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# Patient Outcomes and Factors Associated with Healing in Calciphylaxis Patients Undergoing Adjunctive Hyperbaric Oxygen Therapy



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## KEYWORDS:

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Hyperbaric;  
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**Abstract** Calcific uremic arteriopathy, also known as calciphylaxis, is a rare syndrome of small vessel calcification of unknown etiology causing painful, violaceous skin lesions that progress to form chronic non-healing ulcers and gangrene. Hyperbaric oxygen therapy (HBOT) can be used as adjunctive therapy in the treatment of these ulcers. However, due to paucity of cases, there is limited data on the clinical benefit of HBOT and identifying factors associated with healing. The purpose of this study was to determine patient outcomes and factors associated with healing in patients with calciphylaxis undergoing HBOT. A retrospective chart review was completed on patients who were diagnosed with calciphylaxis and had hyperbaric medicine consultation between May 2012 and January 2016. Clinical outcomes, demographics, risk factors, laboratory values, wound distribution, and HBOT profiles were collected and analyzed. We identified 8 patients. Out of 8 patients consulted for calciphylaxis, five were consented and underwent HBOT (2 males and 3 females). All had coexisting ESRD and Diabetes. All males were able to tolerate being in the chamber and received therapeutic treatments (at least 20 HBOT) with complete resolution of ulcers. HBOT was discontinued in one female due to an inconsistent biopsy report and two others due to death secondary to septic shock or respiratory arrest and severe uremia. Calciphylaxis is a devastating disease with a high mortality rate. Our results demonstrated a positive response to HBOT especially when receiving at least 20 treatments. A majority of calciphylaxis cases are females and indeed female gender has been cited as a risk factor for this disease. However, current literature has not conferred a relationship between gender nor the number of HBOT received and outcomes. Our results showed that males had a more favorable outcome provided they received at least twenty HBOT. Further prospective studies are needed to elucidate these outcomes.

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## Introduction

Calciphylaxis (also known as calcific uremic arteriopathy) is a rare and potentially life threatening syndrome of small vessel calcification of unknown etiology,

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which causes painful violaceous skin lesions that progress to chronic, non-healing ulcers and subsequent gangrene. It is commonly seen in end-stage renal disease (ESRD) patients with a prevalence of 1–4% of those on hemodialysis.<sup>1,2</sup> Incidence has been reported to be increasing recently.<sup>3</sup> With a high mortality between 60 and 80%, most patients die from complications of sepsis secondary to infection of the calciphylaxis wounds, which results from impaired integrity of the epidermis and dermis.<sup>4</sup> The exact pathogenesis is unclear but involves vascular calcification with calcium deposition in the media of the dermal and subcutaneous arterioles and cutaneous necrosis.<sup>5</sup> Although various sites have been reported, the lower extremities are the most commonly involved.<sup>5</sup>

Hyperbaric oxygen (HBO<sub>2</sub>) is a treatment in which the patient breathes 100% oxygen at a pressure higher than ambient sea-level pressure (1 atmosphere absolute – ATA) while inside a sealed chamber. It has been proven successful as adjunctive treatment of problem wounds, defined as those that fail to respond to standard medical and surgical management. These wounds are often severely hypoxic with transcutaneous oxygen pressures (P<sub>tc</sub>O<sub>2</sub>) of less than 40 mmHg. Normal tissue has P<sub>tc</sub>O<sub>2</sub> of greater than 50 mmHg.<sup>6</sup> Impaired healing is noted when tissue O<sub>2</sub> tension is less than 40 mmHg. HBOT improves the oxygen tension and promotes wound healing through effects including increased fibroblast proliferation, collagen production and neogenesis. HBOT also reverses the local tissue hypoxia that inhibits the oxygen-dependent polymorphonuclear leukocyte-mediated bacterial killing of organisms that are most commonly found in wound infections.<sup>7</sup>

The benefits of HBO<sub>2</sub> in the treatment of calciphylaxis have been reported in many case reports and a few retrospective case series.<sup>2,8–10</sup> In Podymow et al 2 out of 5 patients showed complete resolution of extensive necrotic ulcers and improvement in wound area transcutaneous oxygen pressure.<sup>2</sup> Dean and Werman report a case of a female patient with end-stage renal disease and diabetes mellitus who presented with lower extremity calciphylaxis who responded to 7 weeks of HBO<sub>2</sub> treatments after failing to respond to standard care including parathyroidectomy and wound debridement.<sup>9</sup> Vassa et al reported on a case of a woman on continuous ambulatory peritoneal dialysis who presented with lower extremity calciphylaxis who also failed standard care but showed resolution of her skin lesions after 38 HBO<sub>2</sub> therapy sessions.<sup>8</sup> The majority of calciphylaxis patients are females. However, gender has not been reported to confer an advantage (or disadvantage) in treatment. We thus present a retrospective study of eight patients on renal replacement therapy who underwent consultation for calciphylaxis and their outcomes.

## Methods

We obtained IRB exemption for our retrospective case review. We identified patients admitted to Upstate Medical University who received hyperbaric medicine consultation for lesions suspicious for calciphylaxis from May 2012 through Jan 2016. Eight cases were retrospectively studied. Characteristics of each patient including age, gender, dialysis, duration on dialysis, presence of diabetes mellitus, evidence of parathyroidectomy, use of sodium thiosulfate, use of coumadin, distribution of calciphylaxis lesions, serum levels of calcium, phosphate, albumin, hyperbaric oxygen treatment profile, and clinical outcomes were recorded. Patients, who underwent treatment received hyperbaric oxygen at 2.0 atmospheres absolute (ATA) for 90 min, 5 days per week for variable number of treatments. All patients received routine wound care, and the majority of patients who underwent hyperbaric oxygen therapy were also treated with sodium thiosulfate concurrently. Presence of increased granulation tissue, overall reduction in ulcer size dimensions with subsequent epithelialization and formation of scar determined resolution of calciphylaxis lesions.

## Results

Patient characteristics are illustrated in [Table 1](#). Six females and two males were identified. Mean age of females was 52.2 years and males 62.5 years. Five patients (4 females, 1 male) had biopsy confirmed calciphylaxis. All were diagnosed with end-stage renal disease on renal replacement therapy and diabetes mellitus. Average duration on dialysis was 34 months. Five patients were receiving anticoagulation with warfarin for atrial fibrillation, and this was discontinued when clinically appropriate. Out of the eight patients identified, seven received supplemental vitamin D and calcium acetate as part of their treatment for secondary hyperparathyroidism and three underwent parathyroidectomy for refractory secondary hyperparathyroidism. Calciphylaxis lesions were located on the lower extremities in six patients, on the trunk in one and in the lungs in one patient.

[Table 2](#) summarizes the laboratory findings. Average serum PTH level was 693.7 pg/ml, calcium 5.3 mg/dl and phosphate 8.4 mg/dl. Elevated calcium-phosphate product was not identified in any of the patients. Mean serum albumin was 3.3 mg/dl with three patients demonstrating hypoalbuminemia (serum albumin < 3.5 mg/dl).

[Table 3](#) identifies the clinical course of patients. Five patients underwent HBO<sub>2</sub> therapy of which two (both males) received therapeutic treatments (at least 20 HBO<sub>2</sub> treatments). Patients #1 and #5 showed excellent clinical response with resolution of skin ulcers. Healing occurred

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