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Original article

CHRONIC INFLAMMATION IN DIALYSIS PATIENTS AND ITS CORRELATION WITH DERMATOLOGICAL MANIFESTATIONS: A MULTICENTER STUDY FROM SKOPJE

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Abstract

Introduction: Chronic systemic inflammation is a defining feature in dialysis patients, contributing significantly to dermatological manifestations such as pruritus, xerosis, pigmentation changes, and nail abnormalities. These conditions impair quality of life and are linked to markers of systemic inflammation and dialysis-related factors.

Objectives: This study aimed to analyze the prevalence and severity of dermatological manifestations in dialysis patients, and their correlations with systemic inflammation.

Methods: An observational, cross-sectional study was conducted in two dialysis centers in Skopje, North Macedonia, involving 167 chronic dialysis patients. Data collection included dermatological assessments, laboratory markers (e.g., CRP, PTH, MPV), and pharmacological histories. Statistical analyses were used to explore correlations.

Results: Pruritus was observed in 74% of patients and correlated significantly with CRP (R=0.223, p=0.005) and PTH (R=0.219, p=0.008). Xerosis affected 88.62% of patients, with moderate severity in 38.92%, and correlated with CRP (R=0.215, p=0.003). Pigmentation changes (63.47%) were linked to MPV (R=0.219, p=0.004), while nail abnormalities (81.44%) correlated with ferritin (R=0.170, p=0.028).

Conclusion: Dermatological manifestations are prevalent in dialysis patients and closely associated with systemic inflammation markers. A multidisciplinary approach is essential to improve management and patient outcomes.

Keywords: chronic systemic inflammation, dermatological manifestations in dialysis, hemodialysis patients, pruritus and xerosis, inflammatory biomarkers

Introduction

End-stage renal disease (ESRD) is a growing public health concern globally, with an estimated prevalence of 700 million individuals affected by chronic kidney disease (CKD), many of whom progress to ESRD requiring dialysis [1]. Dialysis, while life-saving, fails to replicate the full detoxification and immunomodulatory functions of the kidneys, leading to

systemic complications, including chronic inflammation, which has been identified as a key factor contributing to morbidity and mortality in this population. Chronic inflammation is driven by factors including uremic toxins, oxidative stress, and recurrent infections [2].

In addition to systemic complications, dermatological manifestations are commonly observed in dialysis patients, affecting up to 80% of this population [3,4]. Conditions such as pruritus, xerosis, pigmentation changes, and nail abnormalities are not only prevalent but also significantly impair patients' quality of life [5]. These dermatological symptoms are increasingly recognized as markers of systemic inflammation and indicators of disease burden [6]. While these conditions are commonly reported, their association with chronic inflammation remains underexplored.

This study investigated the correlation between chronic inflammation in dialysis patients and its impact on dermatological health, using data from a comprehensive study of ESRD patients in Skopje.

Objective

The aim of this study was to analyze the relationship between chronic systemic inflammation and dermatological manifestations in dialysis patients. Specific objectives included:

1. Evaluating the prevalence and severity of dermatological manifestations in dialysis patients.
2. Exploring correlations between sociodemographic characteristics, inflammatory markers, laboratory parameters, and pharmacological treatments with dermatological findings.
3. Providing recommendations for improving patient care through a multidisciplinary approach.

Methodology

This observational, cross-sectional study was conducted between March and June 2022 in two dialysis centers in Skopje, North Macedonia. A total of 167 patients with CKD stage 5 on chronic hemodialysis (HD) (≥3 months) aged ≥18 years were included, following informed consent. Patients with pre-existing chronic dermatological conditions or renal transplants were excluded.

Data Collection

- Clinical Evaluations: Comprehensive examinations were performed to identify dermatological manifestations.
- Instrumentation:
- Xerosis severity was graded using a xerosimeter on a 5-point scale [41].
  - Visual Analog Scale (VAS) measured pruritus intensity [40].
- Dermoscopy and histopathology confirmed select diagnoses [42-44].
- Laboratory Parameters: Complete blood count, urea, creatinine, uric acid, serum calcium, phosphate, triglycerides, albumin, parathyroid hormone (PTH), ferritin, and C-reactive protein (CRP) levels were analysed.
- Pharmacological History: Detailed review of prescribed medications, including vitamin D supplementation, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin II receptor blocker (ARB) therapy, and anemia correction drugs.
- Dialysis Duration: The length of time patients were on dialysis was recorded and analyzed.

- Sociodemographic data: Gender, age, nationality, and socioeconomic status, which was defined in four categories: poor (no income, dependent person), medium (disability pension/social assistance), good (regular pension, employed), and excellent (higher education – regular pension, employed, or business owner).

Statistical Analysis

Statistical analysis was performed using a range of methods. Descriptive statistics were used to summarize the baseline characteristics of the study population. Correlations between clinical, laboratory, and sociodemographic variables were evaluated using Pearson and Spearman correlation coefficients. Group differences were assessed through ANOVA and t-tests, while multivariate regression analysis was employed to identify independent predictors of mucocutaneous changes.

Results

Patient Characteristics

The sociodemographic characteristics of the study population, including gender distribution, age, socioeconomic status, and nationality, are summarized in Table 1.

Table 1: Sociodemographic Characteristics of the Study Population

[1]Parameter	Value
Total Patients	167 (100%)
Gender	Male: 108 (64.67%)
	Female: 59 (35.33%)
Age (years)	Mean ± SD: 62.21 ± 12.94
	Range: 26–90
	Median (IQR): 64 (56–71)
Socioeconomic Status	Poor: 18 (10.78%)
	Medium: 45 (26.95%)
	Good: 84 (50.29%)
	Excellent: 20 (11.98%)
Nationality	Macedonian: 119 (71.26%)
	Albanian: 23 (13.77%)
	Roma: 9 (5.39%)
	Turkish: 5 (2.99%)
	Serbian: 5 (2.99%)
	Other: 6 (3.59%)

[1]Patients with CKD stage 5 on chronic HD program; Mean = Average; SD = Standard Deviation; Median (IQR) = Middle value and interquartile range, indicating the variability of the data.

Dialysis Initiation and Duration

The mean age at dialysis initiation was 54.09 ± 15.19 years, with a median age of 56 years (IQR: 44–65). Males initiated dialysis at a mean age of 52.99 ± 16.66 years, while females started at 56.12 ± 11.94 years. No significant gender differences were noted (p=0.184). The mean dialysis duration was 8.06 ± 6.98 years, with females undergoing significantly longer dialysis durations than males (p=0.0284). These findings, summarized in Table 2, highlight the demographic and clinical characteristics of patients undergoing chronic dialysis and underscore the gender differences in dialysis duration.

Table 2. Analysis of the Sample by Age at First Dialysis and Dialysis Duration

[1]Parameters	Age (years)						[1]p
	N	Mean±SD	Min/Max	Percentiles			
				25th	50th (Median)	75th	
Age at First Dialysis							
Men	108	52.99±16.66	18/85	41	54,5	64,5	Z=-1,327; p=0,184
Women	59	56.12±11.94	28/74	49	60	65	
Total	167	54.09±15.19	18/85	44	56	65	
Dialysis Duration (years)							
Men	108	7.50±7.26	0.25/36	2	6	11	Z=-2,191; p=0,0284*
Women	59	9.09±6.34	0.30/29	4	9	12	
Total	167	8.06±6.98	0.25/36	2	7	11	

[1]Patients with CKD stage 5 on chronic HD program, Mean = Average; SD = Standard Deviation; Min/Max = Minimum/Maximum, Z=Mann-Whitney U Test; * significant for p<0.05

Patients in the sample were analyzed regarding their pharmacological status, with the frequency of individual consumption of each of the 14 medications from the basic therapy being evaluated. Additionally, the consumption of medications from other supplementary therapies was also analyzed (Table 3).

Table 3. Sample Analysis by Pharmacological Status – Basic and Supplementary Therapy

[1]Parameters	N (%)	
	No	Yes
Basic Therapy		
Antithrombotics	154 (92.21%)	13 (7.78%)
Anticoagulants	1 (0.60%)	[1]166 (99.40%)
Calcium-channel blockers	97 (58.08%)	70 (41.92%)
ACE inhibitors	137 (82.04%)	30 (17.96%)
Angiotensin receptor blockers (ARB)	139 (82.23%)	28 (16.67%)
Beta blockers	63 (37.72%)	103 (61.68%)
Diuretics	139 (82.23%)	28 (16.77%)
Anemia correction agents	1 (0.60%)	[1]166 (99.40%)
Calcium carbonate/calcium acetate	13 (7.78%)	154 (92.21%)
Vitamin D3	57 (34.13%)	110 (65.87%)
Statins	89 (53.29%)	78 (46.71%)
NSAIDs	122 (73.05%)	45 (26.95%)
Antihistamines	158 (94.61%)	9 (5.39%)
Immunosuppressive therapy	155 (92.81%)	12 (7.19%)
Total – Basic Therapy		
Mean±SD	6.06±1.66	
Min/ Max	3/11	
Median IQR	6 (5-7)	
Supplementary Therapy		
Other therapy	35 (20.96%)	132 (79.04%)
Total – Supplementary Therapy		
Mean±SD	0.83±0.93	
Min/ Max	0/4	
Median IQR	1 (0-1)	

[1]Patients with CKD stage 5 on chronic HD program

The most commonly used medications within the basic therapy were anticoagulants and anemia correction agents, each administered to 166 patients (99.40%). The second most frequently used medication was calcium carbonate/calcium acetate, taken by 154 patients (92.21%). Vitamin D and beta blockers were used by a comparable number of patients, with 110 (65.87%) and 103 (61.68%) patients, respectively. The average number of medications from the basic therapy consumed by patients with chronic kidney disease (CKD) stage 5 on a chronic HD program was 6.06 ± 1.66, with a minimum/maximum of 3/11 medications. In 50% of patients, the total number of consumed medications from the basic therapy was ≥6, while in 25% of them, it exceeded 7. The use of other supplementary therapy was recorded in 132 (79.04%) patients from the sample. The average number of medications from supplementary therapy consumed by patients with CKD stage 5 on a chronic HD program was 0.83 ± 0.93, with a minimum/maximum of 0/4 medications. In 50% of patients in the sample, the consumption of supplementary medications was ≥1, while 25% of them did not consume any supplementary medication (Table 3).

Comorbidities and Pharmacological Factors:

The study documented the prevalence of key comorbidities and their associated pharmacological factors, as summarized in Table 4. Cardiovascular disease (CVD) was the most common comorbidity, observed in 82.23% of patients, as inferred from the combined use of angiotensin receptor blockers (ARB), beta blockers, and diuretics as part of cardiovascular management. Diabetes mellitus was identified in 25 patients (14.97%), based on the use of antidiabetic therapy.

Anemia correction medications were universally used, with nearly all patients (99.4%) receiving these treatments, reflecting the critical need to address dialysis-related anemia.

Additionally, skin and mucosal infections were reported in 13 patients (7.78%), underscoring the importance of routine monitoring and early intervention in this population. Although recurrent infections were not directly measured, they were frequently noted in clinical histories as contributing factors to acute-on-chronic inflammatory episodes.

Table 4. Prevalence of Comorbidities and Associated Pharmacological Factors

Comorbidity	Prevalence	Notes
Cardiovascular Disease (CVD)	82.23%	Based on combined use of ARB therapy, beta blockers, and diuretics.
Diabetes Mellitus	14.97% (25 patients)	Identified from antidiabetic therapy usage.
Anemia	99.4%	Treated universally with anemia correction medications.
Skin and Mucosal Infections	7.78% (13 patients)	Emphasizes the need for monitoring and early interventions.

Dermatological Manifestations

Based on data from the dialysis centers in Skopje, several dermatological manifestations were observed among patients. The prevalence of various dermatological conditions observed in dialysis patients is summarized in Figure 1, highlighting the most common manifestations and their distribution within the study population. Correlations between clinical, and laboratory, and mucocutaneous changes revealed several significant associations, as summarized in Table 5.

Pruritus was reported in 74% of patients and categorized into mild (29%), moderate (41%), severe (24%), and very severe (6%) cases. Significant correlations were identified, including a positive correlation between CRP levels and pruritus severity ($R=0.223$, $p=0.005$). Elevated phosphorus levels were associated with severe pruritus ($p=0.004$), while increased PTH levels also showed a significant link to pruritus severity ($R=0.219$, $p=0.008$). Pharmacological factors, particularly angiotensin receptor blocker (ARB) therapy, were positively associated with pruritus severity ($R(167)=0.173$, $p=0.049$).

Xerosis, or dry skin, was prevalent in 88.62% of patients, with moderate severity being the most commonly observed (38.92%). Correlations showed a weak but significant link between CRP levels and xerosis severity ($R=0.215$, $p=0.003$). Borderline insignificant positive correlations were noted with vitamin D supplementation ($R=0.140$, $p=0.072$) and NSAID use ($R=0.133$, $p=0.088$). Xerosis was significantly associated with ARB therapy ($p=0.038$).

Pigmentation changes, predominantly hyperpigmentation, were observed in 63.47% of patients. These changes demonstrated significant positive correlations with MPV ($R=0.219$, $p=0.004$) and alkaline phosphatase levels ($R=0.213$, $p=0.006$). A negative correlation was identified with creatinine levels ($R=-0.220$, $p=0.004$), while dialysis duration was positively correlated with pigmentation changes ($R=0.205$, $p=0.007$).

Nail changes were present in 81.44% of patients, with "absence of lunula" (51.50%) and onychomycosis (44.91%) being the most frequent findings. MPV exhibited a weak but significant positive correlation with nail abnormalities (R=0.156, p=0.044). Ferritin levels showed a positive correlation with general nail changes (R=0.170, p=0.028), and MCV was linked to specific nail findings such as longitudinal ridging (R=0.236, p=0.002) and onycholysis (R=0.159, p=0.041).

While cardiovascular disease (CVD) was linked to systemic inflammation, this association was not explicitly tested. Diabetes mellitus prevalence was 14.97%, based on therapy records, and skin and mucosal infections were observed in 7.78% of patients.

These findings highlight the diverse dermatological manifestations in patients undergoing dialysis and their complex associations with clinical and laboratory parameters.

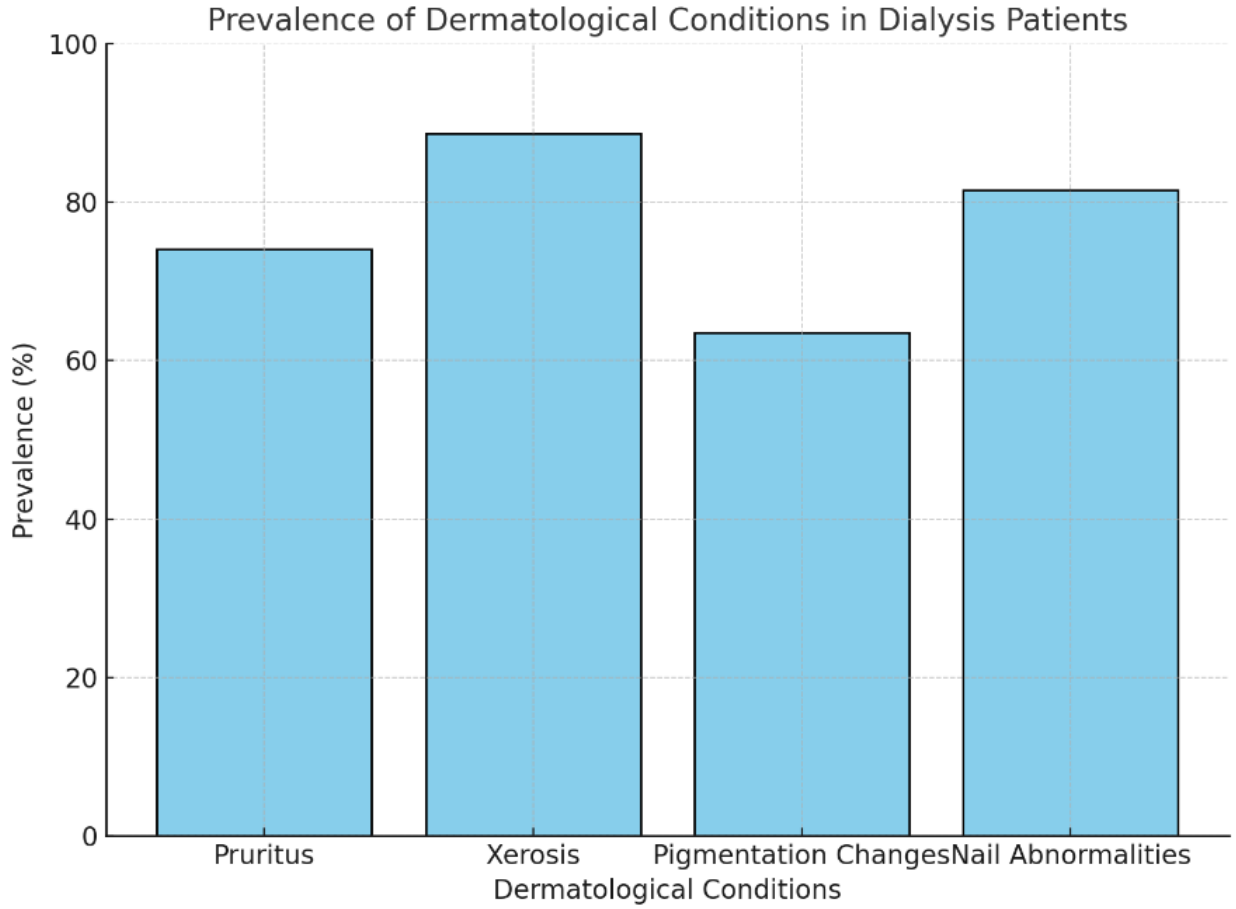

Fig. 1. Prevalence of various dermatological conditions in dialysis patients

Table 5. Overview of Dermatological Findings and Their Correlations with Statistical Analysis

Dermatological Manifestation	Finding/Correlation	Significance (p-value)
Pruritus	Prevalence: 74% (Mild: 29%, Moderate: 41%, Severe: 24%, Very Severe: 6%)	-
Pruritus	CRP (R=0.223)	0.005*
Pruritus	Phosphorus (p=0.004)	0.004*
Pruritus	PTH (R=0.219)	0.008*
Xerosis	Prevalence: 88.62% (Moderate severity: 38.92%)	-
Xerosis	CRP (R=0.215)	0.003*
Xerosis	ARB therapy	0.038*
Xerosis	Vitamin D Supplementation (R=0.140)	0.072
Xerosis	NSAID Use (R=0.133)	0.088
Pigmentation Changes	Prevalence: 63.47% (Predominantly hyperpigmentation)	-
Pigmentation Changes	MPV (R=0.219)	0.004*
Pigmentation Changes	Alkaline Phosphatase (R=0.213)	0.006*
Pigmentation Changes	Creatinine (R=-0.220)	0.004*
Nail Changes	Prevalence: 81.44% ('Absence of lunula': 51.50%, Onychomycosis: 44.91%)	-
Dermatological Manifestation	Finding/Correlation	Significance (p-value)
Nail Changes	MPV (R=0.156)	0.044*
Nail Changes	Ferritin (R=0.170)	0.028*
Nail Changes	MCV (Longitudinal ridging: R=0.236, Onycholysis: R=0.159)	0.002*, 0.041*

Note: Significant results are highlighted for p<0.05*. Observational findings are based on reported frequencies.

Legend for Abbreviations: CRP: C-reactive protein, PTH: Parathyroid hormone, MPV: Mean platelet volume, NSAID: Non-steroidal anti-inflammatory drugs, MCV: Mean corpuscular volume

Discussion

Chronic Inflammation in Dialysis Patients

Chronic systemic inflammation in dialysis patients arises from multiple factors, including comorbidities such as cardiovascular diseases (82.23%), diabetes (14.97%), and recurrent infections (7.78%). These factors significantly exacerbate systemic inflammation and contribute to dermatological manifestations. Inflammation is driven by uremia per se, dialysis-related factors, and genetic predisposition, all of which interact synergistically to exacerbate clinical outcomes in patients with ESRD.

Uremia-Related Factors

Uremic toxins lead to reduced renal clearance of inflammatory cytokines, accumulation of advanced glycation end-products (AGEs), oxidative stress, persistent infections, and endothelial dysfunction. These factors promote chronic heart failure and atherosclerosis, both of which fuel the inflammatory cycle. The most significant uremic toxins are typically divided into three categories based on their molecular size and clearance characteristics. The following

toxins are considered the most clinically relevant due to their role in dermatological manifestations:

1. Small, Water-Soluble Toxins

These are easily diffusible and accumulate as a result of decreased kidney clearance.

- Urea: The most abundant nitrogenous waste product. While not highly toxic itself, it can contribute to skin changes like pruritus and xerosis [32].
- Creatinine: A marker of renal function; elevated levels indicate impaired glomerular filtration [32].
- Uric Acid: Accumulation can contribute to gout, inflammation, and oxidative stress[33].
- Guanidines: Known neurotoxic compounds derived from nitrogen metabolism, linked to systemic inflammation [34,35].

2. Middle Molecules

These toxins have a larger molecular weight, making their removal by conventional dialysis more challenging.

- β2-Microglobulin: Strongly associated with dialysis-related amyloidosis and vascular inflammation [31].
- PTH: Secondary hyperparathyroidism contributes to vascular calcification, pruritus, and bone-mineral disorders [36,37].
- Cytokines: Pro-inflammatory molecules such as interleukin-6 (IL-6) and TNF-alpha are key drivers of systemic inflammation, promoting cardiovascular disease, malnutrition, and dermatological conditions [23].

3. Protein-Bound Toxins

These are among the most significant toxins due to their poor clearance during standard dialysis and strong association with inflammation and cardiovascular outcomes:

- Indoxyl Sulfate: Produced from gut microbial metabolism of tryptophan; it promotes oxidative stress, endothelial dysfunction, and inflammation [30].
- p-Cresyl Sulfate: Derived from phenolic compounds, this toxin exacerbates inflammation, oxidative damage, and cardiovascular complications [30].
- Homocysteine: Elevated levels are linked to cardiovascular risk and endothelial dysfunction [38,39].

Clinical Relevance

The protein-bound uremic toxins (indoxyl sulfate and p-cresyl sulfate) and β2-microglobulin are particularly significant because they [30,31]:

1. Drive systemic inflammation and oxidative stress.
2. Worsen CVD progression.
3. Exacerbate dermatological changes such as pruritus, pigmentation, and xerosis.
4. Are poorly removed by standard hemodialysis, requiring advanced dialysis techniques like hemodiafiltration.

Dialysis-Related Factors

Both hemodialysis and peritoneal dialysis introduce inflammation through bioincompatibility of dialyzer membranes, dialysates, and exposure to endotoxins. Access-related infections, peritoneal infections, and peritonitis further exacerbate systemic inflammatory responses.

Genetic Factors

Pre-inflammatory cytokines such as IL-6, anti-inflammatory mediators like interleukin-10 (IL-10), and CRP play a significant role in determining inflammatory burden in ESRD patients. Individual genetic variability may influence the balance between pro-inflammatory and anti-inflammatory responses, impacting clinical outcomes [23].

Consequences of Inflammation

Inflammation in dialysis patients contributes to two major pathways:

Malnutrition and Wasting: Inflammation leads to decreased dietary intake and protein loss via dialysis, culminating in malnutrition and muscle wasting.

CVD: Inflammatory processes, along with hyperlipidemia, hypertension, and age-related changes, accelerate atherosclerosis and vascular damage, increasing the prevalence of CVD in dialysis patients.

Ultimately, these pathways converge to increase all-cause mortality and cardiovascular-related deaths, highlighting the critical role of inflammation in the poor prognosis of ESRD patients. The findings underscore the need for strategies to reduce inflammation, improve nutritional support, and address cardiovascular risk factors to enhance outcomes in dialysis populations.

Several studies indicate that the kidneys play a key role in clearing pro-inflammatory cytokines. In CKD, reduced renal function is associated with impaired clearance of cytokines such as IL-6 and TNF-α. Evidence shows that CKD patients have lower urinary excretion of IL-6 receptors compared to healthy controls [24]. Even a mild reduction in GFR, as seen in diabetic patients, leads to elevated plasma levels of IL-6 and TNF-α [25]. Experimentally induced renal impairment has further demonstrated reduced clearance of TNF-α and IL-1 [26,27]. Clinical studies have confirmed that circulating IL-6 and CRP levels correlate with declining renal function, even in predialysis populations with moderate reductions in GFR [28,29]. These findings suggest that impaired renal clearance of cytokines is a major contributor to the chronic inflammatory state observed in CKD, highlighting the role of diminished kidney function in systemic inflammation.

Although our study did not measure IL-6 and TNF-α, these cytokines are well-established markers of systemic inflammation in CKD and dialysis populations promoting inflammatory pathways, vascular damage, and immune dysregulation [23-27]. IL-6 and TNF-α are particularly relevant to dermatological manifestations, as they can contribute to pruritus, xerosis, and other skin changes through their effects on keratinocyte proliferation, immune activation, and impaired skin barrier function. Incorporating these markers in future studies could enhance the understanding of inflammatory mechanisms and their direct impact on skin health, offering a more comprehensive perspective on the complex interplay between systemic inflammation and dermatological outcomes in dialysis patients.

CRP is a well-known marker of systemic inflammation and is frequently elevated in dialysis patients. Its association with dermatological symptoms such as pruritus and xerosis has been highlighted in the literature [16]. CRP was significantly associated with pruritus severity in this study, aligning with findings by Stenvinkel *et al.* that link elevated CRP levels to poor clinical outcomes in ESRD patients [2,7].

Increased MPV levels, as observed in our study, were significantly associated with pigmentation changes, consistent with prior research linking MPV to systemic inflammatory processes [8,9,15]. Increased MCV values are associated with macrocytic anemia, which may indicate a reduced capacity for cell division. Additionally, elevated MPV values are considered a marker of increased platelet production and are linked to inflammatory processes and vascular changes. This may be relevant to our findings, as the correlation between MPV and pigmentation changes suggests that anemia or other factors related to hemosiderin deposition

may also play a significant role in the occurrence of pigmentation changes in the patients in our study [8,9]. However, specific research directly linking MPV to skin pigmentation changes in dialysis patients is limited. While systemic inflammation can contribute to various dermatological manifestations, including pigmentation changes, the direct association between MPV and skin pigmentation in this patient population requires further investigation. Therefore, while increased MPV levels in our study may indicate heightened systemic inflammation, attributing these levels specifically to pigmentation changes should be approached with caution due to the current lack of direct evidence.

CVD and diabetes mellitus are common in dialysis patients, exacerbating systemic inflammation and influencing dermatological manifestations. The high prevalence of CVD (82.23%) and diabetes (14.97%) in our cohort underscores the role of metabolic and vascular comorbidities in driving systemic inflammation and associated dermatological conditions. This observation aligns with existing literature indicating that CVD is a major cause of morbidity and mortality in ESRD patients undergoing hemodialysis [10]. Furthermore, diabetes mellitus is a significant risk factor for both CKD and cardiovascular complications. The presence of diabetes in CKD patients amplifies the risk of cardiovascular events, with studies showing that approximately 40% of individuals with diabetes develop CKD, which in turn mediates increased cardiovascular risk. The interplay between traditional risk factors, such as diabetes and hypertension, and non-traditional factors, including inflammation and oxidative stress, contributes to the heightened cardiovascular risk in this population [11]. The interrelationship between diabetes, cardiovascular disease, and kidney dysfunction creates a vicious cycle that exacerbates patient outcomes. Effective management of these comorbidities is crucial to mitigate systemic inflammation and its dermatological manifestations in dialysis patients [14].

Dialysis patients are particularly prone to skin infections, contributing to acute-on-chronic inflammation. Skin and mucosal infections, observed in 7.78% of our cohort, may exacerbate inflammatory responses, a phenomenon well-documented in prior studies [12]. In a study from India by Jeswani *et al*. [13], the overall prevalence of skin infections was 17%, with no significant difference observed between patients undergoing hemodialysis and those with CKD who were not yet on dialysis. This indicates that the occurrence of skin infections may not be directly influenced by the dialysis process itself but rather reflects the systemic and immunological changes associated with advanced CKD.

Medications such as ARB therapy, NSAIDs, and vitamin D supplementation play roles in modulating inflammation and influencing dermatological outcomes. Our findings indicated a weak but significant association between ARB therapy and xerosis and pruritus, supporting evidence that ARBs may influence inflammatory pathways in ESRD [17,18]. Our study found a borderline insignificant positive linear correlation between vitamin D and NSAID treatment and the presence of xerosis ($R(167) = 0.140$, $p = 0.072$ *vs.* $R(167) = 0.133$, $p = 0.088$). While these findings do not meet conventional thresholds for statistical significance ($p < 0.05$), they highlight a potential trend worth further investigation. This correlation may reflect underlying mechanisms, such as the effects of vitamin D supplementation on calcium and phosphate metabolism, which are known to influence dermatological outcomes. Importantly, we analyzed vitamin D supplementation rather than serum levels in our study cohort. High doses of vitamin D are known to induce ectopic calcification due to hypercalcemia and hyperphosphatemia, which could contribute to dermatological changes such as xerosis. The relationship between vitamin D and calciphylaxis is complex, influenced by factors such as CKD stage, hyperparathyroidism, and external calcium/phosphate intake. Studies, such as that by Kechichian and Ezzedine (2018) [19], support the role of vitamin D in skin integrity and immune response regulation. Vitamin D deficiency weakens the skin barrier, increasing susceptibility to inflammatory conditions. Our findings suggest a potential protective role for vitamin D in skin health, but also raise concerns about the effects of over- or under-treatment. This

underscores the need for further research to determine the optimal use of vitamin D in managing xerosis and other dermatological issues in dialysis patients.

Our study found a borderline insignificant positive linear correlation between NSAID treatment and the presence of xerosis ($R(167) = 0.133$, $p = 0.088$). This finding aligns with previous research highlighting the potential impact of NSAIDs on skin hydration and barrier function. NSAIDs exert their effects by inhibiting cyclooxygenase (COX), reducing prostaglandin production. Prostaglandins play a critical role in regulating vascular tone and supporting microcirculation, particularly in the skin. Reduced prostaglandin levels can lead to vasoconstriction, decreased skin perfusion, and impaired hydration, which may exacerbate xerosis. Prolonged NSAID use may alter lipid composition in the skin and disrupt its moisture-retaining ability, further contributing to dryness. Studies such as those by Derry *et al.* (2015)[20] and Combs *et al.* (2015) [21] support this observation, noting that xerosis and related symptoms like dry mouth are common adverse effects associated with NSAID use. Additionally, Udayakumar *et al.* (2006) [22] identified xerosis as the most frequent dermatological issue in patients with CKD, often exacerbated by medications like NSAIDs and vitamin D. These findings underscore the need for cautious use of NSAIDs in patients with compromised skin barrier function, such as those with CKD. Further research is required to elucidate the mechanisms by which NSAIDs influence skin health and to determine whether a causal relationship exists between these medications and xerosis.

The causes of inflammation in dialysis patients are multifactorial, encompassing both dialysis-related and unrelated factors. Chronic inflammation plays a critical role in the development of CVD, while acute-phase reactions contribute to vascular damage through various mechanisms. Addressing the cycle of malnutrition, inflammation, and atherosclerosis (MIA syndrome) in ESRD could potentially improve survival and reduce comorbidities [23]. However, with no established guidelines for managing chronic inflammation in ESRD, further research is essential to evaluate the long-term effects of anti-inflammatory treatments on nutritional and cardiovascular outcomes, as well as to identify key pathways driving the disease process.

Implications for Patient Management

The findings underscore the need for a comprehensive approach to managing systemic inflammation and its associated dermatological manifestations in dialysis patients. Effective management of comorbidities, targeted therapies, and optimization of dialysis strategies are critical for improving patient outcomes.

Given the high prevalence of CVD (82.23%) in the studied cohort, optimizing ARB therapy is essential to manage hypertension and potentially mitigate systemic inflammation. Routine cardiovascular evaluations are recommended to monitor inflammation-related risks and prevent disease progression.

With diabetes mellitus identified in 14.97% of patients, aggressive glycemic control is crucial to minimize microvascular damage, which may exacerbate skin complications. Tailored nutritional interventions can help balance blood glucose levels while addressing the nutritional needs specific to dialysis patients.

Skin and mucosal infections, observed in 7.78% of patients, highlight the importance of prophylactic measures to prevent vascular access-related infections and other inflammatory triggers. Early interventions, including prompt antimicrobial therapies, are necessary to avoid acute inflammatory exacerbations that worsen dermatological conditions.

Inflammation Control

Targeting inflammation remains a central strategy. Anti-inflammatory therapies should be integrated into clinical management plans. These interventions can help reduce inflammatory cytokine levels and improve overall patient outcomes.

Optimizing Dialysis

The use of biocompatible dialyzer membranes and ensuring adequate dialysis dosing are critical to minimize inflammatory responses triggered by dialysis procedures. Long-term dialysis duration, significantly correlated with pigmentation changes ($R=0.205$, $p=0.007$), highlights the importance of optimizing dialysis protocols to limit cumulative inflammation.

Nutritional Support

Malnutrition and hypoalbuminemia, common in dialysis patients, exacerbate inflammation and skin complications. Addressing nutritional deficiencies, particularly through vitamin D supplementation, may improve skin barrier function and overall inflammatory status. However, careful dosing is essential to avoid potential adverse effects such as hypercalcemia and ectopic calcifications.

Symptom Management

Effective symptom-specific management can significantly improve patients' quality of life. Use of antihistamines, gabapentin, or ultraviolet therapy can alleviate itching, which is closely linked to elevated CRP levels and phosphorus concentration. Regular application of emollients and skin hydration therapies is essential to mitigate dry skin, which was observed in 88.62% of patients.

Limitations

This study is limited by its cross-sectional design, which restricts the ability to establish causality between chronic inflammation and dermatological manifestations. Additionally, the lack of longitudinal follow-up prevents the assessment of temporal changes in inflammation markers and their progression alongside dermatological conditions. Future studies investigating dermatological manifestations in dialysis patients should incorporate additional uremic toxins, such as indoxyl sulfate, p-cresyl sulfate, and β2-microglobulin, alongside standard markers like urea and creatinine. Expanding the scope of uremic toxin assessment could provide a more comprehensive understanding of their contribution to chronic inflammation and associated cutaneous changes in this population. Future studies with larger sample sizes and longitudinal designs are recommended to validate these findings.

Conclusion

Chronic systemic inflammation is a key driver of dermatological manifestations in dialysis patients, significantly impairing their quality of life. Findings from the Skopje study reveal a high prevalence of xerosis, pruritus, pigmentation changes, and nail abnormalities, which are strongly associated with systemic inflammation markers, including CRP, MPV, and alkaline phosphatase, as well as factors such as ARB therapy, vitamin D supplementation, NSAID use, and prolonged dialysis duration. Comorbid conditions, including cardiovascular disease (82.23%), diabetes mellitus (14.97%), and skin and mucosal infections (7.78%), further exacerbate the inflammatory burden and its dermatological consequences.

Addressing these challenges necessitates a comprehensive, multidisciplinary approach that integrates nephrological, dermatological, and nutritional expertise. By identifying and managing these interrelationships, healthcare providers can optimize care delivery and improve the overall quality of life for patients undergoing dialysis.

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