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Calciphylaxis arising following bariatric surgery: A case series

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INTRODUCTION

Calciphylaxis is a rare and serious disease that leads to vascular calcification and cutaneous necrosis. This highly morbid condition is characterized by painful nodules and ulcers, which may become superinfected. Calciphylaxis has a predilection for patients with end-stage renal disease (ESRD), with prevalence ranging from 1% to 4% in this population; however, a nonnephrogenic subtype, usually associated with warfarin use, exists.[1]

The pathogenesis, causes, and risk factors of calciphylaxis are poorly understood. Studies have identified certain risk factors, including female sex, obesity, elevated calcium-phosphate product, warfarin use, hypercoagulability, systemic corticosteroid use, and treatment with calcium salts and vitamin D.[1-4] However, although many patients with ESRD possess these risk factors, few develop calciphylaxis, and the overall incidence of calciphylaxis in this patient population remains low. A prior case report presented a fatal case of calciphylaxis following Roux-en-Y gastric bypass (RYGB).[5] In this case series, we report 7 patients without ESRD who underwent bariatric surgery and subsequently developed calciphylaxis. Our findings propose a potential role of nutritional abnormalities and treatments in the pathogenesis of this disease.

Abbreviations used:

BMI:	body mass index
CKD:	chronic kidney disease
ESRD:	end-stage renal disease
RYGB:	Roux-en-Y gastric bypass

CASE SERIES

The demographic, clinical, and laboratory features of all patients are summarized in Table I. The median age was 50 years; most patients were men (n = 5) and Caucasians (n = 5). Bariatric surgery consisted of RYGB (n = 6) and sleeve gastrectomy (n = 1). The median time between bariatric surgery and diagnosis was 10.6 years, ranging from 7 months to 30 years. The mean maximal weight loss was 42.8% of the individual patient's presurgery weight. The median percent excess body weight loss, or the percentage of weight loss relative to achieving a body mass index (BMI) of 25 kg/m^2, was 75.5%. The median BMI at the maximal weight loss was 29.1 kg/m^2, and the median BMI at the time of calciphylaxis diagnosis was 29.5 kg/m^2. At the onset of calciphylaxis, 2 patients were persistently obese with respective BMIs of 34.3 and 31.6 kg/m^2 despite surgery, and 3 patients were persistently overweight with BMIs ranging from 25.3 to 29.8 kg/m^2. Weight loss data were missing in 2 patients.

At the time of calciphylaxis, 3 patients had chronic kidney disease (CKD) stage 2, 1 patient had CKD stage 3, 2 patients had normal kidney function, and 1 patient had an acute kidney injury. Comorbidities included diabetes (n = 5), nonalcoholic fatty liver

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Table I. Summary of clinical findings of 7 patients diagnosed with calciphylaxis after bariatric surgery

Patient	1	2	3	4	5	6	7
Age at diagnosis, y	48	31	49	65	65	36	55
Sex	Female	Female	Male	Male	Male	Male	Male
Race	Black	Black	White	White	White	White	White
Lesion location	P	D	P	P	D	P	D
Bariatric surgery type	RYGB	RYGB	RYGB	RYGB	RYGB	SG	RYGB
Kidney function	Normal	Normal	AKI	CKD2	CKD2	CKD2	CKD3
Time between surgery and calciphylaxis diagnosis (mos)	13	28	264	360	120	7	96
BMI at surgery, kg/m^2	49.3	40.73	N/A	N/A	60.3	52.8	55.9
BMI after surgery at maximum weight loss, kg/m^2	25.2	32.27	N/A	N/A	34.5	26.5	29.8
Percent excess body weight loss	85.9	54.5	N/A	N/A	69.3	88.4	79.3
BMI at calciphylaxis diagnosis, kg/m^2	25.3	34.3	N/A	N/A	31.6	26.4	29.8
Concomitant medications	D2, D3*	D2, D3*	D2	Warfarin, D3*	D2, IV iron	D2	D3*
Calciphylaxis risk factors	DM, NAFLD	DM	NAFLD	DM	NLS, NAFLD	NLS, DM, NAFLD	DM, APLS
Serum calcium level, corrected (reference, 9-10.5 mg/dL)	8.8	9.9	9.3	8.3	10.2	10.1	9.6
Serum phosphorus level (reference, 3.4-4.5 mg/dL)	4.3	2.8	5	4.3	3	3.6	4
Serum parathyroid hormone level (reference, 10-55 pg/mL)	24	95	53	494	34	10	58
Serum 25-hydroxyvitamin D level (reference, 25-802 ng/mL)	26	49	8	18	N/A	47	26
Serum albumin level (reference, 3.4-5.4 g/dL)	3.6	3.4	2.7	1.1	2.8	3.4	3.5
Serum vitamin K level (reference, 0.2-3.2 ng/mL)	N/A	N/A	N/A	N/A	0.10	0.08	0.08
Treatment	IV STS, IL STS, SD	IV STS	IV STS, IL STS	IV STS	SD	IV STS	IV STS, IL STS
Time to healing (mos)	N/A	12	N/A	N/A	25	5	11
Time to death after diagnosis (mos)	N/A	N/A	1	6	N/A	N/A	67
Cause of death	N/A	N/A	Multiple organ failure	GI bleed	N/A	N/A	Sepsis from AV graft

AKI, Acute kidney injury; *APLS*, antiphospholipid syndrome; *AV*, arteriovenous; *BMI,* body mass index, *CKD*, chronic kidney disease; *D*, distal; *D2*, vitamin D2; *D*3, vitamin D3; *DM,* diabetes mellitus; *GI*, gastrointestinal, *IL*, intralesional; *IV*, intravenous; *N/A*, not available; *NAFLD,* nonalcoholic fatty liver disease; *NLS,* nephrolithiasis; *P*, proximal; *RYGB*, Roux-en-Y gastric bypass; *SD*, surgical debridement; *SG*, sleeve gastrectomy; *STS*, sodium thiosulfate.
*Vitamin D 1000 IU/d.

disease (n = 4), nephrolithiasis (n = 2), and antiphospholipid antibody syndrome (n = 1). Five patients received vitamin D2 daily, 4 patients received activated vitamin D 1000 IU/d, 1 patient was treated with intravenous iron, and 1 patient was on warfarin. Vitamin K1 levels were measured in only 3 patients and were below normal levels.

Lesions were located predominantly on the abdomen, breast, and thighs (n = 4), and most were ulcerated (n = 6). Five patients had biopsy-proven calciphylaxis and 2 had suggestive clinical findings consistent with the disease, as determined by a multidisciplinary assessment. Laboratory testing in 2 patients at the time of diagnosis was notable for low 25-hydroxyvitamin D levels (8 ng/mL and 18 ng/mL) and elevated parathyroid hormone levels (95 pg/mL and 495 pg/mL). The mean corrected serum calcium level was 9.5 mg/dL, and the mean phosphate level was 3.9 mg/dL. Albumin level was low, with a mean of 2.9 g/dL.

Six patients were treated with intralesional/intravenous sodium thiosulfate, and 2 patients underwent intraoperative surgical debridement. Four patients had a resolution of their disease, with a median time to wound healing of 7.2 months. The time to wound healing could not be determined in patient 1 because they were lost to follow-up; however, as per chart review, their last note denoted a persistent wound. Three patients died of causes unrelated to calciphylaxis or any secondary infection of their ulcers.

DISCUSSION

Calciphylaxis is a rare disorder of calcification of small- and medium-sized arterioles, leading to subsequent thrombosis and ischemia of the overlying tissue. It clinically presents with extremely painful necrotic ulcers with surrounding retiform purpura and has been associated with high morbidity and 1-year mortality of 45% to 80%.[1,2] Although typically seen in patients with ESRD, other reported risk factors include obesity, hyperparathyroidism, hypoalbuminemia, and the use of warfarin and calcium supplements.[1,6]

To our knowledge, this is the largest case series of calciphylaxis in the setting of bariatric surgery. Only 3 patients have been reported in the literature to have developed calciphylaxis after RYBG, 1 without a history of ESRD and 2 with a history of ESRD.[5,7,8]

Although ESRD may be the strongest risk factor for the development of calciphylaxis, it has also been increasingly reported for nonnephrogenic patients. The most notable associated comorbidities include primary hyperparathyroidism, malignancies, autoimmune disease, diabetes mellitus, and nonalcoholic liver disease.[6] Although none of the patients in this series had ESRD, 4 had CKD and 1 patient had an acute kidney injury. Thus, in these cases, renal effects may still have had an impact on the development of calciphylaxis. The seven patients included in our series had at least 1 other risk factor for calciphylaxis, thereby suggesting a multifactorial etiology.

Obesity has been posited to contribute to the pathophysiology of calciphylaxis.[9] Mechanistically, it is believed that excess adipose tissue causes tensile stress on dermal arterioles, further reducing blood flow in already calcified vessels.[6,9] This could explain why most of the patients in our series had proximal lesions involving the trunk, thighs, and breasts. In addition, rapid weight loss has been implicated in the development of calciphylaxis because of weight loss-induced production of matrix metalloproteinase digesting vascular elastin, which provides an enhanced matrix for calcium deposition.[10]

The prevalence of vitamin D deficiency is reported to be as much as 100% after weight loss surgery.[11] It results in decreased calcium absorption and increases the prevalence of secondary hyperparathyroidism to 35.4% at 1 year after surgery and to 63.3% at 5 years after surgery.[11] In our case series, calcium levels overall were within normal limits. Vitamin D levels were lower in 2 patients, and parathyroid hormone levels were higher in 2 patients who underwent RYGB. Calciphylaxis has been traditionally linked to secondary hyperparathyroidism, in the setting of dysregulated calcium-phosphorous metabolism in patients undergoing dialysis, and the frequent use of high doses of calcium salts and vitamin D that promote calcification.[6] The American Society for Metabolic and Bariatric Surgery recommends a daily calcium intake of 1200 to 1500 mg and 3000 IU of vitamin D daily, until the blood levels of 25-hydroxyvitamin D are >30 ng/mL.[11] We could not measure the level of compliance to daily supplementation in our study. Whether secondary hyperparathyroidism contributes to calciphylaxis in nonnephrogenic bariatric surgery patients remains to be elucidated.

Recently, the role of vitamin K deficiency in the pathogenesis of calciphylaxis has gathered growing evidence. Warfarin, a vitamin K antagonist, has been shown to promote vascular calcification in animal models by the inhibition of carboxylation of endothelial matrix Gla protein.[1] Functional vitamin K deficiency (from warfarin use and other causes) is associated with an increased risk of calciphylaxis among patients undergoing dialysis.[12] Although vitamin K is a fat-soluble vitamin, its deficiency has not been frequently reported, except after biliopancreatic diversion.[13] Of the three patients in this

case series with available data, all had low serum vitamin K levels.

Although uncommon, a subset of patients may develop protein-calorie malnutrition. This complication occurs frequently in RYGB and is associated with the length of the common channel because it determines the length of the small intestine available for the mixture of pancreatic secretions with the dietary protein.[14] Low levels of albumin in 3 patients in our series could suggest malnutrition. However, this is confounded by the underlying inflammation as a result of calciphylaxis itself, as well as other comorbidities.[15]

This case series suggests that clinicians should consider calciphylaxis in the differential for painful skin lesions arising after weight loss surgery. This is particularly true if the patients show signs of micronutrient deficiencies or malnutrition. Overall, bariatric surgery is an effective treatment for obesity that can improve the health-related quality of life for these patients, but careful monitoring of the nutritional status and long-term supplementation with the recommended vitamins and minerals is essential.[11] Recognition of risk factors for calciphylaxis and careful evaluation of therapies for other comorbidities in patients who have undergone bariatric procedures is essential to reduce the risk and improve outcomes for this rare but problematic disease.

Conflicts of interest

None disclosed.

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