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## Foreword from the Editors

We are proud to present Volume 3, Issue 3 of The Journal of European Internal Medicine Professionals (JEIMP), a landmark issue that marks the beginning of our collaboration with the Hypertension, Dialysis and Transplantation Foundation (HDTV). From this issue onward, JEIMP will continue its mission in partnership with HDTV, further advancing our shared commitment to scientific excellence and innovation in internal medicine.

This issue showcases the diversity and clinical relevance of our journal. Highlights include original research on oxidative stress and levothyroxine treatment in Hashimoto's thyroiditis, a comparative study of topical therapies for itchy ear syndrome, and important data on secondary fractures in hemodialysis patients. Additionally, the renal and hemodynamic effects of SGLT2 inhibitors in diabetic kidney disease, and a public health analysis of frailty syndrome trends, reflect the breadth of contemporary internal medicine.

A comprehensive review of gout, along with rare case reports in our Letters to the Editor section, round out this issue—offering both practical guidance and new perspectives for our readers.

We thank our authors, reviewers, and the entire JEIMP community for their dedication. We look forward to growing together with HDTV and continuing to serve as a platform for impactful research and clinical insights.

The Editors;
Mehmet Deniz Aylı, Mehmet Emin Demir, Özant Helvacı
The Journal of European Internal Medicine Professionals (JEIMP)

**In This Issue**



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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

# Assessment of Oxidative Stress in Hashimoto's Thyroiditis Patients: Effects of Levothyroxine Sodium Treatment

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## Abstract

**Background:** Hashimoto's thyroiditis (HT) is a prevalent autoimmune disease characterized by chronic inflammation of the thyroid gland, leading to hypothyroidism. Oxidative stress has been implicated in the pathogenesis of HT, influencing disease progression and therapeutic outcomes. Understanding the dynamics of thiol/disulfide balance, a marker of oxidative stress, in HT patients receiving levothyroxine treatment is crucial for elucidating its role in disease management. Our study has the largest cohort on this topic.

**Methods:** This study enrolled 357 euthyroid HT patients, divided into groups based on levothyroxine treatment status. Thiol/disulfide homeostasis was assessed using the Erel method. Clinical parameters, including thyroid function tests and antibody levels, were measured. Statistical analyses were performed to compare oxidative stress markers between groups.

**Results:** Patients on levothyroxine therapy showed lower native and total thiol levels than untreated patients, indicating potential antioxidant depletion. Higher disulfide/native thiol and disulfide/total thiol ratios in the treated group suggest elevated oxidative stress. There were no correlations between thyroid antibodies (TPO-Ab, TG-Ab) and thiol/disulfide levels.

**Conclusion:** This study highlights alterations in thiol/disulfide balance among euthyroid HT patients, with implications for oxidative stress management in clinical practice. Levothyroxine treatment appears to be associated with oxidative stress markers, suggesting associations that warrant further investigation.

**Keywords:** Autoimmunity, Oxidatvie Stress, Hashimoto Disease

## INTRODUCTION

Hashimoto's thyroiditis (HT), the most prevalent organ-specific autoimmune disease, is characterized by chronic thyroid gland inflammation driven by autoimmune mechanisms. It stands as the leading cause of hypothyroidism in iodine-sufficient areas, impacting approximately 10% of the population, predominantly women, with prevalence rising with age (1). The etiology of HT is believed to stem from a blend of genetic predisposition and environmental influences. Clinically, HT manifests as gradual thyroid failure. This is due to the infiltration of lymphocytes and the autoimmune-induced degradation of thyroid gland tissue, which involves programmed cell death of thyroid epithelial cells (2,3). In the United States National Health and Nutrition Examination Survey (NHANES III), hypothyroidism was found in 4.6% and hyperthyroidism in 1.3% (1). In another study, more than 90% of HT patients have high serum concentrations of autoantibodies to thyroglobulin (TG-Ab) and thyroid peroxidase (TPO-Ab) (4,5). The

failure of immunological self-tolerance initiates a series of cascading events. This includes the dysfunction of T regulatory cells, the activation and proliferation of T-helper cells, and the differentiation of auto-reactive B cells, leading to anti-thyroid autoantibodies. These processes culminate in tissue inflammation and subsequent damage (6). The release of pro-inflammatory cytokines by infiltrating T and B cells exacerbates tissue damage and inflammation, fostering a cycle of worsening pathology (7). In this context, an imbalance arises between the endogenous production of reactive oxygen species (ROS) and the antioxidant defenses, emerging as a significant factor in the onset and advancement of the autoimmune process and associated glandular dysfunction. When thyroid dysfunction occurs, it exacerbates oxidative stress, as changes in thyroid hormone levels can impact the production of ROS and the synthesis of antioxidants, potentially affecting both processes (8). Several studies have investigated the correlation between oxidative stress and HT to gauge the oxidant-antioxidant balance in the body. However, findings have occasionally been conflicting (9-12).

The oxidant radicals cause oxidation of the thiol groups of sulfur-containing amino acids (cysteine) of proteins and form disulfide (-S-S-) bonds (13). These disulfide bonds are the earliest sign of protein oxidation and are reversible (14). Reducing reversible disulfide bonds to thiol groups maintains dynamic thiol/disulfide homeostasis (15). Unlike previous methods, the method developed by Erel et al. allows individual measurement of both thiol and disulfide levels (16). This method is also superior to former methods in terms of fast and accurate results, the possibility of remeasurement, and being both a manual and colorimetric method (17). Abnormal thiol/disulfide homeostasis is implicated in several diseases characterized by chronic inflammation (18-20). In this study, we aimed to investigate dynamic thiol/disulfide homeostasis in euthyroid patients with Hashimoto's thyroiditis, both with and without levothyroxine medication, using the Erel method.

To our knowledge, this represents the largest cohort specifically examining thiol/disulfide homeostasis in euthyroid HT patients using the Erel method.

## METHODS

*Study participants*

A total of 357 subjects aged over 18 years, consecutively referred to our outpatient clinics over six months, were enrolled in the study. HT was diagnosed using the currently accepted laboratory and ultrasonographic criteria (serum anti-thyroid antibodies positivity and/or heterogeneous echo-structure with diffuse or patchy hypoechogenicity at ultrasonography). All patients were euthyroid. 176 (49.3%) of the patients were euthyroid on levothyroxine treatment. We assessed dynamic thiol/disulfide homeostasis in euthyroid patients with Hashimoto's thyroiditis, both with and without levothyroxine medication, using the Erel method.

Exclusion criteria;

1. Unwilling to participate
2. Active malignancy
3. Pregnancy
4. Inflammatory disease
5. Infection disease
6. Trauma or acute injury
7. Smoking, alcohol consumption
8. Taking any form of antioxidant agents or vitamin supplements

Patients who met the study criteria and agreed to participate were given details about the study and signed a free informed consent form.

*Study Design*

The study is a single-centered, cross-sectional clinical trial conducted at the Internal Medicine Department outpatient office of Ataturk Research and Training Hospital in Turkey. The study protocol received approval from the local ethical committee (17 May 2017, Yildirim Beyazit University Faculty of Medicine Ethical Committee, number 26379996/110, decision no 109) following the principles of the Helsinki Declaration.

Demographic data and patients' clinical history were reviewed. We examined thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), TPO-Ab, and TG-Ab. Serum TSH, fT3, and fT4 levels were measured using chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, California and UniCel DXI 800, Beckman Coulter, Brea, California). Normal ranges for TSH, fT3, and fT4 were 0.27–4.2 uIU/mL, 1.57–4.71 pg/mL, and 0.61–1.2 ng/dL, respectively. Venous blood samples from the patients and healthy controls were collected after 12 hours of fasting and put in EDTA tubes.

*Thiol/disulfide Homeostasis*

We conducted thiol/disulfide homeostasis tests following the method described by Erel and Neselioglu (16). First, disulfide bonds were reduced to form free functional thiol groups. Any unused sodium borohydride reducer was neutralized and removed using formaldehyde. Next, we determined native and total thiol levels by reacting with 5,5'-dithiobis-2-nitrobenzoic acid. The dynamic disulfide amount was calculated by determining half of the difference between the total and native thiol. After the native thiol, total thiol, and disulfide amounts were determined, the ratios of disulfide/total thiol, native thiol/total thiol, and disulfide/native thiol were calculated. Plasma disulfide levels were 17.29 ± 5.32 μmol/L, native thiol levels were 397 ± 62 μmol/L, and disulfide/native thiol percent ratios were 4.32 ± 1.49 in healthy subjects (16).

## STATISTICAL ANALYSIS

The data were entered into an Excel spreadsheet (Microsoft, Redmond, Washington) for analysis. Statistical analyses were performed using the SPSS. To assess the normal distribution of the variables, we used both analytic (Shapiro-Wilk test) and visual methods, utilizing histograms and probability plots. Independent t-tests were used to compare continuous variables between groups. Chi-square tests were used for categorical variables. A significance level of 5% (type-I error) was employed to determine statistical significance. Descriptive analyses were presented using means and standard deviations for normally distributed variables and medians with minimum-maximum values for non-normally distributed variables. Statistical significance was established when $p<0.05$. Pearson correlation tests were used to explore the relationships among the variables and determine their significance. For this study, we conducted a power analysis to determine the required sample size for detecting significant differences between group means. We set the alpha at 0.05 and aimed for a power of 95%, which led us to calculate a necessary sample size of 342 participants to detect actual differences between the groups effectively.

## RESULTS

The study included 370 patients. Thirteen patients were excluded from the study due to non-acceptance of informed consent. A total of 357 patients, 313 women and 44 men, were included in the study (**Figure 1**). The study was terminated because a sufficient number was reached.

Diabetes Mellitus (DM) was present in 26 (7.3%) patients and hypertension in 39 (10.9%). The patients had no additional diseases other than DM and hypertension. All patients were euthyroid. One hundred seventy-six (49.3%) patients were using levothyroxine sodium therapy. The average dose of levothyroxine sodium was 76.46±13.97 mcg/d. Regarding thyroid function tests, the mean TSH level was 2.25±1.11 mIU/mL, ranging from 0.50 to 4.20 mIU/mL. The mean fT4 level was 1.26±0,21 ng/dL. The mean fT3 level was 2.95±0,43 ng/dL. The mean TPO-Ab titer was 96±148 IU/mL. The mean TG-Ab titer was 148±351 IU/mL (**Table 1**). When all patients were evaluated, the mean disulfide level was 18.08±10.20 µmol/L, ranging from 0.80 to 45.45 µmol/L. The mean native thiol level was 445.41±46.06 µmol/L, ranging from 256.60 to 594.40 µmol/L. The mean total thiol level was 481.61±50.52 µmol/L, ranging from 331.60 to 623.40 µmol/L. The mean disulfide/native thiol (%) was 4.07±2.33. The mean disulfide/total thiol (%) was 3.84±2.34. The mean native/total thiol (%) was 92.57±3.96 (**Table 1**). The mean disulfide and native thiol levels were higher than healthy subjects (16).

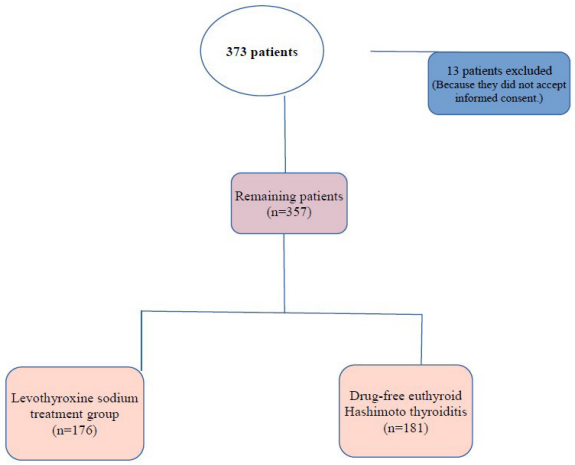


**Figure 1.** Study design, basic flowchart

Then, the patients were divided into two groups: those who received levothyroxine sodium treatment and those who did not. The mean age of the group that received treatment and did not was 44.85±14.03 and 31.17±12.86, respectively ($p<0.001$). While 157 (89.2%) of the patients in the group that received treatment were women, 156 (86.2%) were women in the group that did not ($p=0.38$). The number of patients diagnosed with DM was 15 (8.5%) in the group that received treatment and 11 (6.1%) in the group that did not ($p=0.37$). The number of patients diagnosed with hypertension was 29 (16.5%) in the group that received treatment and 10 (5.5%) in the group that did not ($p<0.001$). The mean

**Table 1.** Characteristics of the study participants

| | |
|---|---|
| **Patient number, n** | 357 |
| **Female gender, n (%)** | 313 (87.7) |
| **Age, years** | 40.96 ± 13.95 (18-79) |
| **Diabetes Mellitus present, n (%)** | 26 (7.3) |
| **Hypertension present, n (%)** | 39 (10.9) |
| **Usage of levothyroxine sodium yes, n (%)** | 176 (49.3) |
| **The average dose of levothyroxine sodium** | 76.46 ± 13.97 |
| **TSH mIU/mL** | 2.25 ± 1.11 (0.5-4.2) |
| **fT3 ng/dL** | 2.95 ± 0.43 (2.0-5.0) |
| **fT4 ng/dL** | 1.26 ± 0.21 (0.8-2.0) |
| **TPO-Ab IU/mL** | 96 ± 148 (5-600) |
| **TG-Ab IU/mL** | 148 ± 351 (9-4000) |
| **Mean disulfide level µmol/L** | 18.08 ± 10.20 |
| **Mean native thiol level µmol/L** | 445.41 ± 46.06 |
| **Mean total thiol level µmol/L** | 481.61 ± 50.52 |
| **Mean disulfide/native thiol (%)** | 4.07 ± 2.33 |
| **Mean disulfide/total thiol (%)** | 3.84 ± 2.34 |
| **Mean native/total thiol (%)** | 92.57 ± 3.96 |

**TSH**, thyroid-stimulating hormone; **fT3**, free triiodothyronine; **fT4**, free thyroxine; **TPO-Ab**, thyroid peroxidase antibody; **TG-Ab**, thyroglobulin antibody; **µmol/L**, micromoles per liter; **ng/dL**, nanograms per deciliter; **mIU/mL**, milli-international units per milliliter; **IU/mL**, international units per milliliter; %, percentage.
Statistical significance was established when $p<0.05$.

**Table 2.** Demographic characteristics and laboratory findings among groups

| | Levothyroxine sodium treatment group | Drug-free euthyroid Hashimoto thyroiditis | p value* |
|---|---|---|---|
| **Patient number, n (%)** | 176 (49.3) | 181 (50.7) | |
| **Female gender, n (%)** | 157 (89.2%) | 156 (86.2%) | 0.38 |
| **Age, years** | 44.85 ± 14.03 | 31.17 ± 12.86 | <0.001 |
| **Diabetes Mellitus present, n (%)** | 15 (8.5%) | 11 (6.1%) | 0.37 |
| **Hypertension present, n (%)** | 29 (16.5%) | 10 (5.5%) | 0.00 |
| **TSH mIU/mL** | 2.28 ± 1.17 | 2.16 ± 1.06 | 0.29 |
| **TPO-Ab IU/mL** | 125 ± 170 | 67 ± 116 | <0.001 |
| **TG-Ab IU/mL** | 180 ± 374 | 117 ± 324 | 0.09 |
| **Mean disulfide level µmol/L** | 17.88 ± 9.73 | 18.27 ± 10.68 | 0.72 |
| **Mean native thiol level µmol/L** | 437.07 ± 48.82 | 453.52 ± 41.77 | <0.001 |
| **Mean total thiol level µmol/L** | 472.63 ± 52.03 | 490.36 ± 47.5 | <0.001 |
| **Mean disulfide/native thiol (%)** | 4.10 ± 2.26 | 4.05 ± 2.41 | 0.83 |
| **Mean disulfide/total thiol (%)** | 3.97 ± 2.60 | 3.72 ± 2.06 | 0.31 |
| **Mean native/total thiol (%)** | 92.48 ± 3.79 | 92.66 ± 4.13 | 0.67 |

TSH level of the group that received treatment and did not was 2.28±1.17 [SD] and 2.16±1.06 mIU/mL, respectively (p=0.29). The mean TPO-Ab titer of the group that received treatment and did not was 125±170 and 67±116 IU/mL, respectively (p<0.001). The mean TG-Ab titer of the group that received treatment and did not was 180±374 and 117±324 IU/mL, respectively (p=0.09). The native and total thiol levels were lower in those who received the levothyroxine sodium treatment group (p<0.001, p<0.001). Although not statistically significant, the disülfide levels and native/total thiol ratio were also lower in the treatment group (p=0.72, p=0.67). The disulfide/native thiol and disulfide/total thiol ratios were higher in the treatment group (p=0.83, p=0.31) (Table 2).

When patients with diabetes were excluded, as this might affect the results, 331 patients were identified. While 161 (48.6%) of these patients received levothyroxine treatment, 170 (51.4%) were not. The mean age of those who received treatment was 43.73±13.95, while the mean age of those who did not receive treatment was 36.44±12.67. The native and total thiol levels were lower in those who received the levothyroxine sodium treatment group (p<0.001, p<0.001). Although not statistically significant, the disülfide levels, disulfide/total thiol, and native/total thiol ratios were also lower in the treatment group (p=0.68, p=0.27, p=0.62). The disulfide/native thiol ratio was higher in the treatment group (p=0.78) (Table 3).

No correlation was detected between TSH levels and native thiol, total thiol, and disulfide levels (p=0.06, p=0.051, p=0.54). No correlation was detected between TPO-Ab titer and native thiol, total thiol, and disulfide levels (p=0.29, p=0.37, p=0.56). No correlation was detected between TG-Ab titer and native thiol, total thiol, and disulfide levels (p=0.65, p=0.71, p=0.41).

## DISCUSSION

HT represents a multifaceted autoimmune condition characterized by persistent inflammation of the thyroid gland, ultimately culminating in hypothyroidism. Our investigation sought to elucidate the dynamic thiol/

**Table 3.** Demographic characteristics and laboratory findings among groups without diabetes

| | Levothyroxine sodium treatment group | Drug-free euthyroid Hashimoto thyroiditis | p value* |
|---|---|---|---|
| **Patient number, n (%)** | 161 (48.6) | 170 (51.4) | |
| **Female gender, n (%)** | 144 (89.4%) | 149 (87.6%) | 0.61 |
| **Age, years** | 43.73 ± 13.95 | 36.44 ± 12.67 | <0.001 |
| **TSH mIU/mL** | 2.30 ± 1.17 | 2.17 ± 1.06 | 0.29 |
| **TPO-Ab IU/mL** | 129 ± 172 | 65 ± 110 | <0.001 |
| **TG-Ab IU/mL** | 184 ± 386 | 123 ± 334 | 0.12 |
| **Mean disulfide level µmol/L** | 17.66 ± 9.47 | 18.11 ± 10.65 | 0.68 |
| **Mean native thiol level µmol/L** | 435.76 ± 48.63 | 454.52 ± 42.11 | <0.001 |
| **Mean total thiol level µmol/L** | 470.83 ± 50.54 | 491.06±47.81 | <0.001 |
| **Mean disulfide/native thiol (%)** | 4.07 ± 2.25 | 4.00 ± 2.39 | 0.78 |
| **Mean disulfide/total thiol (%)** | 3.96 ± 2.66 | 3.68 ± 2.05 | 0.27 |
| Mean native/total thiol (%) | 92.52 ± 3.77 | 92.74 ± 4.12 | 0.62 |

disulfide homeostasis among euthyroid HT patients, with and without medication, utilizing the Erel method. Our findings offer valuable insights into the underlying mechanisms of oxidative stress in HT pathogenesis and management. Our study uncovered significant alterations in thiol/disulfide homeostasis parameters among euthyroid HT patients compared to healthy controls, as defined by established cut-off values (16). Recent studies have elucidated the intricate relationship between thyroid dysfunction and oxidative stress. Studies have highlighted the augmentation of free radical generation and oxidant production in hyperthyroidism (21-24), juxtaposed with the attenuation of antioxidant defense mechanisms in hypothyroidism (23-25), thus exacerbating oxidative stress. Ruggeri RM's study, encompassing a sizable cohort (n=134) of euthyroid HT patients without thyroxine therapy, corroborated these findings by revealing a pro-oxidative shift in the oxidative/antioxidative balance (12). They later published another study examining advanced glycation end products (AGEs) and their receptors(sRAGEs), demonstrating oxidative stress in patients with HT. They showed that sRAGEs were decreased and AGEs increased, suggesting a dysregulation of AGE/sRAGEs-related oxidative homeostasis in euthyroid HT patients (26). Thyroid hormones can target, influence, or alter the metabolism of numerous cells in the body by accelerating cellular reactions and enhancing oxidative metabolism. Excessive generation of free radicals and inadequate antioxidant defense systems lead to oxidative stress. Unchecked, these free radicals eventually harm cell membranes' essential cellular components such as DNA, proteins, and lipids. Each cell possesses mechanisms to mitigate the effects of free radicals through DNA repair enzymes and antioxidants. Poor control of pro-oxidants and oxidative stress can contribute to various chronic and degenerative diseases, aging, and pathological conditions. Specifically, heightened levels of disulfide and native thiol, indicative of oxidative stress imbalance, were observed in our study cohort. Consistent with prior research implicating oxidative stress in autoimmune thyroid disorders, our findings underscore the pertinence of oxidative stress markers in elucidating HT pathophysiology. Notably, the methodology employed in our study, involving the meticulous removal of sodium borohydride using formaldehyde, offers a nuanced approach to delineating thiol/disulfide homeostasis (16). This methodological refinement allows for the distinct measurement of these elemental constituents, potentially enhancing our understanding of the intricate interplay between oxidative stress and HT progression.

Besides inflammatory processes, hormonal imbalances can also contribute negatively to oxidative stress. Therefore, we selected euthyroid patients for our study. It represents the largest cohort in the literature that evaluates a similar patient group. We divided the patients into two groups based on levothyroxine usage (n=176, n=181)and assessed their oxidative stress status (**Table 2**). There was no statistically significant difference between the two groups in terms of age and prevalence of hypertension. While 89.2% of the group using levothyroxine were female, compared to 86.2% in the non-levothyroxine group. TPO-Ab levels did not show a statistically significant difference between the groups, whereas TG-Ab levels were higher in the levothyroxine group. This suggests that patients with higher antibody levels may require more levothyroxine. Native and total thiol levels were statistically significantly higher in the group not using medication, indicating potentially lower antioxidant levels in the medication-requiring group. Although not statistically significant, the higher mean disulfide/native thiol and mean disulfide/total thiol ratios in the levothyroxine group suggest higher oxidative stress in this group. Since a statistically significant difference in the prevalence of diabetes between the groups was observed, patients with DM were excluded, and the two groups (n=161, n=170) were re-evaluated (**Table 3**). Similarly, there was no statistically significant difference between the two groups in terms of age and prevalence of hypertension. TPO-Ab levels did not show a statistically significant difference between the groups, whereas TG-Ab levels were higher in the levothyroxine group. The oxidative stress markers showed similar results in both groups, even after excluding patients with diabetes. DM did not significantly alter the oxidative stress outcomes. Csiha et al. investigated the association between serum AGE, sRAGE, and thyroid function in HT patients receiving levothyroxine substitution and healthy controls. In their study, AGE levels were lower in the patient group than controls, while sRAGE levels were higher. However, not all patients in their study were euthyroid; some had overt or subclinical hypo/hyperthyroidism (27). Another study from Ates I. Et al. investigated the effects of levothyroxine replacement on oxidative stress in HT. Thirty-six patients recently diagnosed with HT-related hypothyroidism and 36 healthy controls were included in the study. Levothyroxine replacement was started for patients with hypothyroidism and had been followed up for 6 months. The study showed that levothyroxine replacement decreased oxidant status and increased antioxidant status following six 6 months of levothyroxine replacement in hypothyroidism developed by the HT (28). The outcomes may differ because the study designs, patient numbers, and methodologies varied among studies evaluating the effects of levothyroxine treatment on oxidative stress. Further studies would be beneficial in evaluating the effect of levothyroxine supplementation on subclinical inflammation in euthyroid HT patients.

No correlation was found between TSH, TPO-Ab, and TG-Ab levels and native thiol, total thiol, and disulfide levels in our study. Ates I. et al. investigated the effects

of oxidative stress on the pathogenesis and progression of HT, and their study revealed significant positive correlations between both TPO-Ab and TG-Ab levels with total oxidant status and negative correlations with total antioxidant status (29). Nanda et al. found a positive correlation of the oxidant molecules malondialdehyde and protein carbonyl with TPO-Ab (30). Highlighting discrepancies in existing literature, our study advocates for further research to clarify the inflammation in euthyroid HT patients.

Strengths of our study: (I). Our study includes a substantial number of participants, enhancing the statistical power and generalizability of findings within euthyroid HT patients. (II). The use of the Erel method for assessing thiol/disulfide homeostasis is detailed and scientifically sound, offering precise measurements and allowing for reproducibility. (III). By focusing on euthyroid HT patients both with and without levothyroxine medication, the study addresses a clinically relevant question about the impact of treatment on oxidative stress markers.

**Limitations of the Study**

This study has several limitations that should be acknowledged. The cross-sectional design precludes establishment of causal relationships between levothyroxine treatment and oxidative stress markers. The significant age difference between treatment groups represents a potential confounding factor that may influence our findings. Additionally, the clinical significance of the observed laboratory differences in thiol/disulfide parameters requires validation through longitudinal studies with clinical endpoints. Despite these limitations, our findings provide valuable insights into oxidative stress patterns in euthyroid HT patients.

## CONCLUSION

Our study delves into the intricate dynamics of thiol/disulfide balance in euthyroid HT patients, offering novel insights into the role of oxidative stress in autoimmune thyroid disorders. By leveraging the robustness of the Erel method, we meticulously evaluated thiol/disulfide homeostasis, uncovering significant alterations influenced by levothyroxine therapy. These findings underscore the relevance of oxidative stress as a pivotal factor in HT pathogenesis and treatment response. Moving forward, further research exploring the interplay between thyroid function, oxidative stress markers, and clinical outcomes will be indispensable in refining therapeutic strategies and advancing personalized medicine for HT patients.

## DECLARATIONS

**Authors' contributions:** All authors contributed to the study conception and design. Material preparation, and analysis were performed by B.C.H. Data collection was performed by B.C.H, and GD. The first draft of the manuscript was written by B.C.H. and all authors commented on previous versions of the manuscript. The study was supervised by O.H, S.N, and O.E. All authors read and approved the final manuscript.

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**Conflict of interest:** The authors declare that they have no conflict of interest. In addition, the authors have no financial relationship with the companies that manufactured the materials used in this study.

**Ethics approval:** All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol received approval from the local ethical committee.

Consent to participate and written consent for publication Informed consent was obtained from all participants.

Availability of data and material Data is available upon reasonable request from the corresponding author.

**AI:** Artificial intelligence tools were used to assist in language editing and improving the clarity of the manuscript. However, all scientific content, data analysis, and interpretations were carried out by the author, who bear full responsibility for the content and conclusions of this work.

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Original Article

# Empirical Treatment Approach for Itchy Ear Syndrome: Topical Steroids or Antifungals?

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**Abstract**

**Background:** "Itchy ear syndrome", defined as ear itching after exclusion of related pathologies with a thorough physical examination, is common in otolaryngology practice. Despite the fact that it is frequent, high quality evidence regarding its etiology and treatment is lacking. We aimed to investigate whether empirical antifungal therapy is effective in this situation in comparison with corticosteroid therapy and the effectiveness of topical mometasone furoate lotion.

**Methods:** This retrospective observational study included 57 patients who applied with recurrent ear pruritus, were treated with mometasone or ciclopirox olamine, and who did not have any pathological findings on examination. The patients were retrospectively scanned through the hospital database, called, and asked to fill out a modified form of the 5D itching questionnaire to assess the degree of itching before and after treatment. The results were compared statistically.

**Results:** Of the 57 patients included, 25 (43.8%) were male and 32 (56.1%) were female. The mean age of the two groups was similar (p=0.915). Twenty-eight (49.1%) patients were treated with ciclopirox olamine, and 29 (50.9%) patients with mometasone. When the scores before and after treatment were compared, the decrease in scores was significant (p<0.001). There was no significant difference between the two cohorts regarding pre-treatment and post-treatment scores (p=0,26 and p=0.22, respectively).

**Conclusion:** Our findings indicate that topical antifungal treatment with ciclopirox olamine and topical steroid treatment with lotion form mometasone furoate are both effective in the treatment of itchy ear syndrome.

**Keywords:** Pruritis, Ear Canal, Memetasone Furoate, Ciclopirox/pharmacology

## INTRODUCTION

Ear itching is one of the most common complaints in otolaryngology practice. Ear itching, as in other dermatological causes, can be caused by inflammatory skin diseases, exogenous trigger factors (e.g. mites, fungi, viruses, etc.), or systemic diseases (e.g. renal insufficiency, liver diseases, diabetes mellitus) (1-4). Although this is a common symptom, the underlying systemic or local cause can not be detected in most patients and this condition is also called " itchy ear syndrome" (5).

Despite the fact that ear itching is a common symptom, there are not enough studies on its etiology and treatment (6,11). It has been reported in previous studies that topical corticosteroid agents, local moisturizers, topical immunomodulators, antihistaminics, and Castellani's paint has been used for treatment, but the treatment of choice, as well as the best empirical treatment approach, remains unclear (3,5). Although the effectiveness of topical steroid therapy is reported in the literature, there are not enough studies on this subject and the choice of the topical agent and pharmaceutical form (lotion, cream, etc.) to use is unclear. It should also be emphasized that before the initiation of empirical treatment with steroids, a thorough physical examination is essential, for absence of funghal infection findings is necessary, in

which steroids may have deleterious effects.

In this study, we aimed to investigate whether empirical antifungal therapy is effective in the itchy ear syndrome in comparison with corticosteroid therapy, the effect of which has already been reported. We also aimed to investigate the effectiveness of the lotion form of topical mometasone furoate on itchy ear.

## METHODS

This study was conducted in compliance with the principles outlined in the "Declaration of Helsinki". The institutional ethics committee approved the study protocol (E.Kurul-E2-22-2304). Given the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived by the ethics committee. All patient data were anonymized and securely stored in an electronic database to ensure confidentiality. Written informed consent to participate was obtained from the patients participated in this study. Personal data privacy has been protected. Patients signed informed consent regarding publishing their data.

*Study Design*

This study was designed as a retrospective observational study in our otorhinolaryngology clinic. Twenty-eight patients who were treated with topical mometasone and twenty-nine patients who were treated with topical ciclopirox olamine were randomly selected. Mometasone was applied as 5 drops, 3 times a day and the ciclopirox olamine was applied as 5 drops, 3 times a day. The patients who were treated with these agents and were eligible were retrospectively scanned and called. Patients were asked to fill out a 5-D pruritus scale to assess the degree of itching before and after treatment7. The results of the questionnaire were compared between the two groups.

*Data Source*

By scanning the outpatient clinic data through hospital data-base, 57 patients who applied to the otorhinolaryngology outpatient clinic within 1 week with recurrent bilateral external ear canal pruritus and were treated with mometasone or ciclopirox olamine were included.

*Case Selection*

During the study period, we identified a total of 232 patients who presented to our otorhinolaryngology outpatient clinic with recurrent bilateral external ear canal pruritus and received either mometasone or ciclopirox olamine treatment. From this initial cohort, 127 patients met our inclusion criteria after exclusion of those with pathological examination findings, recent medication use, or comorbid conditions. Of the 127 eligible patients, 86 were successfully contacted by telephone, and 57 agreed to participate and completed the 5-D pruritus questionnaire. Reasons for non-participation included: inability to reach (41 patients) refusal to participate (14 patients), and incomplete questionnaire responses (15 patients). The patients who did not have any pathological findings that would cause itching on otolaryngological examination were included in the study.

*Exclusion Criteria*

Patients with abnormal physical examination findings were excluded. Long-term use of topical or systemic steroids and. antibiotics, as well as usage of these agents within one week prior to study enrollment date were also determined as exclusion criteria. Patients who had earwax or showed signs of otological diseases such as otomycosis, external otitis, or chronic otitis media on otoscopic examination, a history of ear surgery, any history of systemic diseases including diabetes mellitus, renal failure, hepatic disorders or dermatological diseases such as psoriasis or atopic dermatitis were also excluded.

## STATISTICAL ANALYSIS

Statistical analyzes were performed using SPSS version 26 software. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Descriptive analyzes were given using the mean and standard deviations for normally distributed variables, and the median and interquartile range for non-normally distributed variables. Pre-treatment scores were compared with the Independent Groups T-test since this variable showed a normal distribution. Post-treatment scores that did not show normal distribution were compared using the Mann-Whitney U test. Since it was determined that the post-treatment scores did not comply with the parametric test assumptions, the statistical significance of the change over time for these parameters was examined using the Friedman test. Pairwise comparisons were made using the Wilcoxon test and evaluated using Bonferroni correction. Within-group changes from pre- to post-treatment were analyzed using the Wilcoxon signed-rank test for each group separately. A p-value below 0.05 were considered statistically significant.

## RESULTS

Of the 57 patients included in the study, 25 (43.8%) were male and 32 (56.1%) were female. The mean age of the patients who were treated with mometasone was 43.1 ± 10.4. The mean age of the patients who were treated with ciclopirox olamine was 47.4 ± 12.2 years. The mean age of the two groups was similar (p=0.915).

Twenty-eight (49.1%) patients were treated with ciclopirox olamine and 29 (50.9%) patients with mometasone. When the scores before and after treatment were compared, it was found that the decrease in scores was significant (p<0.001). When the cicloprox olamine

and mometasone treatments were evaluated separately, the decrease in scores was statistically significant (p<0.001) (Table 1 and Figure 1).

Forty-nine of 57 patients (86%) achieved the minimum itch score of 5, with the highest post-treatment score being 8. For pre-treatment scores, the mean of the ciclopirox olamine group was 15.89 (SD±2.94) and the mean of the mometasone group was 16.97 (SD±4.21). There were no significant difference between two groups (p=0.26). There was no significant difference in post-treatment scores in the ciclopirox olamine and mometasone groups (p=0.22). No statistically significant difference in magnitude of itch reduction was found between the two groups (Table 2).

In the ciclopirox group, itch scores improved from a mean of 15.89 (95% CI: 14.76-17.02) to a median of 5, representing a reduction of 10.89 points (paired Cohen's d = 3.70, p<0.001). In the mometasone group, scores improved from a mean of 16.97 (95% CI: 15.37-18.57) to a median of 5, representing a reduction of 11.97 points (paired Cohen's d = 2.84, p<0.001). For pre-treatment scores, there was no significant difference between the ciclopirox group (mean: 15.89, SD: 2.94) and mometasone group (mean: 16.97, SD: 4.21), with a between-group difference of 1.08 points (Cohen's d = 0.30, p=0.26). Similarly, post-treatment scores showed no significant difference between groups (p=0.22), with both groups achieving similar median scores of 5.

**Table 1.** The 5-D itch scale scores of all patients before and after treatment

| | Mean (SD) | Median (Min-Max) |
|---|---|---|
| Score Before Treatment | 16.44 (3.65) | 17 (9-24) |
| Score After Treatment | 5.51 (0.73) | 5 (5-8) |

*p<0.001, Friedman test for overall comparison. SD: standard deviation
Note: 5-D itch scale total score ranges from 5 (minimum, no itch) to 25 (maximum, worst itch)

## DISCUSSION

The "itchy ear syndrome", which is defined as itching in the ear for no apparent reason after a thorough physical examination is a common condition6. Vallur et al. reported the prevalence of ear itching as 9.8% in a series of 2143 cases (2). The same study reported that the predominant etiologies were otomycosis 30%, wax deposition 25.2%, otitis externa 30%, and use of a hearing aid 7.6%2.

Although ear itching can be caused by many dermatological or systemic diseases and its treatment

**Table 2.** Comparison of ciclopirox olamine and mometasone treatment by means of 5-D itch scale scores before and after treatment

| | Ciclopirox Olamine | Mometasone | p |
|---|---|---|---|
| Mean Scores of the Patients Before Treatment (SS) | 15.89 (2.94) | 16.97 (4.21) | 0.26* |
| Median of the Scores After Treatment (Interquartile Range ) | 5 (2) | 5 (1) | 0.22** |
| Score Reduction | 10.89 | 11.97 | - |
| Within Group p-value | <0.001*** | <0.001*** | - |

*Independent T Test **Mann-Whitney U Test ***Wilcoxon signed-rank test
Note: 5-D itch scale total score ranges from 5 (minimum, no itch) to 25 (maximum, worst itch)

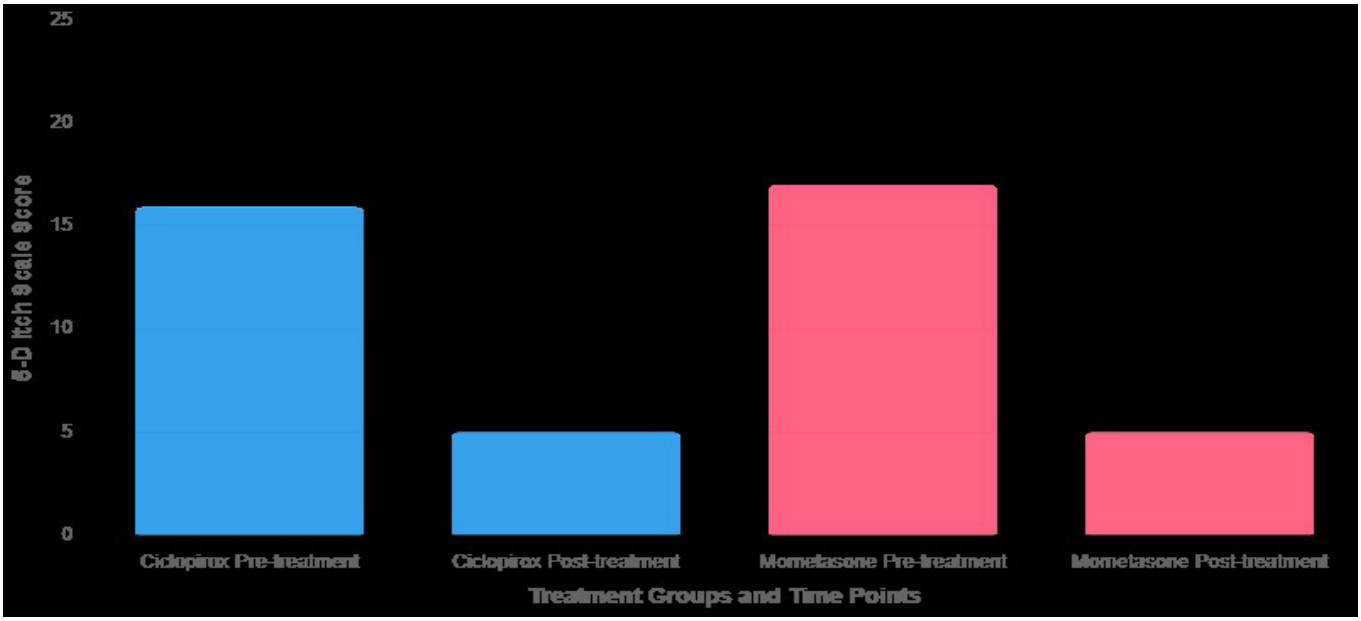


**Figure 1.** Pre- and Post-Treatment Itch Scores by Treatment Group, basic flowchart

depends on the underlying cause, it may be challenging to identify the cause in daily practice. Moreover, prior studies outlined that the underlying cause of isolated ear itching could not be revealed in a substantial proportion of the patients (6). These findings have led to the ideal empirical treatment for symptom relief being a subject of research. Among these, the most frequently recommended treatment is topical corticosteroids, in the absence of strong evidence.

Although there are several studies in the literature on what this ideal empirical treatment might be, as we have noted before, large randomized controlled trials are lacking. Lea SY et al. compared the effects of a topical calcineurin inhibitor and a moisturizing cream. They suggested that chronic low-level inflammation associated with aging (termed "inflaming") may play a role in ear itching (5). They reported a similar result in both groups and concluded that using moisturizers, especially in elderly patients, provides adequate symptomatic relief and protection from the side effects of other pharmacological agents. Babakurban ST et al. stated that Castellani paint is a well-known antiseptic,and is frequently used in otolaryngology to treat external otitis and otomycosis (3). Their study with Castellani paint reported that it can be administered safely, effectively, and easily without affecting normal skin flora in the treatment of itchy ear syndrome (3).

In another study, Svisthuskin VM et al. reported effective symptomatic improvement with a topical empirical treatment containing beclomethasone, gentamycin, and clotrimazole in the treatment of pruritic dermatoses of the external auditory canal (10).

In our study, we found that the topical lotion form of mometasone (a moderately potent corticosteroid) is effective in the symptomatic treatment of itchy ears, in almost all patients. This finding is consistent with other studies in the literature. We also determined that all patients completed the treatment without reporting any side effects.Topical anti-fungals were also found to be safe and were generally well tolerated, without any documented adverse effects. An important point to note is that fungal infections are one of the common causes of ear itching, and may cause itching even when physical examination reveals no apparent findings. Morinaka et al. reported that dermatophyte infections were detected in the normal appearing ears in 8 of 34 patients with ear itching (8,9). This may partially explain the effectiveness of empirical antifungal treatment, and it also suggests that further diagnostic tests are needed to be developed. From a daily practice perspective, there are no specific treatment recommendations for fungal infections in the absence of fungal infection findings on physical examination. Clinical significance of this, in the absence of supporting physical examination findings, remains unclear, and it is possible that this finding may predict response to empirical antifungal treatment. Currently, it is not known whether steroid or antifungal treatment is superior to each other in these occult fungal infections, and these findings indicate that this should be investigated with randomized clinical trials.

Despite the limitations, our investigation offers a contribution to the literature by demonstrating that a new empirical treatment approach may be beneficial for a symptom that commonly seen in daily practice. It also provides new research topics related to better defining populations that may benefit from empirical antifungal therapy.

**Limitations of the Study**

Our study has several limitations inherent to its retrospective design, which is prone to data incompleteness. Another limitation is that since the disease has no measurable physical examination, laboratory or imaging findings, symptomatic evaluation must be made via a questionnaire. Because no baseline itch scores were recorded prospectively, we relied on patient recall using a modified 5-D Itch Scale. We recognize this introduces recall bias and

that the 5-D scale is validated for current itch severity, not past recall. An important methodological consideration is the potential floor effect observed with the 5-D itch scale in our study. With 86% of patients achieving the minimum possible score of 5, the scale may have limited sensitivity to detect mild residual symptoms or subtle differences between treatments in patients with excellent responses. Future studies might benefit from using more sensitive outcome measures or additional scales that can better discriminate between different levels of minimal symptoms. Furthermore, in a small subset of patients, it is not possible to make definitive statements, as our findings need to be confirmed in larger, prospective studies. Finally, although large within-group effect sizes demonstrate substantial clinical improvement, this study had limited statistical power to detect small-to-moderate differences between treatments.

## CONCLUSION

Topical ciclopirox olamine appears to relieve itchy ear symptoms about as effectively as mometasone furoate lotion in our sample, with both treatments leading to significant itch reduction. However, given the study's limitations (small sample, retrospective design), we cannot conclusively establish equivalence; further randomized trials are warranted.

## DECLERATIONS

**Ethics Approval:** This study was approved by Ankara City Hospital No. 2 Clinical Research Ethics Committee (E.Kurul-E2-22-2304).

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**Conflict of Interest Declaration:** The authors declare that they have no conflicts of interest to declare.

**Informed Consent:** Written informed consent to participate was obtained from the patients participated in this study.

**Availability of Data and Material:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**AI:** Artificial intelligence tools were used to assist in language editing and improving the clarity of the manuscript. However, all scientific content, data analysis, and interpretations were carried out by the author, who bear full responsibility for the content and conclusions of this work.

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Original Article

# Investigation of Factors Affecting the Formation of Secondary Non-Traumatic Fractures Due to Mineral Bone Disorder in Hemodialysis Patients: A Single-Center Experience

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## Abstract

**Background:** In our study, we aimed to determine whether demographic data and biochemical parameters of patients undergoing hemodialysis influence the prediction of secondary non-traumatic fractures due to mineral bone disorder caused by chronic kidney disease.

**Methods:** This cross-sectional study was conducted by retrospectively scanning the records of patients aged 18 years and older who had undergone hemodialysis for at least six months at our hospital's hemodialysis unit between 2017 and 2022. A total of 272 patients meeting the inclusion criteria were examined through hospital records.

**Results:** Of the 272 patients included in the study, 57.7% were males, and the median age was 65 years. Non-traumatic fractures were detected in 32 (11.8%) patients. Non-traumatic fractures were significantly more common in female patients compared to males (18.3% vs. 7%; p=0.008). Eight patients had undergone parathyroidectomy, and among them, non-traumatic fractures were significantly more frequent compared to those who had not undergone the procedure (50% vs. 10.6%; p=0.008). Patients using steroids had significantly more non-traumatic fractures compared to non-users (26.9% vs. 10.2%; p=0.021). The duration of dialysis was significantly longer in patients with non-traumatic fractures compared to those without (60.5 months [7 - 324] vs. 39.5 months [7 - 330]; p=0.017). The risk of non-traumatic fractures was found to be 3.66 times higher in women, 4.17 times higher in steroid users, and increased by 0.7% with each additional month of dialysis.

**Conclusion:** This study investigated factors influencing non-traumatic fractures associated with mineral bone disorder in hemodialysis patients. Female gender, steroid use, parathyroidectomy, and dialysis duration were found to increase the risk of fractures. No significant association was found between fractures and other laboratory parameters or medications used by patients to regulate bone mineral metabolism.

**Keywords:** Hemodialysis Units, Hospital, Chronic Kidney Disease-Mineral and Bone Disorders, Non-Traumatic Fracture

## INTRODUCTION

According to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), chronic kidney disease (CKD) is defined as either a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² persisting for at least three months or structural and/or functional abnormalities of the kidney, regardless of GFR decline (1). Renal replacement therapy (RRT) should be considered for patients reaching end-stage kidney disease. RRT options include dialysis and kidney transplantation. Dialysis is further subdivided into two modalities: hemodialysis and peritoneal dialysis, with hemodialysis being the most widely used method worldwide (2).

As GFR declines, abnormalities emerge within the bone-mineral axis. Alterations in plasma calcium, phosphorus, parathyroid hormone (PTH), and vitamin D disrupt

normal bone-mineral homeostasis, adversely affecting bone volume and strength. Consequently, mineral and bone disorders associated with CKD develop (3). PTH influences bone by stimulating osteoblasts and osteoclasts, thereby increasing calcium and phosphorus release from bone. PTH, alongside abnormalities in calcium, phosphorus, fibroblast growth factor-23 (FGF-23), and vitamin D metabolism, contributes to altered bone turnover, impaired mineralization, and extraskeletal calcifications. Kidney Disease Improving Global Outcomes (KDIGO) recommends using the term "chronic kidney disease-mineral and bone disorder (CKD-MBD)" to define this multisystemic condition (4). KDIGO classifies CKD-related bone pathology into four categories: osteitis fibrosa (high-turnover renal osteodystrophy secondary to hyperparathyroidism), osteomalacia (mineralization defect accompanied by low osteoclast and osteoblast activity), adynamic bone disease (low-turnover), and mixed osteodystrophy (mineralization defect with either high or low bone turnover) (5,6).

With progression of renal injury and decreasing GFR, the kidney's ability to excrete phosphorus diminishes, resulting in elevated plasma phosphorus. Increased phosphorus levels stimulate PTH secretion from the parathyroid glands, simultaneously binding calcium and leading to reduced plasma calcium concentrations. Furthermore, declining activity of the renal enzyme 1-alpha hydroxylase, synthesized in proximal tubules, reduces production of calcitriol, the active form of vitamin D, thus decreasing intestinal calcium absorption. Elevated phosphorus levels also enhance FGF-23 secretion, further diminishing calcitriol levels. Reduced plasma calcium concentrations trigger calcium-sensitive receptors (CaSR) within the parathyroid glands, promoting additional PTH secretion. Additionally, ongoing kidney damage weakens the negative feedback provided by vitamin D receptors (VDR) in the parathyroid glands due to decreased calcitriol, further exacerbating PTH secretion. These mechanisms collectively result in secondary hyperparathyroidism (7,8). Bone-mineral abnormalities begin as early as CKD stage 2 and affect nearly all patients by stage 5 (9). Factors contributing to sustained increases in PTH secretion include elevated phosphorus, decreased calcium, reduced calcitriol, elevated FGF-23, reduced vitamin D receptor expression in parathyroid glands, diminished calcium-sensing receptor expression, and decreased fibroblast growth factor receptor and klotho expression (10).

Mineral and bone disorders are closely linked to increased cardiovascular mortality and fracture risk. Bone biopsy remains the gold standard for diagnosing and differentiating mineral-bone disorders. However, due to its invasiveness and potential complications, biopsy is not commonly employed in routine practice. Instead, several laboratory parameters have emerged as practical diagnostic and monitoring tools, including plasma calcium, phosphorus, intact PTH (iPTH), and alkaline phosphatase (bone-specific or total) (11,12).

Radiological assessment is also valuable for diagnosis and differentiation of these disorders. In high-turnover bone disease, subperiosteal resorption and brown tumors may occur, particularly affecting ribs, pelvic bones, and long bones. Osteomalacia may present radiologically with pseudo-fractures. Low-turnover bone diseases may demonstrate osteopenia or appear normal on imaging studies (13).

Bone mineral density (BMD) measurements cannot differentiate between specific bone disorders but are recommended for assessing fracture risk in patients prone to mineral-bone disorders or osteoporosis (14). Extraskeletal calcification can affect vascular structures and soft tissues. Some guidelines advocate abdominal radiography to visualize vascular calcifications, whereas echocardiography assists in detecting cardiac valve calcifications (3).

The aim of this study was to investigate demographic and biochemical parameters that influence the prediction of secondary non-traumatic fractures related to CKD-associated mineral and bone disorders in patients undergoing hemodialysis.

## METHODS

*Study Design*

This study was conducted by retrospectively reviewing hospital records of patients aged 18 years or older who had undergone hemodialysis for at least six months in our dialysis unit between 2017 and 2022. Patients meeting the inclusion criteria—aged at least 18 years and receiving hemodialysis treatment for a minimum of six months—were enrolled. Patients were excluded if they had a history of malignancy, pregnancy, kidney transplantation, peritoneal dialysis, fractures due to high-energy trauma (e.g., traffic accidents, falls from heights), or incomplete clinical data. Fractures were confirmed clinically and documented radiologically.

Demographic data, medications, comorbid diseases, and laboratory parameters of all included patients were recorded. Additionally, hospital records were reviewed to determine whether patients had been hospitalized due to non-traumatic fractures or had undergone parathyroidectomy within the five-year study period.

## STATISTICAL ANALYSIS

Descriptive statistics included mean, standard deviation (SD), median, minimum (min), maximum (max), frequency (n), and percentage (%) values. Normality of quantitative variables was assessed using the Kolmogorov–Smirnov test (if $n > 50$) and the Shapiro–

Wilk test (if n ≤ 50). Comparisons between groups were performed using Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical data were compared using the chi-square test. Binary logistic regression analysis was conducted to identify variables associated with non-traumatic fractures and to calculate estimated relative risks. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 23.0.

## RESULTS

A total of 272 patients were included in the study. Among these, 157 were males and 115 were females. Patient ages ranged from 23 to 97 years, with a median age of 65 years. Non-traumatic fractures were significantly more common in females compared to males (18.3% vs. 7%; p=0.008).

Among the 272 patients, 8 had undergone parathyroidectomy. Non-traumatic fractures were significantly more frequent in patients who had undergone parathyroidectomy compared to those who had not (50% vs. 10.6%; p=0.008). Similarly, non-traumatic fractures were significantly more common among patients using steroids compared to non-users (26.9% vs. 10.2%; p=0.021).

No significant differences were observed between patients with and without non-traumatic fractures in terms of hypertension, diabetes mellitus, coronary artery disease, cerebrovascular events, or medication use, including selective serotonin reuptake inhibitors (SSRIs), angiotensin-converting enzyme inhibitors (ACE-Is)/ angiotensin receptor blockers (ARBs), anticoagulants/ antiplatelets, insulin, oral antidiabetics, active vitamin D, sevelamer, cinacalcet, calcium carbonate, calcium acetate, or lanthanum carbonate. These findings are presented in **Table 1.**

Dialysis duration was significantly longer among patients with non-traumatic fractures compared to those without fractures (60.5 months vs. 39.5 months; p=0.017). However, no significant differences were detected regarding age, BMI, hemoglobin, albumin, corrected calcium, phosphorus, PTH, alkaline phosphatase (ALP), bicarbonate ($HCO_3$), LDL-cholesterol, Kt/V, or dialysate

**Table 1.** Comparison of the frequencies of categorical data according to patients' nontraumatic fracture status

| Variable | | Non-traumatic Fracture | | p value |
|---|---|---|---|---|
| | | Present (n=32) | Absent (n=240) | |
| **Parathyroidectomy** | **Present**<br>**Absent** | 4 (% 50)<br>28 (% 10.6) | 4 (% 50)<br>236 (% 89.4) | 0.008 |
| **Hypertension** | **Present**<br>**Absent** | 31 (% 11.9)<br>1 (% 9.1) | 230 (% 88.1)<br>10 (% 90.9) | 1.000 |
| **Diabetes Mellitus** | **Present**<br>**Absent** | 12 (% 10.4)<br>20 (% 12.7) | 103 (% 89.6)<br>137 (% 87.3) | 0.695 |
| **Coronary artery disease** | **Present**<br>**Absent** | 10 (% 8.8)<br>22 (% 13.8) | 103 (% 91.2 )<br>137 (% 86.2) | 0.286 |
| **Cerebrovascular event** | **Present**<br>**Absent** | 4 (% 6.7)<br>28 (% 13.2) | 56 (% 93.3)<br>184 (% 86.8) | 0.245 |
| **Steroid** | **Present**<br>**Absent** | 7 (% 26.9)<br>25 (% 10.2) | 19 (% 73.1)<br>221 (% 89.8) | 0.021 |
| **SSRI** | **Present**<br>**Absent** | 11 (% 10,4)<br>21 (% 12,7) | 95 (% 89.6)<br>145 (% 87.3) | 0.708 |
| **ACE-İ/ARB** | **Present**<br>**Absent** | 7 (% 17.5)<br>25 (% 10.8) | 33 (% 82.5)<br>207 (% 89.2) | 0.284 |
| **Anticoagulant/ Antiplatellet** | **Present**<br>**Absent** | 15 (% 9.7)<br>17 (% 14.4) | 139 (% 90.3)<br>101 (% 85.6) | 0.320 |
| **Insulin** | **Present**<br>**Absent** | 11 (% 10.7)<br>21 (% 12.4) | 92 (% 89.3)<br>148 (% 87.6) | 0.811 |
| **Oral Antidiabetic** | **Present**<br>**Absent** | 4 (% 13.8)<br>28 (% 11.5) | 25 (% 86.2)<br>215 (% 88.5) | 0.759 |
| **Active vitamin D** | **Present**<br>**Absent** | 26 (% 12.3)<br>6 (% 9.8) | 185 (% 87.7)<br>55 (% 90.2) | 0,760 |
| **Sevelamer** | **Present**<br>**Absent** | 13 (% 15.9)<br>19 (% 10) | 69 (% 84.1)<br>171 (% 90) | 0.242 |
| **Cinacalcet** | **Present**<br>**Absent** | 8 (% 15.7)<br>24 (% 10.9) | 43 (% 84.3)<br>197 (% 89.1) | 0.470 |
| **Calcium Carbonatte** | **Present**<br>**Absent** | 12 (% 12.8)<br>20 (% 11.2) | 82 (% 87.2)<br>158 (% 88.8) | 0.861 |
| **Calcium Acetate** | Present<br>Absent | 16 (% 10.8)<br>16 (% 12.9) | 132 (% 89.2)<br>108 (% 87.1) | 0.730 |
| **Lanthanum Carbonate** | Present<br>Absent | 0 (% 0)<br>32 (% 12.3) | 11 (% 100)<br>229 (% 87.7) | 0.372 |

**Table 1.** Comparison of patients' non-traumatic fracture conditions in terms of quantitative data

| Variable | Non traumatic Fracture | | p value |
|---|---|---|---|
| | Present | Absent | |
| **Age** | 64 (26 - 92) | 65 (23 - 97) | 0.910 |
| **BMI (kg/m²)** | 22.6 (15 – 32.8) | 24.1 (15.6 – 41.4) | 0.225 |
| **Hemoglobin (g/dL)** | 10.77 ± 2.07 | 11.05 ± 1.77 | 0.415 |
| **Albumin (g/dL)** | 3.74 (2.6 – 4.7) | 3.8 (1.4 – 4.9) | 0.592 |
| **Corrected Calcium (mg/dL)** | 8.59 ± 0.8 | 8.53 ± 0.76 | 0.644 |
| **Fosfor (mg/dL)** | 4 (1.1 – 6.3) | 4.3 (0.9 – 9.6) | 0.329 |
| **PTH (pg/mL)** | 309 (27 - 3258) | 304 (1.96 - 2016) | 0.979 |
| **ALP (IU/l)** | 140 (57 - 371) | 114 (36 - 779) | 0.094 |
| **HCO3 (mEq/L)** | 19.55 (14.4 – 25.2) | 20.05 (8.2 – 26.8) | 0.799 |
| **LDL (mg/dL)** | 76.5 (37 - 133) | 76 (20 - 229) | 0.539 |
| **Kt/V** | 1.47 (1.33 – 1.77) | 1.45 (0.99 – 1.75) | 0.261 |
| **Dialysate Calcium (mmol/L)** | 1.5 (1.25 – 1.75) | 1.5 (1.25 – 1.75) | 0.607 |
| **Dialysate Duration (month)** | 60.5 (7 - 324) | 39.5 (7 - 330) | 0.017 |

**BMI**, Body Mass Index; **PTH**, Parathyroid Hormone; **ALP**, Alkaline Phosphatase; **$HCO_3$**, Bicarbonate; **LDL**, Low-Density Lipoprotein; **Kt/V**, Dialysis Adequacy Index.

calcium levels between the two groups. These findings are presented in **Table 2.**

The risk of non-traumatic fractures was found to be 3.66 times higher in female patients, 4.17 times higher in steroid users, and increased by 0.7% with each additional month of dialysis. These findings are presented in **Table 3.**

In the ciclopirox group, itch scores improved from a mean of 15.89 (95% CI: 14.76-17.02) to a median of 5, representing a reduction of 10.89 points (paired Cohen's d = 3.70, p<0.001). In the mometasone group, scores improved from a mean of 16.97 (95% CI: 15.37-18.57) to a median of 5, representing a reduction of 11.97 points (paired Cohen's d = 2.84, p<0.001). For pre-treatment scores, there was no significant difference between the ciclopirox group (mean: 15.89, SD: 2.94) and mometasone group (mean: 16.97, SD: 4.21), with a between-group difference of 1.08 points (Cohen's d = 0.30, p=0.26). Similarly, post-treatment scores showed no significant difference between groups (p=0.22), with both groups achieving similar median scores of 5.

## DISCUSSION

In the advanced stages of chronic kidney disease and among patients undergoing hemodialysis, bone mineral disorders commonly develop. These conditions are closely linked to elevated cardiovascular mortality and an increased fracture risk. To mitigate complications from bone mineral disorders, target laboratory values have been established, and therapeutic approaches are continuously being developed.

Studies investigating fractures in end-stage kidney disease have examined gender influences. Jadoul et al. reported that female hemodialysis patients had a 1.41-fold increased risk for hip fractures and a 1.59-fold increased risk for any non-traumatic fracture compared to males (15). Similarly, Patricia et al. found a 1.81-fold higher risk of non-traumatic fractures among women (16). Stehman-Breen et al. further corroborated these findings, reporting a 2.26-fold greater risk of hip fractures in females (17).

Consistent with prior studies, our study demonstrated significantly higher non-traumatic fracture rates in females compared to males (18.3% vs. 7%; p=0.008). Our adjusted analysis indicated that female gender and steroid use were associated with increased fracture likelihood, although the magnitude of the odds ratios may be inflated due to the limited number of fracture

**Table 3.** Risk factors for non-traumatic fractures and estimated relative risk ratios

| | | OR | % 95 CI | p value |
|---|---|---|---|---|
| **Risk Factors for Non-Traumatic Fracture** | **Age** | 1.012 | 0.985 – 1.040 | 0.396 |
| | **Female Gender** | 3.660 | 1.589 – 8.430 | 0.002 |
| | **BMI** | 0.926 | 0.837 – 1.024 | 0.135 |
| | **Dialysis Duration** | 1.007 | 1.001 – 1.013 | 0.025 |
| | **Steroid Use** | 4.170 | 1.476 – 11.782 | 0.007 |

events. Specifically, the adjusted odds ratio for fracture occurrence in female patients was 3.66 (95% CI: 1.59–8.43).

Previous literature has also examined the relationship between parathyroidectomy and fracture risk in patients with end-stage renal disease. Jadoul et al. identified a significant association between parathyroidectomy and previous hip fractures (15). Elevated PTH levels lead to bone marrow fibrosis, increased osteoblast-osteoclast activity, and osteitis fibrosa cystica (18). Parathyroidectomy, by improving these conditions, can potentially enhance bone quality and reduce the risk of long-term fractures.

In a study by Rudser et al., the risk of hip fractures in hemodialysis patients without prior fractures was 0.68 times lower in those who underwent parathyroidectomy compared to those who did not (19). Similarly, a Sweden-based study by Isaksson et al. found a significant reduction in hip fracture risk among female hemodialysis patients who underwent parathyroidectomy (20). However, in a study by Ishani et al., which examined 4.435 hemodialysis patients, no significant reduction was found in the fracture rate one year before vs. one year after parathyroidectomy (21).

Contrary to some previous findings, our study identified significantly higher non-traumatic fracture rates among patients who underwent parathyroidectomy compared to those who did not. This discrepancy may arise from our smaller sample size and lack of adjustment for fracture timing relative to surgery. Therefore, this association should be interpreted cautiously.

Steroid usage increases fracture risk, even at low doses (prednisolone equivalent 2.5–7.5 mg daily) (22). However, studies evaluating steroid use and fracture risk in hemodialysis patients remain limited. Jadoul et al. reported a 1.4-fold increase in fracture risk among steroid users (15). Our study similarly identified significantly higher fracture rates in steroid users (26.9% vs. 10.2%), with a notably elevated fracture risk (odds ratio: 4.17).

Several studies have linked fracture risk to dialysis duration. Wakasugi et al. observed increased hip fracture risk starting one year post-hemodialysis initiation (23). Alem et al. and Jadoul et al. similarly reported increased fracture risks correlated with longer dialysis duration (15,24). Matias et al. found a significant relationship between dialysis duration and fracture prevalence (median duration 93 months) (16). Our study reinforced these findings, noting significantly longer dialysis durations among patients with fractures (60.5 vs. 39.5 months) and a 0.7% incremental fracture risk per additional dialysis month.

Literature on PTH levels and fracture risk has yielded inconsistent results. Jadoul et al. identified elevated PTH (>900 pg/mL) as an independent fracture risk factor, while Stehman-Breen et al. found no significant association (17). Our study also found no significant difference in median PTH levels between fracture and non-fracture patients (309 vs. 304 pg/mL).

Studies in the literature have reported varying results regarding cinacalcet use and fracture risk. In a study by Geoffrey et al., cinacalcet was shown to lower parathyroid hormone levels more effectively than placebo in hemodialysis patients (26). In the EVOLVE study by Moe et al., which examined the effects of cinacalcet on fractures in hemodialysis patients, cinacalcet was compared to placebo. When factors such as female gender, previous fractures, and advanced age—which increase fracture risk—were excluded, cinacalcet reduced fracture rates by 16-29%. However, when these factors were included in the analysis, no significant relationship between cinacalcet and reduced fracture risk was found (27). Similarly, in our study, no significant relationship was found between cinacalcet use and fractures (p=0.470), consistent with some prior studies. Our findings were calculated without excluding fracture risk factors; thus, a larger sample size and adjusted calculations may yield different results.

Important biochemical parameters indicating renal osteodystrophy include calcium, phosphorus, albumin, and alkaline phosphatase. In our study, we also examined the relationship between these values and fractures. A multicenter study conducted by Jadoul et al., involving 12 countries, found that calcium and phosphorus levels were not significant in predicting newly occurring fractures. However, patients with phosphorus levels above 5.5 mg/dL and calcium levels above 10.2 mg/dL had a higher likelihood of previous fractures (15). Consistent with these findings, our study did not detect a relationship between non-traumatic fractures and calcium or phosphorus levels.

Sevelamer, calcium acetate, calcium carbonate, and lanthanum are phosphate-binding agents. Our study examined the relationship between these medications and fractures. Studies investigating this relationship are limited. Ferreira et al. compared calcium-based phosphate binders with sevelamer and found no significant difference between the two groups in bone turnover and mineralization after one year. Sevelamer was shown to increase bone formation, but the study did not specify whether this was associated with a lower fracture risk (28).

Another study by Ruospo et al. found that sevelamer reduced mortality compared to calcium-based binders, but reported no significant relationship between sevelamer and fracture risk (29). Similarly, our study found no significant association between fractures and the use of sevelamer, calcium acetate, calcium carbonate,

or lanthanum.predict response to empirical antifungal treatment. Currently, it is not known whether steroid or antifungal treatment is superior to each other in these occult fungal infections, and these findings indicate that this should be investigated with randomized clinical trials.

Our investigation offers a contribution to the literature by demonstrating that a new empirical treatment approach may be beneficial for a symptom that commonly seen in daily practice. It also provides new research topics related to better defining populations that may benefit from empirical antifungal therapy.

### Limitations of the Study

The retrospective and observational design limits the ability to establish causal relationships. Second, the relatively small sample size, particularly the limited number of fracture events, may have inflated the magnitude of the reported odds ratios and reduced statistical power. Additionally, we did not adjust for the timing of fractures relative to procedures like parathyroidectomy, potentially introducing temporal bias. The lack of data on bone mineral density, nutritional status, physical activity, and lifestyle factors, which may influence fracture risk could have resulted in residual confounding. Lastly, our findings are from a single-center study, limiting the generalizability to broader hemodialysis populations. Future studies with larger samples, prospective designs, and comprehensive covariate adjustments are required to validate our findings.

## CONCLUSION

This study demonstrated that female gender, steroid use, history of parathyroidectomy, and longer dialysis duration were significantly associated with an increased risk of non-traumatic fractures in hemodialysis patients. Conversely, no significant relationships were identified between fracture risk and biochemical parameters (such as calcium, phosphorus, and PTH levels) or medications used for managing bone-mineral disorders. Given the study's limitations, larger prospective studies are necessary to validate these findings and guide clinical practices aimed at reducing fracture risks among patients undergoing hemodialysis.

## DECLARATIONS

**Ethics Approval:** This study was approved by Giresun University Clinical Research Ethics Committee (IRB no:12-13.02.2025). The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and its subsequent amendments, ensuring full adherence to ethical guidelines for research involving human participants.

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**Conflict of Interest Declaration:** The authors declare that they have no conflicts of interest to declare.

**Informed Consent:**

**Availability of Data and Material:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Original Article

# Renal and Hemodynamic Effects of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease Receiving Varying Doses of Renin-Angiotensin System Blockade

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## Abstract

**Background:** Chronic kidney disease (CKD) in the context of type 2 diabetes mellitus (T2DM) remains a significant global health challenge. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have emerged as a renoprotective therapy, often co-administered with renin–angiotensin system inhibitors (RASi). However, the clinical impact of background RASi intensity on SGLT2i-associated renal and hemodynamic outcomes remains unclear.

**Methods:** This retrospective study included 67 patients with T2DM and CKD initiated on SGLT2i therapy and followed for 12 months. Patients were stratified into three groups based on background RASi use: no RASi, moderate-dose RASi, and full-dose RASi. Clinical, biochemical, and hemodynamic parameters—including blood pressure, eGFR, proteinuria, and glycemic/metabolic markers—were evaluated at baseline, 3 months, and 12 months. Adverse events including acute kidney injury (AKI) and urinary tract infections (UTIs) were recorded.

**Results:** All groups exhibited significant reductions in systolic blood pressure (SBP), with the greatest decline observed in the full-dose RASi group (–13 mmHg at 12 months). A transient significant dip in eGFR was noted at month 3 in the full-dose group, with partial recovery by month 12. Proteinuria decreased significantly in both the moderate-dose and full-dose RASi groups, with the greatest absolute reduction in the moderate-dose group. Glycemic control improved across all groups, with the non-RASi group showing the most pronounced decline in fasting glucose and HbA1c. No significant differences in AKI or UTI incidence were observed among groups.

**Conclusion:** SGLT2i therapy is safe and effective across all RASi backgrounds. However, co-administration with RASi—particularly at full doses—appears to enhance antihypertensive, renal function, and antiproteinuric outcomes. These findings underscore the potential synergistic role of full-dose RAS blockade in optimizing the renoprotective benefits of SGLT2i in diabetic CKD.

**Keywords:** Sodium-Glucose Transporter 2 Inhibitors, Renin-Angiotensin System, Diabetic Nephropathies, Glomerular Filtration Rate, Proteinuria

## INTRODUCTION

Chronic kidney disease (CKD) is a major global health concern, affecting approximately 850 million individuals worldwide. The increasing prevalence of aging, obesity, and diabetes mellitus are key drivers of this growing burden (1,2). In response to this challenge, landmark studies published over the past five years have reignited hope for the nephrology community, which has awaited more effective treatment options since the introduction of renin–angiotensin system inhibitors (RASi) nearly two decades ago. Based on accumulating evidence of their renoprotective effects, sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and nonsteroidal mineralocorticoid receptor antagonists (MRAs) have emerged as promising therapeutic options for patients with CKD (3).

The renin–angiotensin system (RAS) regulates fundamental physiological processes, including

fluid balance, blood pressure, vascular responses to inflammation, and tissue repair (4). Inappropriate RAS activation leads to elevated angiotensin II levels, resulting in direct vascular, renal, and cardiac damage. Consequently, RAS inhibition remains a cornerstone in the treatment of systemic hypertension, heart failure, and kidney disease (5). Among commonly used RAS blockers, angiotensin-converting enzyme inhibitors (ACEis) reduce the conversion of angiotensin I to angiotensin II, whereas angiotensin receptor blockers (ARBs) prevent angiotensin II from binding to the angiotensin type 1 receptor (6).

SGLT2i act by blocking glucose reabsorption in the proximal tubule, where approximately 90% of filtered glucose is reabsorbed. This mechanism promotes urinary glucose excretion and simultaneously increases sodium excretion, thereby activating tubuloglomerular feedback. The resulting reduction in intraglomerular pressure helps mitigate hyperfiltration. In addition, SGLT2i have been shown to improve tubular oxygenation and reduce renal fibrosis, offering further renoprotective benefits (7). Unlike RASi, which induce efferent arteriolar vasodilation, SGLT2i exert afferent vasoconstriction via tubuloglomerular feedback, producing a distinct hemodynamic effect. This occurs despite elevated plasma aldosterone and angiotensin II levels. A study evaluating the impact of SGLT2i on intrarenal RAS activity observed modest increases in systemic and urinary RAS components, likely reflecting volume contraction secondary to osmotic diuresis (8,9).

SGLT2 inhibitors and RAS blockers operate at different sites within the kidney, and their combination has been hypothesized to produce synergistic effects (10,11). In patients with type 1 diabetes, empagliflozin was found to increase circulating angiotensin I levels more than angiotensin II, suggesting a shift in RAS balance. Despite RAS upregulation, afferent arteriolar constriction due to tubuloglomerular feedback emerged as the dominant hemodynamic effect, contributing to reduced glomerular hypertension. The "alternative" RAS axis, characterized by angiotensin-(1–7), is considered a beneficial counter-regulatory pathway to the "classical" RAS. Evidence suggests that combining an ACEi with an SGLT2i may activate this alternative axis (4). Thus, the natriuretic effects of SGLT2i and the vasodilatory actions of RASi may complement each other, potentially reducing systemic oxidative stress and inflammation and thereby lowering the incidence of cardiovascular and renal events (12). Indeed, various clinical trials have demonstrated that the combination of SGLT2i with ACEi/ARBs results in superior cardiorenal protection, with improvements in glycemic parameters, blood pressure, and body weight, while maintaining a favorable safety profile (10,11,13). Supporting this, some studies have shown that the addition of SGLT2i to RASi therapy yields better renal and cardiovascular outcomes compared to the addition of MRAs (14).

Although several pivotal trials comparing SGLT2 inhibitors to placebo have reported outcomes in patient subgroups with and without background RAS inhibition, the findings remain inconclusive. To address this gap, researchers recently conducted a meta-analysis incorporating subgroup data from major trials. The results demonstrated that SGLT2i therapy provides comparable clinical efficacy and safety in patients with or without RAS inhibition. However, they also noted that the combination of SGLT2i and RASi may lead to greater improvements in select renal parameters, including reductions in blood pressure and body weight, compared to SGLT2i monotherapy. Further investigation is warranted to confirm and expand upon these observations (15,16).

This study aims to investigate the potential synergistic effects of SGLT2i and varying doses of RASi on kidney outcomes in patients with DM and CKD.

## METHODS

*Study Design*

The study included patients with DM and CKD who were followed up in the nephrology outpatient clinic between 2022 and 2024 and who were started on SGLT2i for the purpose of treating DM and providing cardiorenal protection. Patients treated with SGLT2 inhibitors were stratified into three groups based on their RASi usage (none, low–moderate dose, and full dose), and evaluated over a one-year follow-up period using biochemical and demographic data. By analyzing these subgroups, the study seeks to contribute to the ongoing debate regarding the clinical benefits and optimization of combination therapy involving SGLT2i and RASi. The clinical and biochemical findings of the patients were subjected to retrospective analysis, resulting in the preparation of a data set. The clinical findings, comorbidities, medications, and current blood and urine tests (urea, creatinine, C-reactive protein (CRP), albumin, hemogram, lipid levels, HbA1c, CRP, proteinuria and albuminuria) were recorded, as were the demographic characteristics of the patients. The laboratuary values of all patients at the 3th and 12th month after the commencement of treatment were analysed and recorded. Furthermore, all hospital admissions within one year from the start of treatment were analysed retrospectively.

The exclusion criteria comprised the following: receiving kidney replacement therapy, eGFR < 25 ml/min/1.73m$^2$, previous use of SGLT2i treatment, diagnosis of type 1 DM, presence of active urinary tract infection, dehydration, hypovolemia, sepsis, or urinary catheterisation, complication-free interruption of SGLT-2i treatment after initiation, insufficient data available

*RASi intensity definition*

Patients were stratified into groups based on the intensity of renin–angiotensin system inhibitor (RASi) therapy. Those in the low-moderate dose group were receiving less than the maximum recommended daily dose of an ACE inhibitor or ARB, whereas the full dose group was treated with target or maximum approved doses commonly used in clinical trials for kidney and cardiovascular protection.

For reference, the following dose ranges were used to define low-moderate versus RASi intensity:

ACE Inhibitors:
- Enalapril: 2.5–10 mg/day (low-moderate), 20 mg/day (full)
- Ramipril: 1.25–5 mg/day (low-moderate), 10 mg/day (full)
- Lisinopril: 5–10 mg/day (low-moderate), 20 mg/day (full)
- Perindopril: 2.5–5 mg/day (low-moderate), 10 mg/day (full)
- Trandolapril: 1–2 mg/day (low-moderate), 4 mg/day (full)

Angiotensin Receptor Blockers:
- Losartan: 25–50 mg/day (moderate), 100 mg/day (full)
- Valsartan: 40–160 mg/day (moderate), 320 mg/day (full)
- Irbesartan: 75–150 mg/day (moderate), 300 mg/day (full)
- Telmisartan: 20–40 mg/day (moderate), 80 mg/day (full)
- Olmesartan: 10–20 mg/day (moderate), 40 mg/day (full)
- Candesartan: 4–8 mg/day (moderate), 16–32 mg/day (full)

This classification was based on therapeutic ranges commonly accepted in nephrology and cardiology guidelines (e.g., KDIGO, ESC, ADA), and reflects real-world prescribing patterns in patients with diabetic kidney disease.

*Complication Definition*

Acute kidney injury (AKI) was characterized by an elevation in serum creatinine of at least 0.5 mg/dL. Due to the retrospective design and fixed laboratory assessment intervals (baseline, 3rd, and 12th months), AKI was defined as ≥0.5 mg/dL increase in serum creatinine, in line with previous studies, to ensure consistency and optimize the balance between sensitivity and specificity for detecting clinically relevant renal events (17,18). Acute cystitis and uncomplicated urinary tract infection (UTI) were identified based on the presence of cystitis symptoms, along with a urinalysis showing ≥10 white blood cells per microliter and positive leukocyte esterase and nitrite results on the dipstick test.

## STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics included the presentation of continuous variables as mean ± standard deviation, regardless of distribution, and categorical variables as frequency and percentage. For comparisons between groups, the Independent Samples T-test was used for normally distributed numerical data, whereas the Mann-Whitney U test was employed for non-normally distributed data. The chi-square test was utilized to analyse categorical variables. Blood pressure and laboratory findings were evaluated at three time points: baseline, 3 months, and 12 months. For parameters showing normal distribution across these repeated measures, repeated measures ANOVA (Greenhouse-Geisser correction) was applied. For parameters not normally distributed, the Friedman test was used for comparisons involving three time points, and the Wilcoxon test for pairwise comparisons. Bonferroni correction was applied for multiple comparisons. Additionally, patients were stratified into two groups based on the presence or absence of SGLT2i-related side effects, and group differences were assessed. A p-value below 0.05 was considered to indicate statistical significance.

## RESULTS

A A total of 67 patients were included in the study. The mean age of the participants was 64.5 ± 8.6 years, and 53% (36) of them were female.

The patients were categorized into three groups based on RAS blockade intensity: no RASi (n=18), moderate-dose RASi (n=27), and full-dose RASi (n=22). The mean age was slightly higher in the non-RASi group (67.8 ± 8.7 years) compared to the moderate (64.1 ± 7.6) and full-dose groups (62.2 ± 9.2). Female representation ranged from 44.4% to 59.1%. 31 of the 49 patients (64%) receiving antihypertensive treatment were using thiazide or thiazide-like diuretics.

There were no significant differences between the groups in terms of comorbidities, duration of diabetes, prevalence of end-organ damage, or the use of glucose-lowering agents other than metformin.

All groups experienced a reduction in systolic blood pressure over time. At 12 months, the decline was statistically significant in all groups ($p<0.05$), with the most pronounced decrease observed in the full-dose RASi group (from 130 ± 17 to 117 ± 10 mmHg). Diastolic blood pressure also decreased slightly in all groups, reaching significance only in the full-dose RASi group (from 76 ± 10 to 71 ± 9 mmHg, $p<0.05$) (**Table 1a and 1b**). These trends are numerically supported in **Table 2**, where the 0–12-month mean change in systolic pressure reached –13 mmHg in the full-dose group.

A significant transient decrease in eGFR was noted in

**Table 1a.** Table 1. Demographic, Clinical, and Laboratory Characteristics and Their Changes Over 12 Months According to RAS Inhibitor Dosage Groups in Patients Receiving SGLT2 Inhibitor Therapy initiation.

| Parameters | Non-RASi (n=18) | Low-Moderate Dose RASi (n=27) | Full Dose RASi (n=22) |
|---|---|---|---|
| Gender, Female n (%) | 8 (44.4) | 15 (55.6) | 13 (59.1) |
| Age (years) | 67.8 ± 8.7 | 64.1 ± 7.6 | 62.2 ± 9.2 |
| Duration of diabetes (years) | 15.1 ± 10.5 | 13.3 ± 9.7 | 13 ± 8.4 |
| Duration of hypertension (years) | 15.8 ± 11.1 | 13.5 ± 9.7 | 13 ± 9.2 |
| Proteinuria n (%) | 12 (66.7) | 19 (70.4) | 15 (68.2) |
| Coronary artery disease n (%) | 8 (44.4) | 12 (44.4) | 8 (36.4) |
| Diabetic Retinopathy/Neuropathy n (%) | 6 (33.3) | 10 (37) | 7 (31) |
| Metformin n (%) | 5 (27) | 17 (63) | 13 (59) |
| Sulfonylurea n (%) | 4 (22.2) | 4 (14.8) | 4 (18.2) |
| DPP-4 inhibitor n (%) | 4 (22.2) | 10 (37) | 8 (36.4) |
| Insulin n (%) | 8 (44.4) | 11 (40.7) | 10 (45.5) |
| SGLT2i (dapagliflozin/empagliflozin %) | 44/56 | 37/63 | 59/31 |
| SGLT2i associated Adverse Effect n (%) | 2 (11.1) | 6 (22.2) | 2 (9.1) |

**RASi**, renin–angiotensin system inhibitor; **DPP-4** inhibitor, dipeptidyl peptidase-4 inhibitor; **SGLT2i**, sodium-glucose cotransporter-2 inhibitor

the full-dose RASi group at month 3 (from 58.0 ± 12.6 to 53.8 ± 14.4 mL/min/1.73 m², p=0.009), but this value recovered to 56.5 ± 15.8 by 12 months. This is also reflected in Table 2, where the GFR decline from baseline to month 3 was greatest in the full-dose RASi group (–8.4 vs –6.1 and –3). Serum creatinine increased slightly across all groups, reaching statistical significance only in the full-dose RASi group at month 3 (p=0.003).

**Figure 1** illustrates the trajectory of eGFR across the three groups. Despite an early drop at month 3, renal function remained largely preserved at month 12, particularly in the full-dose RASi group.

Proteinuria significantly decreased at 12 months in both the moderate-dose (from 1034 ± 608 to 608 ± 630 mg/day, p=0.002) and full-dose RASi (1278 ± 1114 to 916 ± 1058 mg/day, p=0.024) groups, with the greatest absolute reduction observed in the moderate-dose RASi group (–426 mg/day). The non-RASi group exhibited a smaller, non-significant reduction (–159 mg/day).

Fasting glucose levels declined significantly across all groups at both 3 and 12 months (p<0.05 for each), with the most notable early reduction in the non-RASi group (209 → 127 mg/dL at month 3). HbA1c also improved significantly in all groups over 12 months, with the greatest reduction observed in the non-RASi group (from 8.9 ± 1.7% to 7.2 ± 1.1%, p<0.05).

There were no statistically significant changes or differences between groups in serum sodium, potassium, calcium, magnesium, phosphorus, albumin, or hemoglobin over the 12-month period. Similarly, CRP values remained stable across all groups. Lipid profiles (total cholesterol, LDL, HDL) showed minor fluctuations but no statistically significant trends. Ferritin and uric acid levels did not demonstrate meaningful variation.

Regarding SGLT2 inhibitor–associated adverse events (including acute kidney injury in 4 patients and urinary tract infections in 6 patients), no statistically significant differences were observed among the groups. In the patients who developed urinary tract infections (UTIs) or acute kidney injury (AKI), the treatment was temporarily interrupted and then reinitiated after resolution of the complication. However, in none of the cases was permanent discontinuation of the medication required.

## DISCUSSION

This study investigated the clinical outcomes of initiating SGLT-2i in patients with diabetes and CKD, stratified by background RAS blockade intensity: no RASi, moderate-dose RASi, and full-dose RASi. Our findings reveal meaningful differences in hemodynamic, renal, and metabolic responses depending on the degree of background RAS blockade at the time of SGLT-2i initiation.

Reductions in systolic blood pressure (SBP) were observed across all groups, aligning with the well-established antihypertensive properties of SGLT-2i (18). Notably, the most significant SBP decline occurred in the group receiving full-dose RAS blockade, suggesting a synergistic interaction between maximal RAS inhibition and SGLT-2i-induced natriuresis. This finding supports previous data from the DAPA-CKD and EMPA-KIDNEY trials, which demonstrated superior hemodynamic control with combination therapy (19,20).

Renal function, as assessed by estimated glomerular filtration rate (eGFR), exhibited a transient significant dip at 3 months in the full-dose RASi group—an expected early hemodynamic response associated with both SGLT-2i and RASi therapies (21). Importantly, eGFR partially recovered by month 12, highlighting the reversibility and likely benign nature of this

**Table 1b.** Table 1. Demographic, Clinical, and Laboratory Characteristics and Their Changes Over 12 Months According to RAS Inhibitor Dosage Groups in Patients Receiving SGLT2 Inhibitor Therapy initiation.

| Parameters | Time | Non-RASi (n=18) | Low-Moderate Dose RASi (n=27) | Full Dose RASi (n=22) |
|---|---|---|---|---|
| Systolic Blood Pressure (mmHg) | 0 month | 130 ± 20 | 133 ± 17 | 130 ± 17 |
| | 3 months | 129 ± 19 | 124 ± 13* | 119 ± 10* |
| | 12 months | 124 ± 17*,+ | 122 ± 12* | 117 ± 10* |
| Diastolic Blood Pressure (mmHg) | 0 month | 74 ± 9 | 76 ± 8 | 76 ± 10 |
| | 3 months | 72 ± 10 | 72 ± 9 | 74 ± 7 |
| | 12 months | 71 ± 12 | 72 ± 10 | 71 ± 9* |
| Glucose (mg/dL) | 0 month | 209 ± 131 | 162 ± 69 | 156 ± 64 |
| | 3 months | 127 ± 34* | 148 ± 54* | 134 ± 59* |
| | 12 months | 151 ± 59* | 152 ± 61* | 127 ± 42* |
| Creatinine (mg/dL) | 0 month | 1.41 ± 0.4 | 1.28 ± 0.2 | 1.25 ± 0.3 |
| | 3 months | 1.49 ± 0.4 | 1.37 ± 0.3 | 1.35 ± 0.4*(p:0.003) |
| | 12 months | 1.46 ± 0.4 | 1.33 ± 0.3 | 1.31 ± 0.4 |
| Urea (mg/dL) | 0 month | 56.7 ± 24.3 | 47 ± 11.4 | 47.1 ± 13.6 |
| | 3 months | 64.3 ± 24.2 | 53.1 ± 22.1 | 56.5 ± 26.6 |
| | 12 months | 62.8 ± 23.3 | 51.8 ± 20.8 | 49.7 ± 15.8 |
| eGFR (mL/min/1.73 m²) | 0 month | 52.2 ± 14.9 | 56.7 ± 14.9 | 58 ± 12.6 |
| | 3 months | 49.2 ± 14.6 | 52.9 ± 15.7 | 53.8 ± 14.4*(p:0.009) |
| | 12 months | 49.3 ± 13.3 | 54.1 ± 14.3 | 56.5 ± 15.8 |
| Sodium (mEq/L) | 0 month | 139.7 ± 3 | 139 ± 3.2 | 139.9 ± 2.1 |
| | 3 months | 140.5 ± 2.2 | 140.4 ± 2 | 139.4 ± 4.5 |
| | 12 months | 139.3 ± 2.9 | 139.8 ± 2.5 | 140.2 ± 2.3 |
| Potassium (mEq/L) | 0 month | 4.8 ± 0.4 | 4.6 ± 0.4 | 4.8 ± 0.3 |
| | 3 months | 4.8 ± 0.5 | 4.72 ± 0.5 | 4.9 ± 0.5 |
| | 12 months | 4.9 ± 0.3 | 4.7 ± 0.4 | 4.7 ± 0.5 |
| Calcium (mg/dL) | 0 month | 9.6 ± 0.3 | 9.7 ± 0.3 | 9.7 ± 0.4 |
| | 3 months | 9.8 ± 0.5 | 9.6 ± 0.4 | 9.7 ± 0.5 |
| | 12 months | 9.7 ± 0.5 | 9.3 ± 1.4 | 9.7 ± 0.5 |
| Magnesium (mg/dL) | 0 month | 2 ± 0.2 | 2 ± 0.2 | 1.8 ± 0.3 |
| | 3 months | 2.1 ± 0.2 | 2 ± 0.19 | 2.1 ± 0.4 |
| | 12 months | 2.1 ± 0.2 | 2.1 ± 0.3 | 2 ± 0.3 |
| Phosphorus (mg/dL) | 0 month | 3.5 ± 0.4 | 3.7 ± 0.5 | 3.7 ± 0.6 |
| | 3 months | 3.8 ± 0.6 | 3.7 ± 0.5 | 3.8 ± 0.6 |
| | 12 months | 4 ± 0.6 | 3.7 ± 0.5 | 3.9 ± 0.4 |
| Serum Albumin (g/dL) | 0 month | 4.5 ± 0.3 | 4.4 ± 0.2 | 4.3 ± 0.4 |
| | 3 months | 4.5 ± 0.2 | 4.3 ± 0.3 | 4.6 ± 0.4 |
| | 12 months | 4.4 ± 0.3 | 4.2 ± 0.2 | 4.4 ± 0.4 |
| Hemoglobin (g/dL) | 0 month | 13 ± 2.3 | 13 ± 1.7 | 13 ± 1.8 |
| | 3 months | 13.1 ± 1.9 | 13.7 ± 3 | 13 ± 1.5 |
| | 12 months | 13.3 ± 2.3 | 12.9 ± 2.1 | 13 ± 1.3 |
| Total Cholesterol (mg/dL) | 0 month | 188 ± 39 | 183 ± 45 | 193 ± 45 |
| | 3 months | 174 ± 35 | 176 ± 46 | 195 ± 46 |
| | 12 months | 177 ± 31 | 178 ± 51 | 175 ± 27 |
| LDL (mg/dL) | 0 month | 104 ± 35 | 106 ± 41 | 110 ± 38 |
| | 3 months | 95 ± 26 | 92 ± 34 | 116 ± 39 |
| | 12 months | 100 ± 26 | 103 ± 42 | 96 ± 24 |
| HDL (mg/dL) | 0 month | 46 ± 12 | 44 ± 10 | 45 ± 15 |
| | 3 months | 49 ± 12 | 43 ± 11 | 46 ± 14 |
| | 12 months | 47 ± 13 | 43 ± 12 | 43 ± 14 |
| Ferritin (mg/dL) | 0 month | 94 ± 103 | 74 ± 64 | 48 ± 37 |
| | 12 months | 116 ± 109 | 81 ± 68 | 44 ± 33 |
| Uric Acid (mg/dL) | 0 month | 6 ± 1.8 | 6.2 ± 1.8 | 6 ± 1.1 |
| | 12 months | 5.9 ± 1.9 | 6.1 ± 1.5 | 5.8 ± 1.1 |
| Proteinuria (g/day) | 0 month | 966 ± 1061 | 1034 ± 608 | 1278 ± 1114 |
| | 12 months | 771 ± 842 | 608 ± 630 (p=0.002) | 916 ± 1058 (p=0.024) |
| HbA1c (%) | 0 month | 8.9 ± 1.7 | 8.1 ± 1.6 | 8.1 ± 1.5 |
| | 12 months | 7.2 ± 1.1* | 7.3 ± 1.1* | 7.3 ± 1.3* |
| CRP (mg/L) | 0 month | 4 ± 4.3 | 4.5 ± 3.7 | 5.6 ± 4.2 |
| | 12 months | 5.1 ± 4.6 | 5.1 ± 4.9 | 4.2 ± 3.2 |

**RASi**, renin–angiotensin system inhibitor; **eGFR**, estimated glomerular filtration rate; **LDL**, low-density lipoprotein; **HDL**, high-density lipoprotein; **CRP**, C-reactive protein; **HbA1c**, glycated hemoglobin

initial decline, especially in patients with preserved autoregulation. These results reinforce current clinical guidance that early eGFR reductions following SGLT-2i initiation should not prompt treatment discontinuation unless other clinical concerns are present (22). Notably, the percentage reduction in eGFR from baseline to month 12 was smallest in the full-dose RASi group. As shown in Figure 1, this group demonstrated a more favorable

**Table 2.** Changes and percentage reduction in key clinical parameters over time according to RAS inhibitor dosage in patients initiating SGLT2 inhibitor therapy

| | Non-RASi (n:18) | Low-Moderate Dose RASi (n:27) | Full Dose RASi (n:22) |
|---|---|---|---|
| **Systolic Blood Pressure (mmHg)** | | | |
| **Δ(0-3 month)** | -1 | -9 | -11 |
| **Δ(0-12 month)** | -6 | -11 | -13 |
| **Diastolic Blood Pressure (mmHg)** | | | |
| **Δ(0-3 month)** | -2 | -4 | -2 |
| **Δ(0-12 month)** | -3 | -4 | -5 |
| **Creatinine (mg/dl)** | | | |
| **Δ(0-3 month)** | 0.08 | 0.09 | 0.1 |
| **Δ(0-12 month)** | 0.05 | 0.05 | 0.06 |
| **Urea (mg/dl)** | | | |
| **Δ(0-3 month)** | 7.6 | 6.1 | 9.4 |
| **Δ(0-12 month)** | 6.1 | 4.8 | 2.6 |
| **eGFR (CKD-EPI 2021)** | | | |
| **Δ(0-3 month)** | -3 | -6.1 | -8.4 |
| **Δ(0-12 month)** | -2.9 | -4.8 | -2.6 |
| **Potassium (mEq /L)** | | | |
| **Δ(0-3 month)** | 0 | 0.12 | 0.1 |
| **Δ(0-12 month)** | 0.1 | 0.1 | -0.1 |
| **Proteinuria (gr/day)** | | | |
| **Δ(0-12 month)** | -159 | -426 | -362 |

Δ indicates absolute change from baseline (0 month) to 3rd and 12th months. eGFR: Estimated glomerular filtration rate, RASi : Renin angiotensinogen inhibitors.

eGFR trajectory by the end of follow-up, suggesting that long-term kidney outcomes may benefit most from combined full-dose RAS blockade and SGLT-2i therapy.

Proteinuria decreased significantly in both the moderate and full-dose RASi groups, highlighting the additive antiproteinuric effect of SGLT-2i when layered onto existing RAS blockade. This is consistent with the known complementary mechanisms: SGLT-2i reduce intraglomerular pressure via afferent arteriole vasoconstriction, while RASi act via efferent arteriole dilation (23). The largest absolute reduction in proteinuria occurred in the moderate-dose RASi group, potentially reflecting a plateauing effect at maximal RAS inhibition or better tolerability at intermediate dosing.

Glycemic control improved across all groups, with the most pronounced reduction in HbA1c and fasting glucose levels observed in the group not receiving RAS blockade. While SGLT-2 inhibitors primarily exert their glycemic effect through glucosuria, RAS blockers have also been associated with positive or neutral effects on glucose metabolism, improving insulin sensitivity and offering protection against diabetes development (24). The unexpectedly greater glycemic response in the non-RASi group may reflect unmeasured factors such as differences in insulin regimens, dietary adherence, or baseline glycemic burden.

Finally, SGLT-2i therapy was well tolerated across all groups, with no significant differences in adverse event rates, including acute kidney injury or urinary tract infections, further supporting its safety in real-world settings (25).

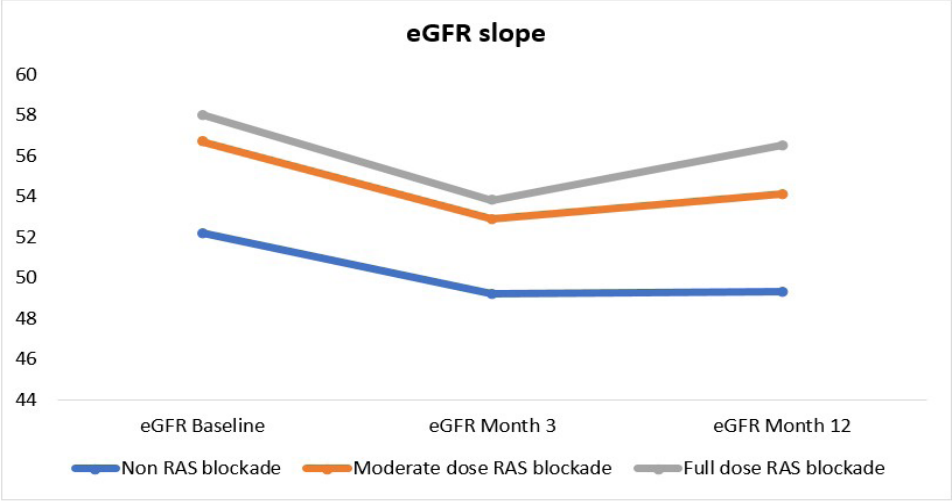


**Figure 1.** Trajectory of Estimated Glomerular Filtration Rate (eGFR) Over 12 Months According to RAS Inhibitor Use and Dosage. eGFR: Estimated glomerular filtration rate, RASi :Renin angiotensinogen inhibitors

### Limitations of the Study

The limitations of this study include a relatively small sample size, which may have reduced the statistical power to detect subtle differences, particularly in safety outcomes. Moreover, factors such as medication adherence, dietary intake, and insulin usage were neither standardized nor prospectively monitored, introducing potential bias—especially in the interpretation of glycemic endpoints.

## CONCLUSION

The findings of this study suggest that initiating SGLT2i in patients with diabetes and CKD is generally safe and associated with favorable renal and metabolic outcomes, regardless of background RAS blockade. However, the combination of SGLT2i with RAS inhibitors—particularly at full doses—appears to confer additional benefits in terms of blood pressure control and eGFR preservation. Moderate-dose RAS blockade may represent an optimal balance between efficacy and tolerability when layering SGLT2i therapy, especially in proteinuric diabetic CKD. These results support the complementary roles of SGLT2i and RASi in renal protection and reinforce current clinical recommendations favoring their co-administration when tolerated. Future studies with longer follow-up are warranted to evaluate whether the more favorable eGFR slope seen in the full-dose RASi group translates into sustained long-term kidney protection..

## DECLARATIONS

**Ethics committee approval:** All procedures performed in the study were conducted in accordance with the ethical standards set forth by the Clinical Research Ethics Committee of Kırklareli University Faculty of Medicine. The protocols in this study (Protocol No. P202300036/02) were approved by the aforementioned committee and are in alignment with the ethical principles set forth in the 1964 Declaration of Helsinki.

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**Author contributions:** Author declares that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

**Conflicts of interest:** Author declares none.

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**AI:** None

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Original Article

# Seasonal, Geographic, and Socioeconomic Patterns of Public Interest in Frailty Syndrome: Insights From Google Trends

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**Abstract**

**Background:** Frailty syndrome is a complex geriatric condition characterized by reduced physiological reserves and increased vulnerability to stressors. While its clinical implications are well established, knowledge on public awareness remains limited. As online search behavior increasingly reflects public interest, tools like Google Trends offer real-time insights into population-level awareness of frailty and its influencing factors.

**Methods:** This observational study analyzed global Google Trends data for the search topic "frailty syndrome" from January 2004 to May 2025. Relative search volume (RSV) was examined across temporal, seasonal, geographic, and socioeconomic dimensions. Seasonal trends were evaluated using time-series decomposition and winter-to-summer amplitude ratios. Geographic patterns were assessed by mapping RSV and classifying countries by World Bank income levels. Pearson correlation was used to assess associations between RSV and socioeconomic indicators including GDP per capita and internet penetration.

**Results:** Global RSV increased from a baseline mean of 8.2 (±3.1) in 2004–2009 to a peak of 78.5 (±15.2) in 2020, followed by sustained elevated interest through 2025 (mean: 45.3 ±12.1). Seasonal analysis showed consistent winter peaks, with amplitude ratios exceeding 1.3. Japan had the highest RSV (100), followed by the United Kingdom (55), Singapore (52), and Ireland (44). All top countries were high-income. RSV was significantly correlated with GDP per capita ($r = 0.62$, $p < 0.01$) and internet penetration ($r = 0.58$, $p < 0.01$).

**Conclusion:** Search interest varied by season and socioeconomic context. Higher wintertime interest may reflect seasonal vulnerability in older adults, while increased search activity in high-income countries suggests better digital access and health literacy. Low visibility in lower-income regions highlights a digital and educational gap. Google Trends provides meaningful insight into frailty awareness. Understanding seasonal and socioeconomic patterns can guide targeted public health campaigns to promote early detection and prevention in aging populations.

**Keywords:** Frailty, Public Health, Social Media/trends, Socioeconomic Factors, Digital Health, Aging

## INTRODUCTION

Frailty syndrome is a complex geriatric syndrome characterized by increased sensitivity to stressors resulting from reduced physiological reserves in several systems, including the immunological, metabolic, and musculoskeletal domains. It is often identified using Fried's phenotype, which requires three or more of the following: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity (1). Frailty affects approximately 5–17% of community-dwelling adults aged 60 and older, with prevalence rising to 30% by age 90 and up to 84% in hospitalized populations (2). A meta-analysis reported a global frailty incidence rate of 43.4 per 1,000 person-years among community-dwelling older adults (3). Prevalence varies by region, with higher rates in southern Europe (e.g., 27% in Spain) compared to northern Europe (e.g., 5.8% in Switzerland), and is influenced by older age, female sex, and lower socioeconomic status (SES) (4). Frailty is associated with many outcomes, including

falls, disability, hospitalizations, and mortality, making it a significant public health concern as populations age, with the older adults projected to make up 20% of developed countries' populations by 2025 (5).

Awareness of frailty syndrome among patients, caregivers, and the public is critical for early intervention and management. Early recognition enables preventive strategies, such as exercise, balanced nutrition, and multidisciplinary care, which can delay frailty progression (6). For patients, understanding frailty makes lifestyle changes that enhance functional independence and quality of life possible. Caregivers benefit by identifying early signs, following through with geriatric assessments, and promoting patient adherence to treatment (7). In addition, public awareness informs health policy, guiding resource allocation to address frailty's growing burden. Public interest in frailty may vary seasonally, potentially driven by health stressors or reduced physical activity in colder months, as observed in conditions like major depression and bipolar disorder (8). Socioeconomic factors, such as income, also influence frailty awareness and prevalence, with low SES linked to higher frailty odds due to chronic inflammation, poor nutrition, and reduced physical activity (9). Exploring these patterns can guide targeted awareness campaigns.

The internet, particularly Google Trends, provides a powerful tool for assessing public interest in frailty syndrome. Google Trends, a free tool by Google LLC (a subsidiary of Alphabet Inc.), analyzes web queries to provide relative search volume (RSV) data on a 0–100 scale, reflecting search interest relative to peak popularity (10). Used in public health to track influenza outbreaks, it offers real-time insights into population behavior, complementing epidemiological data as grey literature (11). For resource-limited organizations, Google Trends is cost-effective for identifying knowledge gaps, monitoring seasonal trends, and assessing socioeconomic influences on health awareness; its accessibility, global reach, and ability to track real-time trends are other advantages to consider (12,13). This study uses Google Trends to explore public interest in frailty syndrome, its seasonal variations, and its relationship with socioeconomic factors like income, aiming to enhance awareness and inform public health strategies.

## METHODS

*Study Design*

This retrospective observational study analyzed public interest in frailty syndrome using Google Trends data to assess temporal, seasonal, and socioeconomic influences. The study period spanned January 2004 to May 2025, capturing long-term trends in search interest to evaluate variations in public awareness, focusing on seasonal patterns and correlations with economic income levels.

*Data Collection*

Data were collected using Google Trends, a publicly accessible tool by Google LLC, analyzing a sample of web queries submitted to the Google Search engine (10). The primary search topic was "frailty syndrome," defined as a topic to include semantically related terms across languages (e.g., "fragilidad" in Spanish). Google Trends provided relative search volume (RSV) data, normalized on a 0–100 scale, where 100 represents peak popularity within the selected time frame and region, and 0 indicates search interest below 1% of the peak (12). Searches were conducted globally and for specific regions to explore differences, particularly in relation to economic income. The time frame covered January 2004 to May 2025, with data aggregated monthly to capture seasonal patterns. Duplicate queries from the same user within a short period were excluded by Google Trends. Data were downloaded as CSV files. Comparative RSV data for "dementia" were collected as a reference. Regional income data from the World Bank were collected to correlate search interest with economic indicators (14).

*Data Analysis*

All analyses were conducted using R statistical software (version 4.3.0) (15). RSV data were analyzed across temporal, seasonal, geographic, and socioeconomic dimensions using descriptive statistics (mean, standard deviation, range) and inferential methods to explore public interest in frailty syndrome.

*Temporal and Seasonal Analysis*

Time-series analysis was performed to assess long-term trends and seasonal patterns, employing the Mann-Kendall test to detect monotonic trends over the 21 years, with Sen's slope estimator quantifying changes. Seasonal decomposition using classical methods identified periodicities, focusing on 12-month cycles, with winter-to-summer amplitude ratios calculated to quantify seasonal fluctuations. Structural breaks, such as the notable 2020 spike potentially linked to the COVID-19 pandemic, were explored using visual inspection and basic breakpoint analysis (16).

*Geographic and Socioeconomic Analysis*

Geographic RSV data were normalized using z-scores to account for regional baseline differences and mapped to visualize variations. Countries were categorized by World Bank income classifications (low-, middle-, and high-income) for comparative analysis (14). Pearson correlation analysis examined relationships between RSV and socioeconomic indicators, including GDP per capita and internet penetration, with partial correlation adjustments for age structure (17). Comparative analysis with "dementia" RSV provided context for frailty awareness patterns.

## STATISTICAL ANALYSIS

Normality of RSV data was assessed using the Shapiro-Wilk test, with non-parametric tests (e.g., Kruskal-Wallis) applied when assumptions were violated. Multiple comparisons were adjusted using the Benjamini-Hochberg procedure to control false discovery rates. Confidence intervals (95%) were estimated using bootstrap resampling (n=1,000). Data quality was ensured through outlier detection via interquartile range (IQR) methods and completeness checks across regions and periods. All statistical tests used a significance threshold of $\alpha = 0.05$.

## RESULTS

*Geographic Distribution of Search Interest*

Analysis of Google Trends data revealed significant regional variations in public interest for frailty syndrome. Japan exhibited the highest relative search volume (RSV) at 100, indicating peak interest within the study period. The United Kingdom and Singapore followed with RSVs of 55 and 52, respectively, while Ireland and Hong Kong showed moderate interest with RSVs of 44 and 29. The global map indicated higher search activity in East Asia, Western Europe, and parts of North America, with many regions, particularly in Africa and Central Asia, showing low search volumes unless explicitly included. The top 10 countries for RSV are represented in **Table 1**, all are high income countries according to World Bank Database (14).

*Temporal Trends and Seasonal Patterns*

The interest over time data demonstrated a general upward trend in searches for frailty syndrome from January 2004 to May 2025, with notable fluctuations (**Figure 1**). Peaks in search volume were observed during winter months (e.g., December–February), suggesting a seasonal pattern potentially linked to increased health concerns or reduced physical activity in colder seasons. The data also showed periodic spikes, with a significant surge in 2020, likely driven by heightened media coverage and public health discussions during the COVID-19 pandemic, which highlighted frailty as a risk factor for severe outcomes in older adults. Temporal trends and significant events affecting the search interest are shown in **Table 2**.

*Related Topics and Search Behavior*

Related topics identified included "frailty index," "old age," "frailty definition," and "frailty meaning." The "frailty index" and "old age" reflect a focus on clinical and demographic aspects of frailty, while "frailty definition" and "frailty meaning" suggest a broader public interest in basic knowledge associated with the condition. This indicates that searches may involve both deeper medical implications and basic knowledge

## DISCUSSION

The geographic distribution of frailty syndrome search interest highlights a concentration in high-income and aging populations, such as Japan, the United Kingdom, and Singapore (3). Japan's peak RSV (100) aligns with its rapidly aging society, where over 28% of the population was aged 65 or older by 2025, driving public health focus on geriatric conditions (18). Lower interest in regions like Africa and Central Asia may reflect limited internet access or lower health literacy, highlighting socioeconomic disparities (19). The moderate interest in Ireland and Hong Kong suggests a middle ground, potentially influenced by healthcare infrastructure and aging demographics (4).

Seasonal patterns, with peaks in winter months, align with findings from other health conditions, such as increased frailty risk due to reduced physical activity and vitamin D deficiency in colder seasons (20). The 2020 surge likely reflects heightened health awareness during the COVID-19 pandemic, when media outlets and public health campaigns frequently highlighted frailty as a risk factor for severe outcomes in older adults, as evidenced by global news coverage emphasizing vulnerable populations (21). These trends suggest that seasonal health campaigns could enhance frailty awareness, particularly during winter.

The related topics search indicates a dual focus: clinical ("frailty index") and educational ("definition", "meaning"). This duality suggests that public interest extends beyond medical definitions to involve a desire to understand frailty's broader context, a finding supported

**Table 1.** Geographic Distribution of Relative Search Volume (RSV) for Frailty Syndrome Population (16)

| Country | RSV | Population 65+ |
|---|---|---|
| **Japan** | **100** | **28.7** |
| **United Kingdom** | **55** | **18.5** |
| **Singapore** | **52** | **15.2** |
| **Ireland** | **44** | **14.4** |
| **Hong Kong** | **29** | **17.9** |
| **United States** | **25** | **16.9** |
| **Canada** | **22** | **17.6** |
| **Australia** | **18** | **16.2** |
| **Germany** | **15** | **22.1** |
| **France** | **12** | **20.3** |

**Table 2.** Temporal Trends and Significant Events in Frailty Syndrome Search Interest

| Year | Mean RSV | Notable Events/ Peaks | Contextual Factors |
|---|---|---|---|
| 2004-2009 | 8.2 + 3.1 | Baseline period | Early internet adoption |
| 2010-2014 | 15.6 + 5.4 | Gradual increase | Aging population awareness |
| 2015-2019 | 32.8 + 8.9 | Steady growth | Clinical research expansion |
| 2020 | 78.5 + 15.2 | Peak year | COVID-19 pandemic impact |
| 2021-2025 | 45.3 + 12.1 | Sustained interest | Post-pandemic awareness |

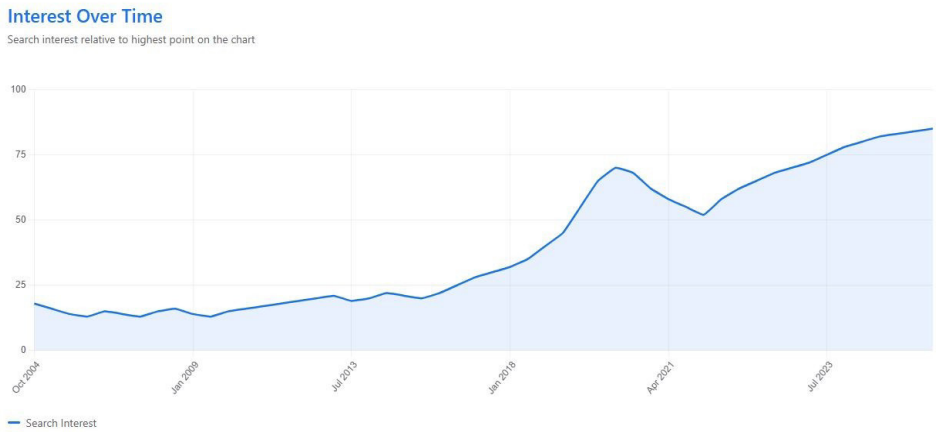


**Figure 1.** Numbers represent search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term.

by studies showing its impact on independence (1). However, the inclusion of general terms like "subject" and "topic" may reflect curiosity or lack of specific knowledge, highlighting the need for targeted education to clarify frailty's implications (13).

Socioeconomic factors, such as income, appear to influence search interest, with higher RSVs in high-income regions. This correlates with evidence that lower SES increases frailty prevalence due to poor nutrition and limited healthcare access (9). The lack of data from low-income regions emphasizes the need for initiatives to bridge this gap, potentially using mobile health tools to reach underserved populations (22). Limitations include the absence of user demographic data in Google Trends, which hinders precise interpretation of search intent, and the relative nature of RSV, which may underrepresent interest in less-searched regions (10).

Several limitations should be considered when interpreting these findings. First, Google Trends provides relative rather than absolute search volumes, which may cover actual public interest in regions with low internet penetration or where frailty is less commonly searched compared to dominant topics (10). Second, the lack of demographic data on search users prevents differentiation between patients, caregivers, or healthcare professionals, potentially causing a bias in the representation of public awareness (12). Third, language variations beyond 'fragilidad' (for example 'weakness' or 'debility' in other languages) and cultural differences in how frailty is conceptualized may lead to underreporting of interest in multilingual or low-income regions, where alternative terms or non-digital sources dominate (11). Fourth, the study's reliance on a single data source (Google Trends) may miss insights from other platforms or languages not captured in the sampled queries, limiting generalizability (11). Finally, the temporal analysis, while spanning 2004 to 2025, is subject to external influences (e.g., the 2020 pandemic spike), which may confound seasonal or socioeconomic trends without further contextual data. Future studies could address these by incorporating multilingual search terms, integrating data from social media platforms like X, or conducting surveys to capture demographic-specific search intent.

## CONCLUSION

This study provides insights into the geographic, seasonal, and socioeconomic dimensions of public interest in frailty syndrome using Google Trends data, an underutilized tool in geriatric research (22). The results highlight the potential of digital epidemiology to identify awareness gaps in aging populations, suggesting that public health strategies could include winter-focused campaigns emphasizing exercise and nutrition in high-income regions with strong digital access, while mobile health interventions, such as SMS-based educational alerts or community-based workshops in local languages, could bridge gaps in low-income regions (9). Multilingual materials explaining frailty in culturally relevant terms could further enhance outreach, offering a foundation for future targeted interventions (5,9). By integrating real-time internet data with epidemiological evidence, this research bridges traditional and digital methodologies, paving the way for more dynamic public health strategies to address frailty in an aging global population.

## DECLARATIONS

**Ethics Committee Approval:** As this study utilized publicly available and anonymized data from Google Trends and did not involve human subjects, Institutional Review Board (IRB) approval was not required.

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**AI:** Artificial intelligence tools were used to assist in language editing and improving the clarity of the manuscript. However, all scientific content, data analysis, and interpretations were carried out by the author, who bear full responsibility for the content and conclusions of this work.

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Review

# Gout: Evaluation and Management

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**Abstract**

Uric acid is a by product of purine nucleotide metabolism, primarily synthesized in the liver and less frequently in other tissues. Hyperuricemia, characterized by elevated uric acid levels, can lead to gout and nephrolithiasis. It is also associated with conditions such as hypertension, metabolic syndrome, cardiovascular disease, and chronic kidney disease. Gout is an inflammatory disease marked by the deposition of monosodium urate (MSU) crystals in joints and tissues. It commonly affects the metatarsophalangeal joint, followed by other lower extremity joints, making it the most prevalent inflammatory arthritis. The pathophysiology of gout involves pro-inflammatory cytokines, lipid mediators, and the complement system, which contribute to the initiation and exacerbation of gout flares. Diagnosis relies on clinical evaluation, the identification of MSU crystals, and radiological imaging. Treatment encompasses acute gout flare management, prophylaxis, dietary modifications, and urate-lowering therapies. Common therapeutic agents include nonsteroidal anti-inflammatory drugs, colchicine, glucocorticoids, adrenocorticotropic hormone, and anti-IL-1β biological agents.

**Keywords:** Hyperuricemia, Gout, Urate Oxidase/metabolism, Arthritis

## INTRODUCTION

Uric acid is the final product of purine metabolism in humans. Its regulation is mediated by xanthine oxidoreductase, which converts hypoxanthine to xanthine and xanthine to uric acid. Uric acid has endogenous and exogenous origins. The endogenous sources include tissues such as the liver, muscles, intestines, kidneys, and vascular endothelium, with the liver being the primary site of synthesis. Exogenous sources mainly come from animal-derived foods but can also originate from fruit-derived fructose. The causes of hyperuricemia are categorized into excessive production (purine-rich diet, fructose-induced hyperuricemia, errors in purine metabolism, and high cell breakdown or turnover) and reduced uric acid excretion (acute or chronic kidney disease (CKD), acidosis, hypovolemia, medications/toxins, sarcoidosis, hyperparathyroidism, hypothyroidism, Bartter syndrome, and Down syndrome). Approximately two-thirds of serum uric acid is excreted through urine, while one-third is eliminated via the gastrointestinal system. Hyperuricemia has been shown to be associated with gout, kidney stones, hypertension, atrial fibrillation, CKD, heart failure, coronary artery disease, and cardiovascular mortality (1,2).

Serum uric acid acts as an antioxidant at normal levels. Normal serum uric acid values are 2-7 mg/dL in men and 2-6 mg/dL in women. Hyperuricemia is usually asymptomatic. Its long-term health effects are still unclear. Hyperuricemia is defined as ≥ 7.0 mg/dL in men and ≥ 5.7 or ≥ 6 mg/dL in women. Hypouricemia refers to serum uric acid levels of ≤ 2 mg/dL (3,4).

## DEFINITION

Gout is the most common cause of inflammatory arthritis worldwide. It is characterized by an inflammatory response resulting from the accumulation of monosodium

urate (MSU) in joints and surrounding tissues, most commonly in the first metatarsophalangeal joint (5).

## HISTORY

Gout disease, initially described by the Egyptians in 2640 BC, was later recognized by Hippocrates in the 5th century BC. Hippocrates referred to this disease as the "disease of the inability to walk." six centuries later, Galen described tophi, which are crystalline MSU deposits resulting from chronic hyperuricemia. Later, the famous English physician Thomas Sydenham, who himself became disabled due to gout and kidney disease, also described the condition. Emperor Charles V, who frequently consumed beer and wine, suffered from repeated gout flares. Gout was considered a disease of the wealthy. German-Swedish pharmaceutical chemist Karl Scheele isolated uric acid in the 1700s, and about half a century later, urate was aspirated from a tophus of a gout patient. In 1961, Daniel McCarty and Joseph Lee Hollander demonstrated the presence of MSU crystals in the synovial fluid of gout patients. MSU crystals were visualized under a microscope in an inflamed joint using polarized light (6,7).

## EPIDEMIOLOGY

Gout disease is a commonly occurring disease, with its prevalence influenced by genetic and environmental factors. The incidence of gout disease has been reported as 190 cases per 100,000 person-years. The prevalence of gout disease ranges between 1.8% and 6.8%. In China, the prevalence of gout in adults has been found to be 3.2%. A study conducted in Australia reported gout prevalence ranging from 4.5% to 6.8%. In Spain, the prevalence of gout was found to be 2.4%. Between 2015-2016, the prevalence of gout in the United States was found to be 3.9%. Gout prevalence varies between genders, being more common in men. The prevalence in men ranges from 4.5% to 5.2%, while in women it ranges from 0.38% to 2.7%. The prevalence of gout is increasing over time. Between 2011 and 2018, the overall prevalence of gout rose from 3.6% in 2011-2012 to 5.1% (8-15).

## RISK FACTORS

There are several risk factors for gout disease. These include: low education level, poverty, obesity, alcohol consumption, medications (especially diuretic use), CKD (estimated glomerular filtration rate <60 mL/min), male gender, high income in both women and men in North America, and diet (purine-rich diet, consumption of high-fructose sugar-sweetened beverages, and increased daily portions of meat and seafood). Studies have reported that conditions such as heart disease, diabetes, hypertension, obesity, hyperlipidemia, menopause, and undergoing surgery increase the risk of gout. Climate can also affect the natural course of gout, particularly the onset of flare-ups. A meta-analysis by Park and colleagues showed that extreme temperature fluctuations (especially increases) can trigger gout attacks. Additionally, environmental air pollution increases the risk of gout flare-ups. Physiological stress can trigger gout flare-ups as well. Infections, contrast medium injections, acidosis, trauma, surgery, psoriasis, chemotherapy, rapid increases and decreases in serum uric acid levels due to discontinuing or initiating allopurinol or febuxostat can also trigger flare-ups. In most studies, no specific trigger is identified for gout attacks in the majority of gout patients. If identified, typically only 1-2 triggers are found. The most frequently reported triggers are alcohol (14.2%), dehydration, injury or excessive activity, extreme temperatures (hot or cold), and red meat. Less commonly identified triggers include fruits or fruit juices, seafood, cheese or cream, Chinese sauces or curry, vegetables, air travel, stress, diuretics, fatigue, infections, and overeating. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) and phosphoribosyl pyrophosphate synthetase 1 (PRS1) are the most important enzymes involved in uric acid production in the liver. Transporters such as GLUT9, ABCG2, and organic anion transporter are key carriers involved in the reabsorption and excretion of uric acid in the kidneys and intestines. Studies suggest that mutations in the HGPRT and PRPPS genes appear to be the main cause of primary gout disease. Additionally, mutations in the SLC22A11 (organic anion transporter 4) gene and ATP-binding cassette transporters G2 (ABCG2) genetic mutation have been associated with gout (16-22).

In patients with gout who also have hypertension, treatment adjustment is important. Losartan is the only angiotensin II receptor blocker shown to significantly reduce uric acid levels. Therefore, it is recommended as an antihypertensive agent in gout patients by clinical guidelines In patients using hydrochlorothiazide as an antihypertensive, uric acid levels may increase, potentially triggering gout flare-ups. This usually occurs within the first few weeks after starting the medication (23,24)

## PATHOPHYSIOLOGY

Several mediators, including pro-inflammatory cytokines, lipid mediators, and the complement system, play a role in the initiation and exacerbation of gout flares. Hyperuricemia and the accumulation of MSU crystals are the key pathophysiological mechanisms leading to gout disease development. The over-saturation of urate is the most important factor in MSU crystal formation, with additional factors such as temperature, pH, and connective tissue components also playing a role. When the urate level exceeds the saturation point of 6.8 mg/dL, MSU crystals form at a pH of 7.0 and a temperature of 37°C. MSU crystals are needle-shaped structures with unequal axes and can be easily identified under compensated polarized microscopy by their strong

negative birefringence. Histologically, a gout flare is characterized by synovial membrane hyperplasia and cellular infiltration of neutrophils. Some monocytes, macrophages, and lymphocytes may also be present. Hyperuricemia above local resolution can lead to the deposition of MSU crystals in joints, hyaline cartilage surfaces, and periarticular soft tissues such as tendons, ligaments, retinacula, and bursae. This results in an inflammatory response. The excessive saturation and crystallization of uric acid within the joint directly damage synovial epithelial cells. The deposition of MSU crystals can trigger a gradual inflammatory response by activating the NLRP3 inflammasome in macrophages and monocytes. Activation of the NLRP3 (NLR family pyrin domain-containing 3) inflammasome leads to the release of IL-1β and IL-1α from macrophages and dendritic cells, which, through IL-1 receptors, activate other cells to produce pro-inflammatory cytokines and chemokines, contributing to local inflammation and sometimes systemic effects. Gout flares are self-limiting inflammations, and several resolution mechanisms have been suggested. These include neutrophil extracellular traps, negative regulators of inflammasome and TLR signaling, and anti-inflammatory cytokines. Some proteins that leak into the joint space during inflammation, such as apolipoprotein B, can coat the crystals and reduce their inflammatory properties. Tophus is a characteristic feature of advanced gout and is clinically seen as a palpable nodule in the subcutaneous tissues, joints, or tendons. Tophus consists of MSU crystals and chronic granulomatous tissue and typically forms in gout patients who have not received urate-lowering therapy for at least 10 years. MSU crystals can accumulate in end organs like the kidneys and heart. Recurrent acute gout attacks eventually lead to chronic synovitis, tophus formation and accumulation, and, ultimately, erosions and joint destruction, resulting in chronic arthropathy (25-32).

## CLINICAL PRESENTATION

Gout disease is typically characterized by recurrent acute inflammatory arthritis attacks, most commonly affecting the first metatarsophalangeal joint. The disease can be classified into four stages: asymptomatic hyperuricemia, acute gout, intercritical gout, and chronic gout arthritis (26). The development of hyperuricemia and the stages and comorbidities of gout disease are given in **Figure 1.**

### Asymptomatic Hyperuricemia

This stage is characterized by elevated serum urate levels without clinical symptoms. It is usually discovered incidentally during serum uric acid measurements. Asymptomatic hyperuricemia can lead to the accumulation of urate crystals when serum urate concentrations exceed 6.8 mg/dL. During this phase, urate deposits may contribute to organ damage. MSU crystal deposition can be detected by microscopy or advanced imaging techniques [such as double contour sign on ultrasound and urate deposition with dual energy computed tomography (DECT)]. In Japan, it is recommended that asymptomatic hyperuricemia and gout be treated with low-dose urate-lowering therapy (ULT) (33-35).

### Acute Gout

Acute gout is characterized by episodic, self-limiting inflammatory arthritis. Initially, only one joint is typically affected (monoarticular arthritis), with the first metatarsophalangeal joint being involved in about 50% of cases. Other commonly affected joints include the foot, ankle, knee, wrist, fingers, and elbow. Severe attacks can affect multiple joints (polyarticular). Recurrent attacks are common in patients with severe gout. Polyarticular attacks are more frequent in patients with poorly controlled gout. The pain starts intensely and peaks within a few hours, often beginning in the middle of the night or early morning. The pain significantly affects the patient's ability to perform daily activities. The skin overlying the affected joints becomes hypersensitive, and there is redness, warmth, tenderness, swelling, and loss of function. The skin is so sensitive that even a bed sheet cannot be tolerated. The attack usually resolves spontaneously. If untreated, the first attack typically resolves within 3 to 14 days (22,33,36).

### Intercritical Gout

After the first acute attack of gout typically resolves within 7 to 14 days, an asymptomatic period follows, referred to as "intercritical gout." The duration of this phase can range from several days to years. This phase is characterized by the absence of symptoms. If appropriate treatment for hyperuricemia is not applied, new attacks can develop suddenly. Despite the apparent inactivity of the disease, hyperuricemia persists, and crystal deposition continues. Subclinical inflammation may also be present in the joints during this period. It has been reported that in patients with intercritical gout or those with MSU crystal deposition on ultrasound, pro-inflammatory cytokine levels are elevated (36-38).

### Chronic Gout

In untreated or inadequately treated gout, chronic tophaceous gout may develop over the years. This condition can lead to gradual and progressive joint destruction. Chronic gout patients exhibit low-grade inflammation. It is characterized by the accumulation of MSU crystal aggregates in joints, bursae, and tendons. Chronic gout arthritis is a permanent condition that presents with bone erosions and tophus (which may appear intra-articular, peri-articular, or extra-articular) in various joints (commonly in the fingers, toes, knees, and olecranon bursa). Tophus can develop in 12% of patients after 5 years and in 55% after 20 years of untreated disease. This condition leads to destructive deforming arthritis, widespread bone destruction, and

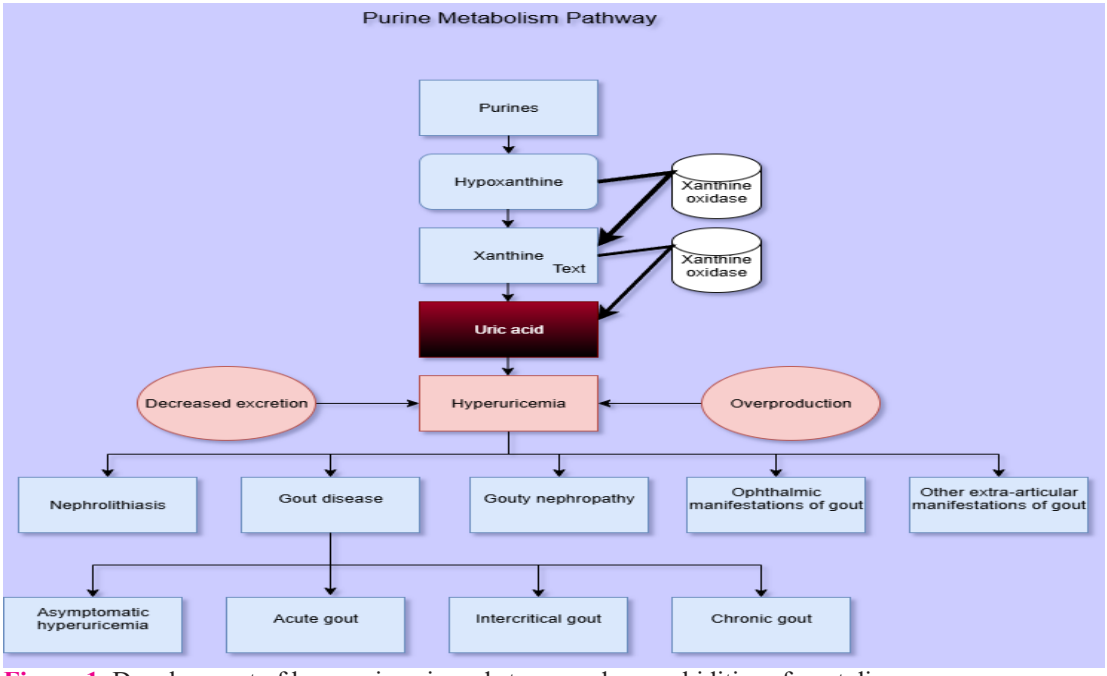


**Figure 1.** Development of hyperuricemia and stages and comorbidities of gout disease.

severe deformities (22,37).

## DIAGNOSIS

Recommendations and expert opinions for the diagnosis of gout emphasize the necessity of MSU crystal examination and identification in patients with clinical suspicion of gout to establish a definitive diagnosis. The gold standard for diagnosis is the detection of negatively birefringent MSU crystals in synovial fluid or soft tissue/tophus aspirate. However, synovial fluid analysis may fail to reveal MSU crystals in a significant portion of patients with acute gout. Therefore, the diagnosis of gout is often made by evaluating laboratory and radiological findings together. In gout patients, serum uric acid, CRP, TNF-α, and IL-6 levels increase. Serum procalcitonin can be a useful serological marker for distinguishing between acute gout arthritis and bacterial infections. Imaging techniques used in gout arthropathy include radiography, ultrasonography, X-ray, computed tomography (CT), dual-energy computed tomography (DECT), and magnetic resonance imaging (MRI). Radiographs taken during acute attacks may reveal nonspecific findings such as soft tissue swelling and joint effusion. On ultrasound, the double contour sign, clusters of crystals, or tophi can be observed. The “double contour sign,” representing MSU crystal deposition on hyaline cartilage seen on ultrasound, has 99% specificity but only a low sensitivity of 43%. DECT of peripheral joints provides a non-invasive method for detecting MSU crystal deposits in the joint and surrounding tissues. Crystals can appear as hyperdensities in both intra- and extra-articular regions compared to surrounding soft tissues. MRI is another option for evaluating arthropathies due to its excellent ability to visualize soft tissue and synovial inflammation associated with gout. MRI can also visualize soft tissue tophi and bone erosions (27,39-42).

Guideline recommendations suggest that in patients with suspected gout, [acute onset joint pain (usually overnight) with severe pain, redness, and swelling in one or both first MTP joints], crystal examination should be performed on synovial fluid or tophus aspirate. Gout should be considered in the diagnosis of any acute arthritis in adults. In patients suspected of having gout, a detailed history and physical examination should be conducted to assess symptoms and signs. For individuals with symptoms and signs of gout, measurement of serum urate levels is recommended to confirm the clinical diagnosis. If serum urate levels are <6 mg/dl during an acute flare, and there is strong suspicion of gout, it is recommended to repeat serum urate level measurement at least two weeks after the acute flare has subsided. The NICE guidelines emphasize that if the diagnosis of gout is uncertain or unconfirmed, joint aspiration and microscopy of synovial fluid should be considered. Synovial fluid aspiration and crystal examination should be strongly considered in any patient with undiagnosed inflammatory arthritis. Gout diagnosis should not be based solely on the presence of hyperuricemia. If joint aspiration cannot be performed or the diagnosis of gout remains uncertain, imaging of the affected joints with X-ray, ultrasound, or DECT should be considered. In patients with painful, red, swollen joints, the possibility of septic arthritis, calcium pyrophosphate crystal deposition, and inflammatory arthritis should be evaluated(43,44).

## COMPLICATIONS AND COMORBIDITIES

A study showed that extra-articular urate deposits were found in various organs, including the heart, blood vessels, kidneys, spine, eyes, skin, and gastrointestinal system. The 2007-2008 NHANES survey revealed that 74% of gout patients had hypertension, 71% had CKD (stage >2), 26% had diabetes, 53% had obesity, 14% had a history of myocardial infarction, 11% had heart failure, and 10% had a history of stroke. Among those with hyperuricemia but no history of gout, 47% had hypertension, 70% had CKD, 54% had obesity, 12% had diabetes, 5% had a history of stroke, and 4% had a history of myocardial infarction. In the normourisemic population without a history of gout, only 24% had hypertension, 37% had CKD, 27% had obesity, 6% had diabetes, 2% had a history of stroke, and 2% had a history of myocardial infarction. A venous thromboembolism was found in 2.1% of gout patients. It has been shown that the greater the severity of hyperuricemia, the more common these comorbidities are. Hypertension is frequently observed in gout patients. Previously, it was demonstrated that uric acid stimulates vascular smooth muscle cell proliferation in vitro and also promotes the production of both angiotensinogen and angiotensin II. Hyperuricemia is associated with an increased frequency of both coronary heart disease and cerebrovascular stroke. Both gout and subclinical hyperuricemia are linked to adverse cardiovascular outcomes. Gout patients have been found to have an increased risk of cardiovascular mortality compared to controls(45-48).

### Kidney Stones

Kidney stones are a common complication of gout disease and are often composed of a combination of uric acid or minerals. Uric acid stones account for approximately 10% of all urinary stones in the United States and 5% to 40% of all stone cases worldwide. A study found the prevalence of nephrolithiasis in primary gout disease to be 35%, with 18.7% of patients being asymptomatic. In acute gout nephropathy, uric acid stones may be observed in 15-20% of patients. These are usually bilateral. It has been found that the condition is more severe in patients with high serum uric acid levels and decreased kidney function. MSU crystals can also precipitate in the kidneys, leading to the formation of uric acid stones. Hyperuricemia is associated with metabolic diseases, hypertension, and diabetes mellitus. In patients with metabolic syndrome and diabetes, ammonia production in the proximal tubule is also reduced. This defect often causes urinary pH to drop below 5.3, which can lead to uric acid precipitation and uric acid stone formation, even without an increase in urinary uric acid excretion (49-51).

### Gout Nephropathy

"Gout nephropathy" is a term used to describe kidney changes in gout disease. The mechanisms of kidney tissue damage in hyperuricemia include urate crystallization in the tubulointerstitial tissue and pelvis; reduced activity of fibrinolytic factors; endothelial dysfunction; and renin secretion by juxtaglomerular cells associated with activation of the local renal renin-angiotensin-aldosterone system. Gout nephropathy is characterized by the deposition of uric acid/urate crystals in the renal medulla. Crystals that accumulate in the renal medulla can directly affect kidney function, contributing to inflammation and fibrosis in the kidney. Acute uric acid crystal-induced urinary tract obstruction (e.g., tumor lysis syndrome) may present as acute kidney injury. Chronic gout nephropathy is characterized by medullary intratubular and/or interstitial microtophi. This microcrystalline nephropathy is associated with kidney dysfunction and features of tubulointerstitial nephritis. Tubulointerstitial fibrosis develops. Glomerular changes may include increased mesangial matrix and double contours of glomerular basement membranes. Electron microscopy reveals epithelial damage in collecting ducts and needle-like crystals in the cytoplasm. Kidney failure is a well-known cause of gout disease because it reduces uric acid excretion in the urine, thereby setting the stage for hyperuricemia and gout. Gout disease is also associated with an increased risk of advanced CKD. The age-standardized prevalence of gout is 2.9% in those with normal GFR, while it is 24% in those with a GFR of 60 mL/min. Other studies report that the prevalence of CKD stage ≥2 in gout patients is over 70%, the prevalence of CKD stage ≥3 is about 24%, and the prevalence of CKD stage ≥4 in gout is 2% (5,52-56).

### Ophthalmic and Other Extra-Articular Manifestations of Gout

Ophthalmic manifestations of gout are rare but varied. The most common eye symptom in gout patients is red eye, which can be partially caused by hyperemic conjunctival and episcleral vessels. The mechanism can develop with or without crystal deposition. Conjunctivitis, uveitis, and corneal deposits have also been described, often affecting the anterior segment. Tophus or MSU crystals associated with gout have been observed in the cornea, sclera, iris, Bowman's layer, conjunctiva, lens, orbital fossa, retina, and eyelids (49,57).

Detection of spinal gout is limited due to radiographically dense urate crystals and non-specific findings on MRI and CT. However, there have been case reports of MSU deposition in the cervical, thoracic, and lumbar spine. The clinical presentations of spinal gout are highly varied, depending on the anatomical involvement, with symptoms being non-specific. Spinal gout typically manifests with back pain. Spinal tophi can also cause neurological impairment by pressing on nerve roots or the spinal cord. These impairments may include radiculopathy, myelopathy, and dysfunction of the bowel and bladder. Several case report studies have

described urate deposition in the gastrointestinal system. In these cases, tophi have been reported in the liver, pancreas, coronary arteries, lungs, prostate, mesentery, peritoneum, small intestine, colon, breast, and bladder. Dermal tophi, caused by intradermal MSU deposits, appear as subcutaneous nodules or hardened plaques. Dermal tophi can cause ulcers and potential joint symptoms (45,49,58,59).

## TREATMENT

In gout disease, treatments can be evaluated as non-pharmacological and pharmacological. Non-pharmacological treatments are individualized therapies that involve patient participation. Within the scope of individualized patient education, the etiology of the disease, potential clinical outcomes, and available treatment options are addressed through a comprehensive approach and tailored to the specific needs of the patient. Lifestyle changes should be achieved by weight control, appropriate diet, and avoidance of alcoholic beverages and sugary drinks. For weight control, exercise and calorie restriction reduce uric acid levels. In addition, during acute attacks, rest and ice application should be recommended, and patients should be advised to avoid dietary factors that may trigger attacks. Dietary recommendations that may reduce the frequency of gout attacks should be shared with the patient. High serum vitamin C levels have a positive effect on purine metabolism, reducing uric acid levels and the accumulation of MSU crystals. However, starting vitamin C may exacerbate gout attacks, so it is not recommended. A vegetarian diet is associated with a lower risk of gout. Plant-based foods contain polyphenols that can reduce uric acid by inhibiting xanthine oxidase activity and increasing uric acid excretion. Purine-containing foods (such as meats, organ meats, seafood, legumes, yeast, mushrooms, and gravies) should be reduced. Fructose is the only carbohydrate known to increase uric acid, so it is strongly advised to avoid fructose-sweetened foods, beer, liquor, and starchy carbohydrates. Alcohol consumption should be reduced in gout patients (60-68).

The treatment of gout consists of acute gout treatment, prophylaxis, and uric acid-lowering therapies. For the treatment of an acute gout attack, one or more anti-inflammatory treatments are used. Anti-inflammatory drugs include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and anti-IL-1β biological agents. The choice of drug is individualized. NSAIDs increase salt and fluid retention, thus raising the risk of hypertension and heart failure. They can also impair kidney function and are not suitable for use in chronic kidney failure. They should be discontinued as soon as possible to control a gout flare. However, premature discontinuation may lead to a recurrence of the gout flare. Colchicine treatment is initiated with 1.2 mg, followed by 0.6 mg. For prophylaxis, colchicine is given 0.6 mg once or twice daily. Colchicine should not be used with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine or clarithromycin), as they inhibit colchicine metabolism. In patients started on colchicine, a hemogram, liver function tests, and kidney function monitoring are recommended. It is not recommended for use in liver disease. In CKD, dosage adjustment is required if the GFR is below 50 mL/dL. Some authors suggest not using colchicine if GFR is less than 10 mL/dL. However, based on information from other diseases, we use adjusted doses of colchicine in patients with GFR <10 mL/dL or on dialysis. The use of glucocorticoids (oral, intra-articular, or intramuscular) is recommended. Prednisone 0.5 mg/kg or an equivalent dose is suggested. Prednisone can be continued at this level until the attack resolves completely, or an alternative dose reduction strategy can be used. A rapid reduction in glucocorticoid dose may lead to a recurrence of the gout flare. Among anti-IL-1β biological therapies, targeted antibodies (canakinumab), modified receptors (rilonacept), and recombinant receptor antagonists (anakinra) are available. While anakinra and canakinumab are effective in acute gout treatment, rilonacept has been found to be less effective than indomethacin in acute gout. Anakinra has a half-life of 6 hours and is applied daily (100 mg/day) for 3-5 days in acute gout treatment. Anakinra can also be used in CKD. For patients with CKD and a GFR <30 mL/min, it is recommended that anakinra be administered every other day. Adrenocorticotropic hormone has been used in the treatment of gout for a long time, especially as an alternative treatment option in difficult-to-treat cases. These anti-inflammatory treatment options are also recommended as short-term prophylaxis when ULT is initiated. Anti-inflammatory prophylaxis is done for 3-6 months. Additionally, in asymptomatic hyperuricemia patients, although the ACR does not provide any recommendations, the Japan Gout and Nucleic Acid Metabolism Society recommends uric acid-lowering treatment in patients with comorbidities and serum uric acid levels greater than 9.0 mg/dL (69-76).

ULT is recommended in the presence of subcutaneous tophi ≥1, radiographic findings suggestive of gout, frequent gout attacks (≥2 per year). If the number of gout attacks is <2 per year, uric acid serum levels >9 mg/dL, CKD, cardiovascular disease, and a risk-benefit evaluation should be considered. In patients experiencing their first gout flare, treatment can be initiated if CKD stage ≥3, uric acid >9 mg/dL, or urolithiasis is present, based on the benefit-risk assessment. The goal of ULT is to achieve a target serum urate concentration (i.e., <6 mg/dL or <5 mg/dL), resolve tophi, reduce or eliminate gout attacks over time, improve quality of life indicators, and correct radiographic changes. ULTs include xanthine oxidase inhibitors (allopurinol, febuxostat, topiroxostat),

uricosuric agents (probenecid, benzbromarone, lesinurad), and uricase (pegloticase). Allopurinol is most commonly used and should be started at a low dose and titrated gradually. The daily dose of allopurinol ranges from 100 to 600 mg, with a maximum dose of 800-900 mg. However, low-dose allopurinol (≤300 mg/day) has been shown to reduce the overall cardiovascular event risk, though high doses do not demonstrate a significant reduction in risk. In CKD patients, dose adjustments are necessary. For CKD stage ≥3, allopurinol ≤100 mg/day is recommended. Detection of HLA-B*5801 increases the risk of hypersensitivity syndrome with allopurinol. The recommended dose of febuxostat is 80–120 mg/day, but 40 mg/day has been found to reduce serum uric acid levels as well. For patients with renal insufficiency (GFR <30 mL/min), febuxostat does not require dose adjustment in dialysis patients, even though it has not been studied in this population. Lesinurad is an oral selective inhibitor of the renal URAT1 and OAT4 uric acid transporters. It increases uric acid excretion and is taken once daily at 200 mg. If the target serum uric acid level is not reached with xanthine oxidase inhibitors, lesinurad can be used in combination. Pegloticase enzymatically breaks down uric acid. Pegloticase reduces uric acid, resolves tophi, reduces the number of tender and swollen joints, alleviates pain, and improves quality of life. Pegloticase is administered IV at 8 mg every 2-4 weeks, and it is typically given for 3-6 months. The treatment algorithm for gout disease is given in **Figure 2**. Studies have also shown that sodium-glucose transport protein 2 (SGLT2) inhibitors reduce serum uric acid levels and decrease the risk of gout disease. SGLT2 inhibitors have been shown to reduce gout flares in gout patients (69-76).

## CONCLUSION

Gout is the most common cause of inflammatory arthritis. The most frequently affected joint is the first metatarsophalangeal joint, with involvement around the joint also being observed. Acute, severe arthritis, and any joint involvement should raise suspicion for gout. Gout has several risk factors, including conditions that can lead to hyperuricemia. The diagnosis of gout involves the identification of MSU crystals. Gout can be confused with septic arthritis and infections, but procalcitonin does not increase in gout. X-ray, ultrasound, and DECT can be used in the diagnosis of gout. The treatment of gout is individualized, and the treatment of patients with CKD is particularly important. In CKD, NSAIDs should be avoided, colchicine, anakinra, and allopurinol require renal dose adjustments.

## DECLERATIONS

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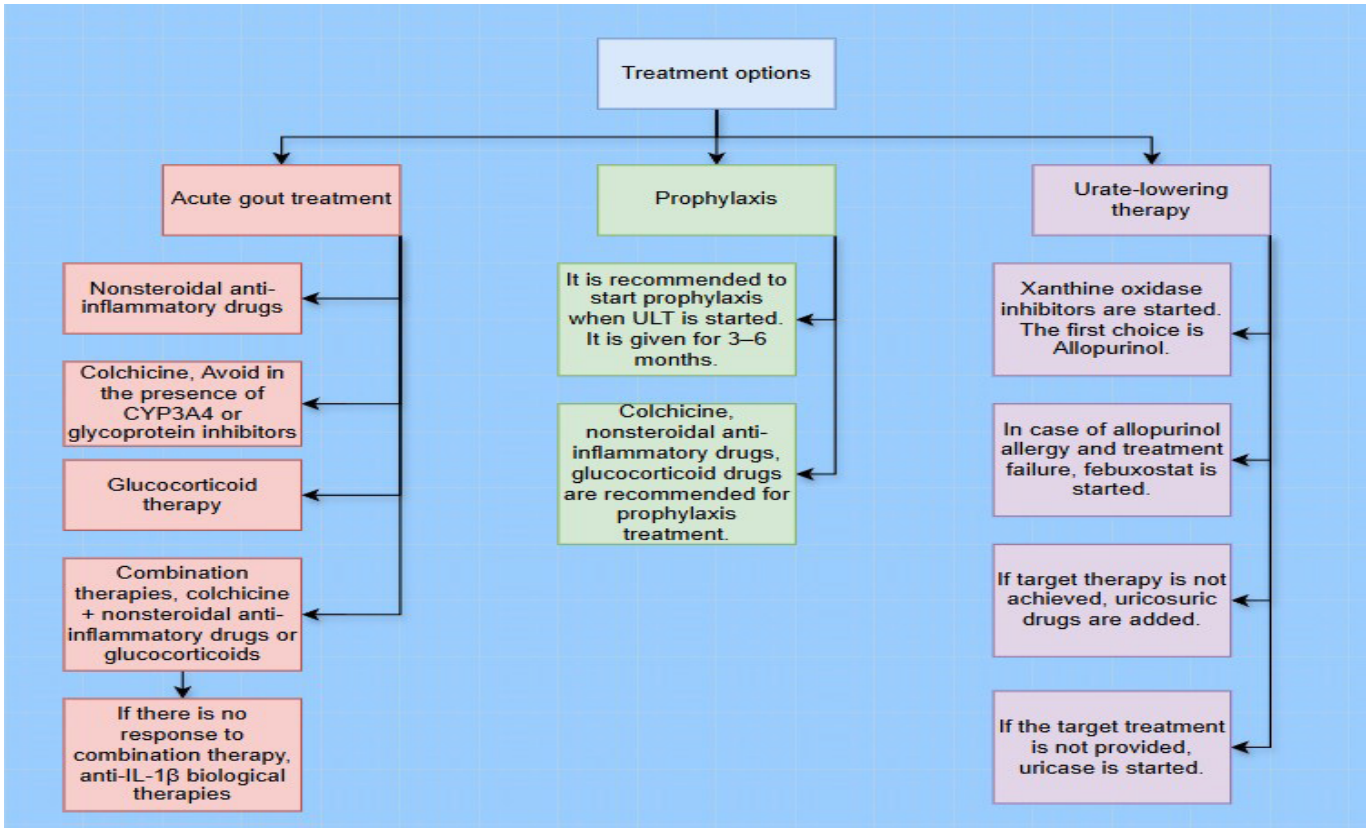


**Figure 2.** Treatment algorithm for gout disease

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Letter to Editor

# A Rare Relapse: Recurrence of Nephrotic Syndrome in an NPHS1 Mutation Post-Kidney Transplant

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*To the Editor,*

Renal transplantation is the most effective treatment for children with end-stage renal disease, offering the best long-term outcomes. However, recurrence of the primary disease can jeopardize graft survival, with post-transplant glomerulonephritis occurring in up to 45% of cases (1). In genetic forms of nephrotic syndrome, recurrence is considered rare, as the underlying defect is corrected with transplantation. Here, we present a case of recurrent focal segmental glomerulosclerosis after kidney transplantation in a patient with a heterozygous NPHS1 mutation, highlighting the need to better understand the mechanisms underlying post-transplant disease recurrence in genetic nephrotic syndrome.

A male patient was diagnosed with nephrotic syndrome at the age of 8 and underwent a renal biopsy at 13, confirming focal segmental glomerulosclerosis (FSGS). Genetic testing identified a p.Thr294Ile (c.881C>T) mutation in the NPHS1 gene. Despite multiple immunosuppressive treatments, the disease progressed to end-stage renal disease by age 20. He subsequently underwent a preemptive kidney transplant from his 55-year-old mother, who had normal renal function, with a 3/6 HLA match. Postoperatively, the patient received standard immunosuppressive therapy, including basiliximab, methylprednisolone, mycophenolate mofetil, and tacrolimus. The lowest serum creatinine level was 1.5 mg/dL within the first 10 days; however, by postoperative day 11, it increased to 1.9 mg/dL, raising concerns for graft dysfunction. Renal Doppler ultrasonography showed normal renal artery flow with a resistive index of 0.62. CMV-DNA was negative, and the spot urine protein-to-creatinine ratio was <300 mg/mg. Given these findings, recurrence of FSGS and de novo glomerulonephritis were initially ruled out.

By postoperative day 12, due to suspected cellular and humoral rejection, the patient was treated with intravenous methylprednisolone (250 mg/day for 3 days), anti-thymocyte globulin (600 mg total), and two plasmapheresis sessions with 12 units of fresh frozen plasma. By postoperative day 21, serum creatinine was 1.87 mg/dL, and the tacrolimus trough level was 8.2 ng/mL. At discharge, the immunosuppressive regimen was adjusted to extended-release tacrolimus (10 mg/day), mycophenolate mofetil (2000 mg/day), and prednisone (20 mg/day).

During follow-up, proteinuria increased to 1960 mg/mg, prompting the decision to perform a renal transplant biopsy at post-transplant month 3. At the time of the biopsy, the measured creatinine level was 2.0 mg/dL. Histopathological findings confirmed recurrent FSGS, leading to five plasmapheresis sessions and a single dose of rituximab (1000 mg). Losartan (100 mg/day) was initiated for its antiproteinuric effect. Maintenance immunosuppressive therapy was administered as extended-release tacrolimus (10 mg/day), mycophenolate mofetil (2000 mg/day), and prednisone (5 mg/day). The patient did not receive any additional doses of rituximab in the following period. Proteinuria gradually decreased, measuring 1000 mg/mg at one year and 380 mg/mg at two years post-transplant, while renal function remained stable (**Figure 1**). By the second year post-transplant, the patient's regimen included extended-release tacrolimus (5.5 mg/day), mycophenolic acid (1440 mg/day), and prednisone (5mg/day). Losartan (100 mg/day) was

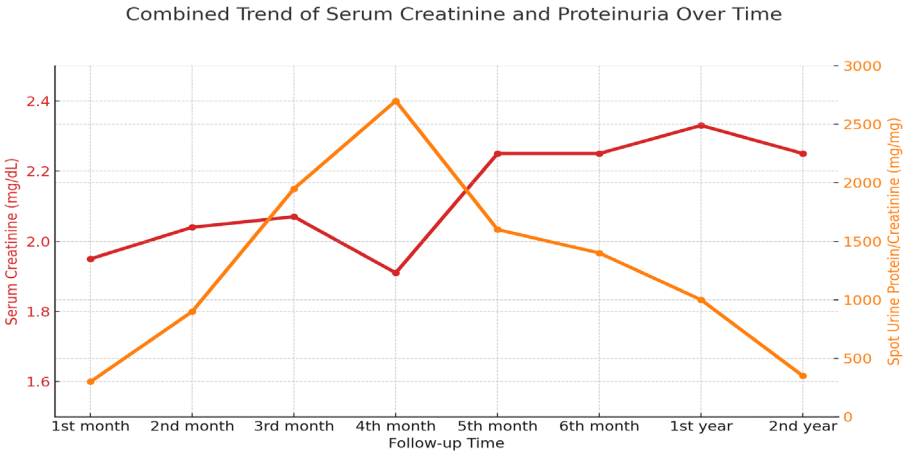


**Figure 1.** Combined trends of serum creatinine and spot urine protein/creatinine ratio over time after kidney transplantation, illustrating changes in renal function and proteinuria during follow-up.

continued for proteinuria management.

In patients with nephrotic syndrome, retrospective analyses of post-kidney transplant relapse cases show that relapses in genetic steroid-resistant nephrotic syndrome are very rare (2-4). In cases where relapse occurs, these relapses appear later compared to patients with non-genetic nephrotic syndrome, and they generally respond well to plasmapheresis treatment. Additionally, the kidney outcomes for these patients are typically good (4). However, the underlying mechanisms for the post-transplant relapse of genetic focal segmental glomerulosclerosis are not well understood. Circulating anti-nephrin antibodies may play a pathogenic role in the development of recurrent FSGS in patients with NPHS1 mutations but without NPHS2 mutations (5). Unlike previous reports where relapses occurred later, this case highlights the potential for early recurrence, underscoring the need for closer post-transplant monitoring in this subgroup. Nevertheless, the good prognosis was in line with the literature, as there was a response to plasmapheresis and no need for hemodialysis. In our case of a patient diagnosed with nephrotic syndrome due to an NPHS1 gene mutation, the occurrence of relapse in the early period post-transplant was unusual.

This case shows the early recurrence of FSGS after kidney transplantation in a patient with a heterozygous NPHS1 mutation, a phenomenon considered rare in genetic nephrotic syndrome. Despite the recurrence, the patient responded well to plasmapheresis and rituximab, with stable renal function and reduced proteinuria during follow-up. These findings demonstrates once the importance of close post-transplant monitoring and further research into the mechanisms of recurrence in genetic FSGS.

Sincerely,

## DECLERATIONS

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Letter to Editor

# Piperacillin-Tazobactam Induced Fanconi Syndrome

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*To the Editor,*

Proximal renal tubular acidosis (pRTA) is a rare condition characterized by impaired bicarbonate reabsorption in the proximal renal tubule, resulting in normal anion gap metabolic acidosis. Often occurring alongside Fanconi syndrome, it is marked by widespread proximal tubular dysfunction. Although genetic disorders and autoimmune conditions are known etiologies, medications have also been implicated (1). We report a unique case of piperacillin-tazobactam (Pip-Tazo) induced pRTA associated with Fanconi syndrome.

A 64-year-old female with hypertension and diabetes underwent surgical repair for a right hip fracture under spinal anesthesia with bupivacaine. Intravenous Pip-Tazo was initiated on postoperative day two for antibiotic prophylaxis and pneumonia treatment, alongside enoxaparin therapy. By postoperative day four, she exhibited polyuria and tachypnea. Laboratory tests indicated normal anion gap metabolic acidosis with hypokalemia and hypophosphatemia, consistent with proximal tubular dysfunction. Pip-Tazo was discontinued on day seven, and supplementation with sodium bicarbonate and potassium resulted in the gradual resolution of electrolyte abnormalities and metabolic acidosis over subsequent days. Laboratory values during follow-up confirmed these observations (Table 1). The temporal relationship between Pip-Tazo initiation and the resolution following its cessation strongly suggests causality. The role of bupivacaine was discounted, as spinal anesthetics generally do not enter systemic circulation.

Proximal RTA has previously been linked to several antimicrobials, including penicillin, cephalosporin, and aminoglycosides, but our literature search revealed no prior association with Pip-Tazo (2). Fanconi syndrome, characterized by increased urinary excretion and decreased plasma levels of substances usually reabsorbed by the proximal convoluted tubule (PCT),

**Table 1.** Laboratory values

| Postoperative: | Day 2. | Day 4. | Day 12. |
|---|---|---|---|
| Plasma chemistry | | | |
| pH | 7,40 | 7,32 | 7,54 |
| HCO3 (mEq/L) | 23,1 | 10,9 | 27,4 |
| CO2 (mmHg) | 41,1 | 11,6 | 31,9 |
| Lactate (mEq/L) | 0,9 | 1,0 | 1,0 |
| Na (mEq/L) | 134 | 126 | 131 |
| Cl (mEq/L) | 102 | 112 | 102 |
| K (mEq/L) | 4,30 | 2,58 | 4,07 |
| Glycose (mg/dL) | 277 | 304 | 189 |
| Creatinine (mg/dL) | 1,34 | 0,91 | 0,78 |
| Urea (mg/dL) | 67 | 45 | 41 |
| P (mg/dL) | 3,6 | 1,8 | 3,2 |
| Ca (mg/dL) | 8,06 | 7,64 | 8,64 |
| Mg (mg/dL) | 1,95 | 1,58 | 1,75 |
| Urate (mg/dL) | 6,5 | 2,5 | 2,9 |
| Albumin (g/dL) | 2,6 | 1,9 | 2,4 |
| Protein (g/dL) | 6,4 | 5,2 | 6,1 |
| PTH (pg/mL) | | 102 | |
| Vitamin D (ng/mL) | | 15 | |
| Urine analysis | | | |
| pH | 5 | 6 | 8 |
| WBC ( per hpf) | 3 | 2 | 1 |
| RBC (per hpf) | 68 | 27 | 14 |
| Glucose | pos | pos | neg |
| Ketone | neg | neg | neg |
| Protein | neg | pos | neg |
| K (mEq/L) | | 22,8 | |
| Na (mEq/L) | | 126 | |
| Cl (mEq/L) | | 33 | |
| Creatinine (mg/dL) | | 18 | |

often coexists with proximal RTA in patients exposed to causative agents (3). Our patient's clinical profile, low plasma potassium, phosphorus, and bicarbonate despite replacement, normal anion gap metabolic acidosis, increased urinary anion gap, and urinary alkalosis, was consistent with Fanconi syndrome.

Glucosuria, typically indicative of Fanconi syndrome, might partially be explained by transient hyperglycemia, given the patient's glucose exceeded 300 mg/dL on the day glucosuria was detected (4). However, the concurrent hypophosphatemia, hypokalemia, non-anion gap metabolic acidosis, alkaline urine, positive urinary anion gap, and rapid biochemical improvement after Pip-Tazo discontinuation collectively supported a diagnosis of drug-induced Fanconi syndrome rather than isolated hyperglycemia-related glucosuria.

Technical limitations prevented analysis of fractional excretion of bicarbonate, phosphorus, uric acid, protein, and amino acids, markers sensitive to proximal tubulopathy. Diagnosis was thus reliant on clinical and biochemical improvement post-drug withdrawal.

Typically, Fanconi syndrome is suspected when proximal tubulopathy arises with medication use, confirmed by symptom resolution upon withdrawal. The temporal relationship is generally clear, though late presentations (months or years later) have been documented with drugs like tenofovir (5). However, Fanconi syndrome linked to Pip-Tazo use is absent from existing literature.

The rapid onset of symptoms within 2-3 days post-administration and resolution following discontinuation strongly supports Pip-Tazo as the cause. Nevertheless, Pip-Tazo's exact pathogenic mechanism remains unclear, particularly since some literature argues against its nephrotoxicity (6). Using the Naranjo Adverse Drug Reaction Probability Scale, we scored a 5 out of 13, indicating a 'probable' association based on timing, symptom resolution upon withdrawal, laboratory confirmation, and exclusion of alternate causes (7).

Clinicians should remain vigilant for Fanconi syndrome in patients receiving Pip-Tazo, especially in postoperative scenarios. Early recognition and medication discontinuation are vital for patient recovery.

Sincerely,

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We obtained written informed consent from the patient to publish this case report.

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