



# Acupuncture Effect on Pruritus in Hemodialysis Patients: A Randomized Clinical Trial

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## Abstract

**Background:** End-stage renal disease (ESRD) is a worldwide growing public health concern. Hemodialysis (HD) is a treatment option for people experiencing ESRD. Because of limited therapeutic methods due to the vague pathogenesis, the control of pruritus is so difficult. Thus, we decided to carry out this study to examine the effect of acupuncture on pruritus.

**Methods:** This multi-centered randomized clinical trial was conducted during 2015 - 2017 in the hemodialysis wards of teaching hospitals in Mashhad, Iran. 30 patients that met the inclusion criteria entered the study by a convenience sampling and were randomized into two groups: One group receiving acupuncture intervention and the other receiving sham acupuncture as the control group. We measured the visual analog scale (VAS) score of pruritus before and after the intervention in the two groups.

**Results:** The mean age of the participants was  $49.04 \pm 14.93$  with a minimum age of 23 years and a maximum age of 65 years. 17 (65.40%) patients were male, and nine (34.60%) were female. We had a significant difference between the scores of both groups before and after the intervention, but the difference of the scores was more significant in the intervention group than in the control group (5.94 versus 1.27, respectively). Our study also showed a significant difference between the two groups after the intervention ( $P$  value < 0.001).

**Conclusions:** Our findings indicate that acupuncture, as a noninvasive, safe, and easy treatment, can be useful and effective for the management of Hemodialysis patients with pruritus. Identifying the pathophysiology of pruritus and neurobiological mechanism of acupuncture to reduce pruritus will remarkably improve the application of new therapies to decrease itching.

**Keywords:** Acupuncture, End-Stage Renal Disease, Hemodialysis, Itching, Pruritus, Uremic

## 1. Background

End-stage renal disease (ESRD) is a worldwide growing public health disease with considerable increasing prevalence, incidence, morbidity, and mortality (1, 2). The mean global prevalence of chronic kidney disease (CKD) was 13.4% (3) and the age-adjusted prevalence of CKD, stages 3 to 5, in Iran was 14.9% (1). Hemodialysis (HD) is a treatment option available for people experiencing CKD (4). Patients with renal insufficiency have different clinical symptoms such as skin presentations. Pruritus is one of these presentations, defined as an unrestricted and unpleasant feeling of discomfort and desire to scratch in the skin (5). Approximately, 50% - 90% of Hemodialysis patients experience pruritus. A global cross-sectional survey men-

tioned that moderate and severe uremic pruritus (UP) was observed in 42% of Hemodialysis patients (6, 7). It usually presents about 3 - 6 months after the beginning of hemodialysis. However, in some patients, UP may occur even before hemodialysis (8, 9). The etiology and mechanism of UP are complex and are not yet fully understood. The pathogenic molecular basis of pruritus in CKD remains uncertain, which limits options for effective treatment (5, 10). Studies showed that inflammation is one of the main factors associated with uremic pruritus in hemodialysis patients, besides metabolic factors and dialysis clearance. Unfortunately, because of the limited therapeutic methods due to vague pathogenesis, the control of pruritus may be so difficult. Common treatments include the applica-

tion of topical products like emollients or moisturizers, ultraviolet irradiation, gabapentin, and oral antihistamines (5, 10, 11), but different studies have failed to show consistent findings. They are often used to decrease pruritus, but their effects usually are temporary or they have side effects. Creams can be useful to relieve the itch. However, it is impractical to use them to a large area of the skin. Antihistamines may relieve acute pruritus but they do not decrease chronic itch, and also the long-term external use of glucocorticoids will have several side effects such as dry skin and atrophic skin (12, 13). Now, the most important approaches to treatment are topical treatments with or without anti-inflammatory compounds, or systemic treatment drugs such as gabapentin with an anti-inflammatory product, phototherapy, or acupuncture. Some patients benefit from pharmacological treatments although the majority does not (5, 14, 15).

Recently, because of high demand for non-pharmacological approaches, complementary and alternative medicine (CAM) is widely used. One of these approaches is the use of acupuncture that can be defined as the insertion of needles into specific sites on the skin for therapeutic purposes. It has a long history of being used as an adjuvant or alternative therapeutic modality for a number of diseases and clinical conditions and has been commonly applied to treat itching for over 2500 years. In CKD, acupuncture has been used to treat different clinical conditions such as UP (12, 16). One of the most widespread hypotheses for the effects of acupuncture is the influence on the endogenous opioid system. Given the role of opioid peptides in antipruritic effects, it is plausible that acupuncture also could modulate the pruritic sensation by involving endogenous opioids (16).

## 2. Objectives

The benefits of acupuncture for uremic pruritus have been mentioned in some reviews but not in some others. Because of inconsistent results, we decided to carry out this study for the first time in Iran to examine the effect of acupuncture on UP.

## 3. Methods

### 3.1. Participants

This multi-centered randomized clinical trial was conducted during 2015 - 2017 in the hemodialysis wards of teaching hospitals as governmental and referral centers in Mashhad, Iran. The study compared one acupuncture intervention group with one sham acupuncture control group. Potential participants were 98 patients who were

under hemodialysis treatment in the academic hemodialysis units located in Mashhad. Nevertheless, 30 patients that met the inclusion criteria entered the study by convenience sampling, and they were randomized into two groups by a simple method. One group was designated to receive the acupuncture intervention, and the other was defined as the control group receiving sham acupuncture (Figure 1). Allocation concealment was adopted by using sequentially numbered, sealed, opaque envelopes matched for equal size and shape. Both randomization and concealment procedures were done by a person who was not concerned with the current trial or in the management of recruited patients. The inclusion criteria were restricted to patients: (1) undergoing dialysis three times a week; (2) older than 18 years and less than 65 years; (3) complained of pruritus for more than 3-months despite conventional treatment; (4) having been on hemodialysis treatment for at least 6-months; (5) with the visual analog scale (VAS) of at least 4 for pruritus; (6) being able to answer questions; and (7) being consent to participate in our study. The exclusion criteria included: (1) having prior itchy-skin disease, psychiatric disease, liver disease, cancer or disease of the soft tissue or vessels at the extremities; (2) having current infections; (3) PTH, calcium, or phosphor levels out of the controlled range so that it could cause pruritus based on the Nephrologist's opinion; (4) having coagulopathy disorders; and (5) history of using any anti-coagulant drugs. Our sample size was calculated by using NCSS software and considering the mean pruritic score of  $2.66 \pm 1.96$  in the intervention group and  $4.98 \pm 1.69$  in the control group, the z value of 1.96, a power of 80%, and a significance level of 0.05 (5); thus, we needed 15 patients in each group. The ethics committee of Mashhad University of Medical Sciences approved the trial protocol (ethical code: IR. Mums, FM. REC. 1394.223). The study was performed according to the principles of the Declaration of Helsinki (Version Edinburgh 2000). The objectives of the study were explained to the participants, and we declared that participating in the study was voluntary. A signed informed consent form was obtained from all participants before registration. The IRCT code was 20160627720282N2.

### 3.2. Procedure

During the study, patients in all involved hemodialysis wards were under the usual treatment and care, and no changes were made to the working conditions of these wards. We prescribed 200 mg oral gabapentin daily for all patients in the two groups for six weeks and referred them to the acupuncture clinic of Imam Reza Hospital.

First, we measured the VAS score of pruritus for all patients for entering the trial and then completed the data

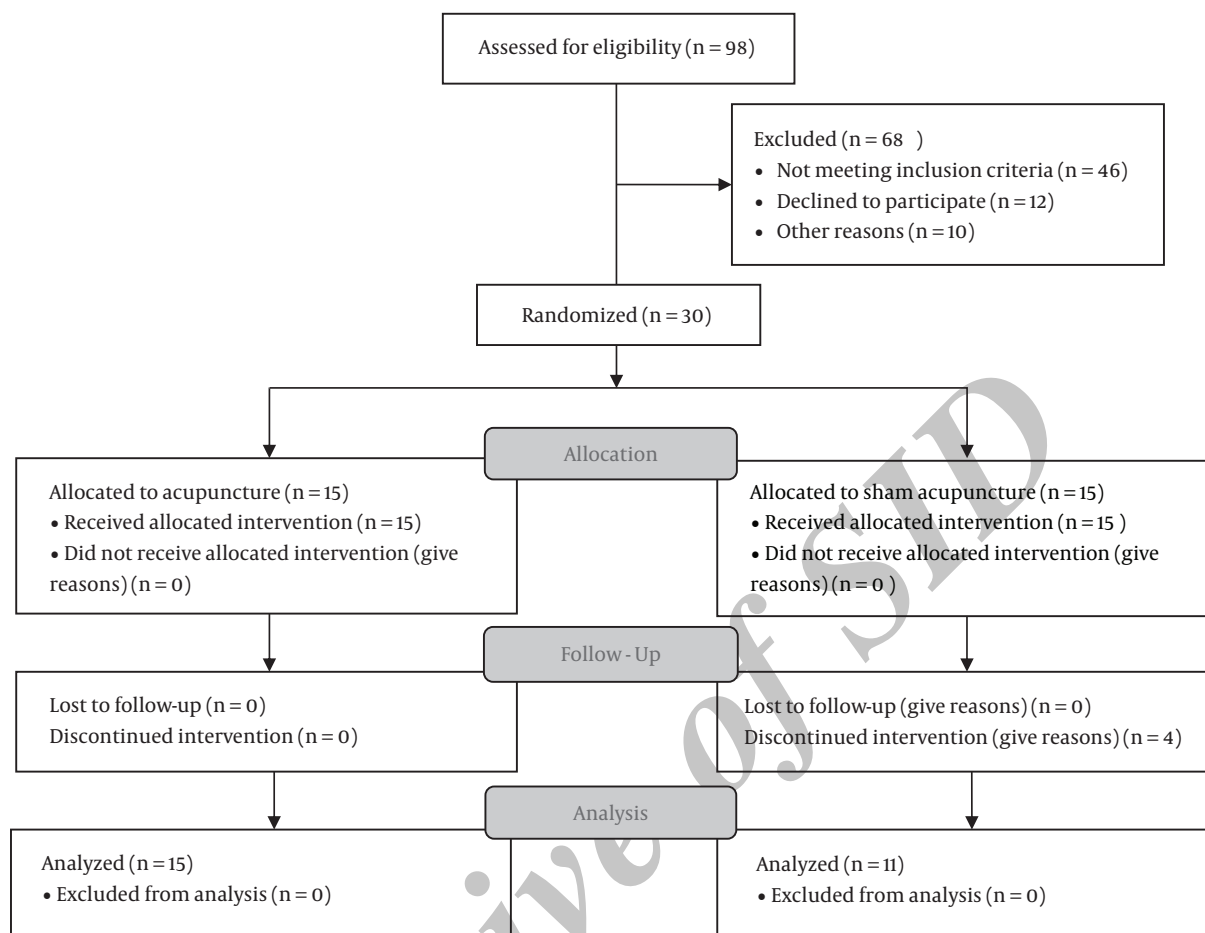


Figure 1. CONSORT flow diagram

collection form that included the demographic characteristics (age, sex, occupation, education level, and marital status) and possible related factors such as dialysis duration. At the end of the trial period, we again measured the VAS score of pruritus.

The pruritus intensity was assessed using the VAS score as the primary outcome. The VAS is an 11-point scale ranging from 0 to 10 in which 0 indicates an absence of pruritus and 10 indicates maximum pruritus. The patient was asked to define the mean level of their itching intensity.

### 3.3. Intervention

For the acupuncture intervention, a specialist of acupuncture who was trained in the Beijing University of Chinese Medicine inserted needles into acupoints by using his fingertips while applying consistent pressure on the correct acupoint with small rotational movements. The

treatment was carried out while the patient was lying in the supine position for 30 minutes.

The depths of body needling depended on the location of the acupoints, as well as on the body build (10 - 30 mm). The sensations that a patient experienced during a correct acupuncture were heaviness, numbness, or soreness.

The sham-acupuncture group received the same sessions with the same duration of minimal acupuncture by the same physician over six weeks. The needles were not supposed to stimulate, and they were inserted superficially with a 1 cm distance from the corresponding acupuncture points outside the meridians.

The acupuncture points of insertion were chosen based on the characteristics of patients and the relevant literature, including Sp6, Sp10, Lv3, Li4, and Li11.

### 3.4. Statistical Analysis

The IBM SPSS Statistical Software for Windows version 22.0 (IBM Corp., Armonk, N.Y., USA) was used for the statistical analyses. The standard descriptive statistics were applied to describe the pattern of the data. The normality of the data was checked with the Kolmogorov-Smirnov test, showing all data had a normal distribution. Independent *t*-test and Paired *t*-test were applied to compare the numerical data with normal distributions between the two groups and before-after intervention, respectively. The Chi-square and Fisher's exact tests were used to examine the significance of associations between categorical data. A covariance analysis was used to assess the effect of confounding factors on pruritus intensity. All tests were two-tailed, and the probability value of 0.05 was considered significant.

### 4. Results

We had 30 patients in our study who randomly were allocated to one of the two groups according to the inclusion and exclusion criteria (15 patients per group). Finally, we analyzed 26 participants in our research (15 in the acupuncture and 11 in the sham acupuncture groups). In the sham acupuncture group, four patients were not included in the analysis because of refusing to continue the study.

The data showed that the mean age of participants was  $49.04 \pm 14.93$  with a minimum age of 23 years and maximum age of 65 years. Among a total of 26 patients, 17 (65.40%) were men. Table 1 summarizes the patients' characteristics. Except for age, there were no significant differences between the two groups in other characteristics. Thus, we carried out a covariance analysis to assess the effect of age on the treatment response.

There was no statistically significant difference between the acupuncture and sham acupuncture groups before the intervention in the intensity of pruritus (*P* value: 0.18). The VAS scores of pruritus before and after the intervention are summarized in Table 2. Our study showed significant differences between the two groups after the intervention (*P* value < 0.001). As shown in Table 2, we also had a significant difference in the control group when comparing before-after data, but the difference in the scores of the intervention group was more significant compared to the control group (5.94 versus 1.27, respectively).

After a covariance analysis, we found that the age of participants and initial intensity of itching did not affect the intensity of pruritus and treatment response. Patients with a dialysis duration of less than one year experienced a higher intensity of pruritus, and the pruritus score was higher in men than in women, but none of them were statistically significant (Table 3).

### 5. Discussion

Pruritus is one of the most common and painful complaints in patients with end-stage renal disease (ESRD) that sometimes is accelerated or exacerbated by dialysis (14, 17, 18). Different therapies are proposed based on different theories such as xerosis, which is seen in the majority of itchy patients on HD; increased serum levels of magnesium, phosphorus, and calcium have also been proposed to involve in uremic pruritus and Hyperparathyroidism (19-21). Recently, the use of complementary therapies has been a new approach in the management of pruritus although there were investigated only in a few studies with inconsistent results. Acupuncture with the involvement of the opioid system ( $\kappa$ ,  $\mu$ ) could be effective in controlling pruritus (22-25). Because of insufficient evidence in this context, we aimed to evaluate the effect of acupuncture in controlling pruritus of HD patients in this survey.

The results of the study showed that there were statistically significant differences in the severity of pruritus between the intervention and control groups and the reduction in the intensity of pruritus after treatment was significantly higher in the acupuncture group than in the control group. Alleviated pruritus in the control group may be because of gabapentin effect.

Concordance with our result, in a clinical trial by Yan et al. on Hemodialysis patients in two groups of 30 controls (sham acupuncture) and 32 auricular acupuncture cases (three times a week for six weeks), the VAS score of pruritus was measured in both groups. A significant difference was observed between the two groups in the mean VAS score. The results showed that, generally, auricular acupuncture as part of the combination therapy of uremic pruritus is beneficial (10).

In a clinical trial conducted by Kilic Akca et al. in four dialysis centers in Turkey, the intervention group consisting of 38 Hemodialysis patients with symptoms of pruritus received the stimulation of the acupuncture points of Li11, sp10, st36, and sp6. The intervention group was compared with 40 Hemodialysis patients complaining of itching as the control group. The frequency and severity of pruritus in patients who received acupuncture significantly reduced compared to controls (5).

Che-Yi et al. randomly allocated 40 patients with uremic refractory pruritus into two control and intervention groups. The intervention group was treated by acupuncture on the Li11 acupoint while the control group was treated with Sham Acupuncture. The control of pruritus showed a significant difference between the intervention and control groups after three months of follow-up (26).

Hypotheses about the pathophysiology of pruritus in uremic patients are multifactorial and built based on im-

**Table 1.** The Basic Characteristics of Participants in the Control and Intervention Groups<sup>a</sup>

Characteristics	Intervention Group (Acupuncture)	Control Group (Sham Acupuncture)	P Value
Age, y	54.67 ± 11.40	41.36 ± 16.21	0.03
Sex			0.68
Male	9 (60)	8 (72.70)	
Female	6 (40)	3 (27.30)	
Education level			0.30
Illiterate	3 (20)	3 (27.40)	
Non-academic	10 (66.70)	4 (36.30)	
academic	2 (13.30)	4 (36.30)	
Occupation			0.37
Unemployed	2 (13.30)	5 (45.40)	
Employed	4 (26.70)	0	
Retired	5 (33.30)	2 (18.20)	
Housewife	4 (26.70)	2 (18.20)	
Marital status			0.05
Single	1 (6.70)	5 (45.50)	
Married	14 (93.30)	6 (54.50)	
Dialysis duration, y			0.85
≤ 1	5 (33.30)	5 (45.50)	
> 1 or ≤ 5	8 (53.30)	5 (45.50)	
> 5	2 (13.30)	1 (9.10)	

<sup>a</sup> Values are expressed as mean ± SD or No. (%).

**Table 2.** Pruritus Scores Before and After the Intervention in Two Groups

Group	Intensity of Pruritus (VAS Score)	P Value	
		Within Groups	Between Groups
<b>Intervention</b>		< 0.001	
Before	9.87 ± 0.35		
After	3.93 ± 2.85		< 0.001
<b>Control</b>		0.01	
Before	9.45 ± 0.93		
After	8.18 ± 1.40		

munological and opioid systems. The immunological hypothesis proposes that itching is a systemic inflammation of the body, rather than a local skin disorder, and treatments such as thalidomide and UVB are introduced as the controllers of uremic pruritus. Some studies have shown increased inflammatory factors, such as CRP, IL-6, and IL-2, in HD patients with pruritus compared to HD patients without itching (27-30). The hypothesis of opioids considers the impaired MU and Kappa receptors as the most important factor and indicates that the proportion of

agonist-receptor MU (beta-endorphin) to agonist receptor Kappa (Dynorphin A) increases in HD patients compared to healthy subjects and the severity of itching depends on increasing this ratio (31).

Acupuncture might modulate pruritus by influencing endogenous opioids both centrally and peripherally and by affecting the hypothalamus-pituitary-adrenal axis, the autonomic nervous system, and brain-derived neurotrophic factor. These might show a guide for prospecting the antipruritic effects of acupuncture on UP. How-



**Table 3.** ANCOVA of Probable Influential Parameters

Parameter	B	Std. Error	t	P Value	95% Confidence Interval	
					Lower Bound	Upper Bound
<b>Intercept</b>	-7.52	7.40	-1.02	0.32	-23.02	7.98
<b>Group</b>						
Intervention	-5.23	0.96	-5.48	< 0.001	-7.24	-3.24
Control	0 <sup>a</sup>					
<b>Dialysis duration</b>						
≤ 1	3.63	1.52	2.39	0.03	0.45	6.82
1 < dialysis duration ≤ 5	1.82	1.41	1.30	0.21	-1.12	4.77
> 5	0 <sup>a</sup>					
<b>Sex</b>						
Male	-2.38	1.16	-2.04	0.05	-4.82	0.06
Female	0 <sup>a</sup>					
<b>Age</b>	0.029	0.035	0.834	0.415	-0.044	0.101
<b>Primary itching score</b>	1.45	0.81	1.80	0.09	-0.24	3.15

<sup>a</sup> Reference group.

ever, none of the proposed theories are completely affirmed, and the pathophysiology of UP is not sufficiently explicit to contemplate about the mechanism through which acupuncture might affect this condition (32).

The strong points of this project were blindness of patients by using the superficial acupuncture and designing a multicenter study. The main limitations of the current study were the small sample size and that our study did not examine the laboratory findings to detect the changes in the pruritus score but it was based on subjective findings.

### 5.1. Conclusions

Our findings indicated that acupuncture, as a noninvasive, safe, and easy treatment, could be useful and effective for the management of HD patients with pruritus. Identifying the pathophysiology of pruritus and neurobiological mechanism of acupuncture to reduce pruritus will remarkably improve the application of new therapies to decrease itching. Future studies with larger sample sizes and objective measurements are recommended to generalize the findings.

### References

- Hosseiniapanah F, Kasraei F, Nassiri AA, Azizi F. High prevalence of chronic kidney disease in Iran: A large population-based study. *BMC Public Health*. 2009;9:44. doi: [10.1186/1471-2458-9-44](https://doi.org/10.1186/1471-2458-9-44). [PubMed: [19183493](https://pubmed.ncbi.nlm.nih.gov/19183493/)]. [PubMed Central: [PMC2658666](https://pubmed.ncbi.nlm.nih.gov/PMC2658666/)].
- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-47. doi: [10.1001/jama.298.17.2038](https://doi.org/10.1001/jama.298.17.2038). [PubMed: [17986697](https://pubmed.ncbi.nlm.nih.gov/17986697/)].
- Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease: A systematic review and meta-analysis. *PLoS One*. 2016;11(7): e0158765. doi: [10.1371/journal.pone.0158765](https://doi.org/10.1371/journal.pone.0158765). [PubMed: [27383068](https://pubmed.ncbi.nlm.nih.gov/27383068/)]. [PubMed Central: [PMC4934905](https://pubmed.ncbi.nlm.nih.gov/PMC4934905/)].
- Harwood L, Wilson B, Locking-Cusolito H, Sontrop J, Spittal J. Stressors and coping in individuals with chronic kidney disease. *Nephrol Nurs J*. 2009;36(3):265-76. 301. [PubMed: [19588694](https://pubmed.ncbi.nlm.nih.gov/19588694/)].
- Kilic Akca N, Tasci S. Acupressure and transcutaneous electrical acupoint stimulation for improving uremic pruritus: A randomized, controlled trial. *Altern Ther Health Med*. 2016;22(3):18-24. [PubMed: [27228268](https://pubmed.ncbi.nlm.nih.gov/27228268/)].
- Wu CF, Hsiao YC, Ko PC. The effects of nonpharmacological treatment on uremic pruritus patients: A systematic review. *Adv Nurs*. 2015;2015:1-9. doi: [10.1155/2015/258263](https://doi.org/10.1155/2015/258263).
- Castello M, Milani M. Efficacy of topical hydrating and emollient lotion containing 10% urea ISDIN(R) plus dexpanthenol (ureadin Rx 10) in the treatment of skin xerosis and pruritus in hemodialyzed patients: An open prospective pilot trial. *G Ital Dermatol Venereol*. 2011;146(5):321-5. [PubMed: [21956268](https://pubmed.ncbi.nlm.nih.gov/21956268/)].
- Susel J, Batycka-Baran A, Reich A, Szepletowski JC. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. *Acta Derm Venereol*. 2014;94(3):276-81. doi: [10.2340/00015555-1749](https://doi.org/10.2340/00015555-1749). [PubMed: [24217858](https://pubmed.ncbi.nlm.nih.gov/24217858/)].
- Ibrahim MK, Elshahid AR, El Baz TZ, Elazab RM, Elhoseiny SA, Elsaie ML. Impact of uraemic pruritus on quality of life among end stage renal disease patients on dialysis. *J Clin Diagn Res*. 2016;10(3):WC01-5. doi: [10.7860/JCDR/2016/16273.7488](https://doi.org/10.7860/JCDR/2016/16273.7488). [PubMed: [27134981](https://pubmed.ncbi.nlm.nih.gov/27134981/)]. [PubMed Central: [PMC4843366](https://pubmed.ncbi.nlm.nih.gov/PMC4843366/)].
- Yan CN, Yao WG, Bao Y, Shi XJ, Yu H, Yin PH, et al. Effect of auricular acupressure on uremic pruritus in patients receiving hemodialysis treatment: A randomized controlled trial. *Evid Based Complement Alternat Med*. 2015;2015:593196. doi: [10.1155/2015/593196](https://doi.org/10.1155/2015/593196). [PubMed: [26495017](https://pubmed.ncbi.nlm.nih.gov/26495017/)]. [PubMed Central: [PMC4606162](https://pubmed.ncbi.nlm.nih.gov/PMC4606162/)].

11. Chen HY, Chiu YL, Hsu SP, Pai MF, Lai CF, Yang JY, et al. Elevated C-reactive protein level in hemodialysis patients with moderate/severe uremic pruritus: A potential mediator of high overall mortality. *QJM*. 2010;**103**(11):837-46. doi: [10.1093/qjmed/hcq036](https://doi.org/10.1093/qjmed/hcq036). [PubMed: [20350963](https://pubmed.ncbi.nlm.nih.gov/20350963/)].
12. Yu C, Zhang P, Lv ZT, Li JJ, Li HP, Wu CH, et al. Efficacy of acupuncture in itch: A systematic review and meta-analysis of clinical randomized controlled trials. *Evid Based Complement Alternat Med*. 2015;**2015**:208690. doi: [10.1155/2015/208690](https://doi.org/10.1155/2015/208690). [PubMed: [26064156](https://pubmed.ncbi.nlm.nih.gov/26064156/)]. [PubMed Central: [PMC4430643](https://pubmed.ncbi.nlm.nih.gov/PMC4430643/)].
13. Biro T, Ko MC, Bromm B, Wei ET, Bigliardi P, Siebenhaar F, et al. How best to fight that nasty itch - from new insights into the neuroimmunological, neuroendocrine, and neurophysiological bases of pruritus to novel therapeutic approaches. *Exp Dermatol*. 2005;**14**(3):225-40. doi: [10.1111/j.0906-6705.2005.0321a.x](https://doi.org/10.1111/j.0906-6705.2005.0321a.x). [PubMed: [15740597](https://pubmed.ncbi.nlm.nih.gov/15740597/)].
14. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis*. 2007;**50**(1):11-20. doi: [10.1053/j.ajkd.2007.03.010](https://doi.org/10.1053/j.ajkd.2007.03.010). [PubMed: [17591521](https://pubmed.ncbi.nlm.nih.gov/17591521/)].
15. Davidson S, Giesler GJ. The multiple pathways for itch and their interactions with pain. *Trends Neurosci*. 2010;**33**(12):550-8. doi: [10.1016/j.tins.2010.09.002](https://doi.org/10.1016/j.tins.2010.09.002). [PubMed: [21056479](https://pubmed.ncbi.nlm.nih.gov/21056479/)]. [PubMed Central: [PMC2991051](https://pubmed.ncbi.nlm.nih.gov/PMC2991051/)].
16. Kim KH, Lee MS, Choi SM. Acupuncture for treating uremic pruritus in patients with end-stage renal disease: A systematic review. *J Pain Symptom Manage*. 2010;**40**(1):117-25. [PubMed: [21796811](https://pubmed.ncbi.nlm.nih.gov/21796811/)].
17. Nielsen T, Andersen KE, Kristiansen J. Pruritus and xerosis in patients with chronic renal failure. *Dan Med Bull*. 1980;**27**(6):269-71. [PubMed: [7006933](https://pubmed.ncbi.nlm.nih.gov/7006933/)].
18. Shakiba M, Sanadgol H, Azmoude HR, Mashhadi MA, Sharifi H. Effect of sertraline on uremic pruritus improvement in ESRD patients. *Int J Nephrol*. 2012;**2012**:363901. doi: [10.1155/2012/363901](https://doi.org/10.1155/2012/363901). [PubMed: [22973512](https://pubmed.ncbi.nlm.nih.gov/22973512/)]. [PubMed Central: [PMC3437632](https://pubmed.ncbi.nlm.nih.gov/PMC3437632/)].
19. Akhyani M, Ganji MR, Samadi N, Khamesan B, Daneshpazhooh M. Pruritus in hemodialysis patients. *BMC Dermatol*. 2005;**5**:7. doi: [10.1186/1471-5945-5-7](https://doi.org/10.1186/1471-5945-5-7). [PubMed: [15975150](https://pubmed.ncbi.nlm.nih.gov/15975150/)]. [PubMed Central: [PMC1184066](https://pubmed.ncbi.nlm.nih.gov/PMC1184066/)].
20. Wikstrom B. Itchy skin: A clinical problem for haemodialysis patients. *Nephrol Dial Transplant*. 2007;**22** Suppl 5:v3-7. doi: [10.1093/ndt/gfm292](https://doi.org/10.1093/ndt/gfm292). [PubMed: [17586843](https://pubmed.ncbi.nlm.nih.gov/17586843/)].
21. Simpson NB, Cunliff WJ. *Rooks textbook of dermatology*. 59. 7th ed. Oxford: Blackwell Science; 2004. p. 49-50.
22. Cabyoglu MT, Ergene N, Tan U. The mechanism of acupuncture and clinical applications. *Int J Neurosci*. 2006;**116**(2):115-25. doi: [10.1080/00207450500341472](https://doi.org/10.1080/00207450500341472). [PubMed: [16393878](https://pubmed.ncbi.nlm.nih.gov/16393878/)].
23. Chen CY, Chern RS, Liao MH, Chang YH, Hsu JY, Chien CH. The possible neuronal mechanism of acupuncture: Morphological evidence of the neuronal connection between groin A-Shi point and uterus. *Evid Based Complement Alternat Med*. 2013;**2013**:429186. doi: [10.1155/2013/429186](https://doi.org/10.1155/2013/429186). [PubMed: [23533481](https://pubmed.ncbi.nlm.nih.gov/23533481/)]. [PubMed Central: [PMC3603327](https://pubmed.ncbi.nlm.nih.gov/PMC3603327/)].
24. Zhang WB, Wu A, Litscher G, Chae Y. Effects and mechanism of acupuncture based on the principle of meridians. *Evid Based Complement Alternat Med*. 2013;**2013**:684027. doi: [10.1155/2013/684027](https://doi.org/10.1155/2013/684027). [PubMed: [24379888](https://pubmed.ncbi.nlm.nih.gov/24379888/)]. [PubMed Central: [PMC3860140](https://pubmed.ncbi.nlm.nih.gov/PMC3860140/)].
25. Lee JH, Li DX, Yoon H, Go D, Quan FS, Min BI, et al. Serotonergic mechanism of the relieving effect of bee venom acupuncture on oxaliplatin-induced neuropathic cold allodynia in rats. *BMC Complement Alternat Med*. 2014;**14**:471. doi: [10.1186/1472-6882-14-471](https://doi.org/10.1186/1472-6882-14-471). [PubMed: [25481535](https://pubmed.ncbi.nlm.nih.gov/25481535/)]. [PubMed Central: [PMC4295325](https://pubmed.ncbi.nlm.nih.gov/PMC4295325/)].
26. Che-Yi C, Wen CY, Min-Tsung K, Chiu-Ching H. Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uraemic pruritus. *Nephrol Dial Transplant*. 2005;**20**(9):1912-5. doi: [10.1093/ndt/gfh955](https://doi.org/10.1093/ndt/gfh955). [PubMed: [15985509](https://pubmed.ncbi.nlm.nih.gov/15985509/)].
27. Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transplant*. 2006;**21**(3):749-55. doi: [10.1093/ndt/gfi204](https://doi.org/10.1093/ndt/gfi204). [PubMed: [16249205](https://pubmed.ncbi.nlm.nih.gov/16249205/)].
28. Fallahzadeh MK, Roozbeh J, Geramizadeh B, Namazi MR. Interleukin-2 serum levels are elevated in patients with uremic pruritus: A novel finding with practical implications. *Nephrol Dial Transplant*. 2011;**26**(10):3338-44. doi: [10.1093/ndt/gfr053](https://doi.org/10.1093/ndt/gfr053). [PubMed: [21372257](https://pubmed.ncbi.nlm.nih.gov/21372257/)].
29. Virga G, Visentin I, La Milia V, Bonadonna A. Inflammation and pruritus in haemodialysis patients. *Nephrol Dial Transplant*. 2002;**17**(12):2164-9. [PubMed: [12454228](https://pubmed.ncbi.nlm.nih.gov/12454228/)].
30. Pisoni RL, Wikstrom B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: International results from the dialysis outcomes and practice patterns study (DOPPS). *Nephrol Dial Transplant*. 2006;**21**(12):3495-505. doi: [10.1093/ndt/gfl461](https://doi.org/10.1093/ndt/gfl461). [PubMed: [16968725](https://pubmed.ncbi.nlm.nih.gov/16968725/)].
31. Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat Rev Neurosci*. 2006;**7**(7):535-47. doi: [10.1038/nrn1950](https://doi.org/10.1038/nrn1950). [PubMed: [16791143](https://pubmed.ncbi.nlm.nih.gov/16791143/)].
32. Shirazian S, Aina O, Park Y, Chowdhury N, Leger K, Hou L, et al. Chronic kidney disease-associated pruritus: Impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis*. 2017;**10**:11-26. doi: [10.2147/IJNRD.S108045](https://doi.org/10.2147/IJNRD.S108045). [PubMed: [28176969](https://pubmed.ncbi.nlm.nih.gov/28176969/)]. [PubMed Central: [PMC5271405](https://pubmed.ncbi.nlm.nih.gov/PMC5271405/)].