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Muco-Cutaneous Changes/Symptoms in Patients with Stage 5 Chronic Kidney Disease on Haemodialysis

Ivana Dohcheva Karajovanov[1], Suzana Nikolovska[1], Katerina Damevska[1], Irena Rambabova Bushljetikj[2], Sasho Dohchev[3] and Goce Spasovski[2]

[1]University Clinic for Dermatology, [2]University Clinic for Nephrology, [3]University Clinic for Urology, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia

Abstract

Introduction. Chronic Kidney Disease (CKD) is defined when the glomerular filtration rate is reduced (GFR) <60 mL/min per 1.73 m2 (GFR categories G3a-G5) for more than 3 months and with the presence of albuminuria: the albumin-creatinine ratio (ACR) is ≥30 mg/g and the albumin excretion rate is (AER) ≥30 mg/d. Stage 5 of Chronic Kidney Disease (Stage 5 CKD) is the stage with a need for renal replacement therapy or kidney transplantation. CKD is characterized by numerous muco-cutaneous manifestations. Our aim was to determine the frequency of non-specific and specific muco-cutaneous changes in patients with Stage 5 CKD on haemodialysis.

Methods. We conducted a cross-sectional study at the University Clinic for Nephrology, Skopje and PHI Special Hospital for Nephrology with Dialysis DIAMED, Skopje from March to June 2022. The study involved 42 patients from both dialysis centers. A detailed medical history for each patient was used to obtain data on demographic characteristics, the cause of the renal insufficiency, dialysis duration, and the latest findings of routine laboratory parameters.

Results. The most common muco-cutaneous changes/symptoms were xerosis 88.1%, pruritus 73.81%, hyperpigmentation 45.24%, echymosis in 42.86%, onychomycosis 40.47%, absence of lunula 23.81%, "longitudinal ridge" 21.43%, sparse hair 21.43%, "Half-and-half nails" 19.05%, brittle nails 19.05%, subungval hyperkeratosis 19.05%, photosensitivity 19.05%, etc.

Conclusion. Muco-cutaneous changes/symptoms were a common finding in patients with Stage 5 CKD on haemodialysis. All respondents were diagnosed with at least one muco-cutaneous change/symptom. Interdisciplinary management involving dermatologists is essential.

Keywords: chronic kidney disease, Stage 5 CKD, haemodialysis, muco-cutaneous changes/symptoms

Introduction

Chronic kidney disease (CKD) is in fact a progressive irreversible loss of kidney function syndrome. It is defined when the glomerular filtration rate (GFR) is reduced below 60 mL/min per 1.73 m2 (GFR categories G3a–G5) for more than 3 months alongside with the presence of albuminuria: the albumin-creatinine ratio (ACR) is ≥30 mg/g and the albumin excretion rate is (AER) ≥30 mg/d [1]. The End Stage Renal Disease (ESRD) or the Stage 5 CKD is the point at which life can no longer be sustained without renal replacement therapy or kidney transplantation.

The muco-cutaneous changes are with high prevalence in Stage 5 CKD patients who undergo dialysis [2]. Affecting the skin, its adnexa and mucosa can be rather extensive and that impacts the quality of life in these patients. In a study by Pico *et al*., it was found that all 102 patients had at least one noted skin change [3]. It is very difficult to deduce whether a certain muco-cutaneous manifestation is affected by the CKD itself or only by the hemodialysis process with all its distinctive features, as many of them can be related to both factors [4].

In all publications pertaining to this subject matter, the muco-cutaneous changes are classified into two groups-non-specific and specific, with pre-defined terms. The entities of interest in terms of certain cutaneous changes "having preference for" Stage 5 CKD patients who undergo chronic dialysis program allude to the specific, and the other ones, non-specific, are found amongst the rest of the population, in which case these patients are also not spared [5].

The muco-cutaneous changes are in actual fact a clinical tool for evaluation of patients' life quality and are a reflection of the general health condition of this population.

This study has the purpose of measuring the frequency of the non-specific and specific muco-cutaneous changes (pre-defined terms) in 42 ESRD patients undergoing dialysis from two dialysis centers in Skopje: University

Correspondence to: Ivana Dohcheva Karajovanov, University Clinic for Dermatology, 1000 Skopje, R. N. Macedonia; E-mail: idohcheva@gmail.com

Clinic for Nephrology - Skopje and PHI Special Hospital for Nephrology with Dialysis, DIAMED Skopje.

Materials and methods

Study design, duration and location: the research was a cross-sectional study conducted in two already mentioned dialysis centers (UC of Nephrology, Skopje and PHI Special Hospital for Nephrology with Dialysis, DIAMED) in Skopje. The research was carried out in the period between March and June 2022. The research sample was comprised by patients on hemodialysis. Inclusion criteria: patients with glomerular filtration <15 ml/min/1.73m2 undergoing chronic hemodialysis program for more than 3 months; age: ≥18; irrespective of sex, ethnic or religious background; and willingness to participate in the study with given informed consent.
Exclusion criteria: patients with chronic dermatological diseases history prior to the commencement of dialysis. The selection of respondents was made in accordance with the inclusion and exclusion criteria by the method of random choice, i.e. the first 42 patients examined from the two previously mentioned dialysis centers (21 patients from each center). All patients were on hemodialysis program, three times weekly, four-hour sessions.
The muco-cutaneous changes/symptoms were classified in two groups, i.e. non-specific and specific with the goal of pre-defining those who were about to be monitored. Non-specific muco-cutaneous changes and symptoms: photosensitivity, paleness, xerosis, hypo and hyperpigmentation, ecchymosis, various changes in nails (Half-and-half nails, Terry's nails, absence of lanula, onycholysis, Beau's lines, clubbing, longitudinal ridging, onychomycosis, subungual hyperkeratosis, koilonychia, total leukonychia, nail pitting, splinter hemorrhage, pincer nail deformity etc.), various changes in hair (brittleness, lack of shine, thinning hair, effluvium, alopecia etc.), mucosal changes (gingivitis, stomatitis, dryness, angulus infectiosis oris etc.), cutaneous infections (bacterial, viral, fungal, parasitic), neck elastosis, cutaneous carcinoma (basocellular, squamocellular, melanoma, etc.), venous dilation near the fistula, eczematous changes around the fistula, etc. Specific muco-cutaneous changes and symptoms: CKD-associated pruritus, pseudoporphyria, porphyria cutanea tarda, acquired perforated dermatosis, calciphylaxis, nephrogenic systemic fibrosis.
The detailed medical history of each patient was reviewed to obtain data on the demographic features (sex, age, nationality, socio-economic background), the original kidney disease, the duration of dialysis and the latest findings from the routine biochemical and hematological analyses (hemoglobin, ferritin, calcium, urea, phosphates creatinine, albumins, parathormone, HCV, HBV, HIV). All patients were subjected to a clinical dermatological exam to record changes in the skin, hair, nails and the accessible mucous membranes. The patients were examined by a dermatovenerologist during the course of one dialysis session. Each patient was informed about the study, and was granted a guarantee for anonymity, as well as a guarantee for use of their personal data for scientific purposes only. Each participant signed an informed consent form. The diagnosis of dermatological changes was made according to the good clinical practice criteria and the directions for evidence-based medical practice. For the purpose of evaluation of the itching intensity, a horizontal visual analog scale (VAS) was used, from 0-no itching, to 10 -severe/unbearable itching. The responses on the VAS were grouped into: mild itching ≥0, but <3, medium itching (≥3, but <7), severe itching (≥7, but <9), and very severe (≥9) [39]. In order to assess the weight of xerosis, a xerosimeter was used: 0-no xerosis, 1-mild xerosis, 2-medium xerosis, 3-severe xerosis, 4-very severe xerosis [38]. The duration of the clinical exam lasted between 20 to 40 minutes per patient.
The analysis was made by utilizing a SPSS software package, version 20.0 for Windows (SPSS, Chicago, IL, USA). The data was presented by means of simple measurements such as frequency, percentage points, average, standard deviation and rank (minimum-maximum values).
The study was approved by the Ethics Committee at the Faculty of Medicine at the Ss. Cyril and Methodius University, Skopje, N. Macedonia.

Table 1. Basic sample data

Parameters		n - number	%
Age	Average value in years ± SD (range)		63.8±13.3 (34-90)
Sex	Male	31	73.81
	Female	11	26.19
Nationality	Macedonian	36	85.71
	Albanian	2	4.76
	Roma	2	4.76
	Serbian	1	2.38
	Turkish	1	2.38
Socio-economic background	poor	1	2.38
	medium	9	21.43
	good	23	54.76
	excellent	9	21.43
Hemodialysis duration	Average value in years ± SD (range)		9.26±8.36 (0.3-36)

Results

Basic sample data are presented in Table 1.
The most frequent muco-cutaneous changes/symptoms included xerosis-88.1% (n=37), followed by pruritus-73.81% (n=31). Any changes in nails were identified in 66.67% (n=28), out of which the most common place was onychomycosis 40.47% (n=17), followed by absence in the nail lunula 23.81% (n=10), after that the longitudinal ridging 21.43% (n=9), half-and-half nails 19.05% (n=8), brittle nails 19.05% (n=8) and subungual hyperkeratosis 19.05% (n=8). Hyperpigmentations were identified in 45.24% (n=19), ecchymoses in 42.86% (n=18), and paleness in 28.57% (n=12). Changes in hair were observed in 23.81% (n=10), out of which the most common finding was thinning hair 21.43% (n=9). Photosensitivity was reported in 19.05% (n=8) of the patients. In 16.67% (n=7) other muco-cutaneous changes were found, which include: Poikiloderma Civatte 7.14% (n=3), prurig simplex 2.38% (n=1), dermatitis around the fistula 2.38% (n=1), xanthoma 2.38% (n=1), Raynaud syndrome 2.38% (n=1). Mucous membrane changes were found in 7.14% (n=3) of the patients. Only in 2.38% (n=1) of the patients who undergo hemodialysis Morbus Kyrle (acquired perforating dermatosis) was diagnosed. All sample patients had a varying degree of dilatation of the arterio-venous fistula (Table 2).

Table 2. Frequency of muco-cutaneous changes in Stage 5 CKD on hemodialysis in this sample

Muco-cutaneous changes/symptoms	%	n=42
Photosensitivity	19.05%	n=8
Xerosis	88.10%	n=37
Changes in nails (one or more than one could be observed in a single patient)	66.67%	n=28
Half-and-half nails	19.05%	n=8
Terry's nails	7.14%	n=3
Absence of lunula	23.81%	n=10
Onycholysis	14.28%	n=6
Brittle nails	19.05%	n=8
Beau's lines	4.76%	n=2
Clubbing	4.76%	n=2
Longitudinal ridging	21.43%	n=9
Onychomycosis	40.47%	n=17
Subungual hyperkeratosis	19.05%	n=8
Koilonychia	7.14%	n=3
Total leukonychia	11.90%	n=5
Pincer nail deformity	2.38%	n=1
Hyperpigmentations	45.24%	n=19
Paleness	28.57%	n=12
Hypopigmentations	11.90%	n=5
Ecchymoses	42.86%	n=18
Skin infections	4.76%	n=2
Bacterial skin infections	2.38%	n=1
Fungal skin infections	2.38%	n=1
Changes in hair (one or more than one could be observed in a single patient)	23.81%	n=10
Effluvium	4.76%	n=2
Alopecia	4.76%	n=2
Thinning hair	21.43%	n=9
No shine	7.14%	n=3
Brittle hair	7.14%	n=3
Changes in the oral mucosa (one or more than one could be observed in a single patient)	7.14%	n=3
Dryness of mucous membranes	2.38%	n=1
Stomatitis	4.76%	n=2
Gingivitis	2.38%	n=1
Neck elastosis	9.52%	n=4
Other skin diseases	16.67%	n=7
Poikiloderma civatte	7.14%	n=3
Dermatitis around the fistula	2.38%	n=1
Dilatation of the arteriovenous fistula	100%	n=42
Prurigo	2.38%	n=1
Xanthomas	2.38%	n=1
Raynaud syndrome	2.38%	n=1
CKD associated pruritus	73.81%	n=31
Acquired perforating dermatosis (Morbus Kyrle)	2.38%	n=1

None of the patients was diagnosed with skin and mucous membranes cancer, pseudoporphyria, calciphylaxis and nephrogenic systemic fibrosis.
The most common cause of renal insufficiency was nephro-arteriosclerosis (NAS) found in 28.57% (n=12) of the respondents (Table 3).

Table 3. Etiology of CKD

Reasons for CKD	%	n=42
Diabetes	7.14	3
NAS	28.57	12
Glomerulonephritis	11.90	5
Infectious and obstructive nephropathy	9.52	4
Hereditary nephropathy	23.81	10
Other	7.14	3
Unknown	11.90	5

The analysis of the lab parameters are expressed as follows with mean ±SD and range: a) elevated values of parathyroid hormone in 97.62% (n=41) of patients -375.9±240.39 pg/mL (52.3-1034); b) elevated values of ferritin in 42.86% (n=18)-329.9±206.58 ng/mL (31-841.25); c) hypercalcemia was noted in 9.52% (n=4), and hypocalcemia in 11.9% (n=5)-2.28±0.24 mmol/L (1.91-2.9); d) only 9.52% (n=4) of patients had hemoglobin reference values, whereas in other patients anemia was observed at the rate of 90.48% (n=38)-113.40± 11.97 g/l (78-135); e) elevated inorganic phosphate levels were noted in 50% (n=21) of patients-1.54±0.53 mmol/L (0.7-3.9); f) the urea levels were elevated in all patients-18.18±4.28 mmol/L (10.2-29); g) elevated creatinine levels were observed in all patients-688.25 ±173.85 μmol/L (273.2-1092); h) 11.9% (n=5) of patients were HBV positive, 9.52% (n=4) tested positive for HCV, and only one patient tested positive for HIV (2.38%). Albumin values in all patents from this sample were within reference values.
Xerosis was found in 88.1% (n=37) of patients. In 30.95% (n=13) of the respondents there was mild xerosis, in 33.33% (n=14) medium xerosis, in 16.67% there was severe xerosis (n=7) and in 7.14% very severe xerosis was found (n=3). In 46.15% (n=6) there was a mild localized xerosis, 53.85% (n=7) with mild generalized xerosis. Medium generalized xerosis was found in 64.29% (n=9), while severe generalized xerosis was found in 70% (n=7) of the respondents (Table 4).
Pruritus was found, irrespective of whether it was localized or generalized, in 73.81% (n=31) of patients. Localized pruritus was observed in 47.62% (n=20), whereas 26.19% (n=11) of patients had generalized pruritus. Mild pruritus had 30.95% (n=13) of patients, 26.19% (n=11) of the patients had medium pruritus and 16.67% (n=7)-severe pruritus. Neverheless, none of patients referred to severe pruritus (Table 4).

Table 4. Intensity and distribution of pruritus and xerosis in Stage 5 CKD on hemodialysis

Intensity / Distribution	Severe						Medium						Mild						Total	
	Total		Local		General		Total		Local		General		Total		Local		General			
	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Pruritus	22.58	7	28.57	2	71.43	5	35.48	11	54.55	6	45.45	5	41.94	13	92.31	12	7.69	1	73.81	31
Xerosis	23.81	10	30	3	70	7	37.84	14	35.71	5	64.29	9	30.95	13	46.15	6	53.85	7	88.10	37

Table 5. Distribution of pruritus with varying intensity in cases of severe xerosis in Stage 5 CKD on hemodialysis patients

	Severe xerosis		total
	%	n	
Mild pruritus	7.69	1	13
Medium pruritus	45.45	5	11
Severe pruritus	57.14	4	7

Distribution of pruritus with varying intensity in cases of severe xerosis in Stage 5 CKD on hemodialysis patients is presented in Table 5.Xerosis was found in all patients diagnosed with diabetes (n=3), infectious and obstructive nephropathy (n=4), as well as the other pa-

Table 6. Distribution of selected muco-cutaneous changes/symptoms according to the causes of CKD

Muco-cutaneous changes/symptoms	Causes of CKD													
	HTN		Diabetes		Hereditary nephropathy		Glomerulo-nephritis		Infectious and obstructive nephropathy		Other		Unknown	
	%	n	%	n	%	n	%	n	%	N	%	n	%	n
Xerosis	83.33	10	100	3	90	9	80	4	100	4	100	3	80	4
Changes in nails	66.67	8	100	3	60	6	40	2	75	3	100	3	60	3
Half-and-half nails	8.33	1	66.67	2	20	2	0	0	0	0	33.33	1	40	2
Absence of lunula	25	3	0	0	20	2	0	0	25	1	33.33	1	60	3
Longitudinal ridging	16.67	2	66.67	2	30	3	0	0	25	1	0	0	20	1
Onychomycosis	41.67	5	33.33	1	50	5	0	0	50	2	33.33	1	60	3
Hyperpigmentations	50	6	66.67	2	20	2	20	1	75	3	66.67	2	60	3
Changes in hair	33.33	4	33.33	1	20	2	40	2	0	0	0	0	20	1
CKD associated pruritus	91.67	11	0	0	60	6	100	5	50	2	100	3	80	4
Acquired perforating dermatosis	0	0	0	0	0	0	0	0	0	0	0	0	20	1

tients from the category-other causes of CKD (chronic pyelonephritis, cancer, reflux nephropathy) (n=3). Pruritus was found in all patients from the glomerulonephritis categories (n=5) and the other etiologies (n=3) (Table 6).

Table 7. Duration of hemodialysis in patients with pruritus, xerosis and hyperpigmentations

Cutaneous changes/symptoms	Hemodialysis duration average±SD (rank)
No pruritus	5.97±6.31 (0.3-18)
With pruritus	10.43±8.77 (0.3-36)
Generalized pruritus	10.36±8.99 (3-30)
Localized pruritus	10.46±8.89 (0.3-36)
Severe pruritus	12.86±10.25 (4-30)
Medium pruritus	7.3±5.17 (0.3-20)
Mild pruritus	11.76±10.16 (1-36)
Severe xerosis	6.28±2.21 (3-9)
Very severe xerosis	18±8.18 (9-25)
Severe and very severe xerosis together	9.8±7.08 (3-25)
With hyperpigmentations	10.59±10.6 (0.3-36)
No hyperpigmentations	8.51±5.85 (0.33-22)

The longest duration of hemodialysis was registered in patients with severe pruritus 12.86±10.25 years (4-30). The patients with no pruritus were undergoing hemodialysis by a half duration compared to the hemodialysis duration in patients where pruritus was actually found, 5.97±6.31 years (0.3-18) and 10.43±8.77 years (0.3-36), respectively (Table 7).

In patients with very severe xerosis, the average duration of hemodialysis in years has shown the highest values 18±8.18 years (9-25) (Table 7).

The duration of hemodialysis in patients with hyperpigmentations was on average 10.59±10.6 years (0.3-36) and has shown higher values compared to the patients with no hyperpigmentations, i.e. 8.51±5.85 years (0.33-22) (Table 7).

Anemia was found in all patients where paleness was noted 100% (n=12), especially in the group with hemoglobin values ranging 78-108 g/l. Pruritus was found in 90.32% (n=28) of the patients with anemia. Xerosis was found in 89.19% (n=17) of the patients with anemia. In 89.48% (n=17) of the respondents, both anemia and hyperpigmentations were found. Absence of lunula and anemia was found in 80% (n=8) of patients with anemia. Changes in nails, the likes of which include half-and-half nails (Lindsay's nails) and anemia was found in 75% (n=6) of patients (Table 8).

Table 8. Distribution of selected cutaneous changes/symptoms according to hemoglobin values

Cutaneous changes/symptoms	Hemoglobin (78-108 g/l)		Hemoglobin >108 (<120 female and <130 male)		Total		
	%	n	%	n		%	n
Paleness	100	12	0	0	12	100	12
Xerosis	29.73	11	59.46	22	37	89.19	33
Hyperpigmentations	26.32	5	63.16	12	19	89.48	17
Pruritus	35.48	11	54.84	17	31	90.32	28
Absence of lunula	30	3	50	5	10	80	8
Half-and-half nails	37.5	3	37.5	3	8	75	6

Patients with pruritus also had hyperphosphatemia 85.71% (n=18), hypercalcemia 100% (n=4) and hypocalcemia 60% (n=3). Hyperphosphatemia 61.11% (n=11) and hypercalcemia 50% (n=2) were noted in patients with localized pruritus, whereas hypocalcemia 60% (n=3) was noted in patients with generalized pruritus. The patients with severe generalized pruritus 50% (n=2) had hypercalcemia (Table 9).

Table 9. Pruritus distribution according to calcium and inorganic phosphates values in Stage 5 CKD patients on hemodialysis

	Calcium				Inorganic phosphates	
	Hypocalcemia		Hypercalcemia		Hyperphosphatemia	
	%	n	%	n	%	n
Pruritus	60	3	100	4	85.71	18
Mild pruritus	20	1	25	1	38.89	7
Mediam pruritus	40	2	25	1	33.33	6
Severe pruritus	0	0	50	2	27.78	5
Localized pruritus	0	0	50	2	61.11	11
Generalized pruritus	60	3	50	2	38.89	7
Mild localized pruritus	0	0	25	1	33.33	6
Medium localized pruritus	0	0	25	1	16.67	3
Severe localized pruritus	0	0	0	0	11.11	2
Mild generalized pruritus	20	1	0	0	5.55	1
Medium generalized pruritus	40	2	0	0	16.67	3
Severe generalized pruritus	0	0	50	2	16.67	3

Table 10. Distribution of Half-and-half nails (Lindsay's nails) according to anaemia and hyperparathyroidism findings in Stage 5 CKD patients on hemodialysis

Cutaneous change	Anemia		Hyperparathyroidism		Total
	%	n	%	n	n
Half-and-half nails	75	6	100	8	8

Nail changes such as half-and-half nails (Lindsay's nails) were found in all patients (100%, n=8) with hyperparathyroidism, and 75% (n=8) of them were also anemic. (Table 10).

Discussion

In the latest ERA-EDTA (the European Renal Association-European Dialysis and Transplantation Association) report from 2019, the register reported 1853 patients with Stage 5 CKD on a chronic dialysis program from N. Macedonia. The Prevalence per million population (Pmp) for N. Macedonia for the year of 2019 was 893 Pmp [25].

The dialysis centers in N. Macedonia do not have data registry for muco-cutaneous manifestations in patients with ESRD on dialysis. The prevalence of muco-cutaneous changes in patients with Stage 5 CKD on dialysis has been determined in several studies of respondents who are not European residents. The occurrence and development of muco-cutaneous changes in patients with ESRD largely depend on the regional climate factors, the race and socio-economic status of the patients, as well as on the accuracy of the diagnosis according to the study from Iran [24].

In our study, 100% of the patients had at least one muco-cutaneous change/symptom, and xerosis was the most common finding, i.e. 88.10%. In many other studies, xerosis is described as the most prevalent cutaneous change in patients with Stage 5 CKD on hemodialysis [26,27]. In the Anees *et al*. study, xerosis 83% ranks second in prevalence behind pigmentations 86% [6]. In the Adégbidi H. *et al.* study from 2020, xerosis has lower prevalence 48% [28]. In the Böhme et al. study, the xerosis frequency is 90% [15]. A study that examined the relation of xerosis and pruritus reported the intensity of the pruritus grows dramatically alongside with the severity of the xerosis [34]. In our study, in the patients with very severe xerosis, the average of the dialysis duration showed the highest values 18± 8.18 (9-25) with the prevalence of 89.19% (n=17) in patients with anemia.

The second ranking in frequency in our sample was the pruritus 73.81%. The pruritus varies in its prevalence in different studies, i.e. ranging between 50-90% [11]. In the study from 2019 published by Rehman I. U. *et al.*, the prevalence of pruritus was 61.4% [29], whereas in a study from 2021 by Tajalli F. *et al*. it showed prevalence of 57.14% and it was not yet considered as the most common cutaneous manifestations [30]. The CKD associated pruritus causes anxiety, depression and sleep disturbance, whereas the severe pruritus is described as an independent risk factor for an increased mortality and poor prognosis in this population [12]. Clinically speaking, it can be divided into localized and generalized pruritus. In our study 47.62% of the patients had localized pruritus and 26.19% of the patients had generalized pruritus. The intensity/severity of the pruritus was assessed according to the visual analog scale -VAS [31,39]. In 30.95% of the patients, mild pruritus was recorded (ranged between VAS ≥ 0, but <3), in 26.19% of the patients-medium pruritus (ranged between VAS ≥3, but <7), and in 16.67% of the patients-severe pruritus (ranged between VAS ≥7, but <9). In patients where no pruritus was found, the duration of their hemodialysis in years was only a half compared to the patients with pruritus 5.97±6.31 (0.3-18) and 10.43±8.77 (0.3-36), respectively. The longest duration of hemodialysis was registered in patients with severe pruritus 12.86±10.25 (4-30). Pruritus was found in 90.32% of the patients with anemia. Patients with pruritus had hyperphosphatemia 85.71%, hypercalcemia 100% and hypocalcemia 60%. In one study, the hyperphosphatemia is more frequent in patients with severe pruritus [32]. Pruritus is commonly a prolonged condition and deteriorates by heat exposure, sweating and xerosis. The cause of its occurrence may be multifactorial. The risk factors include male sex, elevated levels of uremic nitrogen, calcium, phosphorus, ß2 microglobulin, magnesium, aluminum, Vitamin A, histamine and fats. It is considered to be a manifestation of a chronic inflammatory condition which includes the TNF, IFN-γ, and IL2 cytokines, as well as CRP (C-reactive protein). Additional possible mechanisms for pruritus have suggested abnormal innervations, nerve damage and central sensitization, as well as a genetic predisposition associated with HLA B35 [13,14].

The hypercalcemia and hypocalcemia can cause certain cutaneous manifestations in this population. A study from 2018 has shown that 20.6% of the patients with Stage 5 CKD on hemodialysis suffer from hypocalcemia, compared to patients on hemodialysis with reference values of calcium in serum, which can be considered as an important complication in this population. The hypocalcemia and hypercalcemia can be detected via certain cutaneous manifestations [33]. In our study, hypercalcemia was noted in 9.52%, whereas hypocalcemia in 11.9% of patients.

The most common cause of renal insufficiency in this sample is NAS with 28.57% prevalence, followed by hereditary nephropathy with 23.81%, glomerulonephritis and unknown etiology with the same percentage point

prevalence 11.91%, infectious and obstructive nephropathy with 9.52%, and diabetes with 7.14%, the same as the other etiology group with 7.14%. On the other hand, in the Anees *et al*. study, the most common causes for CKD include: diabetes mellitus 41.5%, hypertension 40%, nephrolithiasis 7.5% and chronic glomerulonephritis 2.5% [6].

In our study, the hyperpigmentation was diagnosed in 45.24% of patients. Hyperpigmentation as a finding has varying prevalence percentage points in various studies amongst this population, from 40% to 80% [7-10]. In majority of studies, it was shown that the degree of pigmentation is in direct correlation with the duration of dialysis. Our results have shown a double duration of dialysis in terms of years in patients with hyperpigmentations, compared to those with no such findings. Hyperpigmentation is the result of high levels of the melanocyte-stimulating hormone (MSH) which causes elevated levels of melanin and it deteriorates by photo exposure [18].

Paleness is a result of chronic disease associated anemia and the erythropoietin deficiency, noted in 40% of the patients [18]. In our study, paleness was noted in 28.57% of the respondents, with 100% prevalence in patients with anemia. Paleness can be corrected by administering erythropoietin and correction of the anemia. Ecchymoses are extremely common and occur due to the platelet dysfunction, secondary to elevated urea and creatinine levels. In our study, ecchymoses were found in 42.86% of the respondents. There are several studies focusing on hemosiderin deposits treatment, reporting treatment success rate by means of Q-Switched (QS) 650-nm Nd:YAG laser, 50-ns QS 755-nm alexandrite laser, QS ruby laser and 700-picosecond alexandrite laser [19-21].

Half-and-half nails (Lindsay's nails) are characterized by whitening of the proximal half up to two-thirds of the nail, and the distal part is either pinkish or brownish in color. Such nail changes were found in approximately 20% of the patients with Stage 5 CKD on chronic dialysis program [22]. The precise mechanism remains unknown, however one hypothesis maintains that it is due to the increased concentration of MSH (melanocyte stimulating hormone), while another hypothesis claims that this occurs due to an edema on the nail bed [23]. In our sample "Half-and-half nails" were diagnosed in 19.05% of the respondents. All patients with hyperparathyroidism had these changes in their nails, and 75% of them were also anemic. These findings are similar to those of the a Dyachenko *et al*. (study from 2007), that showed the prevalence of nails changes in patients with CKD are not significantly dependent on the age, sex, the CKD duration, medications or the primary disease that is the cause of CKD. In this study, a significant correlation is established between changes in nails and the levels of PTH >220 pq/ml (p=0.03) [40]. PTH is the major uremic toxin responsible for the long-term consequences, such as renal osteodystrophy, vascular calcification, alterations in the cardiovascular structure and function, immune system dysfunction and anemia. These side effects contribute to an increased mortality and morbidity caused by cardiovascular disease in Stage 5 CKD patients. PTH has a vasorelaxant effect on cells of the smooth muscles of blood vessels and is in fact a potent synthesis activator of the endothelial nitric oxide [36], leading to vasodilatation of the small blood vessels.

Absence of lunula on the nail was recorded in 23.81% of the respondents. 80% of the patients with anemia had this finding. Onychomycosis was found in 40.47% in this sample and is one of the most common cutaneous changes in patients with Stage 5 CKD on hemodialysis. Thinning hair was found in 21.43% of the respondents, a similar finding as in numerous other studies [6, 7].

Morbus Kyrle was diagnosed in 2.38% of the respondents. Some authors consider it as a serious disorder of keratinization, while the majority believes that Morbus Kyrle belongs in the acquired perforating dermatitis (APD) category with prevalence of 11% in patients with Stage 5 CKD on chronic dialysis program. APD is characterized by disseminated papules, plaques and nodules with a hyperkeratotic plug on spots susceptible to pressure or manipulation. The lesions can be linearly arranged secondary to kebnerization. This should be clinically differentiated from prurigo nodularis, arthropod bites, multiple keratoacanthomas, psoriasis and lichen planus. The APD's pathophysiology is not entirely clarified. It could be due to: a) slow healing of the skin in diabetes-induced microangiopathy; b) local trauma caused by itching or dermal necrosis, microangiopathy, which results in extrusion of dermal material through the epidermis; c) foreign body reaction to altered dermal collagen and deposition of calcium salts [17].

None of the respondents was diagnosed with skin and mucous membranes cancer, pseudoporphyria, calciphylaxis and nephrogenic systemic fibrosis.

Conclusion

The muco-cutaneous changes/symptoms were a common finding in patients with Stage 5 CKD on hemodialysis. In all patients, at least one muco-cutaneous change/symptom was diagnosed. The causes of CKD do vary, however in this sample the most common cause was the NAS associated nephropathy. The most common muco-cutaneous changes/symptoms were xerosis, pruritis and hyperpigmentations.

Many of the skin changes/symptoms, its adnexa and mucosa are benign and do not affect the course of CKD. However, some of them may be considered as serious systemic disorders in the patients. Studies investigating the muco-cutaneous changes/symptoms in patients with Stage 5 CKD on hemodialysis are quite necessary so that the quality of life in these patients can be impro-

ved. Interdisciplinary management that involves dermatologists is of vital importance.

Conflict of interest statement. None declared.

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