse shoulder arthroplasty, and 7 patients underwent other types of arthroplasties. Ten percent (5 of 51) of the patients reported taking supplemental testosterone. The mean total serum testosterone was 3.4 ± 1.7 ng/mL (range, 0.5 to 8.8 ng/mL) for men (normal range, 2.4 to 9.2 ng/mL) and 0.2 ± 0.1 ng/mL (range, 0.1 to 0.4 ng/mL) for women (normal range, 0.1 to 0.6 ng/mL) (difference, $p < 0.001$). The mean free testosterone was 72 ± 54 pg/mL (range, 0 to 296 pg/mL) for men (normal range, 39 to 147 pg/mL) and 1 ± 3 pg/mL (range, 0 to 10 pg/mL) for women (normal range, 0.6 to 8.7 pg/mL) (difference, $p < 0.001$). Free testosterone was highly correlated with total serum testosterone ($R = 0.925$) (Fig. 1). The mean SHBG was 35 ± 16 nmol/L (range, 10 to 73 nmol/L) for men (normal range, 13 to 90 nmol/L) and 68 ± 42 nmol/L (range, 13 to 159 nmol/L) for women (normal range, 17 to 136 nmol/L) (difference, $p = 0.003$).

Swab specimens had mean Cutibacterium specimen values of 1.2 ± 1.1 (range, 0 to 4) obtained in the clinic, 1.0 ± 1.1 (range, 0 to 4) obtained after Hibiclens showers and before the skin preparation in the operating room, and 0.4 ± 0.8

(range, 0 to 3) for the wounds after administration of intravenous antibiotic prophylaxis (Rocephin and vancomycin).

The first hypothesis was that testosterone levels are strongly related to the loads of Cutibacterium in concurrently collected culture specimens from the unprepared skin surface obtained in the clinic from patients undergoing an elective shoulder arthroplasty.

Clinic skin Cutibacterium loads were strongly correlated with both clinic free testosterone levels (tau, 0.569; $p < 0.001$) and total serum levels (tau, 0.591; $p < 0.001$) (Figs. 2 and 3, Table II). Multivariate analysis demonstrated that serum testosterone level was an independent predictor of Cutibacterium values ≥ 1 when age and sex were taken into account (Table III).

The prepreparation skin and wound Cutibacterium levels at the time of the surgical procedure were also significantly associated with both the clinic total serum and the clinic free testosterone levels (Table II). SHBG had a negative and weaker association with skin and wound edge Cutibacterium values compared with the free and total testosterone levels.

The second hypothesis was that serum testosterone levels are higher in patients who undergo a ream-and-run procedure than in patients who undergo other types of shoulder arthroplasties.

Patients who underwent the ream-and-run procedure, compared with patients who underwent other types of arthroplasties, had significantly higher total serum testosterone levels (3.8 ± 2.4 compared with 1.7 ± 1.7 ng/mL; $p = 0.011$) and

TABLE III Multivariate Analysis of Factors Associated with a Skin Cutibacterium Value of ≥ 1

Variable	Odds Ratio*	P Value
Age†	0.98 (0.88 to 1.08)	0.663
Male sex‡	0.32 (0.01 to 20.27)	0.588
Serum testosterone in ng/mL†	9.68 (1.05 to 89.36)	0.045

*The values are given as the odds ratio, with the 95% confidence interval in parentheses. †Per 1-unit increase. ‡Reference group: female sex.

TABLE IV Demographic Characteristics, Testosterone Levels, SHBG Levels, and Culture Results for 51 Patients Undergoing Elective Arthroplasty: Either the Ream-and-Run Procedure or Other Types of Arthroplasties

	Procedure		P Value*
	Ream-and-Run	Other Arthroplasties	
No. of patients	13	38	
Age† (yr)	53 ± 13	66 ± 9	0.005
Male sex	85%	55%	
BMI† (kg/m ²)	29 ± 5	32 ± 7	0.188
ASA class†	1.9 ± 0.5	2.5 ± 0.6	0.001
Supplemental testosterone	31%	3%	
Serum testosterone† (ng/mL)	3.8 ± 2.4	1.7 ± 1.7	0.011
SHBG† (nmol/L)	34.2 ± 19.2	51.4 ± 35.0	0.033
Free testosterone† (pg/mL)	92.5 ± 79.6	29.8 ± 31.9	0.016
Clinic values†			
Cutibacterium	1.8 ± 1.0	1.0 ± 1.1	0.036
Coagulase-negative Staphylococcus	0.2 ± 0.6	0.3 ± 0.8	0.646
Other bacteria	1.0 ± 1.0	1.4 ± 1.1	0.279
Percentage of Cutibacterium	62% ± 20%	32% ± 29%	<0.0001
Operating room values for Cutibacterium†			
Prepreparation	1.9 ± 0.8	0.8 ± 1.1	<0.0001
Wound	0.8 ± 1.0	0.2 ± 0.7	0.055

*Unpaired t test. †The values are given as the mean and the standard deviation.

free testosterone levels (92.5 ± 79.6 compared with 29.8 ± 31.9 pg/mL; $p = 0.016$), as well as significantly higher clinic skin loads of Cutibacterium (1.8 ± 1.0 compared with 1.0 ± 1.1 ; $p = 0.036$) and prepreparation skin loads of Cutibacterium (1.9 ± 0.8 compared with 0.8 ± 1.1 ; $p < 0.001$) than patients undergoing other types of arthroplasties (Table IV).

The third hypothesis was that patients taking supplemental testosterone had higher serum testosterone levels and higher loads of Cutibacterium on the unprepared skin surface than patients not taking supplemental testosterone.

Five patients acknowledged taking supplemental testosterone (Fig. 1). Their mean serum testosterone level was 5.9 ± 1.9 ng/mL (range, 4.4 to 8.8 ng/mL) compared with 2.2 ± 2.1 ng/mL (range, 0.1 to 8.8 ng/mL) for those not acknowledging taking testosterone supplements ($p = 0.007$). Their mean free testosterone levels were 171.6 ± 71.8 pg/mL (range, 118 to 296 pg/mL) compared with 32.2 ± 31.0 pg/mL (range, 0.0 to 103.0 pg/mL) for those not acknowledging taking testosterone supplements ($p = 0.012$). The mean skin Cutibacterium values for the patients who took supplemental testosterone (1.8 ± 0.8 [range, 1 to 3]) averaged 50% higher than the values for patients who did not take supplemental testosterone (1.2 ± 1.1 [range, 0 to 4]), but with the numbers of subjects available, this difference was not significant ($p = 0.174$). Notably, of the 9 patients with serum testosterone levels of ≥ 4.4 ng/mL, 5 were male and acknowledged the use of supplemental testosterone and 4 were male and did not ac-

knowledge the use of supplemental testosterone. Four of the 5 patients acknowledging the use of supplemental testosterone underwent a ream-and-run arthroplasty.

Discussion

This investigation is unique in that it demonstrates that serum testosterone levels are strongly associated with the load of Cutibacterium on the skin of patients undergoing an elective shoulder arthroplasty and that these testosterone levels are predictive independent of patient sex and age. These results are of clinical importance because they suggest hormonal control of the levels of Cutibacterium on the skin. Also, these results encourage further investigation into use of serum testosterone levels as a risk stratification tool as well as a potential target for intervention for preoperative prophylaxis^{16,17}.

As pointed out earlier, it is well known that male patients are at a greater risk for Cutibacterium PJIs than their female counterparts. Our study suggests a hormonal basis for this effect: higher serum testosterone levels are associated with an increased load of Cutibacterium in the skin. Prior studies have shown that male sex and androgenic steroids such as testosterone affect the size of sebaceous glands that harbor Cutibacterium^{7,26-31}. Our study suggests that levels of free and total testosterone obtained at a preoperative visit may have use in predicting the load of Cutibacterium in the skin of patients undergoing a shoulder arthroplasty.

This study also indicates that supplemental testosterone leads to higher levels of total and free testosterone and that higher levels of serum testosterone are associated with higher levels of Cutibacterium on the anterior skin of the shoulder. We could find only 1 other study showing that self-administered high doses of testosterone and other anabolic steroids increase the Cutibacterium concentration on the skin; this was a 1988 investigation of Finnish power athletes³².

This study had some limitations. The sample consisted of only 51 patients; as a result, the significance of some of the effects may not have been demonstrated. It was not possible to be certain whether patients accurately reported whether they were taking supplemental androgenic hormones. We did not collect data on the dosages of supplemental testosterone. With the limited follow-up time, we were unable to determine whether testosterone levels were actually correlated with the occurrence of subsequent Cutibacterium PJIs³³. Although free testosterone had the highest association with skin Cutibacterium loads, free testosterone levels can vary throughout the day; as a result, standardization of the time that the blood sample is obtained may be necessary. Although our study suggests that levels of free and total testosterone obtained at a preoperative visit may have use in predicting the load of Cutibacterium in the skin of patients undergoing shoulder arthroplasty, we do not have sufficient information to recommend the discontinuation of supplemental testosterone prior to arthroplasty or the effectiveness of testosterone blockers.

In conclusion, this research shows that serum testosterone levels are independently predictive of skin Cutibacterium levels even when patient sex and age are taken into account. In turn, higher skin loads of Cutibacterium are known to be strongly associated with Cutibacterium PJI. If these associations are supported by additional clinical research, serum testosterone levels may be useful in stratifying patients for the risk of Cutibacterium PJI. ■

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