



An Update on Natural Remedies for Calciphylaxis in Home Management

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Abstract

Calciphylaxis, a rare but severe condition characterized by calcification and thrombosis of small blood vessels, leads to ischemic skin necrosis and presents significant therapeutic challenges for healthcare providers. Recent investigations into holistic and natural remedies have emerged as potential adjunctive therapies to traditional treatments, offering patients at-home management options. This review synthesizes the latest findings on dietary modifications, topical applications, and lifestyle changes that may enhance patient outcomes in managing calciphylaxis. Specific dietary interventions, such as incorporating magnesium-rich foods (e.g., leafy greens, nuts) and omega-3 fatty acids (found in fatty fish and flaxseeds), show promise in modulating calcium metabolism and reducing systemic inflammation. Furthermore, antioxidants from fruits and vegetables, particularly those rich in vitamins E and C, may help mitigate oxidative stress associated with tissue damage. Topical agents like aloe vera, with its anti-inflammatory and wound-healing properties, and calendula, known for its soothing effects on damaged skin, are explored for their potential benefits in improving skin integrity and promoting healing. Additionally, lifestyle modifications, including stress management techniques such as mindfulness, yoga, and acupuncture, can enhance overall well-being and contribute to improved skin health through their effects on systemic inflammation and vascular function. Although the evidence supporting these natural remedies remains preliminary, their integration into a comprehensive management plan offers promise for enhancing the quality of life for patients with calciphylaxis. Emphasizing holistic approaches can empower patients to actively engage in their treatment journey, enhancing their ability to navigate the complexities of calciphylaxis effectively.

1. INTRODUCTION

Calciphylaxis is a progressive inflammatory disease that affects small and medium-sized arteries, where calcification leads to thrombotic ischemia. This ischemia manifests as painful nodules, plaques, or necrotic ulcerations on the skin. While most commonly seen in patients with end-stage renal disease (ESRD), calciphylaxis can also occur in individuals with acute kidney injury or even in those without any known renal

disease. With a one-year mortality rate as high as 50%, calciphylaxis is challenging to diagnose and treat due to its systemic effects and highly variable clinical presentation [1]. The appearance of calciphylaxis lesions depends on the stage of the disease, the patient's skin tone, and the anatomical location of the affected area. Early on, lesions can range from subcutaneous nodules without epidermal changes to retiform purpura or branching purpuric plaques and patches. As the

disease progresses, these lesions often evolve into painful ulcers with overlying eschar. The vasculopathic nature of calciphylaxis contributes to the dry appearance of the lesions, in contrast to the moist pathology seen in conditions like pyoderma gangrenosum. Lesions are typically found in areas rich in adipose tissue, such as the thighs, pannus, and breasts, though they may also occur in less fatty areas like the lower legs, fingers, and penis. Diagnosing calciphylaxis can be particularly challenging in individuals with darker skin tones, as retiform changes may present as hyperpigmentation rather than the more classic purple hue, and skin induration may be subtler [2]. Diagnosis is based on both clinical presentation and histological findings, making early recognition crucial for improving outcomes. High clinical suspicion is necessary to initiate timely intervention and management.

The histopathological changes in calciphylaxis evolve alongside the progression of the clinically apparent lesions. In the early stages, when symptoms such as erythema and tenderness dominate, histopathological findings are often subtle. These may include trace calcifications in adipose tissue and focal calcification of cutaneous and subcutaneous elastic fibers. As the disease advances, with ulceration and necrosis becoming more prominent, the histopathologic changes also become more pronounced. Key diagnostic features include intimal hyperplasia, calcification of small and medium-sized arteries, extravascular soft tissue calcification, epidermal necrosis with subepidermal bullae formation, and dermal necrosis [3]. These advanced findings are critical for confirming a diagnosis of calciphylaxis, but they may only appear once the disease has reached later stages, suggesting a potential delay in diagnosis. Some authors argue that this delay can be significant, with the presence of fibrin thrombi in skin biopsies correlating with more severe pain and later-stage disease. Research indicates that, on average, there is a nine-week lag between the onset of symptoms and the formal diagnosis of calciphylaxis, highlighting the need for earlier recognition and intervention [4]. Addressing this diagnostic gap is essential for improving outcomes, as well as being able to accurately stage the disease at the time of presentation in order to better direct therapeutic treatment.

The management of calciphylaxis primarily focuses on treating the underlying cause, highlighting the critical need for an accurate diagnosis of the systemic condition. Identifying this cause, however, can be particularly

challenging, especially in normo-uremic patients, where traditional renal-related explanations may not apply. To guide clinicians, a general algorithm categorizes treatments into four key areas: targeting vascular calcification, addressing thrombosis, wound care, and pain management [5]. Despite these frameworks, the incomplete understanding of calciphylaxis' pathophysiology has hindered the development of more targeted treatments. This challenge is compounded by the difficulty in recruiting patients for clinical trials due to the disease's high mortality rate and the numerous comorbidities typically present in affected individuals. As a result, there are currently no established guidelines for the standard of care in calciphylaxis, with most treatment recommendations relying on case studies and expert consensus [6]. This absence of definitive guidelines underscores the need for exploring alternative and adjunctive therapies to improve patient outcomes and provide more effective management strategies for this complex disease. This review examines the currently recommended management strategies for calciphylaxis while exploring potential adjunctive therapies that could enhance treatment outcomes. In addition to established protocols, alternative approaches may offer promising benefits, particularly in cases where traditional treatments are less effective. These options include dietary modifications aimed at reducing systemic inflammation, as well as the use of natural topical agents that could promote localized healing and skin regeneration. Furthermore, lifestyle changes, such as incorporating mindfulness practices and yoga, may help to modulate stress and lower inflammation levels, which could play a role in supporting the body's healing pathways. By integrating these complementary therapies alongside conventional treatment, there may be opportunities to optimize care for patients with this challenging condition.

2. PATHOPHYSIOLOGY OF CALCIPHYLAXIS

The pathophysiology of calciphylaxis remains poorly understood, and much of the current knowledge comes from case reports. Some researchers suggest that the disease is driven by calcification in and around subcutaneous blood vessels, resulting from the transformation of vascular smooth muscle cells into osteoblast-like cells [7]. This process is particularly evident in patients with ESRD, where elevated serum calcium-phosphate levels accelerate calcification. This creates a snowball effect,

worsening the disease over time. As these vessels become calcified, they are at greater risk of thrombosis, driven by both endothelial dysfunction caused by calcification and the hypercoagulable state often seen in ESRD. This hypercoagulable state is thought to be due in part to a deficiency of protein C, which inhibits the normal breakdown of clots, making clot formation easier in calcified vessels [8]. Together, these mechanisms allow the disease to progress, ultimately resulting in ischemic tissue. The combination of calcification and thrombosis leads to vessel occlusion and subsequent tissue necrosis. Clinically, these changes manifest as painful, non-healing ulcers on the skin, which are highly susceptible to secondary infections. If left untreated, these infections can lead to sepsis, significantly increasing the risk of mortality [9]. Understanding these underlying mechanisms is essential to guide treatment and prevent disease progression.

Chronic kidney disease (CKD) is the primary underlying mechanism contributing to the development of calciphylaxis. As previously noted, ESRD creates an imbalance in the calcium-phosphate ratio, leading to the formation of the insoluble byproduct hydroxylapatite, which contributes to vascular calcification. This imbalance also disrupts the normal regulation of calcification promoters and inhibitors. Calcification promoters include factors such as BMP-2, BMP-4, BMP-6, osteocalcin, alkaline phosphatase, and inflammatory cytokines, while inhibitors include proteins like Fetuin-A, Matrix Gla protein, osteoprotegerin, and osteopontin [10]. In ESRD-related calciphylaxis, the altered phenotype and dysregulation of vascular smooth muscle cells (VSMCs) play a central role in the pathogenesis. These processes are influenced by osteochondrogenesis, vascular aging and senescence, and the formation of extracellular vesicles that drive mineralization. VSMCs contribute to calcification by producing extracellular vesicles that act as nucleation sites, and they undergo phenotypic transformation from a contractile state to an osteochondrogenic state in response to inflammation, oxidative stress, and the natural aging process. Prelamin A, a protein linked to cellular aging, is thought to be a key driver of this transformation, inducing DNA damage, osteogenic differentiation, and further calcification in VSMCs [10]. This complex interplay of molecular and cellular mechanisms underscores the multifaceted nature of calciphylaxis, particularly in patients with

CKD, and highlights the importance of targeting these pathways for effective management.

Hyperparathyroidism is another significant factor that can contribute to the development of calciphylaxis, functioning in a manner similar to chronic kidney disease. While secondary or tertiary hyperparathyroidism related to CKD is the most common cause in this context, calciphylaxis can also arise in patients without CKD due to primary hyperparathyroidism, often resulting from a parathyroid adenoma or carcinoma. In patients with end-stage renal disease (ESRD), the levels of parathyroid hormone (PTH) rise due to the presence of hypocalcemia, hyperphosphatemia, and vitamin D deficiency. This triggers chronic stimulation of the parathyroid glands, leading to persistent hypersecretion of PTH. Over time, the elevated PTH levels promote the deposition of hydroxyapatite and contribute to the pathological processes of vascular calcification, thrombosis, and tissue ischemia characteristic of calciphylaxis [11]. Even after renal transplantation, this hypersecretion can persist in tertiary hyperparathyroidism, maintaining the risk for calciphylaxis. In primary hyperparathyroidism, the condition is driven by an intrinsic dysfunction in one or more of the parathyroid glands, leading to excessive PTH secretion and elevated calcium levels. Conversely, secondary hyperparathyroidism arises as a compensatory response to external factors, such as low calcium or high phosphate, commonly seen in CKD. This sustained increase in PTH creates an environment conducive to vascular calcification, making hyperparathyroidism a critical player in the progression of calciphylaxis, regardless of the underlying renal status [11]. Understanding these distinct pathways highlights the importance of managing hyperparathyroidism effectively, especially in patients with CKD, to prevent or mitigate the risk of calciphylaxis.

Obesity and diabetes, which are increasing at an alarming rate in developed countries, also contribute significantly to the development of calciphylaxis in patients with chronic kidney disease. In diabetes, the hyperglycemic state disrupts phosphate transporter function, promoting calcification in the podocytes and glomeruli. These transporters, which normally reabsorb phosphate back into renal cells in the proximal tubule, are regulated by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). When their function is impaired, it leads to increased intracellular phosphate

retention and extracellular phosphate buildup, which sets the stage for calcification [12]. In addition, the proteins that make up the phosphate transporters are also involved in cell signaling, and their dysfunction can induce podocyte injury, further promoting calcification. Diabetes mellitus (DM) and obesity are associated with increased oxidative stress, which rises in parallel with the severity of CKD. This oxidative stress plays a key role in the pathogenesis of calciphylaxis. Studies have shown that DM is one of the most significant risk factors for developing calciphylaxis in patients with end-stage renal disease (ESRD) [13]. NADPH oxidases, which are upregulated during oxidative stress, contribute to endothelial dysfunction, inflammation, cardiac hypertrophy, fibrosis, apoptosis, and vessel wall remodeling, all of which exacerbate vascular damage. Moreover, advanced glycation end products (AGEs), which accumulate in both CKD and DM, amplify oxidative stress and induce vascular injury, further encouraging the calcification process [13]. These interrelated mechanisms highlight the complex role that diabetes and obesity play in calciphylaxis, particularly in the context of CKD. By promoting both phosphate dysregulation and oxidative stress, these conditions accelerate vascular calcification and contribute to the progression of this life-threatening disease.

3. CURRENT TREATMENT APPROACHES

Conventional treatments for calciphylaxis primarily focus on managing symptoms and addressing underlying conditions. Current pharmacological interventions target bone-mineral disorders, as factors like elevated calcium-phosphate product, increased parathyroid hormone levels, and deficiencies in vascular calcification inhibitors are associated with calciphylaxis. The article notes a correlation between elevated calcium levels and the development of calciphylaxis [14]. Maintaining phosphorus levels below 5.5 mg/dL and avoiding hypercalcemia can help mitigate conditions contributing to vascular calcification. One commonly used treatment is sodium thiosulfate, which has chelating properties that may help reduce free calcium levels in the bloodstream, potentially alleviating the vascular calcification characteristic of calciphylaxis [15]. This drug may also form water-soluble complexes with various metals, assisting in managing calcifications associated with this condition. Such pharmacological interventions are essential since disruptions in bone-mineral metabolism play a key role in the disease's pathophysiology.

Medications from another group, known as bisphosphonates (e.g., pamidronate), may help lower calcium levels and reduce bone resorption, benefiting patients with elevated calcium levels. The primary action of bisphosphonates involves inhibiting osteoclasts, which may assist in mobilizing intravascular calcium over time [16]. Another relevant medication, cinacalcet, may lower parathyroid hormone (PTH) levels and assist in managing calcium levels. By reducing PTH levels, cinacalcet can help decrease serum calcium and phosphate levels, both of which can contribute to the vascular calcification observed in calciphylaxis, exacerbating the condition [16]. Current recommendations also suggest switching calcium-based phosphate binders to non-calcium alternatives [17]. This approach stems from the understanding that excess calcium can contribute to vascular calcification, and eliminating such sources may reduce the risk of exacerbating calciphylaxis.

Surgical options for treating calciphylaxis generally aim to manage ulcers, alleviate pain, and prevent further complications. Debridement, which involves the surgical removal of necrotic (dead) tissue from ulcers, is crucial. This procedure can improve local blood flow, reduce the risk of infection, and create a healthier environment for healing [5]. Additionally, parathyroidectomy may benefit calciphylaxis treatment by suppressing or eliminating serum PTH, which is believed to play a role in the disease's pathology [16,18]. Lowering PTH levels can help mitigate associated risks like adynamic bone syndrome, hypocalcemia, and hyperphosphatemia, potentially leading to improved patient management. Overall, surgical interventions can address underlying conditions such as severe hyperparathyroidism, reducing the factors that cause excessive calcium and phosphate deposition, which may help mitigate the severity of the condition. When combined with medical treatments, these procedures may enhance patient outcomes by providing a more comprehensive approach to managing the multifaceted pathology of calciphylaxis.

Supportive care is essential for managing calciphylaxis, as the emotional and psychological impact can be significant. Education and counseling are vital components in this management, greatly influencing both patient outcomes and quality of life. Counseling offers a safe space for patients to express their feelings about their diagnosis, helping them address fears and emotional distress [19]. Mental health is crucial in navigating chronic conditions, and

supportive counseling can enhance overall well-being. This type of care also promotes healing through careful wound management and adequate nutrition, while psychological support helps alleviate anxiety and depression. Encouraging self-care, maintaining social connections, and providing regular follow-up allow patients to actively participate in their recovery [19]. This involvement ultimately leads to improved health outcomes and a better quality of life. Furthermore, counseling reinforces the importance of adhering to medical recommendations, including medications, wound care routines, and dietary adjustments [19]. By educating patients about their condition and associated risk factors, healthcare providers help them adopt preventive measures to reduce complications such as infections or worsening skin lesions. Current treatment strategies for calciphylaxis, while grounded in clinical practice, may not always be effective for various reasons compared to natural remedies or holistic approaches. Calciphylaxis involves multifactorial pathophysiology, including vascular calcification and imbalances in calcium and phosphorus levels. Conventional treatments may not address all underlying factors or individual patient variations, leading to inconsistent outcomes. For example, responses to parathyroidectomy can vary significantly among patients. While some may experience marked improvement, others may continue to face issues related to calciphylaxis. One case report described a patient developing painful necrotic skin lesions approximately four weeks post-surgery, later confirmed as calciphylaxis through biopsy [20]. This highlights a critical and unexpected complication that can arise after surgical intervention. Although parathyroidectomy can reduce PTH levels, it carries risks, such as hypoparathyroidism, which can lead to further disturbances in calcium and phosphorus metabolism, potentially exacerbating calciphylaxis [20]. This underscores the need for an in-depth understanding of calcium and phosphorus management, especially in the context of renal failure, along with vigilant postoperative monitoring to mitigate risks like calciphylaxis. Additionally, some pharmaceutical interventions may have side effects that complicate the overall health status of patients. For instance, the use of sodium thiosulfate can present challenges in patient management by contributing to metabolic acidosis, whereas natural remedies might be perceived as less invasive and have fewer side effects [8]. While further research is needed to

establish the efficacy of natural remedies in treating calciphylaxis, their holistic approach may provide benefits that conventional treatments alone cannot always achieve.

4. DIETARY MODIFICATIONS

Dietary management is a critical component in addressing the complex pathophysiology of calciphylaxis. This condition, characterized by vascular calcification, thrombosis, and ischemic tissue damage, is strongly influenced by metabolic imbalances, including disrupted calcium-phosphate homeostasis and systemic inflammation. Nutritional interventions provide an opportunity to modulate these processes and complement conventional medical and surgical treatments. Specifically, incorporating magnesium-rich foods, omega-3 fatty acids, and antioxidant-dense fruits and vegetables into the diet offers a multifaceted approach to managing calciphylaxis. These dietary elements work synergistically to reduce systemic inflammation, improve vascular health, and enhance wound healing, which are all critical for mitigating the progression of this severe condition and improving patient outcomes [6, 10]. Magnesium plays a pivotal role in preventing vascular calcification, a hallmark of calciphylaxis, by acting as a natural antagonist to calcium deposition in soft tissues. It inhibits the transformation of vascular smooth muscle cells into osteoblast-like cells, which is a key process driving calcification in small and medium-sized arteries. Foods rich in magnesium, such as leafy greens (e.g., spinach, kale), nuts, seeds, and whole grains, have been shown to maintain vascular integrity and reduce arterial stiffness. Research highlights that increased magnesium intake is associated with decreased vascular calcification in patients with chronic kidney disease, a population particularly susceptible to calciphylaxis [7, 10]. Furthermore, magnesium exhibits anti-inflammatory properties, reducing levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), which are implicated in systemic inflammation and vascular damage. By integrating magnesium-rich foods into the diet, patients may benefit from both metabolic and inflammatory regulation, enhancing the effectiveness of other therapeutic interventions [5].

Omega-3 fatty acids, predominantly found in fatty fish like salmon, mackerel, and sardines, as well as in plant-based sources such as flaxseeds and walnuts, offer significant anti-inflammatory benefits. These polyunsaturated fatty acids

modulate inflammatory pathways by reducing the production of pro-inflammatory eicosanoids and cytokines while promoting the synthesis of anti-inflammatory resolvins and protectins. In patients with calciphylaxis, omega-3 fatty acids may play a dual role in improving vascular health and mitigating systemic inflammation. For example, studies have demonstrated that omega-3 supplementation reduces markers of endothelial dysfunction, a precursor to vascular calcification and thrombosis, which are central to calciphylaxis pathology [5, 6]. Additionally, omega-3 fatty acids support skin health by promoting collagen synthesis and reducing oxidative stress, which are essential for wound healing in patients with ischemic skin lesions [5]. Antioxidant-rich fruits and vegetables, such as berries, citrus fruits, broccoli, and bell peppers, provide essential vitamins like vitamin C and vitamin E, which combat oxidative stress and enhance tissue repair. Oxidative stress, a key driver of vascular injury and calcification, results from an imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses. By neutralizing ROS, dietary antioxidants can reduce endothelial damage and inflammation, both of which are exacerbated in calciphylaxis [5, 7]. Vitamin C supports collagen synthesis, crucial for maintaining skin integrity and healing wounds, while vitamin E protects cell membranes from oxidative damage and enhances immune function. Research has shown that diets rich in these antioxidants correlate with improved wound healing and reduced inflammation in patients with chronic conditions, suggesting their potential benefit for calciphylaxis management [5, 6]. These dietary interventions collectively target the metabolic and inflammatory pathways implicated in calciphylaxis, offering a complementary strategy to standard treatments. By addressing the root causes of vascular calcification and enhancing tissue repair mechanisms, a diet rich in magnesium, omega-3 fatty acids, and antioxidants holds promise for improving patient outcomes. Empowering patients with nutritional education and guidance is an essential step in integrating these approaches into their care plans, fostering a holistic and patient-centered strategy for managing calciphylaxis.

5. TOPICAL APPLICATIONS

Topical treatments for skin health are structured around the strategies of protection and regeneration. Protection involves mechanisms such as UV blocking and anti-inflammatory

action. Natural compounds in sunscreens, including zinc oxide, titanium dioxide, aloe vera, and calendula, play a vital role in shielding the skin from harmful UV radiation [21]. He et al. (2021) compile the exact sun protection factor (SPF) values for these ingredients, allowing for a comparison of single and combination formulations [22]. Notably, the review by He et al. highlights that combination formulations exhibit stronger absorption and SPF capacities, suggesting that utilizing multiple natural ingredients enables topical formulations to offer a comprehensive approach to sun protection [22]. In addition to UV blocking, antioxidants protect the skin from oxidative stress caused by UV exposure. Karimi 2023, reports that melatonin significantly reduces skin damage by scavenging free radicals, while He et al. (2021), note that polyphenols are key factors in neutralizing harmful reactive oxygen species [22,23]. Therefore, incorporating these antioxidants into skin care products not only improves skin health by offering protection but also reduces injury-inducing agents. Activation and regeneration strategies focus on optimizing skin regeneration processes to enhance internal cell functions and increase cell turnover. Topical peptide technologies such as carrier and signal peptides enhance these processes by facilitating the delivery of bioactive compounds into the skin. For instance, GHK-Cu, a copper peptide, stimulates collagen production and promotes tissue repair by acting as an activator of tissue remodeling factors such as elastin, proteoglycans, and glycosaminoglycans [24]. By breaking down scar tissue and upregulating these cell factors, GHK-Cu and similar peptides can significantly improve skin health. Together these approaches form a holistic framework for enhancing skin health and resilience against environmental stressors.

Among the various natural compounds utilized in topical formulations, aloe vera stands out for its anti-inflammatory and wound-healing properties, making it a key ingredient in advancing skin health. The therapeutic potential of Aloe vera has been attributed to a complex mixture of bioactive compounds, primarily polysaccharides such as partially acetylated mannan (acemannan). These compounds exhibit immunomodulatory effects by activating macrophages to produce nitric oxide, cytokines including TNF- α , and interleukins [25]. Aloe vera's ability to modulate immune responses post-UV exposure enhances its protective effects against skin damage,

particularly in inflammatory contexts. Additionally, Aloe vera accelerates wound healing through mechanisms that include maintaining moisture at the injury site, promoting epithelial cell migration, and facilitating collagen maturation [26]. Recent randomized control trials have shown that Aloe vera gel significantly enhances keratinocyte proliferation, as evidenced by Sabaghzadeh et al. (2021) research, where patients treated with Aloe vera gel exhibited faster epithelialization and granulation tissue formation compared to those treated with nitrofurazone for superficial second-degree burns ($P < 0.05$) [27]. Furthermore, Hekmatpou et al. (2018) found that Aloe vera gel applied to pressure ulcer-prone areas resulted in a significantly lower incidence of pressure ulcers in patients with similar efficacy as 2% Nitrofurazone ointment, demonstrating its ability to enhance keratinocyte proliferation and migration, thereby contributing to skin barrier restoration [28].

Calendula is another natural compound that offers anti-inflammatory, antioxidant, and wound-healing properties. In a randomized controlled trial involving 72 primiparous women, the use of calendula ointment significantly accelerated cesarean wound healing compared to standard care. The results demonstrated a mean wound healing time of 4 days in the calendula group, compared to 8.14 days in the control group, highlighting a substantial reduction in the duration of healing [29]. Wound assessment was conducted using the REEDA scale, which evaluates redness, edema, ecchymosis, discharge, and approximation, providing a comprehensive measure of wound recovery. In a related study, the application of a cream containing calendula extract combined with zinc oxide nanoparticles was examined in a rat model of burn injuries. This formulation not only demonstrated enhanced antibacterial properties but also facilitated wound healing through histopathological improvements and increased gene expression of the anti-apoptotic Bcl-2 gene, promoting fibroblast cell proliferation [30]. The treated rats exhibited complete re-epithelialization and mature granulation tissue by day 14, with no signs of infection or hemorrhage. Together, these findings underscore the potential of Calendula as a therapeutic agent in enhancing wound healing across different contexts, supporting its application in modern topical treatments.

Since there is no standard guidance for the application and formulation of Aloe vera and

Calendula, initial recommendations are to follow standard wound management guidelines and practices. These guidelines suggest using products that support tissue repair, protect the wound bed, and prevent infection [31]. For topical Aloe vera, a consistent approach involves applying prepared formulations to affected areas at least twice daily, particularly after cleansing the skin. However, due to variations in Aloe vera formulations and active ingredient percentages in both the literature review and a randomized controlled trial, specific recommendations cannot currently be made, except to use high-quality Aloe vera products [28, 32]. Similarly, while there is no standard guidance for Calendula formulation, topical ointments or creams should be applied to clean, dry skin twice daily. This approach aligns with Jahdi et al. (2018), where Calendula ointment was applied post-operatively every 12 hours for optimal wound healing [29]. In both cases, formulations were consistently applied to wound sites and rubbed in shortly after application, making these practices recommended for best results. Additionally, according to standard wound care guidelines, both treatments can be layered under protective dressings to enhance effectiveness and prevent contamination [31]. Ensuring consistent application and adherence to these practices will help maximize the tissue repair benefits of Aloe vera and Calendula.

6. LIFESTYLE MODIFICATIONS

Lifestyle, along with related social and economic factors, is an important determinant of mental and physical health. Lifestyle modifications like dietary changes, increased physical activity, and reduced substance use play a critical role in not only the prevention but also the management of chronic conditions like diabetes and hypertension. A study conducted in Sweden, including 23,108 participants, investigated the relationship between lifestyle and weight gain, finding that increasing leisure-time physical activity and decreasing alcohol intake decreased weight gain over the 8 years of follow-up [33]. This implies that lifestyle changes can improve overall health, as they can help prevent the various comorbidities associated with obesity. With proper patient education and health maintenance via daily lifestyle choices, we can combat the rising obesity rates and health decline. Similarly, research on 610 Dutch citizens 50 years old and over-assessed patients' lifestyles in relation to their age found that older age was associated with healthy lifestyle choices

like less tobacco or alcohol use, increased fruit and vegetable intake, and eating breakfast in the morning [34]. This reinforces the notion that healthy habits improve physical health to foster better health outcomes and longevity in patients. In addition to improving physical health, having a healthy lifestyle can also improve quality of life by enabling individuals to engage in fulfilling activities without being hindered by health issues.

Chronic diseases affect patients not only physically but also emotionally. This emotional burden can have a compounding effect by exacerbating the physical symptoms of the disease, highlighting the importance of holistic treatment approaches. Mindfulness and meditation have been shown to alleviate stress and can be explored as a potential therapeutic. In a study conducted with 30 college students, mindfulness and meditation effectively reduced stress, anxiety, and depression, whether used alone or in combination with aerobic exercise [35]. When applied to chronic disease management, improving the psychological manifestations of disease and alleviating the stress associated with managing chronic disease can enhance overall quality of life. Furthermore, mindfulness and meditation can supplement or even replace traditional pharmacotherapy. A study conducted with 67 adult participants with primary anxiety disorder revealed that at 24 weeks of treatment, mindfulness and meditation improved work performance comparably to escitalopram, a common SSRI used to manage anxiety [36]. Considering the potential side effects associated with medications, incorporating mindfulness and meditation as therapeutic options can help reduce medication doses and mitigate adverse effects. Notably, meditation can influence other lifestyle habits like diet. Research on 1400 school children aged 9 to 12 years old in Mexico found that students who practiced meditation were more likely to choose a healthy snack than their peers who did not meditate despite receiving the same information about healthy snacks [37]. These results indicate that meditation has the potential to positively impact broader lifestyle habits and overall health. While mindfulness and meditation are effective stress reducers, emerging research shows that meditation can also promote healthier lifestyle choices.

In addition to mindfulness and meditation, exercise is an important component of comprehensive treatment plans. Yoga, in particular, has demonstrated unique benefits

when compared to other physical activities. Li et al. reported that yoga was a more effective treatment for binge eating disorder in young inactive females compared to high-intensity interval training (HIIT), despite HIIT having a greater effect on physical fitness [38]. These findings suggest that yoga may provide a spiritual or emotional benefit that addresses non-physical aspects of chronic disease processes that HIIT does not. This is corroborated by a study involving 158 medical and nursing students in Brazil, which compared circuit training, yoga, and no intervention. This study found that while both circuit training and yoga reduced self-reported stress and physical markers of stress, including systolic blood pressure, only yoga significantly reduced serum cortisol levels [39]. This emphasizes that while yoga shares some benefits with other forms of exercise, it has additional benefits in reducing stress and improving mental and physical health. A long-term study on the effect of yoga over a 3-year period found that yoga significantly reduced the risk of developing type 2 diabetes in individuals with prediabetes when combined with lifestyle modifications compared to lifestyle modifications alone [40]. This may be due to yoga's impact on stress and cortisol, as lowered cortisol levels can prevent the development of insulin resistance. Additionally, yoga has been found to reduce pain and improve sleep quality in patients with temporomandibular joint dysfunction [41]. This further supports yoga's role in the management of chronic disease and pain. Overall, yoga offers distinct advantages in addressing both physical and emotional aspects of health, making it a valuable addition to holistic treatment plans to improve overall well-being.

Another potential treatment approach is acupuncture, which has gained recognition for its application in chronic pain management. In a study involving 30 patients with long heads of biceps brachii tendinopathy, acupuncture was found to produce results equivalent to transcutaneous electrical nerve stimulation in reducing pain and disability. Furthermore, acupuncture led to a greater improvement in biceps peritendinous effusion compared to transcutaneous electrical nerve stimulation [42]. These findings suggest that acupuncture overall affects the body's healing and homeostasis, indicating that acupuncture not only has a role in treating chronic pain but can also be considered when managing chronic conditions. In a study involving 158 women with breast cancer undergoing endocrine therapy, acupuncture was

found to improve the adverse effects related to treatment, including hot flashes [43]. This further emphasizes acupuncture's role in regulating body homeostasis. Incorporating acupuncture alongside traditional treatments can help alleviate adverse effects and make treatment more tolerable for patients. A recent double-blind, randomized control trial conducted with 50 patients post-acute ischemic stroke utilized acupuncture as an intervention in the acute stage of acute ischemic stroke. The study found that acupuncture improved neurological function after an acute ischemic stroke, potentially due to the anti-inflammatory effects [44]. This illustrates that acupuncture not only has a role in the treatment of chronic conditions but can also promote healing in acute conditions. Despite the benefits, acupuncture is not frequently integrated into the standard of care. However, a study conducted in the emergency department demonstrated that supplementing care with acupuncture reduced pain 1 hour after treatment and resulted in higher patient satisfaction [45]. This study shows that acupuncture is not only beneficial to patients, but it is also feasible to implement even in acute care settings. Acupuncture should not be limited to outpatient practice as it can be implemented effectively in various settings.

Lifestyle factors can also have a significant benefit when applied to systemic inflammation and skin health. Mindfulness and yoga not only reduce stress but also reduce inflammation, which can be beneficial for skin conditions. A study involving 95 participants who underwent a mindfulness retreat found that participants had a decrease in self-reported stress and anxiety, as well as a decrease in pro-inflammatory cytokines IL-6 and IL-8 and an increase in anti-inflammatory cytokine IL-10 [46]. These findings suggest that reduction in stress and anxiety via mindfulness can also reduce inflammation and restore homeostasis. Mindfulness is a seemingly simple therapeutic approach that can significantly impact patient outcomes in mental and physical health. Furthermore, a study conducted with yoga showed that even one session of yoga can reduce inflammatory lipid mediators like lipoxin B4, prostaglandin D2 and resolvin D3 [47]. This shows that even the implementation of yoga over a short-term period can have a beneficial effect, making it a feasible treatment in both acute and chronic settings. In addition, while many lifestyle modifications take time to see the effects of yoga, it can make patients feel more emotionally

balanced and have a systemic effect after just one session. Ultimately, these lifestyle changes work synergistically to not only improve overall well-being but also support a healthier inflammatory response to improve skin condition.

7. INTEGRATIVE CARE STRATEGIES

Calciphylaxis is a devastating disease that is routinely associated with high rates of morbidity and mortality. Consequently, treating calciphylaxis demands a multidisciplinary approach that typically involves collaborative efforts from an interprofessional team. For example, this can involve input from a nephrologist, dermatologist, dietician, wound surgeon, wound nurse, pain management specialist, palliative care team, and hyperbaric oxygen provider [17]. For patients with calciphylaxis, early surgical debridement is crucial, as it is linked to higher 6-month survival rates compared to forgoing debridement [48]. The benefits of debridement, especially with respect to calciphylaxis, can help reduce inflammation, improve microcirculation and increase the growth of healthy tissue. Hyperbaric oxygen therapy, when used as an additional treatment, has been demonstrated to improve wounds by 58% and resolve wounds by 50% in patients with uremic calciphylaxis [49,50]. Further evidence of these interventions primarily derives from case reports and retrospective analyses. One retrospective study done by Lajoie et al. reported the cases of 12 end-stage kidney disease patients from a hospital in Québec, Canada who were diagnosed with calciphylaxis and treated with a multimodality clinical approach using sodium thiosulfate (STS), an inorganic compound that has been shown to inhibit medial arterial calcification [51,52,53]. The therapeutic approach used included increasing the frequency and/or duration of hemodialysis, temporarily decreasing calcium dialysate, termination of the use of vitamin D, calcium-based phosphate binders, warfarin, and administering STS with or without bisphosphonate or cinacalcet. Additionally, the 12 patients were also under the medical supervision of chronic wound care specialists who monitored the healing process throughout the study duration. The results showed STS treatment combined with a multimodality approach successfully led to a complete or partial remission in 75% of the patients in the study [53]. Assembling a team of experienced healthcare professionals can enhance the coordination of calciphylaxis care. By leveraging the diverse

expertise of team members, they can deliver a range of effective treatments.

The mainstay nutritional management for calciphylaxis involves keeping blood levels of calcium and phosphorus under control, as high levels of calcium and phosphate worsen the disease through the formation of calcium-phosphate deposits in small blood vessels. As a result, this narrows blood flow, particularly to the skin, which leads to tissue ischemia and necrosis [14,54]. A published dermatologic case report described a patient hospitalized for calciphylaxis secondary to chronic renal failure. Following 3 months on a low-phosphate diet, along with phosphate binders and low-calcium dialysis, the patient showed evidence of recovery [55]. Another study examined the use of nurse-led, multidisciplinary collaborative therapy to prevent calciphylaxis in patients with end-stage renal disease. The researchers specifically looked at the approach of providing nutritional supplementation. Skin damage, wound ulceration, and severe pain can accelerate protein energy consumption, causing calciphylaxis patients to suffer from loss of appetite as a result. To combat this, patients were provided with a low salt, low fat, high protein, high vitamin diet based on a nutritional calculation tool for chronic kidney disease to ensure adequate energy demands, achieve nutrient balance, and enhance immunity [56]. In addition to wound care and STS treatment, vitamin D and vitamin K supplementation is also essential. Specifically, vitamin K deficiency is directly linked to calciphylaxis development as a result of its role in activating matrix Gla protein, a known inhibitor of vascular calcification [19,57,58]. Vitamin D and K deficiencies also serve as a risk factor for uremic vascular calcification [59,60]. Currently, our understanding of calciphylaxis in response to holistic treatments and multidisciplinary collaboration with holistic practitioners remains limited. Compounding the problem is a striking lack of high-quality research and randomized controlled trials using alternative medicine to guide effective treatment approaches. Notwithstanding this dilemma, there are large pieces of evidence in the literature of yoga proving to be beneficial in increasing the quality of life in patients with chronic health conditions. One study demonstrated a proven positive benefit of yoga in ameliorating the physical and psychological symptoms of chronic kidney disease, a condition that is known to increase the risk of calciphylaxis [61]. Mindfulness meditation, a noninvasive and safe

practice, may provide physiological benefits for individuals with chronic kidney disease (CKD), such as reduced hypertension and decreased sympathetic nervous system overactivity [62]. Possible future studies include the use of yoga and other meditational practices in calciphylaxis prevention among patients with long-term kidney disease.

On account of the rarity of calciphylaxis and the incomplete knowledge of its etiopathogenesis, documented efforts surrounding the raising of awareness about this highly serious condition remain limited. One existing piece of this in current literature is in the form of a recent case series, which looked at 17 patients enrolled in the UK Calciphylaxis Study (UKCS) that were recruited from two NHS Hospital Trusts in the UK. These patients presented with end-stage renal kidney failure and clinical features of calciphylaxis. Within this participant cohort, a history of hyperphosphatemia was common, as well as the usage of calcium-based binders, alfacalcidol, and warfarin. Only 52% of the patients survived, and 66% of those surviving patients presented with completely healed lesions caused by calciphylaxis. Out of all the patients who participated, only one was enrolled in the UK registry of rare kidney diseases (RaDaR) [63]. This discovery highlighted a vital need for the establishment of national patient calciphylaxis registries that could collect data to advance public understanding of this condition. The hope is that with the increase of patient recruitment to existing registries and the creation of similar registries in countries around the world, more information can be elucidated on calciphylaxis incidence that will adequately inform prevention and treatment strategies to empower both at-risk patients and sufferers of the disease.

8. CONCLUSION

In summary, chronic diseases profoundly impact patients, causing both physical and emotional distress. Holistic treatment approaches can prove useful in the management of comorbid conditions and complications that accompany calciphylaxis. The immunomodulatory properties of plants such as aloe vera promote wound healing by retaining moisture at sites of injury, increasing epithelial cell migration, and aiding in collagen maturation [26]. In multiple studies incorporating the use of aloe vera gel, results showed evidence of increased keratinocyte proliferation and restoration of the skin barrier [28,64]. Widely used in homeopathic applications, calendula is

another herbaceous plant known for its anti-inflammatory, antioxidant, and wound-healing properties. Topical uses of calendula in the form of creams and ointments have demonstrated significant benefits in the healing of cesarean wounds in new mothers compared to standard treatment, as well as complete re-epithelialization and formation of granulation tissue in burn injury rat models [29,30]. Mindfulness and meditation can help alleviate the stress and emotional distress that often accompanies chronic conditions, thereby enhancing patient quality of life. Haag et al. demonstrated that while both circuit training and yoga can reduce stress, yoga is uniquely effective at lowering cortisol levels [39]. Furthermore, a long-term study conducted by Madhu et al. found that yoga combined with lifestyle changes greatly reduces the risk of type 2 diabetes in prediabetic individuals, likely due to its benefits for stress and cortisol management [40]. Acupuncture has also emerged as a valuable method for managing both chronic and acute pain, with studies indicating that acupuncture is as effective as transcutaneous electrical nerve stimulation (TENS) in reducing pain and disability, and it can also alleviate treatment-related side effects for cancer patients, such as hot flashes [42,43]. Acupuncture's anti-inflammatory properties may also explain its ability to improve neurological function in post-acute ischemic stroke patients [44]. Despite the demonstrated benefits of these holistic treatments, they are not consistently integrated into standard care practices. This is particularly evident in the current literature on calciphylaxis treatment, especially considering the possibility that some patients may prefer a regimen that reduces reliance on certain medications like opioids for pain management.

Empowering patients with calciphylaxis involves cultivating an environment where patients feel confident, informed, and actively engaged in their treatment journey. This can be achieved by involving patients in the decision-making process and considering their goals and therapy options. Depending on the severity and prognosis of calciphylaxis, patients may opt for lifestyle modifications through diet rather than relying solely on conventional medical therapies. Regardless of their treatment approach - alternative, conventional, or combination - patients should receive clear, comprehensive education on the risks and benefits of each option from a multidisciplinary care team. Additionally, educating at-risk populations, such as those with chronic kidney, liver, or endocrine conditions

(i.e., diabetes mellitus) about calciphylaxis may serve as a prophylactic measure. Adopting these holistic approaches can enhance patient outcomes, satisfaction, and overall well-being, potentially leading to increased rates of calciphylaxis remission. Healthcare providers should prioritize strategies that promote patient empowerment, including personalized education, open communication, and community support.

The main objective of this review is to make known the potential benefits of incorporating natural remedies into the treatment and management of calciphylaxis. Out of all the current studies on multidisciplinary care in calciphylaxis, there has not been any clear evidence of the incorporation of holistic practitioners alongside medical professionals. One reason for this can be attributed to the public perception of alternative remedies being labeled as 'pseudoscience' and associated with minimal evidence of evidence-based efficacy from a medical standpoint. Another reason, albeit from a more valid perspective, is the possibility of certain types of natural remedies causing negative drug interactions with certain prescription medications and causing harmful side effects [65,66]. Compounding the problem is the fact that despite the easy availability of natural remedies to consumers, there is minimal federal oversight and regulation of these products in the United States [66]. Therefore, more focus should be targeted towards holistic remedies backed by existing scientific literature that have the potential for integration into calciphylaxis management. Biologically based therapies such as turmeric have been proven to show significant benefits in mediating inflammation in chronic diseases. Its anti-inflammatory properties are attributed to its active compound, curcumin, which works by inhibiting multiple inflammatory pathways in the body. One notable target of curcumin is the NF- κ B signaling cascade [67,68]. Numerous studies have demonstrated that turmeric's anti-inflammatory properties can effectively treat various dermatologic conditions, including eczema, acne, and psoriasis, further supporting its potential therapeutic benefits for skin health [69,70,71]. Despite its benefits, there is equal evidence to show that turmeric also has additional anticoagulant properties, which can potentiate the effects of medications such as blood thinners and lead to an increased risk of bleeding [72,73,74]. Careful monitoring of the use of turmeric supplements with medications used to treat calciphylaxis is highly necessary to avoid further patient harm.

Ultimately, involving holistic practitioners alongside physicians, nurses, nutritionists, and other medical specialists in creating a treatment plan for calciphylaxis patients will allow for the easy integration of alternative therapies with conventional medical treatments, advancing the shared goal of delivering comprehensive, safe, and effective care through a collaborative, interdisciplinary approach.

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