



Nonuremic calciphylaxis - A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Calciphylaxis, also known as calcific uremic arteriopathy, is a well-described condition in renal transplant and end-stage kidney disease (ESKD) patients; however, little is known about calciphylaxis induced by nonuremic causes. This systematic study aimed to determine the causes, prognosis of nonuremic calciphylaxis, clinical features and laboratory abnormalities.

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Patients and methods:A comprehensive review of the literature for nonuremic calciphylaxis case reports and case series published between 2016 and 2021 was performed. Cases included satisfied the criteria for a histological diagnosis of nonuremic calciphylaxis in the absence of ESKD, renal transplantation, or acute kidney injury requiring renal replacement therapy.

Results: The authors identified 53 cases of nonuremic calciphylaxis (83.14 % women, Caucasian 13.33 %, aged 25 to 83 years). The most prevalent documented associations were of patients having multiple conditions 18 (33.33 %), warfarin-induced (7.4 %), calcium and Vitamin D supplementation (3.7 %), primary hyperparathyroidism (3.7 %), liver disease (3.7 %), Acenocumarol use (3.7 %), Systematic lupus erythematosus (3.7 %), alcoholic cirrhosis (3.7 %), respectively.

Conclusion:When investigating skin lesions in patients with sensitive conditions, calciphylaxis must often be addressed in the absence of ESKD or renal transplantation. Obese women with various underlying illnesses such as alcohol intake, smoking, diabetes, liver disease, and so on are more likely to develop nonuremic calciphylaxis (NUC).Calciphylaxis is linked with high mortality; however, sodium thiosulfate (ST) has made clear progress in terms of treatment, yet there are still areas that need to be addressed to describe the effectiveness of ST.

Keywords: Calciphylaxis; nonuremic; calcium; warfarin; supplements.

1. INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriopathy (CUA), is a disease that has a 60–80% one-year mortality rate [1,2]. It's more common in those with end-stage renal illness (ESRD). Calciphylaxis is a condition that causes painful skin lesions that eventually turn into ulcers [3-8]. The calcification of small and medium-sized dermal and subcutaneous veins, intimal hyperplasia, and thrombosis distinguishes this rare disease histologically. The prevalence of calciphylaxis in ESRD patients is increasing [1]. There are now registries and clinical studies underway to investigate the etiology of calciphylaxis in ESRD patients and to discover new treatments. The cause of the increase in occurrence is unknown. Patients with ESRD, a challenging group, are the ones who are most impacted by this disease. Calciphylaxis affects 35 out of every 10,000 hemodialysis patients in the United States, 4 out of 10,000 in Germany, and less than 1 out of 10,000 in Japan [2]. Given the high morbidity and death rates associated with calciphylaxis, as well as the lack of FDA-approved treatments, identifying and removing the risk factors associated with the disease is critical.

While abnormal bone and mineral metabolism, hyperparathyroidism, and vitamin D supplementation are commonly suspected as causes of CUA, the disease procedures are seldom acknowledged; as a result, therapeutic attempts remain untested, and mortality continues to grow [3]. Despite this, nonuremic calciphylaxis (NUC) can occur in people who

have normal kidney function; the risk factors, etiology, consequences, and therapies for NUC remain unknown.[4]. The causes, clinical characteristics, laboratory abnormalities, and prognosis of calciphylaxis from NUC were all investigated thoroughly. A thorough examination of the clinical features of NUC might aid our understanding of CUA.

2. MATERIALS AND METHODS

2.1 Research Questions

The research questions posed in this systematic review concern:

- What are the conditions associated with nonuremic causes of calciphylaxis?
- What are the clinical features, laboratory abnormalities and prognosis of calciphylaxis from NUC?
- What are the treatment options for NUC patients?

To answer these above questions, the following procedure/methodology was followed in the research.The study was conducted using the standard reporting requirements for systematic reviews and meta-analyses (PRISMA). Methodology for doing a literature search: PubMed, Embase, Ovid, Google Scholar, and Science Direct were used to perform a thorough review of the literature. The search was conducted between June 2 and June 10, 2021. The keywords used for retrieval of articles were "calciphylaxis," "nonuremic calciphylaxis," cause and aetiology." To enhance the quality of search, the keywords were combined with "laboratory

abnormalities, treatment options, and clinical features of calciphylaxis".The titles and abstracts of the produced results were used to filter the findings. Articles that were duplicated were deleted.

2.1 Inclusion and Exclusion Criteria

Studies depicting any association of a risk factor with the development of NUC were included in the review. Case studies and case series were the types of articles that were included. Cases that met the objective measure of NUC–histopathologic finding of calciphylaxis in the nonappearance of (ESKD), severe chronic kidney illness delineated as serum creatinine 3 mg/dl or creatinine clearance 15 ml/min, acute kidney injury permitting renal substitution therapy, and renal transplantation–were all included. There were no language prerequisites.

2.2 Data Extraction

The papers were chosen separately by different investigators based on the aforementioned inclusion and exclusion criteria. If the number of articles chosen by the investigators differed, an agreement was established after discussion. Next, both investigators separately studied the

complete contents of the publications and extracted the pertinent data into excel sheets. Finally, a third investigator evaluated the findings. The following data linked to the studies were obtained; authors, race, histopathologic findings, lesion location, treatment strategy, death or alive, and reasons (if available).

3. RESULTS

We identified 53 cases of NUC [5]–[6-7]which included 46 (86.79 %) individual case reports and 7 (13.20 %) case series Fig. 1. Depicts an overview of the literature survey. The histopathologic findings in all of the individuals investigated were consistent with calciphylaxis. Calcifications of medium and/or small arteries (n = 34), fat necrosis (n = 17), thrombosis (9), panniculitis (n = 5), and ischemia (n = 2) were the most commonly observed histopathologic abnormalities. Other observations also include the occurrence of endovascular fibrosis (n = 1), pseudoxanthoma elasticum-like fibers and fibrointimal hyperplasia (n = 1). Participants were between 25 to 83 years old; 62 were over 60 years old, 25 were between 30 and 60 years old, and one was under 30. The majority of patients were women, 73 (86.90 %), while only 15 were males (17.04 %), respectively.

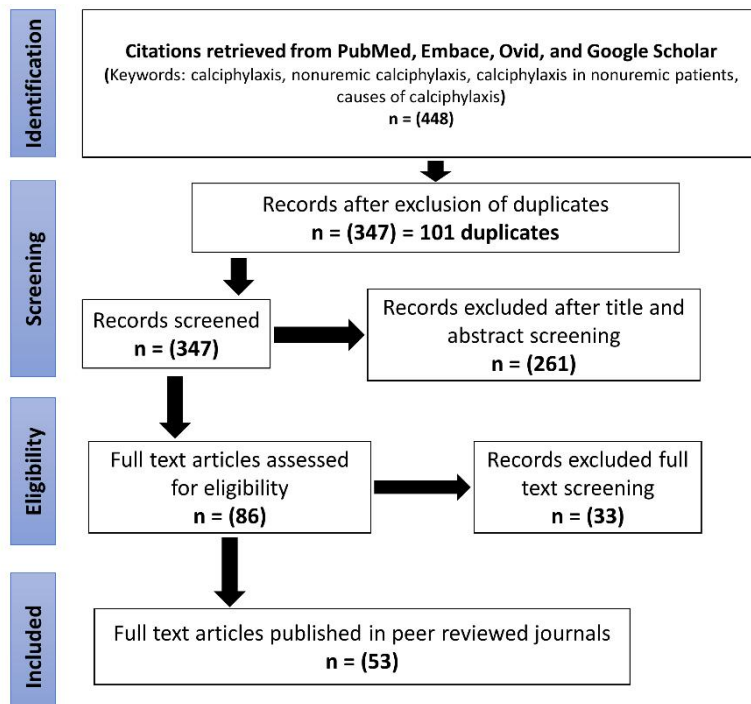


Fig. 1. An overview of the approach for doing a literature search

Most of the studies reported multiple conditions 18 (33.96 %) [8,5,9,10,11,12–14,6,15,16,17,18,19,20,21,22], [7]; define herein as patients suffering from more than two morbidities were assembled in multiple conditions. Other morbidities among the included studies were warfarin induced (7.54 %) [23,24,25,26], calcium and Vitamin D supplementation (3.77 %) [27,28], liver disease (3.77 %) [29,30], Systematic lupus erythematosus (3.77 %)[31,32] and alcoholic cirrhosis (3.77 %) [33,34], respectively (Table 1). Similarly, other remaining etiological conditions were; primary hyperparathyroidism [35], malignancy [36], glucocorticoid [37], stage IV non-Hodgkin lymphoma [38], chronic kidney disease [39], acenocumarol use [40], weight loss and hypotension [41], rheumatoid arthritis and hypotension [42], diuretic therapy [43], diabetes mellitus type-II [44], psoriasis [45], rheumatologic disease [46], multiple myeloma and rheumatoid arthritis [47], alcoholic hepatitis [48], covid-19 [49], liver transplant [50], SLE and

antiphospholipid antibody syndrome (APS) [51], recombinant human parathyroid hormone therapy (PTH) [52], autoimmune disease [53], coumarin necrosis and vasculitis [54], neuroendocrine tumor (NET) [55], rheumatoid arthritis [56].

In addition, majority of the wounds of NUC were seen on legs (n = 20, 37.73 %), thighs (n = 16, 30.18), calves (n = 7, 13.20 %), breast (n = 4, 7.54 %) as well as buttocks (n = 4, 7.54 %), respectively. However, there was no mention of penis participation in any of the NUC. The skin lesions mirrored those reported in CUA in terms of morphology, including indurated nodules, necrotic eschars, ulcerations, dry gangrene, and livedo reticularis. Table 2 shows an overview of laboratory parameters in NUC instances. Mostly, studies had normal calcium (56.60 %), normal phosphorus (50.94 %); the normal calcium-phosphorus product was reported only in 7 cases (13.20 %), while only 17 cases (32.07 %) reported normal values of serum parathyroid hormone. Likewise, normal serum creatinine and

Table 1. Conditions associated with nonuremic calciphylaxis

Cause	No of Cases (%)
Multiple conditions	18 (33.96)
Warfarin induced	4 (7.54)
Acenocumarol induced	2 (3.77)
Calcium and Vit D supplementation	2(3.77)
Alcoholic cirrhosis	2 (3.77)
Systematic lupus erythematosus (SLE)	2 (3.77)
Liver disease	2 (3.77)
Stage IV non-Hodgkin lymphoma	1 (1.88)
Chronic kidney disease [§]	1 (1.88)
Hyperparathyroidism	1 (1.88)
Weight loss and hypotension	1 (1.88)
Rheumatoid arthritis and steroid use	1 (1.88)
Diuretic therapy	1 (1.88)
Glucocorticoid	1 (1.88)
Diabetes mellitus type-II	1 (1.88)
Psoriasis	1 (1.88)
Numerous rheumatologic disease	1 (1.88)
Multiple myeloma and rheumatoid arthritis	1 (1.88)
Alcoholic hepatitis	1 (1.88)
Covid – 19	1 (1.88)
Liver transplant	1 (1.88)
Malignancy	1 (1.88)
SLE and antiphospholipid antibody syndrome	1 (1.88)
Coumarin necrosis and vasculitis	1 (1.88)
Autoimmune disease	1 (1.88)
Neuroendocrine tumor	1 (1.88)
Rheumatoid arthritis	1 (1.88)

Multiple condition:* patients have more than two morbidities at a time, *chronic kidney disease[§]:* patient not on dialysis.

vitamin D level were only seen in 19 (35.84 %) and 6 (11.32 %) cases, respectively. In contrast, the elevation of calcium (>12.0 mg/dl) was seen in 3 (5.6 %), phosphorus (>6) was seen in only 1 (1.88 %), whereas high serum PTH and vitamin D were seen in 10 (18.86 %) and 3 (5.66 %) cases, respectively. Most of the cases (35.84 %) had normal (≤ 1.2 mg/dl) serum creatinine values, while one (1.88 %) case had higher serum creatinine than 2.5 mg/dl.

Moreover, mortality rate among patients with NUC was 26.66% [5,31,47,48,41,6,35,33, 37,17,57,22,32,25,53] While sepsis was the leading cause of mortality, accounting for 6.6% of all fatalities. Other mortality rates documented throughout the instances covered, however, were a multiorgan failure, cardiac fibrillation, and pneumonitis.[33,35]. Treatment procedures varied among the cases depending on the degree and intensity of the lesion formed on the skin. Palliative wound nursing with discomfort management, empiric antibiotic treatment,

treating core causative disorders (e.g., parathyroidectomy for hyperparathyroid patients), and decreasing, potentially triggering issues were all documented treatment (e.g., corticosteroids, albumin infusions). In three cases (5.66 %), vitamin D supplementation and two cases (3.77 %), vitamin K supplementation was used as a therapy. Similarly, corticosteroid therapy was used in only five cases (9.43 %), while most of the studies (54.71 %) reported intravenous sodium thiosulfate (IV - ST) injection as a baseline treatment for NUC. Some other treatment strategies among the included cases were hyperbaric oxygen therapy [51,50,7], cannabis-based medicine [21], IV – pamidronate [45], doxycycline combined with zoledronic acid and Rivaroxaban [15], as well as heparin [31,51,57] individually or combined with other medicines, respectively. Moreover, the duration of complete resolution of skin lesion ranged from 2 months to 3 years. Table 3 summarizes the Characteristic of the studies included and patient-related information.

Table 2. Laboratory parameter in patients with NUC

Laboratory parameter	Data available (%)
Serum calcium (mg/dl)	
Low ≤ 8.5	2 (3.77)
Normal (8.5 – 10.2)	30 (56.60)
Mild elevation (10.3 – 12.0)	0 (0.00)
Marked elevation (>12.0)	3 (5.66)
Not reported	18 (33.96)
Serum phosphorus (mg/dl)	
Low (<2.2)	1 (1.89)
Normal (2.2 – 4.5)	27 (50.94)
Mild elevation (4.6 - 6.0)	3 (5.66)
Marked elevation (>6)	1 (1.89)
Not reported	22 (41.51)
Calcium-phosphorus product	
<50	7 (13.21)
>50	0 (0.00)
Not reported	46 (86.79)
Serum PTH	
Low	1 (1.89)
Normal	17 (32.08)
High	10 (18.87)
Not reported	25 (47.17)
Serum creatinine (mg/dl)	
≤ 1.2	19 (35.85)
1.3 - 1.5	3 (5.66)
1.6 - 2.5	1 (1.89)
2.6 - 3.0	4 (7.55)
Not reported	26 (49.06)
Vitamin D	
Low	5 (9.43)
Normal	6 (11.32)
High	3 (5.66)
Not reported	39 (73.58)

Table 3. Characteristic of the studies included

Reference	Caucasian	AF/AM/IN/H S	Histopathologic findings	Location of lesion	Treatments	Dead/Aliv e	Reason
[8]	NA	NA	IVC, WN, Panniculitides	Proximal inner thighs and inferior abdominal Pannulus	IV - ST	A	NA
[5]	all (8)	NA	IU, STN, CD, TN	Breast, Thigh, Legs	IV - ST, fluidione IV - ST, fluidione	4D/4A	NA
[56]	NA	NA	VMC, LT	Vesicular lesion of left leg	NA	A	NA
[7]	NA	1	CD, AT	Right lower leg	PB, HBOT, AGT,	NA	NA
[31]	1	NA	CD, Necrosis	Calves	Heparin, Steroid, Vit D	D	sepsis
[33]	NA	NA	CD	Left calve and right leg	Prednisone	D	Cardiac fibrillation
[6]	NA	NA	CD, Panniculities, Thrombosis	Both legs	Prednisone, Enoxaparin	D	Sepsis
[37]	NA	NA	CD	Left leg	AB, Steroid	D	Sepsis
[51]	1	NA	CD, Fat necrosis	Right leg	ST, HBO, Heparin, Prednisone	A	NA
[15]	NA	NA	Vascular calcification, Nephrocalcinosis	Both lower legs	Doxycycline, Zoledronic acid, Rivaroxaban	A	NA
[16]	NA	NA	Cutaneous vasculitis	Left leg	NA	A	NA
[52]	NA	NA	TN	Right breast lesion	ST, Opiods	A	NA
[27]	NA	NA	Thrombosis, CD, Fat necrosis	Calves	ST, Skin drafting	A	NA
[38]	NA	NA	CD, VN	Lower limbs	ST	A	7 months
[23]	NA	Indian	CD, Thrombosis, Panniculitis	Right leg	Local wound treatment	A	4 months
[39]	NA	NA	Necrosis, calcification	Both thighs	ST, Antibiotics	A	NA
[40]	NA	NA	Microthrombosis, Fibrointimal	Below knees	Topical treatment	A	6 to 14 months

Reference	Caucasian	AF/AM/IN/H S	Histopathologic findings	Location of lesion	Treatments	Dead/Alive	Reason
[29]	1	NA	hyperplasia, CD Necrotic leukocytic, Thrombosis, CD	Both thighs	ST	A	5 months
[36]	NA	NA	Cellulitis of small vessels	Left lower leg	Antibiotic, Skin grafting	A	NA
[17]	all (8)	NA	CD	Peripheral leg	ST, Bisphosphonate	2D/6A	NA
[65]	NA	NA	CS	Lower peripheral abscess	IV - ST, IL - ST, steroid	A	6 month
[41]	1	NA	Thrombosis, CD, necrosis	Thigh, buttocks, right shoulder	IV - ST, Alendronate	D	NA
[12]	NA	1-Hispanic, 1- African/American	Thrombosis, fat Necrosis, CD	Calf	IV - ST,	A	6 weeks
[13]	NA	NA	CD, Fat Necrosis	NA	NA	NA	NA
[18]	NA	1	CD, Necrosis	Sacral region, Bilateral thighs, Flanks, lower epigastrium	ST, DuoDERM, Tube supplementation	A	1 year
[42]	NA	NA	CD, Thrombosis, Panniculitis, fat necrosis	NA	NA	NA	NA
[43]	NA	NA	Thrombosis, Calcification of Vessels, Panniculitis	Buttocks, thighs	IV - Pamidonate, Calcium carbonate, Cholecalciferol	A	5 months
[54]	NA	NA	CD,	Left lower leg	IV - ST, Topical ST	A	7 months
[19]	NA	NA	CD	Abdominal wall	IV - ST, Opioids	NA	NA
[20]	NA	NA	CD of small vessels	Lower leg	Vit K, D, Bisphosphonate, opioid	NA	NA
[57]	NA	NA	CD	Right leg	Heparin, Vit D, Cinacalcet	D	NA
[49]	1	NA	CD of small vessels, Fat necrosis	Bilateral flanks, Hips, Lower	NA	NA	NA

Reference	Caucasian	AF/AM/IN/H S	Histopathologic findings	Location of lesion	Treatments	Dead/Aliv e	Reason
[21]]	1	NA	CD	abdomen Right leg	Cannabis based medicine, Analgesic	A	2 months
[22]	NA	NA	CD small and medium, Fat Necrosis	Thigh, Ankle	IV - ST, Skin draft	2A/1D	3 months
[32]	NA	1	CD connective tissues	Trunk, Upper extremities	IV - ST, IV - Bisphosphonate, Plasmapheresis	D	NA
[44]	NA	NA	Epidermal, Superficial dermal necrosis, Fat Necrosis	Lower limb	NA	NA	NA
[24]	NA	NA	CD small and medium, Fat Necrosis, Neovascularization	Both thighs	IV - ST	A	2 months
[14]	NA	NA	Inflammation, Fat necrosis, Thrombosis, CD	Right thigh	Tramadol	A	3 months
[25]	NA	NA	CD	Thigh and lower abdomen, Calf	STS	2D/3A	5 months
[45]	NA	NA	CD subcutaneous adipose tissue	Right calf	IV - ST, IV - Pamidronate, IL - ST, IV - Vit K	A	4 months
[34]	NA	NA	CD	Bilateral groin and thigh	NA	NA	NA
[46]	NA	NA	Intravascular and perivascular CD, Pseudoxanthoma elasticum-like fibers	Left calf	IV - ST, Cinacalcet	A	6 month
[53]	NA	NA	CD	Both legs	IV - ST, cinacalcet	1D/1A	5 years
[66]	1	NA	CD, Vasculitis	Both thighs	IV - ST	A	NA
[28]	NA	NA	CD small and medium size vessel, Tissue	Left breast	IV - ST, IV - Ibandronate	A	3 years

Reference	Caucasian	AF/AM/IN/H S	Histopathologic findings	Location of lesion	Treatments	Dead/Aliv e	Reason
[47]	NA	NA	Necrosis Endovascular fibrosis, Fat necrosis, Thromobosis, Ischmia, CD	Back of both legs	NA	D	NA
[9]	NA	NA	Fat necrosis, CD small vessels	Abdomen and proximal thighs	IV - ST, Sevelamer	NA	NA
[26]	NA	NA	Fat Necrosis, CD small and medium vessels	Both breasts	Surgery	A	NA
[48]	1	NA	CD large veins and adipose tissue	abdomen, Hips, and thighs	IV - ST, Surgical debridement	D	sepsis
[10]	NA	NA	CD in arterioles in the dermis and subcutaneous adipose tissue	Left arm and bilateral legs	NA	NA	NA
[11]	NA	NA	CD	Legs	IV - ST	NA	NA
[55]	NA	NA	CD in small and medium size vessels, ischemia, necrosis of skin	NA	IV - ST	NA	NA
[35]	NA	NA	CD	Bilateral lower limbs	Vacuum assisted closure, Skin graft	D	sepsis, multiorgan failure, pneumonitis
[50]	NA	1	CD	Both thighs and right buttocks	Surgical debridement, IV - ST, Cinacalcet, Hybaric oxygen	A	4 months

NA (Not available), IVC (Intravascular calcification), WN (Warfarin necrosis), IV-ST (Intra vascular sodium thiosulfate), D/A (Dead or alive), IU (Ischemic ulceration), STN (Soft tissue necrosis), CD (Calcium deposit), TN (Tissue necrosis), VMC (Vascular mular calcification), LT (Luminal thrombosis), AT (Arteriolar thrombi), PB (Phosphate binders), HBOT (Hyperbolic oxygen therapy), AGT (Allografts), UNP (Ulcerated necrotic plaques), VN (Vascular narcosis), IL (Intra lesional), AF (African), AM (American), HS (Hispanic), IN (Indian).

4. DISCUSSION

Calciphylaxis was initially characterized as a systemic hypersensitivity response by Selye et al. [58] in 1961. They used animal studies to cause calcification in a variety of areas after exposing the animals to a variety of reactive chemicals known as "calcifiers" (e.g., vitamin D2, vitamin D3, dihydrotachysterol, parathyroid hormone), followed by exposure to a "challenger" (e.g., metallic salts such as egg albumin, aluminum, iron, and trauma). Calciphylaxis, on the other hand, was originally reported in humans some years ago by Selye et al. as a condition characterised by small mural calcification, uremic kidney thrombosis ischemia, extravascular calcification, skin and soft tissue necrosis, and a high mortality rate.[4].

In this systematic review, we reported 53 reported cases of NUC during the last five years. Thus, reporting of NUC has increased significantly, implying an increasing frequency of the syndrome; conversely, increased knowledge that the illness might arise beyond the ESKD and in renal transplant patients, on the other hand, may have resulted in a more significant number of cases getting detected and finally discussed in the literature. As a consequence, while some have speculated that the rise in CUA is due to more rigorous mineral metabolism management and secondary hyperparathyroidism among dialysis patients, the growth in CUA appears to be in lockstep with the rise in NUC. It might be because of greater understanding and relatively early skin surgery.

Secondary hypercalcemia, hyperparathyroidism, hyperphosphatemia, calcium-based phosphate binders, and vitamin D supplements, among other uremia-related metabolic diseases and medicines, are thought to worsen CUA risks.[59]. That idea appears to be supported by the histopathologic picture, which revealed substantial soft tissue calcification. As a consequence, it's worth mentioning that the majority of study participants had normal calcium, phosphate, and parathyroid hormone levels, while just five were vitamin D deficient. Because calcium and phosphorous "intake" during the precipitation method may represent part of the normal or low blood levels of these minerals. Anomalies in bone and mineral metabolism, as well as associated therapies, may have a role in calciphylaxis in certain individuals; the pathogenesis is likely far more complex than we now comprehend. It might reflect a similar

histopathologic characteristic of tissue damage in retort to several diverse stimuli. Inadequacies in vascular calcification antagonists e.g., fetuin-A and matrix Gla protein [60–62] are now thought to have a role in CUA, adding to our approach to the analysis of vascular calcification. Because this system is implicated in the etiology of CUA, irrationalities of receptor activator of NF- κ B (RANK), RANK ligand, and osteoprotegerin could be implicated [63]. Many of the factors associated for NUC (corticosteroid, liver disease, parathyroid hormone) have been shown to enhance the synthesis of RANK ligand while decreasing the manifestation of osteoprotegerin, activating NF- κ B or damaging the regulatory protein of NF- κ B (or a blend of these)[64].

As with every systematic review, there is a lack of comprehensive information, potential selection, publishing biases, and a controlled method to reporting in this one. Though NUC has become more widely recognized in recent years, a lack of understanding of the disease, as evidenced by patients' lack of awareness of the disease, may have resulted in under-recognition and, [60-68] as a result, confidential reporting of the disease, limiting the representativeness of this systematic review. In addition, we did not disclose attempting to contact the authors of original reports to collect missing data (e.g., time to death, laboratory parameters, histopathologic confirmation, or bone scans), which may lead to some of the stated words being "associated" with the NUC. While our method may have overlooked some real NUC instances, many more are likely to have gone unreported, a shortcoming that continues to hinder efforts to precisely estimate the syndrome's prevalence and thoroughly evaluate its health consequences.

5. CONCLUSION

NUC is a rare disorder that is becoming more prevalent. The four Ws (woman, white race, overweight, and warfarin) are the most common ethnic and concomitant features in NUC. The majority of cases in our review were caused by warfarin usage, calcium and vitamin D supplements, Acenocoumarol, and alcoholic cirrhosis, emphasizing the importance of maintaining a consistent ratio of concern while assessing skin abnormalities in NUC patients. While sodium thiosulfate is the therapy of choice among nephrologists, there is still more work to be done to effectively treat NUC.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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