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CLINICAL REPORT

Clinical Findings and Provision of Care in Haemodialysis Patients with Chronic Itch: New Results from the German Epidemiological Haemodialysis Itch Study

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The German Epidemiological Haemodialysis Itch Study (GEHIS) has shown that more than one-third of haemodialysis patients have chronic itch (CI). As part of GEHIS, 216 patients with current CI were offered a dermatological examination, of whom 177 were investigated. According to the clinical classification of the International Forum for the Study of Itch (IFSI), 43.5% (*n*=77) of the patients examined had CI with no skin lesions (IFSI II), 37.9% (*n*=67) had secondary scratch lesions (IFSI III), and 18.6% (*n*=33) primarily had diseased skin (IFSI I). Severity of CI and itch-related quality of life (ItchyQoL) showed a significant association only with IFSI III. Of the patients in this study, 89.8% (*n*=159) had xerosis cutis. Only 40.4% (*n*=80) had ever sought medical help for CI, 46.4% (*n*=32) of whom were in the category IFSI III. Only 32.4% (*n*=77) had ever received any treatment for CI and these patients had significantly more severe CI. The current analyses demonstrate that CI is a frequently disregarded symptom in haemodialysis patients. *Key words: haemodialysis; IFSI classification; itch; pruritus; uremic itch; xerosis.*

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Itch is a frequent and bothersome symptom in haemodialysis (HD) patients, and has been described for decades as a major challenge in this group of patients (1). However, the comparability of studies of itch is limited by several factors: the undulating pattern of itch, a lack of definition of the prevalence period, differing study time periods without clear definitions of itch, and regional variations in dialysis quality limits. These factors contribute to large variations in the reported prevalence of itch in HD (1). With the aim of closing this gap, a representative cross-sectional prospective prevalence study on itch in HD patients (GEHIS: German Epidemiological Haemodialysis Itch Study) was initiated (2). Precise and different prevalence estimates of chronic itch (CI) (>6 weeks) were determined, showing that 25.2% of the HD patients had current CI and 35.2% reported having had CI at least once in their lifetime (2). General health status and health-related quality of life (HRQOL) was significantly impaired in the patients with CI, which makes it a distressing and impairing symptom (2), facts that put CI problematic forward for HD patients.

It has been reported that HD patients with CI face a 23% higher risk of mortality (3). In addition, improved medical care and increased survival rates, as well as demographic changes, especially in Western countries, will increase the number of patients with end-stage renal disease (ESRD) who will require HD treatment in the coming years. It is therefore important to expand our knowledge of this symptom.

The pathogenesis of itch in HD patients remains elusive, although various molecules have been implicated (4), and there are therefore few treatments that substantially relieve this symptom.

Clinical classification of itch was developed by the International Forum for the Study of Itch (IFSI) to serve as a diagnostic tool for better evaluation of patients with CI and to improve patient care (5). Classification comprises 3 groups, based on the clinical presentation of CI according to skin changes: group I are subjects with primarily diseased skin, group II have normal-looking skin, and group III have a clinical picture of chronic secondary scratch lesions (5). However, to date, this classification has not been applied in HD patients.

As part of GEHIS, HD patients with current CI were offered a dermatological examination, with the aim of classifying CI in HD patients according to the IFSI classification. The dermatological aspects and features of CI were documented. In addition, the provision of care in HD patients with CI was investigated.

MATERIALS AND METHODS

GEHIS was established as a prospective observational cross-sectional study taking place in Germany in 2013 and including 860 HD patients. Eligible patients were diagnosed with ESRD and underwent chronic HD treatment. The study was described in detail elsewhere (2) and all results were reported in line with STROBE recommendations (6). The primary outcome measures

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of GEHIS were different prevalence measures of itch (point, 12-month- and lifetime prevalence). Secondary outcome measures were HRQOL assessed with the Short Form Health Survey (SF-12) (7) and the Hospital Anxiety Depression Scale (HADS) (8). Comorbidities (according to the Charlson Comorbidity Index (CCI)) (9), laboratory values and dialysis characteristics (e.g. start of HD treatment, efficacy of dialysing, dialyser membrane) were assessed. Measures of daily washing (shower or bathe, frequency: daily or every other day) and moisturizing habits (once or twice a day, every other day) were obtained.

In patients with CI the following characteristics of itch were assessed: severity, measured by visual analogue scale (VAS) ranging from 0 (no itch) to 10 (maximum imaginable itch); affected body localization(s); quality of itching (e.g. burning, tingling, etc.); frequency of CI (daily, weekly, monthly); triggers of CI (e.g. stress, rest, sweat, heat); measures to combat CI (e.g. scratching, etc. rubbing, using brushes, moisturizing the skin, applying heat or cold); and itch-related quality of life (ItchyQoL) (10). Patients were asked whether they had ever consulted a physician and/or a dermatologist for their CI, undergone treatment for CI, and whether this had relieved CI.

The current analyses are based on an additional part of the GEHIS. HD patients with current CI were offered a skin examination by a dermatologist. This included the following: (*i*) dermatological history including present or past dry skin, atopic eczema, atopic diathesis, contact allergies, psoriasis and/or any other skin disease; (*ii*) whole-body examination in order to classify CI according to the clinical IFSI classification; (*iii*) dermatological examination documenting: (a) skin phototype (SPT, I-VI) according to Fitzpatrick and any signs of actinic skin damage, actinic keratosis, basal cell carcinoma, squamous carcinoma; and (b) xerosis cutis, atrophy of the skin, seborrhoeic eczema, nail disorders (dystrophy, onychomycoses), tinea pedum, varicose veins and leg ulcers.

Statistical analyses

A Microsoft Access 2003 database was used for data entry and management. Data entry was conducted twice by 2 independent persons. All observed inconsistencies within the resulting data were resolved to maximize data quality. Statistical analyses were performed using SPSS (version 20) for Windows. Nominal and ordinal data were analysed by computing absolute (n) and relative frequencies (%). χ^2 statistics were used to identify variables that were significantly associated with CI and the IFSI classification in univariate analysis. p-values < 0.05 were considered significant. Comparisons between IFSI categories were conducted by independent t-tests/analysis of variance (ANOVA) for the continuous variables (e.g. laboratory values) and by χ^2 test for binary distributions.

Associations between laboratory findings and the dermatological characteristics of CI are reported by Pearson's correlation coefficients. For multiple testing, e.g. when analysing differences in laboratory values, a Bonferroni correction was conducted, setting the significance cut-off at α/n (adjusted alpha).

RESULTS

Socio-demographic data

A total of 216 HD patients had current CI, of whom 82% ($n = 177$) agreed to a dermatological examination. The remainder declined the offer of examination because of feelings of shame, tiredness, sleepiness, or because of a physical handicap. Analyses of the socio-demographic data did not reveal any significant differences between patients with current CI and those without current CI or CI in the last 12 months regarding age, sex, origin, occupational, and marital status (Table I).

In previous research, we had shown a significant positive association between the history of eczema, allergic rhinitis/conjunctivitis and the occurrence of CI (2); however, this was not confirmed when considering classification according to the IFSI. There was a history of atopic diathesis in 19.2% ($n = 34$) of patients and psoriasis in 7.9% ($n = 14$). There was a history of contact allergy in 31.6% ($n = 56$) of patients; however, no itemization of these allergies could be elicited.

Clinical classification of itch according to IFSI

Clinical classification according to IFSI revealed that 43.5% ($n = 77$) of the patients who underwent dermatological examination were classified as IFSI II (normal-looking skin), 37.9% ($n = 67$) were classified as IFSI III (secondary scratch lesions), and 18.6% ($n = 33$) as IFSI I (CI caused by dermatoses). Of the 33 patients classified as IFSI I, 8 had itchy psoriasis, and this was the most frequent diagnosis in the IFSI I group. Of the patients classified as to IFSI I, seven patients had any type of eczema (atopic, seborrhoeic, nummular) and 6 had mycoses. The remainder had a variety of itchy dermatoses, such as lichen planus, lupus erythematosus, pseudoporphyria, mycosis fungoides, acne vulgaris, erythema ab igne (1 or 2 cases each). IFSI II was equally prevalent in males and females, but IFSI I and IFSI III were more prevalent in males than in females; however, this difference was not significant.

The body sites most affected by CI, in 196 patients who answered this question, were the legs, 54.6% ($n = 107$),

Table I. *Socio-demographic data for hemodialysis patients with and without chronic itch (CI)*

	Patients with CI ($n = 177$)	Patients without CI[a] ($n = 551$)
Age, years, mean ± SD	64.7 ± 13.7	68.6 ± 13.0
Female, % (n)	39.5 (70)	43.4 (239)
Occupational status, % (n)		
Working	11.9 (21)	7.7 (42)
Retired	61.6 (109)	75.4 (413)
Other	26.5 (47)	17.0 (93)
Schooling, % (n)		
Elementary	79.1 (140)	81.9 (451)
Advanced	16.9 (30)	14.9 (79)
Marital status, % (n)		
Married/in partnership	58.2 (103)	55.5 (306)
Widowed	18.6 (33)	23.4 (129)
Divorced	7.9 (14)	7.3 (40)
Single	14.1 (25)	12.3 (68)
Origin, % (n)		
Germany	88.1 (156)	89.7 (494)
Other	10.7 (19)	8.5 (47)

[a]Point- and 12-month prevalence.
SD: standard deviation.

followed by the back, 52% ($n=102$), and the scalp, 43.2% ($n=86$). CI on the back was significantly associated with IFSI II and CI of the lower extremities was significantly associated with IFSI III. The shunt-arm was no more affected by CI than the other body sites and there was no difference with respect to IFSI classification (see Table II).

Analyses of the whole cohort of GEHIS ($n=860$) regarding habits of daily washing and using emollients showed that 40.6% ($n=333$) showered once or twice a day, whilst 34.6% ($n=284$) showered every second day, and 24.8% ($n=204$) showered less often (total $n=821$). When analysing these habits for HD patients with and without CI, no significant differences were detected. Statistical analyses also showed no differences in the habits of washing/using emollients according to the IFSI classification. Of those HD patients using emollients $n=629$ in total), 57.7% ($n=363$) did so once or twice a day, 19.2% ($n=121$) every second day, and 23.1% ($n=145$) less often. Patients with CI stated that they applied creams more often (60.4% once or twice a day) compared with those not affected by CI (56.2%); however, this was not significant. Likewise, there were no differences in habits of emollient use when considering IFSI classification of itch. There was no association between the frequency and type of skin care habits and the occurrence of xerosis cutis or between xerosis cutis and IFSI classification.

Of all patients with CI, 60.4% ($n=113$) had CI for more than one year. Twenty-two patients (9.3%) had their CI for less than 6 months, 11.8% ($n=28$) less than 12 months and longer than 6 months, and 9.3% ($n=22$) longer than 10 years. Our previous analyses refer to GEHIS ($n=860$), identified a significant association between the duration of HD treatment and the occurrence of CI (2), but the current analysis on CI paitents ($n=177$) shows that there was no significant association between the different IFSI groups and the duration of HD treatment. Nevertheless, there was a tendency that the longer the patients are on HD the more likely it was that they would present as IFSI III; however, this was not significant. There was no association between IFSI classification and the type of dialysis membrane. In an earlier study from GEHIS ($n=860$), we showed a significant association between the laboratory values creatinine, phosphate and parathormone (PTH) and CI in HD patients (11), but no difference in terms of clinical categories of IFSI.

Characteristics of chronic itch and itch-related quality of life

The severity of itch was significantly higher in patients classified as IFSI III (mean ± SD VAS 4.4 ± 1.7) compared with IFSI II (3.8 ± 2.0) and IFSI I (3.7 ± 1.8) (Fig. 1).

Table II. *Sociodemographic data, clinical characteristics and quality of life according to IFSI classification of itch (I: primarily diseased skin; II: normal-looking skin; III: secondary scratch lesions) in 177 haemodialysis patients suffering from chronic itch (CI)*

	IFSI I 18.6% ($n=33$)	IFSI II 43.5% ($n=77$)	IFSI III 37.9% ($n=67$)
Female sex, % (n)	27.3 (9)	47.4 (36)	35.8 (24)
Age, years, mean ± SD	62.5 ± 13.7	65.8 ± 14.0	64.6 ± 13.6
Duration of haemodialysis-therapy, mean (months)	75.8	63.2	82.9
Duration of CI, % (n)			
> 6 weeks to 6 months	30.0 (6)	30.0 (6)	40.0 (8)
6–12 months	7.7 (2)	50.0 (13)	42.3 (11)
> 1–10 years	18.9 (18)	41.4 (46)	32.6 (31)
> 10 years	27.8 (5)	33.3 (6)	38.9 (7)
Severity of itch (visual analogue scale), mean ± SD	3.7 ± 1.7	3.8 ± 2.0	4.4 ± 1.8*
Localization of itch (top 3), % (n)			
Legs	37.5 (12)	52.1 (38)	65.1 (41)*
Back	43.8 (14)	56.2 (41)*	50.8 (32)
Scalp	40.6 (13)	43.8 (32)	42.9 (27)
Skin phototype, % (n)			
Skin photo-type I & II	19.2 (28)	41.8 (61)	39.0 (57)
Skin photo-type III & IV	16.1 (5)	52.6 (16)	32.3 (10)
Measures to combat itch, % (n)			
Moisturizing	48.5 (16)	57.9 (44)	60 (39)
Scratching	66.7 (22)	68.0 (51)	72.3 (47)
Rubbing	48.5 (16)	40.0 (30)	24.6 (16)
Itch-related quality of life, mean ± SD	1.9 ± 0.6	1.9 ± 0.7	2.2 ± 0.6*
HRQOL (SF-12), mean ± SD (n)			
Physical SF-12	37.1 ± 7.75 (28)	35.5 ± 11.15 (64)	32.8 ± 10.75 (60)
Mental SF-12	51.2 ± 11.60 (28)	52.4 ± 9.35 (64)	51.6 ± 11.01 (60)
Hospital Anxiety and Depression Scale, mean ± SD (n)			
Subscale anxiety	9.16 ± 2.38 (31)	8.23 ± 2.25 (65)	8.92 ± 2.17 (65)
Subscale depression	9.53 ± 1.98 (32)	9.52 ± 2.26 (68)	9.81 ± 2.46 (65)

*Significantly different at $p<0.05$.
SD: standard deviation; SF-12: Short-Form Health Survey.

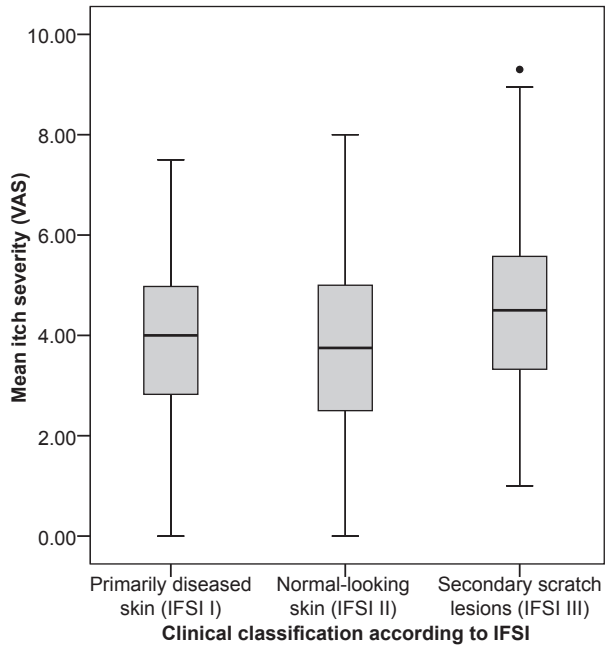

Fig. 1. Severity of itch (VAS) according to the clinical classification of itch (International Forum for the Study of Itch; IFSI).

Sensations of tingling, sharp, burning and painful itch, aspects that are specific to neuropathy, were reported by 54.2% ($n=96$) of patients. Daily/almost daily itch was reported by 63.4% ($n=123$), and 23.7% ($n=46$) had itch at least weekly. Having itch "sometimes" during the day was reported by 44.4% ($n=84$), and 31.7% ($n=60$) had itch "often". The majority of patients, 71.6% ($n=169$), experienced itch in the evening/night. An undulating pattern of CI, which they did not characterize as permanent, was reported by 80.4% ($n=135$). The most frequent triggers of itch were rest in 33.6% ($n=80$), being in bed in 29.5% ($n=70$) and sweating in 22.8% ($n=54$). Other triggers, such as stress, strain and cold, were reported by less than 10%. Measures to combat itch were scratching in 60.3% ($n=143$), using emollient in 46.2% ($n=110$), and rubbing in 29.5% ($n=70$). There was no significant association between the IFSI classification and the triggers or countermeasures of itch.

We reported previously that patients with CI who had the worst itch had significantly higher impairments in ItchyQoL (2), with ItchyQoL being significantly worst (2.2) in IFSI III patients. However, no such associations were detected between the HADS score and SF-12 score and IFSI classification. There was a significant association between CI and quality of sleep (2); however, there was no difference between IFSI I, II or III (see Table II).

Provision of care

Of the investigated patients ($n=177$, missing $n=7$), 40.6% ($n=69$) answered to have ever consulted a physician/dermatologist. 46.4% ($n=32$) of them were classified as IFSI III (itch with secondary scratch lesions). In another question, only 32.4% ($n=77$) of all CI patients answered to have received any kind of antipruritic therapy, and these patients had significantly higher mean VAS scores (4.4 vs. 3.8; $p<0.03$) than those who had not received any treatment for CI. There was no difference when considering IFSI classification. Most of the treated patients received corticosteroids, 24.7% ($n=19$), and urea-containing agents, 20.8% ($n=16$), as topical treatments. Antihistamines were the most frequently prescribed systemic treatment for CI in 39% ($n=30$), whereas other therapies were systemic cortisones in 3.9% ($n=3$), antibiotics in 1.3% ($n=1$), gabapentin/pregabalin in 7.8% ($n=6$) and ultraviolet (UV) phototherapy in 7.8% ($n=6$).

When asked about the efficacy of the treatment in CI patients ($n=195$), 60% ($n=117$) stated that they had not yet received any treatment for CI, 9.2% ($n=18$) that it did not help, 23.1% ($n=45$) that it helped "a little" and 7.7% ($n=15$) "a lot".

Patients with the worst ItchyQoL score were classified as IFSI III and sought medical help (physician, dermatologist) more than those classified as IFSI I and IFSI II. This is consistent with the mean severity of itch, which was also significantly higher in IFSI III compared with the others.

Dermatological evaluation

The results showed herein are obtained in 177 CI patients who had a full body dermatological examination. The most frequent skin finding was xerosis cutis, in 89.8% ($n=159$) of the HD patients with CI. Interestingly, 85.5% ($n=130$) of these patients reported dry skin. Dermatological diagnoses not related to CI were also documented, as follows: skin atrophy was present in 46.3% ($n=82$) of the patients, onychomycosis or tinea pedis in one-third ($n=54$), generalized hyperpigmentations in 49.3% ($n=89$), seborrhoeic dermatitis in the predilection sites (scalp, face, chest, back) in 22.6% ($n=40$), leg ulcers in 8.5% ($n=15$), and varicose veins were in 20.9% ($n=27$). There was no association between CI and these skin findings and no differences between the different IFSI groups. 10.2% ($n=18$) had excoriations and scratched nodules consistent with the typical clinical picture of prurigo nodularis. These patients with prurigo nodularis were classified as to IFSI III. 32.8% ($n=58$) had signs of actinic skin damage, 19.8% ($n=35$) had actinic keratosis (AKs) and 10.8% ($n=21$) of non-melanoma skin cancers (NMSCs), such as basal cell (BCC) or squamous cell carcinoma (SCC). There was no association between the IFSI classification and the skin phototype (SPT), AKs or NMSCs. There was no significant association between the occurrence, the mean severity of itch and the SPT or any signs of actinic skin damage, AKs, BCC or SCC.

DISCUSSION

This is the first study to apply the IFSI clinical classification to a cohort of HD patients affected by CI. The results show that 43.5% of these patients have normal-looking skin (IFSI II), which may explain why CI in HD patients is not well perceived by nephrologists (12). The study also demonstrated that nearly 60% of HD patients with CI did not seek medical help, which may also be explained by the lack of skin lesions and the fact that 57.1% of patients consider HD treatment to be the cause of CI (2), an assumption that was also reported more than 30 years ago (13). It is notable that 18.6% of patients had CI with a clinical picture of a specific skin disease (IFSI I), which shows that there is a lack of dermatological care in this group of patients. This may be explained in part by the overwhelming HD therapy, and reduced general health status and HRQOL (2) in these patients, facts that make consulting another physician redundant. Despite attending HD units 3 times a week and receiving nephrological care, only a minority of HD patients ever received any type of topical or systemic treatment for their itch. However, a stepwise therapeutic approach has previously been proposed for HD patients (4, 14). In presenting the current data we would like to help improve the medical and, in particular, the dermatological, care of HD patients with CI and to help avoid underestimation of the patients' itch (for example due to a lack of skin lesions or the less severe intensity of CI).

The vast majority of HD patients with and without CI had xerosis cutis, with no significant difference between these 2 groups. Interestingly, 85.5% self-reported the condition, and a history of dry skin was significantly associated with CI (2). More than three-quarters of HD patients stated that they use creams and emollients for the skin, the majority of them on a daily basis; however, the presence of xerosis cutis in 89.8% of patients brings the effect of this treatment into question. No association has been found between xerosis cutis and the patients' skin care and body washing habits. The role of xerosis cutis in HD patients has long been investigated in several studies and "uraemic xerosis" has been shown to be associated with reduced QOL (15). A randomized controlled trial showed successful management of uraemic xerosis and "antipruritic effect" through moisturizing the skin (16); however, in the current study the results from everyday life situations do not confirm this, and this is a frequent finding in health services research. The pathophysiology of xerosis cutis in HD patients is complicated and generally considered as multifactorial; this includes: intrinsic changes in keratinization and lipid content, use of diuretics and similar acting medications, and environmental factors, such as overuse of heaters or air conditioners. HD therapy seems to contribute to the pathophysiology of xerosis in these patients. Based on the current study, and since the majority of HD patients, with or without CI, has xerosis cutis, it is unlikely that xerosis would contribute to the origin and chronicity of CI in HD patients.

We hypothesized that the longer the duration of HD treatment and the longer CI continues, the more likely it is that these patients would be categorized as IFSI III (itch with secondary scratch lesions). There was indeed a tendency for CI patients categorized as IFSI III to be on HD therapy longer; however, this was not significant. Furthermore, we previously identified younger age (< 70 years) to be significantly associated with CI (2), which makes it unlikely that the duration of HD treatment would be significantly associated with IFSI classification of itch. A significantly higher mean severity of itch (measured by VAS) was detected in patients with scratch lesions (IFSI III). This is of importance, as the severity of itch in HD was shown to be mild to moderate, but constant (2). It is noteworthy that patients classified as IFSI III had the worst ItchyQoL scores. More than 50% of HD patients with CI who sought medical help had scratch lesion on the skin (IFSI III). In the Dialysis Outcomes and Practice Patterns Study (DOPPS), patients with severe itch had lower QOL (17), whilst another investigation showed mental and physical composite scores to be lower in patients with severe itch than in patients with no/mild pruritus. Forty-nine of the CI patients (64.5%) showed impaired skin-related QOL on DLQI, and this impairment was correlated with itch intensity assessed with VAS and the 4-item itch questionnaire (18). Similar results have been demonstrated by others (19); however, our study is the first to use a more specific and itch-related quality of life measure (ItchyQoL).

Skin diseases and cutaneous findings in ESRD patients are frequent (20). This could also be shown in our study, with a high number of common dermatoses, e.g. seborrhoeic dermatitis, tinea pedum and onychomycoses. Dermatological findings due to pathophysiological changes and previous treatments of ESRD as well as HD treatment may lead to skin atrophy and hyperpigmentation, which were seen quite frequently. It may be assumed that skin atrophy can contribute to CI; however, this should be investigated in a larger cohort, and in comparison with HD patients without CI.

More than half of the patients reported sensations consistent with neuropathy. This may suggest that CI in HD could be considered as a variant of "neuropathic itch"; however, no further data on neuropathy could be retrieved from our study. Nevertheless, this finding may encourage investigation of neuropathy in CI in HD patients. The fact that CI is quite rare in children undergoing HD therapy (21) may also speak for a role of neuropathy, age-related skin changes, xerosis cutis, laboratory abnormalities (PTH, creatinine, phosphate) and dialysis material (11). All this contributes to the

assumption that that the pathogenesis of CI in HD may be multifactorial (11).

Based on the aforementioned results, and the fact that the majority of CI patients had no skin lesions (IFSI II), an effective interdisciplinary approach is strongly recommended. According to a recently published survey on research priorities for patients who are undergoing, or about to undergo, dialysis, the question about itch "What are the cause, prevention and treatment for itching in dialysis patients?" was placed second on the list of research priorities for these patients (22), a fact that emphasizes the importance of this frustrating symptom.

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