Altered Monocytic Phenotypes are Associated with Uraemic Pruritus in Patients Receiving Haemodialysis

Mei-Ju KO1,2, Wan-Chuan TSAI1, Yu-Sen PENG1, Shih-Ping HSU3, Mei-Fen PAI1, Ju-Yeh YANG3, Hon-Yen WU3,4# and Yen-Ling CHIU1,3,7,10#

INVESTIGATIVE REPORT

Uraemic pruritus is one of the most bothersome symptoms in patients receiving haemodialysis. A total of 175 patients receiving maintenance haemodialysis, with 74 patients experiencing uraemic pruritus, were prospectively recruited to assess the influence of the phenotype of blood monocytes and various cytokines on uraemic pruritus. The phenotype of blood monocytes was determined by flow cytometry as classical (CD14++CD16−) monocytes, non-classical (CD14+CD16+) monocytes, and intermediate (CD14++CD16+) monocytes. Eight cytokines, including interleukin (IL)-2, interferon-γ, IL-12p70, IL-4, IL-5, IL-6, tumour necrosis factor-α, and IL-10, were simultaneously detected with a multiplex bead-based immunoassay. Multivariate linear regression analysis showed that a higher percentage of intermediate monocytes (effect estimate 0.08; 95% confidence interval 0.01–0.16) were independent predictors of a higher visual analogue scale score for pruritus intensity. Eight cytokines, including interleukin-2, interferon-γ, interleukin-12p70, -4, -5, -6, tumour necrosis factor-α, and interleukin-10, showed no differences between patients with and without uraemic pruritus. The results indicate that altered monocytic phenotypes could play a role in uraemic pruritus.

Key words: cytokines; CD14++CD16− monocytes; haemodialysis; itch; intermediate monocytes; uraemic pruritus.

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Corr: Hon-Yen Wu, Division of Nephrology, Department of Internal Medicine, and Yen-Ling Chiu, Department of Medical Research, Far Eastern Memorial Hospital, No. 21, Sec. 2, Nanya S. Rd., Banciao Dist., New Taipei City 220, Taiwan. E-mails: honyenwu@ntu.edu.tw; yenlingchiu@ntu.edu.tw

Uraemic pruritus is one of the most common and bothersome symptoms in patients receiving haemodialysis, with 74 patients experiencing uraemic pruritus, were prospectively recruited to assess the influence of the phenotype of blood monocytes and various cytokines on uraemic pruritus. The phenotype of blood monocytes was determined by flow cytometry as classical (CD14++CD16−) monocytes, non-classical (CD14+CD16+) monocytes, and intermediate (CD14++CD16+) monocytes. Eight cytokines, including interleukin (IL)-2, interferon-γ, IL-12p70, IL-4, IL-5, IL-6, tumour necrosis factor-α, and IL-10, were simultaneously detected with a multiplex bead-based immunoassay. Multivariate linear regression analysis showed that a higher percentage of intermediate monocytes (effect estimate 0.08; 95% confidence interval 0.01–0.16) were independent predictors of a higher visual analogue scale score for pruritus intensity. Eight cytokines, including interleukin-2, interferon-γ, interleukin-12p70, -4, -5, -6, tumour necrosis factor-α, and interleukin-10, showed no differences between patients with and without uraemic pruritus. The results indicate that altered monocytic phenotypes could play a role in uraemic pruritus.

Uraemic pruritus is one of the most common and bothersome symptoms in patients receiving haemodialysis (HD) (1–3). This persistent, debilitating symptom can significantly affect the quality of life in multiple aspects, including mood, sleep, and social relationships. However, the treatment options for uraemic pruritus are few (4–6).

The mechanisms of uraemic pruritus mostly remain unclear, and many hypotheses have been postulated, including xerosis, hyperparathyroidism, opioid system derangements, etc. (7–9). Evidence has indicated that immune dysregulation plays a central role in the pathophysiology of uraemic pruritus. Increased serum levels of high-sensitivity C-reactive protein, proinflammatory cytokines, and Th1-dominant immune activation have been reported to be associated with uraemic pruritus (10–14). Furthermore, uraemic pruritus is of prognostic importance for dialysis patients, and inflammation related to uraemic pruritus could lead to higher mortality (15, 16). Monocytes are key players in the immune system. Human peripheral blood monocytes can be classified into 3 subsets based on the surface expression of the lipopolysaccharide receptor (CD14) and the low-affinity Fcγ-III receptor (CD16); namely, classical (CD14++CD16−), intermediate (CD14++CD16+), and non-classical (CD14+CD16+) monocytes (17, 18). Among them, intermediate monocytes have been reported to show the highest levels of major histocompatibility complex class II and produce the most tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 after being treated with lipopolysaccharides (19–21). In addition, intermediate monocytes are known to expand in multiple inflammatory and infectious conditions, including rheumatoid arthritis, asthma, peripheral arterial disease, and sepsis (22–25). However, the relationships between human monocyte phenotypes and uraemic pruritus have not been assessed.

SIGNIFICANCE

Uraemic pruritus is one of the most common and bothersome symptoms in patients receiving haemodialysis, but its pathophysiology remains obscure. Altered human monocyte phenotypes have been implicated in many chronic inflammatory diseases. This study found that a higher percentage of intermediate monocytes (CD14++CD16+) independently predicts a higher visual analogue scale score for pruritus intensity. Eight cytokines, including interleukin-2, interferon-γ, interleukin-12p70, -4, -5, -6, tumour necrosis factor-α, and interleukin-10, showed no differences between patients with and without uraemic pruritus. The results indicate that altered monocytic phenotypes could play a role in uraemic pruritus.
The aims of this study were to assess the phenotype of blood monocytes using surface markers and to examine its relationship with the severity of uraemic pruritus in patients receiving HD. Furthermore, the study analysed 8 cytokines, including IL-2, interferon (IFN)-γ, IL-12p70, IL-4, IL-5, IL-6, TNF-α, and IL-10, using a multiplex bead-based immunoassay to elucidate the interactive behaviour of monocytes and cytokines to understand immune reactions in uraemic pruritus.

MATERIALS AND METHODS

Study participants

The immunity in ESRD (iESRD) study is a prospective multicentre cohort study investigating the effects of immunological factors on the long-term outcomes of patients receiving HD (26). The current study assessed the participants of the iESRD cohort who received HD in the Far Eastern Memorial Hospital, a tertiary medical centre in Taiwan. Eligible patients were at least 20 years old and had received maintenance HD for more than 3 months in December 2014. The patients received 3–5 h of HD 3 times a week with adequate dialysis doses. All study participants used biocompatible dialyzers. Exclusion criteria were: (i) primary skin disorders; (ii) active infection; (iii) malignancy; (iv) cholestatic liver disease; (v) acute hepatitis; or (vi) communication problems. The Institutional Review Board of the Far Eastern Memorial Hospital approved this study, and all participants provided written informed consent.

Pruritus evaluation

Uraemic pruritus was defined if the patient receiving HD had met any of the following criteria: (i) they were bothered by at least 3 episodes of pruritus within 2 weeks, with each episode of pruritus symptoms occurring a few times a day and lasting for a few minutes; or (ii) they had pruritus symptoms within 6 months, but with a lower frequency than in (i) (15, 27, 28). The participants marked the intensity of their itch on a 10-cm line, measuring the current general severity of pruritus using a visual analogue scale (VAS) from 0 to 10 (0=no pruritus, 10=worst pruritus imaginable) (29). The extent of the body surface area affected by pruritus was also evaluated (28).

Demographics and laboratory parameters

Demographic data, including age, sex, comorbid diseases, aetiology of ESRD, dialysis regimens, and duration of dialysis, were recorded for each participant. Venous blood samples were obtained in the fasting state before the patient’s midweek HD session, and were used to assess laboratory parameters, monocyte phenotypes, and blood levels of cytokines. All laboratory tests were performed in the central laboratory of the Far Eastern Memorial Hospital. The adequacy of dialysis doses, as assessed by Kt/V, was calculated using a single-compartment model (30, 31).

Monocyte differentiation panel

On the day of blood sampling, the mononuclear cell interphase was isolated by Ficoll-Paque PLUS gradient centrifugation according to the manufacturer’s instructions (GE Healthcare, South Plainfield, NJ, USA). Phycoerythrin-conjugated anti-CD86 antibody (clone IT2.2, eBioscience, San Diego, CA, USA) was used to gate the CD86+ monocytes. The surface expression of CD14 and CD16 on peripheral blood monocytes was analysed by staining with fluorescein isothiocyanate-conjugated anti-CD14 antibody (clone M5E2, BioLegend, San Diego, CA, USA) and allophycocyanin-conjugated anti-CD16 antibody (clone 3G8, eBioscience) for 30 min at 4°C in the dark. The gating strategy is shown in Fig. 1. Monocytes were classified into 3 subsets: classical (CD14++CD16−), intermediate (CD14++CD16+), and non-classical (CD14−CD16−) monocytes, according to the Nomenclature Committee of the International Union of Immunological Societies (17). All experiments were performed in the central laboratory of the Far Eastern Memorial Hospital and analysed using a Beckman Coulter MoFloTM-XDP multicolour flow cytometer (Beckman Coulter, Krefeld, Germany).

Multiplex bead-based cytokine analysis

Plasma samples were collected at the time of monocyte isolation and frozen at –80°C until cytokine analyses. The blood levels of the Th1/Th2 Essential Th1/Th2 Cytokine 6-Plex (IFN-γ, IL-12p70, IL-4, IL-5, IL-6, and TNF-α) with the addition of IL-2 and IL-10 were detected using Luminex®-based multiplexed immunoassays (ProcartaPlex, eBioscience, USA) following the manufacturer’s protocol. The limit of detection was 0.8 pg/ml for IL-2, 0.2 pg/ml for IFN-γ, 0.04 pg/ml for IL-12p70, 1.5 pg/ml for IL-4, 0.3 pg/ml for IL-5, 0.4 pg/ml for IL-6, 0.4 pg/ml for TNF-α, and 0.1 pg/ml for IL-10. Acquisition was performed on a Luminex® 100/200™ analyzer (Luminex, Austin, TX, USA). Data analysis was performed using ProcartaPlex Analyst 1.0 (eBioscience, USA).

Statistical analysis

Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA). The data are expressed as the means with standard deviations (SDs) for continuous variables and as numbers with percentages for categorical variables. The diffe-
RESULTS

A total of 175 patients receiving maintenance HD participated in the study. Table I shows the demographic characteristics of the study participants. The mean age of the participants was 60.5 years, and 43% were female. There were 74 patients (42.3%) who had uraemic pruritus, with a mean VAS score of 5.8. Among patients with uraemic pruritus, 68.9% (51/74) had more than 25% of their body surface area affected by pruritus. The median duration of pruritus symptoms was 12 months (first quartile, 3 months; third quartile, 60 months). The clinical characteristics and laboratory parameters of participants with and without pruritus are shown in Table II. Patients with uraemic pruritus had a lower percentage of classical monocytes than those without uraemic pruritus. Patients with uraemic pruritus also had higher blood levels of triglycerides and were more likely to have diabetes than those without pruritus symptoms.

-effects of patient characteristics on the subsets of blood monocytes

Table III shows the influence of patient characteristics on the subsets of blood monocytes. Men had a higher percentage of classical monocytes than did women (72.48 ± 9.20% vs 69.68 ± 9.09%, p = 0.03). Patients with diabetes had a lower percentage of non-classical monocytes (8.80 ± 4.56% vs 10.29 ± 4.99%, p = 0.05). The subsets of blood monocytes did not differ significantly regarding viral hepatitis B, viral hepatitis C, or cigarette smoking.

-effects of the subsets of monocytes and plasma cytokines on pruritus intensity

Linear regression models were used to explore the effects of blood monocytes, proinflammatory cytokines (IL-2, IFN-γ, IL-12p70, IL-4, IL-5, IL-6, TNF-α), and anti-inflammatory cytokine IL-10 on uraemic pruritus. In the univariate linear regression models, a higher VAS score for pruritus intensity was significantly associated with a higher percentage of intermediate monocytes (effect estimate 0.072; 95% CI, 0.0002 to 0.144; p = 0.05), a lower percentage of classical monocytes (effect estimate –0.067; 95% CI –0.0002 to 0.144; p = 0.05).

| Variable | With pruritus | Without pruritus | p-value |
|----------|--------------|------------------|---------|
| Participants, n | 74 | 101 | 0.0001 |
| VAS score for pruritus intensity, mean ± SD | 5.8 ± 2.5 | 0.0 ± 0.0 | <0.0001 |
| Clinical characteristics | | | |
| Age, years, mean ± SD | 61.4 ± 11.9 | 59.9 ± 10.4 | 0.27 |
| Female, n (%) | 34 (45.95) | 42 (51.58) | 0.57 |
| Duration of dialysis, years, mean ± SD | 7.08 ± 5.87 | 7.96 ± 6.10 | 0.25 |
| Kt/V, mean ± SD | 1.57 ± 0.24 | 1.54 ± 0.29 | 0.38 |
| Haematocrit, %, mean ± SD | 35.56 ± 3.35 | 34.85 ± 4.01 | 0.20 |
| Creatinine, mg/dl, mean ± SD | 10.74 ± 2.11 | 10.78 ± 2.06 | 0.99 |
| Uric acid, mg/dl, mean ± SD | 7.68 ± 1.48 | 7.57 ± 1.33 | 0.99 |
| Albumin, g/dl, mean ± SD | 4.14 ± 0.31 | 4.15 ± 0.37 | 0.82 |
| Fasting glucose, mg/dl, mean ± SD | 121.88 ± 62.70 | 116.67 ± 60.58 | 0.22 |
| Total cholesterol, mg/dl, mean ± SD | 166.93 ± 40.10 | 159.61 ± 39.78 | 0.22 |
| Triglyceride, mg/dl, mean ± SD | 180.61 ± 111.47 | 140.64 ± 108.86 | 0.0001* |
| Aspartate transaminase, U/l, mean ± SD | 17.11 ± 8.05 | 18.23 ± 9.80 | 0.45 |
| Alanine transaminase, U/l, mean ± SD | 14.82 ± 8.31 | 17.75 ± 19.60 | 0.72 |
| Alkaline phosphatase, U/l, mean ± SD | 110.85 ± 62.13 | 136.15 ± 192.01 | 0.98 |
| Total bilirubin, mg/dl, mean ± SD | 0.40 ± 0.14 | 0.42 ± 0.11 | 0.08 |
| Ferritin, ng/ml, mean ± SD | 42.24 ± 254.42 | 408.18 ± 230.48 | 0.81 |
| Calcium, albumin adjusted, mg/dl, mean ± SD | 8.98 ± 0.76 | 8.92 ± 0.81 | 0.59 |
| Phosphorus, mg/dl, mean ± SD | 4.96 ± 1.30 | 4.78 ± 1.36 | 0.37 |
| Ca x P mg/dl × mg/dl, mean ± SD | 44.58 ± 12.06 | 42.93 ± 13.75 | 0.27 |
| Intact parathyroid hormone, pg/ml, mean ± SD | 358.54 ± 336.29 | 398.01 ± 462.25 | 0.84 |
| High-sensitivity C-reactive protein, mg/l, mean ± SD | 0.77 ± 0.97 | 0.84 ± 2.01 | 0.17 |
| Diabetes mellitus, n (%) | 43 (58.11) | 40 (35.69) | 0.02* |
| Hepatitis B, n (%) | 9 (12.16) | 18 (17.82) | 0.31 |
| Hepatitis C, n (%) | 5 (6.76) | 11 (10.89) | 0.35 |
| Monocytes subsets | | | |
| Classical monocytes, %, mean ± SD | 69.19 ± 9.88 | 72.79 ± 8.47 | 0.01* |
| Intermediate monocytes, %, mean ± SD | 13.55 ± 7.86 | 11.78 ± 5.72 | 0.22 |
| Non-classical monocytes, %, mean ± SD | 10.15 ± 5.24 | 9.17 ± 4.49 | 0.21 |
| Cytokines | | | |
| Interleukin-2, pg/ml, mean ± SD | 0.09 ± 0.58 | 0.31 ± 1.20 | 0.07 |
| Interferon-γ, pg/ml, mean ± SD | 0.88 ± 2.30 | 1.18 ± 4.53 | 0.92 |
| Interleukin-12p70, pg/ml, mean ± SD | 0.91 ± 1.14 | 1.00 ± 1.98 | 0.41 |
| Interleukin-4, pg/ml, mean ± SD | 0.69 ± 2.01 | 0.50 ± 1.99 | 0.17 |
| Interleukin-5, pg/ml, mean ± SD | 0.08 ± 0.36 | 0.06 ± 0.33 | 0.66 |
| Interleukin-6, pg/ml, mean ± SD | 6.40 ± 8.99 | 7.45 ± 20.29 | 0.83 |
| Tumour necrosis factor-α, pg/ml, mean ± SD | 0.52 ± 0.62 | 0.51 ± 0.66 | 0.95 |
| Interleukin-10, pg/ml, mean ± SD | 1.55 ± 1.91 | 1.74 ± 2.02 | 0.42 |

*p ≤ 0.05
SD: standard deviation; VAS: visual analogue scale; Ca × P: product of albumin-adjusted serum calcium (Ca) and serum phosphorus (P).
−0.119 to −0.015; \( p = 0.01 \)), and the presence of diabetes (effect estimate 1.111; 95% CI 0.149 to 2.073; \( p = 0.02 \)) (Table IV). In addition, none of the 8 cytokines was associated with the VAS score for pruritus intensity (Table IV). Table V shows the results of the multivariate linear regression model for assessing the predictors of pruritus intensity. After adjusting for age and sex, a higher percentage of intermediate monocytes (effect estimate 0.08; 95% CI 0.01 to 0.16; \( p = 0.03 \)) and the presence of diabetes (effect estimate 1.52; 95% CI 0.42 to 2.61; \( p = 0.01 \)) were independent predictors of a higher VAS score for pruritus intensity (Table V). In addition, cigarette smoking (effect estimate 1.88; 95% CI −0.07 to 3.83; \( p = 0.06 \)) was borderline significantly associated with higher pruritus intensity (Table V).

**DISCUSSION**

This is the first study to investigate the association of monocyte phenotypes and uraemic pruritus. Patients receiving HD who had uraemic pruritus were found to have altered monocytic phenotypes. Among the subsets of monocytes, a higher percentage of intermediate monocytes was independently associated with a higher VAS score for pruritus intensity. The results may indicate the subset-specific involvement of monocytes and the distinct role of intermediate monocytes in the pathogenesis of uraemic pruritus.

Patients with maintenance HD are subject to chronic low-grade inflammation owing to multifactorial causes, including uraemic toxins, oxidative stress, underlying comorbidities, and the dialysis process, etc. (32). Compared with non-dialysis patients, patients receiving HD showed a higher prevalence of hypoalbuminaemia, hyperferritinaemia, and elevated C-reactive protein levels (32, 33). There is increasing evidence that immune dysregulation plays a critical role in uraemic pruritus. Kimmel et al. (11) showed that patients with uraemic pruritus had an increased proportion of TH1 cells, as

| Covariates          | Effect estimate | 95% CI          | \( p \)-value |
|---------------------|-----------------|-----------------|--------------|
| Age (years)         | −0.006          | −0.050 to −0.039| 0.81         |
| Men                 | −0.544          | −1.524 to 0.436 | 0.28         |
| Cigarette smoking  | 1.061           | −0.816 to 2.937 | 0.27         |
| K/V                 | 0.495           | −1.326 to 2.316 | 0.59         |
| Duration of dialysis| −0.026          | −0.107 to −0.056| 0.54         |
| Diabetes mellitus   | 1.111           | 0.149 to 2.073  | 0.02*        |
| White blood cell, \(10^9/\mu l\) | 0.029           | −0.209 to −0.267| 0.81         |
| Aspartate transaminase, U/l | 0.004           | −0.050 to 0.058 | 0.89         |
| Total bilirubin, mg/dl | −2.133          | −6.072 to 1.807 | 0.29         |
| Total cholesterol, mg/dl | 0.012           | −0.001 to 0.024 | 0.06         |
| Triglyceride, mg/dl | 0.004           | −0.0003 to 0.0008 | 0.07        |
| Fasting glucose, mg/dl | 0.001           | −0.007 to 0.009 | 0.77         |
| Ca × P, mg/dl × mg/dl | 0.014           | −0.024 to 0.051 | 0.48         |
| Ferritin, ng/ml     | 0.0005          | −0.002 to 0.002 | 0.66         |
| Tranferrin saturation, % | −0.023          | −0.063 to 0.018 | 0.27         |
| Intact parathyroid hormone, pg/ml | −0.0003         | −0.001 to 0.0001 | 0.67        |
| hsCRP, mg/l         | −0.028          | −0.324 to 0.269 | 0.86         |
| Hepatitis B         | −0.759          | −2.104 to 0.585 | 0.27         |
| Hepatitis C         | −0.280          | −1.971 to 1.410 | 0.75         |
| Classical monocytes, % | −0.067          | −0.119 to −0.015| 0.01*        |
| Intermediate monocytes, % | 0.072          | 0.0002 to 0.144 | 0.05*        |
| Non-classical monocytes, % | 0.075          | −0.025 to 0.176 | 0.15         |
| IL-2, pg/ml         | −0.214          | −0.709 to 0.281 | 0.40         |
| IFN-\(\gamma\), pg/ml | −0.069          | −0.201 to 0.062 | 0.30         |
| IL-12p70, pg/ml     | −0.060          | −0.354 to −0.235| 0.69         |
| IL-4, pg/ml         | 0.115           | −0.132 to 0.361 | 0.36         |
| IL-5, pg/ml         | −0.120          | −1.549 to 1.308 | 0.87         |
| IL-6, pg/ml         | −0.011          | −0.041 to 0.019 | 0.49         |
| TNF-\(\alpha\), pg/ml | −0.160          | −0.933 to 0.614 | 0.69         |
| IL-10, pg/ml        | −0.167          | −0.415 to 0.082 | 0.19         |

*p ≤ 0.05. CI: confidence interval; Ca × P: product of albumin-adjusted serum calcium (Ca) and serum phosphorus (P); hsCRP: high-sensitivity C-reactive protein; IL: interleukin; IFN: interferon; TNF: tumour necrosis factor.

| Covariate               | Parameter estimate | 95% CI          | \( p \)-value |
|-------------------------|--------------------|-----------------|--------------|
| Age (years)             | −0.01             | −0.06 to 0.04   | 0.67         |
| Men                     | −0.63             | −1.81 to 0.56   | 0.30         |
| Cigarette smoking       | 1.88              | −0.07 to 3.83   | 0.06         |
| Diabetes mellitus       | 1.52              | 0.42 to 2.61    | 0.01*        |
| Intermediate monocytes  | 0.08              | 0.01 to 0.16    | 0.03*        |

*p ≤ 0.05. CI: confidence interval.
measured by intracytoplasmic cytokines and the expression of chemokine receptors. Evidence also showed that the serum levels of histamine, IL-2, IL-6, and IL-31 were elevated in patients receiving HD with uraemic pruritus (10, 11, 14). However, there is debate regarding whether uraemic pruritus is a primary inflammatory itch, as it is not uncommon for dialysis patients to report severe itching without obvious clinical inflammation of the skin (34). Based on our findings that altered monocytic phenotypes are associated with the severity of uraemic pruritus, further investigations are needed to identify the role of monocytes in itch signalling and to explore the immunopathogenic mechanisms that underlie pruritus occurrence and severity.

Monocytes represent a heterogenic and dynamic cell population continuum of diverse differentiation stages. Intermediate CD14++CD16+ monocytes comprise approximately 11–14% of circulating monocytes in patients receiving HD, which is higher than the 2–8% of intermediate monocytes in normal subjects (35). Our previous study also reported that patients receiving HD, compared with healthy individuals of the same age, had significantly increased levels of intermediate and non-classical monocytes, and both monocyte subsets increased with the duration of dialysis (26). In patients receiving HD, intermediate monocytes are known to be associated with an increased risk of cardiovascular disease, but the association between intermediate monocytes and pruritus has not been reported (36). As dialysis adequacy is an independent predictor of pruritus intensity in patients on maintenance HD (7), and uraemic toxins induce DNA epigenetic changes involving the differentiation of monocytes toward intermediate monocytes (37), the accumulation of uraemic toxins may link monocyte phenotypes with uraemic pruritus.

The current study did not find a significant association between uraemic pruritus and cytokines, including IL-2, IFN-γ, IL-12p70, IL-4, IL-5, IL-6, TNF-α, and IL-10. The results indicate that altered monocytic phenotypes with uraemic pruritus.

In conclusion, altered monocytic phenotypes are associated with the pruritus intensity of uraemic pruritus in patients receiving HD, and a higher percentage of intermediate monocytes independently predicts higher VAS scores for pruritus intensity. No significant association was found between uraemic pruritus and cytokines, including IL-2, IFN-γ, IL-12p70, IL-4, IL-5, IL-6, TNF-α, and IL-10. The results indicate that altered monocytic phenotypes could play a role in uraemic pruritus.

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