Vegetarian diet may ameliorate uremic pruritus in hemodialysis patients

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 objectives: Systemic inflammation has been reported to be associated with uremic pruritus (UP). Although a vegetarian diet can reduce systemic inflammation in hemodialysis patients, the effect of vegetarian diet on UP is not clear. The purpose of the study was to know the possible effects of vegetarian diet on UP.

Methods: A cross-sectional study was done to compare the severity of UP and blood levels of systemic inflammatory markers between vegetarian and non-vegetarian hemodialysis patients. Six non-vegetarian patients with uremic pruritus changed their non-vegetarian diet to vegetarian diet for 2 months. Visual Analogue Scale (VAS) and pruritus score (PS) were used to measure the UP severity. The serum high-sensitivity C-reactive protein (hs-CRP), and interleukin-2 (IL-2) were used as markers of inflammation.

Results: Both the median VAS scores ($p = 0.043$) and the median PS scores ($p < 0.001$) were lower in the Vegetarian than in the non-vegetarian group. The median values of hs-CRP in Vegetarian were lower than that for the non-vegetarian ($p = 0.020$). The median value of IL-2 was also lower in Vegetarian than that of the non-vegetarian ($p = 0.016$). There were 6 non-vegetarian patients shift to vegetarian for 2 months. The pruritus score improved and IL-2 level decreased after change to vegetarian diet.

Conclusion: We concluded that vegetarian diet might be associated with the amelioration of the uremic pruritus severity in hemodialysis patients.
Materials and methods

A cross-sectional study was performed. All the vegetarians or non-vegetarian uremia patients on a 4-h session thrice-weekly hemodialysis therapy for more than one year in two different dialysis centers were enrolled for our study. We excluded patients with abnormal liver function, hepatitis B or hepatitis C carrier, or patients under long-term steroid treatment secondary to systemic or dermal inflammatory disorders; these diseases perhaps will affect the severity of pruritus. A 24-h diet recall method was used for diet evaluation [8]. Vegetarians without consuming any meat, milk, or egg products were deemed strict vegetarian. Vegetarians taking also milk or egg products were deemed lacto-ovo vegetarian. All vegetarians started their vegetarian diet before the commencement of maintenance hemodialysis and all the vegetarians adhered to vegetarian diet more than one year. Both strict and lacto-ovo vegetarians were included into the vegetarian group.

Patients with serum potassium above 5.5 meq/L were given polystyrene sulfonic acid powder for potassium control. Calcitriol was used to control secondary hyperparathyroidism. All patients underwent hemodialysis treatment using high-flux artificial kidneys with low molecular weight heparin as anticoagulant. The quality of water for hemodialysis was monitored regularly following the standards of Association for the Advancement of Medical Instrument (AAMI) guidelines for dialysis water.

The blood sampling was performed before hemodialysis after getting inform consents of patients following regulations of the institutional review board. Patients’ fasting complete blood counts, serum biochemistry, electrolytes, and iPTH were checked. Serum hs-CRP was measured using the nephelometry methods. Serum IL-2 were examined using commercial ELISA kits according to the manufacturer’s manual (abcam®, Cambridge UK). All the samples were checked in triplicate. UP was evaluated by the subjective VAS (Visual Analogue Scale), and the pruritus score (PS) by different hemodialysis nurses as we previously described but with a minor modification [3–5]. In brief, the VAS measures the severity of pruritus with a reported score range from 0 to 10. Patients without UP have a score of 0 and patients with intolerable UP have a score of 10. PS grades the UP distribution, severity, frequency, and effects on sleep disturbances. For UP distribution, itch sensation confined to one spot receives one point, confined to one area 2 points, and generalized itch 3 points. For UP severity, itch sensation resolved without the need to scratch receives one point, itch sensation with the need to be scratched but with no degree of skin excoriation 2 points, itch scratched to the degree of skin excoriation 3 points, itch cannot be resolved even scratched to the degree of skin excoriation 4 points, and itch leading to restlessness 5 points. For UP frequency, itch sensation lasting shorter than 5 min and happening less than 4 times per day receives a score of one. Itch sensation lasting longer than 10 min each episode receives one point with a maximum of 5 points for this part. For the effects of UP on sleep, awakening due to pruritus gives 2 points per episode with a maximum of 6 points. The scores from above four parts (distribution, severity, frequency, effect on sleep disturbance) are summed up with a maximum score of 19. The antipruritic medication including oral antihistamine and anti-pruritic ointments used by patients within previous one year were also recorded from medical chart review.

Statistical analysis

IBM®SPSS® Statistics version 21 for Macintosh was used for statistical analysis. Continuous variables were expressed as mean ± SEM (standard error mean), or median ± IQR (inter-quartile range). Student’s t-test was used generally used for comparison between groups, but for with marked skew distributions a Mann–Whitney test was applied. For categorical variables, Chi-Square or Fisher exact tests were used. Paired sample t-test used for compare biomarker and pruritus scale after diet change in cohort. A p value <.05 was deemed statistically significant.

Results

Demographic data

There were 241 patients receiving maintenance hemodialysis (4-h session hemodialysis therapy thrice-weekly) longer than one year, excluding those with hepatitis B, hepatitis C, and chronic steroid use. A total of 155 patients were enrolled for study.

Among these 155 patients, there were 15 vegetarian (Veg) and 140 non-vegetarian (non-Veg) hemodialysis patients. The two groups were age and sex matched, and there was no difference between hemodialysis vintage. There were 3 diabetes mellitus (DM) patients among the 15 Veg group and 48 DM among the 140 non-Veg group. The proportions of DM between these two groups were not statistically different (p = .388, by Fisher Exact test). Body mass index (BMI) of the non-vegetarian group was higher than of the in vegetarian group (p < .001), but the mean BMI of both groups can
Table 1. Demographic characters of non-vegetarian and vegetarian hemodialysis patients.

|                         | non-Vegetarian | Vegetarian | p-value |
|-------------------------|----------------|------------|---------|
| Age (year)              | 58.5 ± 1.3     | 63.2 ± 2.5 | .275    |
| Male: Female            | 63:77          | 7:8        | .510    |
| HD vintage (months)     | 69.9 ± 5.2     | 71.2 ± 13.8| .924    |
| DM: non-DM             | 46.92          | 9.12       | .263    |
| BMI (kg/m²)            | 22.4 ± 0.2     | 20.2 ± 0.5 | <.001   |

HD: hemodialysis; DM: diabetes mellitus; BMI: body mass index.

Blood test results

The hemoglobin and hematocrit were similar in both groups. The white blood cell count (WBC) was higher in non-Veg than Veg (6685 ± 211/µL vs 4870 ± 316/µL, p < .001). The serum ferritin of Non-Veg was also similar to that of Veg. The normalized protein catabolic rate (nPCR), an indicator of protein intake, was lower in Veg patients (1.22 ± 0.28 g/kg/day vs 1.09 ± 0.31 g/kg/day; non-Veg vs Veg, p < .05). The serum uric acid was significantly higher in non-Veg 7.1 ± 0.1 mg/dL vs 6.4 ± 0.3 mg/dL; non-Veg vs Veg, p < .05) whereas, serum potassium and calcium were similar between these two groups. The serum uric acid was significantly higher in Non-Veg patients (72.8 ± 1.8 mg/dL vs 61.2 ± 3.2 mg/dL; non-Veg vs Veg, p < .001) (Table 3).

Inflammatory markers and uremic pruritus severity

The median value of hs-CRP in Non-Veg was 0.75 (0.30, 1.26) mg/dL, which was significantly higher than that for the Veg 0.40 (0.30, 0.50) mg/dL (p = .020). Similar to the result for hs-CRP, the median value of IL-2 was also higher in Non-Veg 4.83 (2.1, 9.1) µg/mL than that of the Veg 2.53 (1.5, 3.2) µg/mL (p = .016).

The subjective pruritus scale VAS, which produces a score ranging from 0 to 10, was significantly higher in non-Veg [4.0 (1.6, 6.0)] than that of Veg [3.0 (0.0, 4.0)] (p = .022). The other pruritus scaling scoring system, PS, was also significantly higher in non-Veg [5 (4, 7)] than in Veg [4 (0, 5)] (p = .001) (Table 3).

Anti-pruritic agents use

Anti-histamine oral pills or steroid-containing ointments are the most frequent medications used for pruritus. In parallel with the results of the above scoring, the frequency of anti-pruritic agents used within one year before blood testing was higher in non-Veg than in Veg. There were 59 patients in the 140 non-Veg who had previously used oral anti-histamine in the past one year but there were only 2 patients who had previously used oral anti-pruritic agents in the 15 Veg (p = .020). Similar results can be seen in the numbers of patients who had used topical steroid ointment in the previous one year (55/140 vs 2/15; non-Veg vs Veg, p = .048). The median number of topical steroid ointments (clobetasol propionate 0.5 mg/tube) used by non-Veg was significantly higher than that of Veg 4.83 (2.08, 9.12) pg/mL, which was significantly higher than that of the Veg 2.53 (1.48, 3.19) pg/mL (p = .016) (Table 2).
Table 4. The proportion of patients in non-vegetarian and vegetarian hemodialysis patients used oral, topical, or intravenous medication in the previous one year.

|                     | non-Vegetarian (n = 140) | Vegetarian (n = 15) | p-value |
|---------------------|--------------------------|---------------------|---------|
| Oral (patient number)\(^{a}\) | 59/140                   | 2/15                | .020    |
| Topical (patient number)\(^{a}\) | 55/140                   | 2/15                | .048    |
| Ointment (tube)\(^{b}\)       | 0 (0,0)                  | 2 (0,4)             | .003    |

\(^{a}\): Chi-square test; \(^{b}\): Mann–Whitney test.

Table 5. The serum inflammatory markers and pruritic scores of non-diabetic non-vegetarian and non-diabetic vegetarian receiving maintenance hemodialysis for more than one year.

|                     | non-Vegetarian (n = 92) | Vegetarian (n = 12) | p-value |
|---------------------|--------------------------|---------------------|---------|
| hs-CRP (mg/dL)      | 0.75 (0.30, 1.19)         | 0.40 (0.30, 0.50)   | .049    |
| IL-2 (pg/mL)        | 4.89 (2.21, 8.95)         | 2.35 (1.17, 3.05)   | .014    |
| VAS                 | 4.0 (1.6, 7.0)            | 2.0 (0.0, 3.7)      | .030    |
| PS                  | 5.0 (4.0, 8.0)            | 3.0 (0.0, 4.8)      | .003    |

hs-CRP: high sensitivity C-reactive protein; IL-2: Interleukin 2; VAS: visual analog scale (0–10); PS: pruritus score (0–19).

Table 6. The values of inflammatory indicators and pruritus severity in 6 non-vegetarian hemodialysis patients and after their changing to vegetarian diets for 2 months.

|                     | Vegetarian diet | non-Vegetarian diet | p-value |
|---------------------|-----------------|---------------------|---------|
| hs-CRP (mg/dL)     | 1.90 ± 0.29     | 0.64 ± 0.09         | <.001   |
| IL-2 (pg/mL)       | 8.0 ± 0.6       | 2.9 ± 0.2           | .003    |
| VAS                 | 8.8 ± 0.5       | 3.0 ± 0.2           | <.001   |
| PS                  | 8.8 ± 0.4       | 3.8 ± 0.3           | <.001   |

hs-CRP: high sensitivity C-reactive protein; IL-2: interleukin 2; VAS: visual analog scale (0–10); PS: pruritus score (0–19).

than that of Veg [2 (0.4) tube vs 0 (0.0) tube; non-Veg vs Veg, p = .003, Mann–Whitney test] (Table 4). These data indicate that the severity of UP was greater in non-Veg than in Veg.

Non-diabetic hemodialysis patients

As diabetic hemodialysis patients are frequently have uremic pruritus, we then excluded diabetic hemodialysis patients and did further analysis. There were 92 non-diabetic non-vegetarian and 12 non-diabetic vegetarian hemodialysis patients. The hs-CRP was lower in non-diabetic vegetarians ([0.40 (0.30, 0.50) mg/dL vs 0.75 (0.30, 1.19) mg/dL, p = .049]). The IL-2 level of non-diabetic non-vegetarian [4.89 (2.21, 8.95) pg/mL] was higher than that of non-diabetic vegetarian [2.35 (1.17, 3.05) pg/mL] (p = .014). The VAS of non-diabetic non-vegetarian was higher than VAS of non-diabetic vegetarian [4.0 (1.6, 7.0) vs 2.0 (0.0, 3.7) non-Veg vs Veg, p = .030], and the PS of non-diabetic non-vegetarian was also higher than PS of non-diabetic vegetarian [5.0 (4.0, 8.0) vs 3.0 (0.0, 4.8) p = .003] (Table 5).

Diet change

To further demonstrate the effect of vegetarian diet on inflammatory markers and its possible effects on UP, six hemodialysis patients with uremic pruritus shifted their non-vegetarian diets to vegetarian diets for 2 months. Their blood hs-CRP and IL2 levels decreased after diet changed and so did the UP severity scores (Table 6).

Discussion

The current study findings demonstrate that the hemodialysis patients on a vegetarian diet were less likely to have uremic pruritus. In HD patients, the severity of uremic pruritus for the vegetarians, determined by both subjective and objective scoring methods, was lower than that of the non-vegetarians. The percentage of patients using anti-pruritic agents was also lower than that of the non-vegetarians. Finally, vegetarian hemodialysis patients had lower levels of hs-CRP and IL-2 than those of the non-vegetarian hemodialysis patients. When exclude diabetes patients for subgroup analysis, the above findings can also be applied to non-DM hemodialysis patients. The above study results were further validated by a small-scale cohort study.

The cause of UP is still not clear. Uremic toxin, inadequate dialysis, hyperphosphatemia, secondary hyperparathyroidism, iron deficiency anemia, heparin, biocompatible membrane, and skin xerosis have all been postulated as possible mechanism [9]. In our study, mean Kt/V, heparin, and biocompatible membrane use were similar in both groups. Thus, dialysis clearance, heparin, and artificial kidney may not be a key factor of UP difference between Veg and non-Veg group. Serum phosphate and iPTH were lower in our vegetarian patients, but the mean serum phosphate level and iPTH of the non-vegetarian patients were within an acceptable range [10]. The reason for higher serum phosphate in non-vegetarian patients was not clear. As non-vegetarians are more liberal for daily diet selection, they are more inclined to eat processed and convenience foot rich in phosphate contents. The higher serum phosphate led to higher calcium-base phosphate binder use and resulted in higher serum calcium and iPTH in non-vegetarians. There were several studies reported that serum phosphate levels and iPTH did not associate with pruritus [11,12]. It seemed that the differences between serum phosphate and iPTH were not able to fully explain the UP differences between these two groups.

Previous studies have suggested an association of UP with systemic inflammatory process as manifested by high serum hs-CRP in UP patients [13]. Recently serum IL-2, a systemic inflammatory cytokine, has also found to be elevated in UP patients [7]. IL-2 is a pruritic cytokine secreted by T helper 1 (Th1) cells and systemic
Enhanced systemic inflammation in dialysis patient may be related to process associated with renal failure itself, may be a consequence of the treatment for renal failure (dialysis-related), or maybe even unrelated to either renal failure or the dialysis process specifically. There were studies showed that renal failure can cause accumulation of pro-inflammatory compounds and the products of metabolism in renal failure can reduce plasma antioxidant activity [21,22].

Long-term vegetarians have lower oxidative stress and systemic inflammation [23]. Vegetarian diet has been reported to alleviate T-cell mediated inflammatory skin disease [24]. We have previously also reported that blood systemic inflammation markers such as hs-CRP and white blood cell count were lower in vegetarian hemodialysis patients than in non-vegetarian hemodialysis patients [8]. It is reasonable to infer that hemodialysis patients on a vegetarian diet may also have a lower T-cell inflammation as well as its down-stream IL-2 secretion. This may help in explaining the improvement of UP that we saw in our study group. Recently, vegetarian diet in hemodialysis patients has been found to be able decrease the production of indoxyl sulfate, another possible marker of uremic pruritus [25]. We did not check the indoxyl sulfate level of our study subjects and the correlation of IL-2 with indoxyl sulfate was not known either.

In our study, it is limited by small patient number and difficulty for patients to shift from non-vegetarian to vegetarian diets. The study results can be biased by the small case numbers and relatively small size number in vegetarian diet changing (from non-vegetarian to vegetarian). The possible benefits of vegetarian diet versus non-vegetarian diet needs to be further evaluated in more randomized double-blind placebo-controlled trials with larger sample sizes.

**Conclusion**

Hemodialysis patients on a vegetarian diet have a lower severity of uremic pruritus. The biomarkers of uremic pruritus (serum hs-CRP and IL-2) and severity of pruritus (scale by VAS and PS) are lower in vegetarian diet patients and vegetarian diet conversion. Vegetarian diet might be associated with the amelioration of the uremic pruritus severity in hemodialysis patients.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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