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# Effects of Uremic Pruritus on Dermatological and Kidney Disease Quality of Life in Patients Receiving Hemodialysis

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#### Abstract

**Aim:** This study was conducted in order to determine the dermatological and kidney disease quality of life of patients with uremic pruritus receiving hemodialysis treatment.

**Material and Methods:** The present study was a descriptive study. The sample comprised 200 of HD patients. The participants were required to complete patient information form, 5-D-Itch scale, Dermatological Quality of Life Index (DLQI) and Kidney Disease Quality of Life Form (KDQOL-36) were used to collect the data of the study.

**Results:** It was determined that the DLQI score average of the patients with pruritus was  $11.57\pm4.74$  and that the dermatological quality of life of 60.6% of the patients was largely or extremely affected. It was revealed that the average KDQOL-36 score of the patients with pruritus was  $59.36\pm12.27$ , and their kidney disease quality of life was of moderate level. Pruritus severity explained a moderate amount of the variability of DLQL (crude  $R^2 = .181$ ) and KDQOL-36 (crude  $R^2 = .184$ ).

**Conclusion:** It was determined that as the severity of uremic pruritus increased, DLQI and KDQO-36 decreased. Therefore, timely treatment, nursing care and counseling are recommended to monitor level of pruritus, dermatological and general quality of life to improve the quality of life in HD patients.

Keywords: Dermatology quality of life, general quality of life, hemodialysis, itch

### INTRODUCTION

In addition to affecting all systems, chronic kidney diseases (CKD) and Hemodialysis (HD) used in its treatment cause serious dermatological problems. HD prolongs the life of patients, but on the other hand, it leads to various dermatological symptoms and complications and affects dermatological and kidney disease quality of life (1,2). Patients receiving HD treatment suffer from some skin problems such as dryness, uremic itching, hyperpigmentation, pallor, skin ulcers, purpura, ecchymosis, and uremic frost. Such skin problems also lead to deterioration in skin structure and physical, psychosocial, and emotional distortion in the general health perception of patients (3-6).

Uremic pruritus is not only one of the most typical and

disturbing skin problems of CKD and HD, but also it is a common and severe skin-related symptom affecting 40-60% of patients receiving HD treatment (7-8). Pruritus, which is not encountered in acute kidney diseases cases and is treated after kidney transplantation in CKD, occurs in various severity in patients receiving HD treatment. Although it is thought that uremic pruritus is caused as a result of eliminating toxins from the body through the skin, it is stated that the reason behind it might be secondary hyperparathyroidism, hyperphosphatemia, calciumphosphate deposition in the skin, changes in skin pH, dry skin due to atrophy in sweat and sebaceous glands, the proliferation of mast cells in the skin and consequently increased plasma histamine level, inadequate dialysis, anemia, iron deficiency, dialysis with devices that have low hypersensitivity, as well as antiseptic solutions used

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for disinfection, nickel-containing needles, epoxy resin, colophony, formol, and thiuram, as well as other allergenic substances. Due to the obscurity of the pathogenesis of uremic pruritus, the use of limited therapeutic methods is not enough to take the pruritus under control (8,9).

Pruritus is described as the worst and most disturbing symptom by patients receiving HD treatment (3,6,9). Uremic pruritus can cause physical, psychosocial, and emotional deterioration in general health perceptions of patients (1,6). Uremic pruritus generally reduces the dermatological quality of life of HD patients due to the continuous sense of itching and lesions and dryness occurring due to itching (10). Uremic pruritus causes sleeplessness, fatique/exhaustion, anger, anxiety, depression as well as decreased self-esteem, social isolation, a decline in self-care and guality of life, along with the scratching behavior during the day and especially at night, making the disease management more difficult (4-8,11-13). Due to these itching-related problems, patients have a 17% higher mortality rate, along with pruritus and sleep problems, than regular HD patients (14). In a study conducted on HD patients, it was indicated that the dermatological quality of life of patients with uremic pruritus was low (4,10,15).

The impact of uremic pruritus on guality of life, which affects at least half of HD patients, is a critical issue that should be properly addressed by clinicians. No study was found regarding dermatological and general guality of life and their relationship in patients with uremic pruritus. The effects of HD on the dermatological and general quality of life of the patients are not adequately assessed, especially in Turkey. The results of assessments can help the HD healthcare team question and treat the pruritus experienced by patients so that dermatological and kidney disease quality of life of patients can be improved. The HD healthcare team plays an important role particularly in the identification of the presence and severity of uremic pruritus, its care, and treatment, as well as in the holistic assessment of patients and improvement of their dermatological and kidney disease guality of life.

# MATERIAL AND METHOD

#### **Patient selection**

The study was carried out in a descriptive fashion to determine the dermatological and kidney disease quality of life of patients with uremic pruritus receiving haemodialysis treatment.

The study population consisted of 224 patients treated in a private provincial HD center and an HD unit of a university hospital. No sample selection method was used in the study; the entire universe, 200 patients, were included in the sample (89.2% of the invited participants). After the study, post-hoc power analysis was conducted. The power of the test was measured using the G\*Power 3.1 tool. According to the relational findings of the study, the effect size was found to be 0.42, and the power of the

study was measured as 99%.

Inclusion and exclusion criteria; Patients who were 18 years of age or older, had cognitive competence to answer questions, had been receiving HD treatment for at least 6 months due to CKD, did not have a chronic skin disease, and who gave their verbal and written consent to participate in the study were included in the sample.

#### Data collection and measures

Before collecting data, the patients were informed about the purpose of the study, and their written and verbal informed consent was acquired. The questionnaire was filled out in an average of 15-20 minutes for an average patient immediately after the HD treatment was initiated. The research was carried out between January-30 November 2020.

The related literature was examined when creating the patient information form. The form consists of 8 questions regarding socio-demographic characteristics of the patient, 11 questions regarding characteristics of the disease, CKD and HD duration, patient's compliance to diet and treatment, presence and intensity of itching, 19 questions in total (1-6).

5-D Itch Scale was developed by Elman, Hyman, Gabriel, and Mayo in 2010. Five dimensions of itching beginning with letter "D" are included in 5-D pruritus scale and are evaluated during the previous 2 weeks. The first three items (duration, degree, direction) are single-item domains and are scored from 1 ('less involvement according to the item') to 5 ('most involvement according to the item'). Disability represents a multiple-item domain and includes the effects of itching on daily activities such as sleep, leisure/social activities, housework/errands and work/ school. The score for the disability domain is obtained by obtaining the highest score within four evaluated sub domains. The fifth item (Distribution) evaluates the presence of itching within 16 body parts over the previous 2 weeks. Regarding the number of affected parts, five scoring bins are constructed. 5-D scores range from 5 (no pruritus) to 25 (most severe pruritus). Altınok Ersoy and Akyar performed the validity and reliability analyses of the scale in Turkey, and its internal consistency was ensured with Cronbach's Alpha coefficient of 0.608. The items and dimensions of the scale remained the same following the validity and reliability analyses, and no changes were made in the scoring or calculation (16,17). In this study, Cronbach's Alpha of the scale was found to be 0.853.

The Dermatological Quality of life Index, DLQI, created by Finlay and Khan in 1994, is a simple, short, understandable test and is the most important and commonly used across dermatology-related tests. Its Turkish validity and reliability analyses were performed by Öztürkcan et al. in 2006. It consists of 10 questions with possible answers each and is based on the patient's feelings regarding skin-related symptoms, their daily activities, free time occupations, school/work life, personal relationships, and treatment. DLQI is scored between 0-30 points. A higher score means quality of life is affected negatively. Öztürkcan et al. (2006) measured Cronbach's Alpha of the scale as 0.85 in their study (18,19). In this study, Cronbach's Alpha of the scale was measured as 0.766.

Kidney Disease Quality of Life Form (KDQOL-36) is the most commonly used scale among the disease-specific scales in CKD cases. KDQOL-36 was developed in the USA in 1994 by Ron Hays et al. This is a scale used to monitor patients with CKD and various treatment effects, and well-being of the patients are evaluated in the light of their own expressions. The scale originally consisted of 134 items. However, since it took too much time to complete the scale, it was reduced to 80 items by expert researchers (20). The scale was revised by the Kidney Disease Quality of Life Development Center (Research and Development-RAND) in 2000, reducing the scale to 36 items and naming it KDQOL-36. The guestionnaire contains 36 items divided into 5 dimensions. SF-12 (12 items); Items related to kidney disease (5 dimensions/24 items): List of symptoms/issues (12 items), Effects of the kidney disease (8 items), Burden of the kidney disease (4 items), SF12 physical component (6 items), SF12 mental component (6 items). The scale is used to determine the quality of life of individuals with CKD between stages 1-5 and receiving HD treatment (https://www.rand.org, access date: January 1, 2020). Yıldırım et al. performed the Turkish validity and reliability study of the scale, and Cronbach's Alpha value of the study was measured to be 0.84-0.91. Scores range from 0 to 100 in each dimension, and higher scores reflect better health quality in life (21). Cronbach's Alpha of the scale was found to be 0.868 in our study.

#### Data analysis

The data were evaluated using the Statistical Package for Social Science 22.0 (SPSS) software. Descriptive statistics were given as the number of units (n), percent (%), average and standard deviation values. The conformity of the data to normal distribution was determined by Shapiro-Wilk and Kolmogorov-Smirnov tests. Parametric tests were used for normally distributed data, and nonparametric tests were used for non-normally distributed data. Cronbach's a values of the scales used were calculated. p<0.05 value was considered statistically significant in the comparisons.

#### **Ethical considerations**

To be able to conduct the study in institutions, permission (no: 20/232) was acquired from a University Non-Invasive Clinical Research Ethics Committee (Approval no: 20/114). Written permissions were acquired from the institutions where the research was conducted after submitting a written application with a form including information regarding the purpose and scope of the study. Throughout the study, the ethical principles of the Declaration of Helsinki were complied with, and the confidentiality of individual information was maintained. Out of the consideration of the willingness to participate and voluntariness principles, the process took off by acquiring the verbal and written consents of the participants.

# RESULTS

It was determined that the age average of patients with pruritus was 56.83±12.55 years, 46.6% of them were between 51-64 years old, 61.2% were male, 30.1% were primary school graduates, 84.5% were married, 85.4% were unemployed, 65% were from the middle class. 58.3% of them did not receive social support. The average age of the patients without pruritus participating in the study is 52.69±13.69 years, 44.3% of them were between 51-64 years old, 55.7% were male, 26.8% were high school graduates, 79.4% were married, 77.3% were unemployed, 63.9% were from the middle class, 67% did not receive social support. It was stated that patients with and without pruritus had similar sociodemographic characteristics (p>0.05). It was found that 87.4% of the patients with pruritus had a secondary chronic disease, 19% had diabetes as their secondary chronic disease, 11.7% did not comply with treatment, 54.4% did not comply with their diet, 46.6% had been receiving dialysis treatment for 1-5 years. As for patients without pruritus, it was stated that 86.6% of them had a secondary chronic disease, 22.4% had diabetes and hypertension as their secondary chronic disease, 14.4% did not comply with the treatment, 47.4% did not comply with their diet, 39% had been receiving dialysis treatment for 1-5 years. It was stated that the patients with and without pruritus had similarities in terms of the presence of the secondary diseases, types of secondary chronic diseases, the average number of drugs used, and compliance with their treatments and diets (p>0.05; Table 1).

It was revealed that 51.5% of the patients with pruritus began itching after initiation of the HD treatment and had pruritus and itching in the two weeks prior to this study, and 37.9% of them still suffered from itching on the day of the study. It was revealed that 36.9% of the patients intensely experienced pruritus during the evening prior to the day they underwent HD on their back (10.9%), abdomen (8.8%), and upper arm (7.6%). 70% of the patients were found to use medication to cope with pruritus, and 58.9% of them benefitted from the medication (Table 3). 5-D Itch scale score average of the patients measured to be 13.05±4.29, and it was revealed that patients experienced moderate severity itching (Table 2).

It was determined that the DLQI score average of the patients with pruritus was  $11.57\pm4.74$  and that the dermatological quality of life of 60.6% of the patients was largely or extremely affected. The average DLQI score of the patients without pruritus was measured to be  $11.95\pm5.86$ , and in this regard, it was determined that the dermatological quality of life of 49.3% of the patients

Table 1. Distribution of socio-dem	ographic characterist	ics of the patients (n=2	200)		
Characteristics	Itching (n=103)		No itchin	No itching (n=97)	
	n	%	n	%	Test
Gender					
Female	40	38.8	43	44.3	x <sup>2</sup> =0.621
Male	63	61.2	54	55.7	p=0.431
Age (year) X±SD (min-maks.)	56.83±12.55	(30.00 - 90.00)	52.69±13.69 (2	21.00 - 82.00)	t=2.228 n=0.270
Educational level					p 0.210
Illiterate	7	6.8	8	8.2	
Literate	12	11.7	4	4.2	
Primary school graduates	31	30.1	20	20.6	$x^2 = 7.614$
Secondary school graduates	21	20.4	25	25.8	p=0.179
High school graduates	22	21.3	26	26.8	
University	10	9.7	14	14.4	
Marital status					
Married	87	84.5	77	79.4	x <sup>2</sup> =0.875
Single	16	15.5	20	20.6	p=0.350
Employment					
Employed	15	14.6	22	22.7	x <sup>2</sup> =2.183
Unemployed	88	85.4	75	77.3	p=0.140
Income status					
Well class	23	22.3	23	23.7	x <sup>2</sup> =0.054
Middle class	6/ 12	65.0	62	63.9 12.4	p=0.973
Low class	13	1	ΙZ	12.4	
	12	41.7	22	22.0	w <sup>2</sup> -1 625
No	43 60	41.7	52	55.0 67.0	p=0.201
Secondary chronic disease	00	00.0	00	01.0	P
Yes	90	87.4	84	86.6	x <sup>2</sup> =0.027
No	13	12.6	13	13.4	p=0.870
Number of drugs used X±SD (minmaks.)	6.41±2.21 (1.00-12.00)		6.27±2.58 (2.00-17.00)		t=0.412 p=0.681
Compliance to treatment					
Yes	91	88.3	83	85.6	x <sup>2</sup> =0 342
No	12	11.7	14	14.4	p=0.559
Diet compliance					
Yes	47	45.6	51	52.6	x <sup>2</sup> =0 962
No	56	54.4	46	47.4	p=0.326
Dialysis time					
1 years and less	15	14.6	30	30.9	
1- 5 years	48	46.6	38	39.2	
6- 10 years	18	17.4	19	19.5	x <sup>2</sup> =10.519 n=0.033
11-15 years	11	10.7	5	5.2	p=0.000
16 years and more	11	10.7	5	5.2	
X <sup>2</sup> = chi square test, t= t test					

Table 2. Distribution of pruritus characteristics of h   (n=103)	emodialysi	s patients
Characteris	n	%
Itch duration, presence (month) X±SD (minmax.)	14.40±9.7	5 (3-48)
Presence of itch in the last two weeks		
Yes	103	51.5
No	97	48.5
The presence of itch today (n=103)		
Yes	39	37.9
No	64	62.1
Time the itch of most intense (n=103)		
During hemodialysis	22	21.4
The night of hemodialysis	38	36.9
The day left hemodialysis	13	12.6
Continually	30	29.1
Locations of itch*		
Back	67	10.9
Abdomen	54	8.8
Upper arms	47	7.6
Lower legs	46	7.5
Chest	42	6.8
Soles	38	6.2
Tops of feet/toes	38	6.2
Tops of hand/fingers	36	5.8
Forearms	35	5.7
Face	34	5.5
Buttocks	33	5.3
Points of contact w/ Clothing (e.g waistband, undergarment)	33	5.3
Head and scalp	31	5.0
Thighs	29	4.7
Groin	27	4.4
Palms	27	4.4
Medication for itch (n=103)		
Yes	73	70.9
No	30	29.1
Benefit status of drugs (n=103)		
Yes	43	58.9
No	30	41.1
* More than one answer was given		

was largely or extremely affected. The dermatological quality of life of the patients with pruritus was determined

to be 20% worse on average. It was revealed that the average KDQOL-36 score of the patients with pruritus was 59.36±12.27, and their kidney disease quality of life was of moderate level. The average KDQOL-36 score of the patients without pruritus was measured to be 60.08±12.97, and the kidney disease quality of life of the patients was found to be of moderate level (Table 3).

Table 3. Distribution of 5-D itch     hemodialysis patients (n=200)	, DLQI and KDQOL-	36 scales scores of				
Scale and subsections	X±SD (min-max)					
5-D Itch Scale	13.05±4.29	13.05±4.29 (6.25-25.00)				
Duration	2.14±1.36	(1.00-5.00)				
Degree	3.01±0.90 (2.00-5.00)					
Direction	3.11±1.16	3.11±1.16 (1.00-5.00)				
Disability	2.39±0.98 (1.00-5.00)					
Distribution	2.41±1.61	(1.00-5.00)				
	Itching X±SD (min-max)	No itching X±SD (min-max)				
DLQI	11.57±4.74	11.95±5.86				
Dermatological quality of life impact states	n (%)	n (%)				
No effects (0-1)	0 (0)	1 (1)				
Small effects (2-5)	3 (3.1)	9 (8.7)				
Moderate effects (6-10)	36 (35.0)	41 (42.3)				
Very large effect (11-20)	55 (53.4)	45 (46.4)				
Extremely large effect (21-30)	7 (7.2)	3 (2.9)				
	X±SD (min-max)	X±SD (min-max)				
KDQOL-36	59.36±12.27	60.08±12.97				
Subsections						
Physical component	44.30±28.18	53.57±26.66				
Mental component	48.10±21.03	47.81±23.68				
Burden of the kidney disease	41.50±19.86	41.43±20.40				
List of symptoms	73.89±11.37	75.73±11.17				
Effects of the kidney disease	66.23±12.47	60.02±13.97				

It was stated that the average DLQI score of the patients who had been consistently suffering from pruritus and was also experiencing pruritus on the day of the study ever since the initiation of the haemodialysis treatment was significantly higher (p<0.05). It was found that the average KDQOL-36 score of the patients who experienced consistent pruritus since the initiation of haemodialysis treatment was statistically significantly lower (p<0.05).

When general scores of the scales are correlated, it was discovered that there was a moderately positive and significant correlation between the average 5-D itch scale score and the average DLQI score (r=0.425, p=0.001). It was determined that there was a moderately negative

Table 4. Correlation between 5-D ltch. DLOL and KDOOL-36 scales score of patients

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		5-D itch scale 1 duration	5-D itch scale 2 degree	5-D itch scale 3 direction	5-D itch scale 4 disability	5-D itch scale 5 distribution	5-D itch score
KDQOL-36 physical component	r	-0.251*	-0.133	-0.053	-0.297**	-0.081	-0.212*
	р	0.011	0.179	0.596	0.002	0.414	0.031
KDQOL-36 mental component	r	-0.353**	-0.123	-0.237*	-0.354**	-0.138	-0.299**
	р	0.001	0.215	0.016	0.001	0.163	0.002
KDQOL-36 burden of the kidney disease	r	-0.367**	-0.167	-0.261**	-0.383**	-0.219*	-0.355**
	р	0.001	0.091	0.008	0.001	0.026	0.001
KDQOL-36 list of symptoms	r	-0.301**	-0.273**	-0.289**	-0.257**	-0.153	-0.345**
	р	0.002	0.005	0.003	0.009	0.123	0.001
KDQOL-36 effects of the kidney disease	r	-0.198*	-0.089	-0.149	-0.096	-0.055	-0.128
	р	0.045	0.369	0.133	0.334	0.580	0.197
KDQOL-36 score	r	-0.401**	-0.207*	-0.229*	-0.347**	-0.158	-0.429**
	р	0.001	0.036	0.020	0.001	0.112	0.001
DLQI score	r	0.268**	0.304**	0.117	0.287**	0.234*	0.425**
	р	0.006	0.002	0.241	0.003	0.017	0.001

r= spearman rank correlation coefficient \*significant correlation at the 0.05 level \*\*significant correlation at the 0.001 level

and significant correlation between the average 5-D itch scale score and the average KDQOL-36 score (r=-0.429, p=0.001). It was revealed that, as the severity of pruritus increased, dermatological and kidney disease quality of life accordingly decreased (Table 4).

Effects of itching on dermatological and kidney disease quality of life: regression analysis table 5. Model 1-2 The analysis of the t test results for the significance of the regression coefficients revealed that itch was significant predictors for dermatological quality of life ( $R^2$ =.181) and kidney disease quality of life ( $R^2$ =.184).

Table 5. Effect of itch severireceiving hemodialysis: regress	ity on DI sion analy	_QI and ysis (n=`	KDQO 103)	L-36 in	patients
Variables	В	SE	В	t	р
Model 1					
Constant	21.955	1.904		11.528	<.001
Kidney disease quality of life	.150	.031	.429	4.776	<.001
R=.429 R <sup>2</sup> =.184	Ļ		F=2	2.811 p<0	0.001
Model 2					
Constant	8.590	1.019		8.431	<.001
Dermatological quality of life	.385	.082	.425	4.723	<.001
R=.425, R <sup>2</sup> =.181, F=22.307, p	< 0.001				

# DISCUSSION

with Itching (n-102)

Uremic pruritus, which is considered a symptom that is an important health problem that affects the dermatological and general guality of life of patients receiving HD. It was determined that 51.5% of the patients experienced pruritus in the last two weeks and 37.9% of the patients on the day of the study. In a study focused on skin problems of HD patients, it was revealed that 65.1% of the participants experienced itching stated that 49.1% of the patients stated that they experienced itching in a study they conducted on patients receiving HD treatment (1,13). Our results are in parallel with those of these studies. More than half of patients receiving HD treatment were seen to experience pruritus on various severities. We determined in our study that the 5-D Itching scale score of HD patients was moderate severity and the patients experienced moderate itching. Other studies concluded that HD patients experience moderate itching, similar to our findings (12,22). We observed in our study that HD patients mostly experienced severe pruritus on their back region. When other studies in the literature are examined (24,25), it is seen that Kılıc Akca and Tascı (2014) concluded in their study that patients experienced pruritus on their arm and back where the fistula is located (23). Other studies revealed that pruritus was mostly localized on the extremities and back (22,24). We observed in our study that HD patients mostly experienced pruritus in the evening prior to the day they would undergo haemodialysis (36.9%). When other studies in the literature are examined,

it is seen that they reveal that pruritus reaches its peak in the evening prior to the day of HD treatment and continues during HD (5,6). Our results are in parallel with those of these studies.

The dermatological guality of life of more than half of the HD patients was found to be low, and those who experienced consistent itching were found to have even lower quality of life as a result of severe and widespread itching. It was revealed in our study that the DLQI of the patients with pruritus was largely and extremely affected by 60.6%. In a study conducted in Turkey, it was concluded that the dermatological guality of life of the patients was low after the initiation of the haemodialysis treatment (1). Kücükünal et al. stated in their study that the dermatological quality of life of patients undergoing HD was low.10 Adejumo et al., (2016) reported in their study that the dermatological quality of life of 12.4% of the patients with ESRD was moderately affected, and 3.8% of the patients' quality of life was severely affected (2). Satti et al., (2019) found in their study that the DLQI score of the patients was 9.8±1.7, 34.1% of them were moderately affected, and they exhibited depressive symptoms (13). Similarly, studies examining the guality of life of dialysis patients with uremic pruritus revealed that the dermatological quality of life decreased significantly in pruritus cases (15,25). Some sources support our findings. However, the dermatological guality of life of HD patients in studies conducted in other countries was reported to be higher compared to our study. One can say that the reason behind this difference is cultural differences that shape treatment compliance, living conditions and quality of life perceptions of HD patients.

In our study, when the KDQOL-36 scale was examined in terms of pruritus, it was observed that the general quality of life the patients was moderate, but it was found that the general quality of life decreased as the severity of pruritus increased. In a study conducted in Turkey in 2015, which supports our results, it has been observed that pruritus significantly decreases the quality of life of HD patients.10 Similarly, in other studies, it was determined that HD-related pruritus reduced the quality of life patients (2,4-6). The literature also points out that pruritus affects the overall quality of life HD patients (26-29).

# CONCLUSION

In this study, it was concluded that more than half of the HD patients experienced moderate uremic pruritus. It was determined that uremic pruritus decreased the dermatological and kidney disease quality of life of the patients. In this regard, it is recommended that patients with uremic pruritus receiving HD treatment should be thoroughly evaluated for the reasons behind pruritus and relative problems. It can additionally be recommended to carry out more comprehensive studies by ongoing counseling HD patients in order to help them cope with this situation and to increase their dermatological and general quality of life.

## Limitations of the study

The results of this study are valuable in terms of discussing in dermatological and general quality of life HD and influential factors such as pruritus. However, there were some limitations in the study. Firstly, the study was completed with relatively small samples and may only be generalized for its of population. Secondly, a cross-sectional study design is limited in establishing a causal association between dermatological quality of life and pruritus. In order to be able to show causality, longitudinal studies are needed.

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**Conflict of Interest:** The authors declare that they have no competing interest.

**Ethical approval:** The study in institutions, permission (no: 20/232) was acquired from a Hacettepe University Non-Invasive Clinical Research Ethics Committee (Approval no: 20/114).

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