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Research Article

Imbalance of Endogenous Opioids and Its Association With Pruritus Among Renal Transplant Recipients: A Cross-Sectional Study

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Background: Chronic pruritus (CP) is a common and distressing symptom among renal transplant recipients (RTRs), yet its pathogenesis remains poorly understood. Recent evidence suggests that dysregulation of the endogenous opioid system may contribute to pruritus in various conditions, but its role in RTRs has not been thoroughly investigated.
Objective: This study aimed to assess the concentrations of specific endogenous opioids (β-endorphin, dynorphin A, met-enkephalin, and leu-enkephalin) in RTRs with and without pruritus to explore their potential role in pruritus pathogenesis.
Methods: A total of 129 RTRs and 47 healthy controls were included in the study. Serum levels of β-endorphin, dynorphin A, met-enkephalin, and leu-enkephalin were measured using enzyme-linked immunosorbent assays (ELISAs). Pruritus severity was assessed using the Worst Pruritus Numerical Rating Scale (WP-NRS) and the 4-Item Itch Questionnaire (4IIQ).
Results: Pruritic RTRs had significantly lower serum β-endorphin levels compared to nonpruritic RTRs ($p = 0.008$). However, there were no significant differences in dynorphin A, met-enkephalin, or leu-enkephalin levels between pruritic and nonpruritic RTRs or between RTRs and healthy controls. The β-endorphin to dynorphin A ratio also did not differ significantly between groups.
Conclusion: The study suggests that disturbances in the endogenous opioid system, particularly involving β-endorphin, may play a role in the pathogenesis of pruritus in RTRs. Further research is needed to elucidate the precise mechanisms and to explore potential therapeutic interventions targeting the opioid system in this population.

Keywords: β-endorphin; chronic pruritus; dynorphin A; endogenous opioids; kidney transplantation; renal transplant recipients

Summary

Why carry out this study?

- CP is a significant burden in RTRs, affecting quality of life and remaining poorly understood.
- No research exists on the role of the endogenous opioid system in pruritus among RTRs, despite its recognized involvement in other forms of pruritus.

What did the study ask?

- The study aimed to assess the concentration of specific endogenous opioids in pruritic RTRs to explore their potential role in pruritus pathogenesis.

What was learned from the study?

- The study found that pruritic RTRs have significantly lower β-endorphin levels compared to nonpruritic

RTRs, suggesting a potential link between opioid system disturbances and pruritus in this population.

What has been learned from the study?

- While the findings support the involvement of the opioid system in RTR-associated pruritus, they also highlight the complexity of the condition, indicating a need for further investigation into other contributing factors.

1. Introduction

Chronic pruritus (CP) is a sensation causing the desire to scratch, which lasts for at least 6 weeks [1]. CP is a common symptom affecting approximately 13.5% of the general adult population, with an increasing prevalence among the elderly [2, 3]. It has also been reported that every fifth adult suffered from CP at least once in their life [1]. CP is frequently associated with dermatological disorders. In various chronic dermatoses, including atopic dermatitis (AD) and urticaria, its prevalence may reach up to 100% [4]. Nevertheless, in nondiseased skin, it may also be a symptom of systemic, neurological, malignant, or psychiatric conditions, as well as a side effect of numerous medications [1, 3, 5]. The burden of CP has been vastly studied. According to the available knowledge, it is associated with impaired quality of life (QoL), sleep disturbances, depression, and anxiety [6]. Given its multifactorial nature, CP remains challenging to diagnose, and its treatment is often unsatisfactory for both patients and clinicians.

Recent research has highlighted the significant role of opioid system dysregulation in the pathophysiology of pruritus in chronic kidney disease (CKD) [7–10]. The primary opioid receptors implicated in itch transmission include μ-opioid receptors (MORs), κ-opioid receptors (KORs), and δ-opioid receptors (DORs). Notably, activation of MOR has been associated with the promotion of itch, whereas KOR activation appears to exert an inhibitory effect [11]. Furthermore, recent findings have corroborated the involvement of opioid receptors in the pathogenesis of CKD–associated pruritus (CKD–aP), a common and distressing symptom among patients with advanced or end-stage renal disease (ESRD) [7, 8, 12].

Kidney transplantation (KTx) remains an essential therapeutic intervention for ESRD patients, offering substantial improvements in survival and QoL compared to long-term hemodialysis. Nevertheless, renal transplant recipients (RTRs) are not exempt from long- and short-term complications, with CP being a particularly challenging issue [6, 13]. Our previous studies indicated that pruritus affects up to 21.3% of RTRs, with most cases developing after KTx [13]. Moreover, our group recently found that IL-31 and neurotrophin 4 (NT-4) may play an important role in the development of CP in RTRs [14, 15]. Nevertheless, despite unveiling the prevalence, burden, and several possible pathomechanisms behind CP in RTRs, its precise etiology remains poorly understood, reflecting a critical gap in the current knowledge.

Given the limited research and the complex mechanisms underlying pruritus, effective management of CP remains a significant challenge. Consequently, this study aimed to assess the concentration of endogenous opioids (met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin A) in pruritic patients following KTx.

2. Materials and Methods

The study complied with the Declaration of Helsinki and received ethical approval from the Wroclaw Medical University Institutional Review Board (number: KB-750/2021). Informed, written consent was obtained from all participants prior to their inclusion in the study. The research was carried out between March and November 2021 at the Department of Nephrology and Transplantation Medicine and the Department of Dermatology, Venereology and Allergology of Wroclaw Medical University, Wroclaw, Poland.

2.1. Participants. A total of 129 RTRs participated in the study, all of whom were adults with functioning renal transplants. Patients with chronic dermatological disorders or other conditions potentially contributing to pruritus were excluded to ensure the accuracy of the results. The participants' demographic and clinical data, such as sex, age, body mass index (BMI), duration of CKD, time spent on dialysis, time posttransplantation, atopic predisposition, and family history, were meticulously recorded. The exclusion criteria comprised patients under 18, those who could not cooperate or complete the questionnaire, individuals with active skin disorders, other itchy conditions, and nonfunctioning kidney transplants. Moreover, all patients receiving treatments that possibly affect serum opioid levels (phototherapy, pain medication, and opioid analgesics) were excluded. The RTRs were stratified into two groups based on the presence or absence of pruritus within the preceding three days, while 47 healthy volunteers from the Wroclaw Blood Donation Center served as the healthy control (HC) group.

2.2. Pruritus Assessment. Pruritus severity was evaluated using the Worst Pruritus Numerical Rating Scale (WP-NRS) and the 4-Item Itch Questionnaire (4IIQ) [16, 17]. The WP-NRS is an 11-point scale where participants rate their worst pruritus over the past three days, with scores ranging from 0 (*no pruritus*) to 10 (*worst imaginable pruritus*). The following cut-off points were applied: 1–2 points indicate mild pruritus, 3–6 points indicate moderate pruritus, 7–8 points indicate severe pruritus, and scores of 9 or above represent very severe pruritus [16]. The 4IIQ was used to further assess pruritus, measuring intensity, frequency, extent, and the impact of itch on sleep. Each parameter was scored on a six-point scale, with 0 points indicating no pruritus or disturbance and 5 points indicating the most severe pruritus, highest frequency, broader involvement, or greatest sleep disturbance. Higher overall scores on the 4IIQ correspond to more severe pruritus [17]. In addition, the Itchy QoL (ItchyQoL) questionnaire was employed to assess

the impact of CP on patients' QoL [18]. This tool includes 22 items divided into three domains: symptoms, functional limitations, and emotional impact. Responses for frequency items were scored on a scale from 1 (*never*) to 5 (*all the time*), while bother items were scored from 1 (*not bothered*) to 5 (*severely bothered*) [18].

2.3. Laboratory Tests. Blood samples (9 mL) were collected from each RTR (129 subjects) and from 47 HCs. To ensure the integrity of the samples, all blood draws were performed under standardized conditions. Following collection, the samples were immediately centrifuged at 3000 rpm for 15 min to separate the serum. The serum was then aliquoted and stored at −80°C until further analysis to preserve the stability of the analytes.

To quantify endogenous opioid peptides, enzyme-linked immunosorbent assays (ELISAs) were conducted according to the manufacturer's protocols. Specifically, the concentrations of met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin A were measured using commercially available ELISA kits: met-enkephalin (S-1419 Met-Enkephalin ELISA Kit, BMA Biomedicals, Augst, Switzerland), leu-enkephalin (Leu-Enkephalin EIA Kit, Phoenix Pharmaceuticals, Inc., Burlingame, California, United States of America), β-endorphin (Nori Human β-endorphin ELISA Kit, GR111460-1, Genorise Scientific, Inc., Pennsylvania, United States of America), and dynorphin A (RayBio Human Dynorphin A EIA Kit, Ray Biotech, Inc., Peachtree Corners, Georgia, United States of America). The absorbance was read at 450 nm using an EPOCH multiplate reader (BioTEK Instruments, Inc., Winooski, Vermont, United States of America). Met-enkephalin, leu-enkephalin, and dynorphin A concentrations in the serum were expressed in ng/mL, while β-endorphin concentrations were reported in pg/mL.

To explore the balance between opioid receptor agonists, the ratio of MOR agonists to KOR agonists was calculated. This ratio was determined by dividing the plasma concentration of β-endorphin by that of dynorphin A, providing insight into the relative activation potential of these two pathways.

In the same blood samples.

For the comparison, the serum levels of IL-31, NT-4 and brain-derived neurotrophic factor (BDNF) were measured using the ELISA technique with commercially available kits from Genorise Scientific, Inc. (Glen Mills, Pennsylvania, United States of America). Specifically, the Nori Human IL-31 ELISA Kit (catalog number: GR 111374) was used to measure IL-31, while the Nori Human NT-4 ELISA Kit (catalog number: GR111502) and the Nori Human BDNF ELISA Kit (catalog number: GR111085) were used for NT-4 and BDNF, respectively. All procedures were carried out according to the manufacturer's instructions. The absorbance of the samples was measured at a wavelength of 450 nm using the EPOCH microplate reader (BioTEK Instruments, Inc., Winooski, Vermont, United States of America). IL-31 had a test range of 50–3200 pg/mL with a sensitivity of 10 pg/mL. The ingredients were used in previous studies [14, 15].

2.4. Statistical Analysis. The statistical analysis was performed using IBM SPSS Statistics Version 26 (SPSS Inc., Chicago, llinois, United States of America). Initially, all datasets were tested for normality using the Shapiro–Wilk test. Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Comparisons between groups were conducted using the independent samples *t*-test for normally distributed data, while the Mann–Whitney *U* test was applied for non-normally distributed data. Correlations between variables were assessed using Pearson's correlation coefficient for parametric data and Spearman's rank correlation coefficient for nonparametric data.

For group comparisons involving more than two groups, the Kruskal–Wallis test was utilized for nonparametric data and analysis of variance (ANOVA) was applied for parametric data. Where applicable, post hoc analyses with Bonferroni correction were performed to adjust for multiple comparisons. The chi-square test was used to analyze the association between categorical variables. The significance level for all statistical tests was set at $p \leq 0.05$, and all results were interpreted within this threshold to determine statistical significance.

3. Results

3.1. Baseline Characteristic of the Study Group. Overall, 129 RTRs were enrolled in the study. Among them, 74 (57.4%) were male, and 55 (42.6%) were female. The mean age of the entire cohort was 52.01 ± 13.54 years, with no significant difference between the pruritic and nonpruritic groups (51.24 ± 14.58 years vs. 53.07 ± 12.0 years, respectively). The study participants were slightly overweight, with an average BMI of 25.92 ± 5.3 kg/m^2. BMI was comparable between groups, with no significant differences.

The duration of kidney disease and the time spent on dialysis before transplantation were similar between the two groups, with the entire cohort averaging 19.90 ± 12.23 years of disease duration and 2.38 ± 1.97 years on dialysis. The time since renal transplantation was slightly longer in the pruritic group (8.7 ± 6.54 years) compared to the nonpruritic group (7.1 ± 7.45 years), but this difference was not statistically significant. 16.3% of participants declared a predisposition to atopy, and 17.1% had a higher propensity for atopy to appear in the family. A notable difference between the groups was observed in the history of pruritus during dialysis and after transplantation. While 35.7% of the entire cohort reported pruritus during dialysis, a significantly higher percentage of pruritic RTRs (61.1%) had experienced pruritus during dialysis compared to the nonpruritic group (17.3%) ($p < 0.001$). During hemodialysis, 38.57% of RTRs experienced pruritus. After transplantation, this number dropped significantly, with only 21.3% continuing to report itch. Among these, 73.7% saw complete resolution post-transplant, mostly with immediate relief. For those who still had pruritus after transplantation, 52.4% reported a new onset, while 47.6% experienced residual itch from hemodialysis, though generally with lower severity.

The thorough characteristics of studied populations have already been published in our previous study [15].

3.2. Pruritus Assessment in Pruritic RTRs. On average, pruritic RTRs scored 4.98 ± 2.41 points on the NRS, indicating moderate pruritus. Most cases reported mild or moderate pruritus (38.9% and 37%, respectively). Patients with severe and very severe pruritus accounted for 13% and 11.1% of the whole pruritic group, respectively. The mean 4IIQ score was 6.61 ± 2.51 points. The detailed characteristics of the studied populations have already been published [15].

3.3. Serum Levels of Met-Enkephalin, Leu-Enkephalin, β-endorphin, and Dynorphin A in RTRs and in the Control Group. The analysis of serum opioid concentrations revealed significant differences in β-endorphin levels between pruritic and nonpruritic RTRs. β-Endorphin levels were significantly lower in the pruritic group (211.6 ± 56.6 pg/mL) compared to the nonpruritic group (253.2 ± 78.0 pg/mL, $p = 0.008$). However, no significant differences were observed between the pruritic group and HCs (244.6 ± 79.5 pg/mL), as well as nonpruritic RTRs and HCs.

Other opioids, such as met-enkephalin and leu-enkephalin, showed no statistically significant difference between all pruritic RTRs, nonpruritic RTRs, and HCs. In addition, pruritic RTRs had numerically lower dynorphin A concentrations compared to nonpruritic RTRs (152.0 ± 83.6 ng/mL vs. 164.1 ± 68.5 ng/mL), but the difference was not statistically significant. Dynorphin A levels did not significantly vary between RTRs and HCs. The ratio of β-endorphin to dynorphin A also showed no significant differences between the studied groups. The results of serum opioid concentrations in the studied groups are presented in Table 1.

Correlation analysis further highlighted significant associations involving β-endorphin levels. A moderate, positive correlation was found between β-endorphin levels and the pruritus severity according to the NRS ($r = 0.306$, $p = 0.025$) (Figure 1), and a negative, weak correlation was observed with interleukin-31 (IL-31) levels ($r = -0.209$, $p = 0.006$) (Figure 1). In addition, β-endorphin levels correlated positively with BDNF ($r = 0.150$, $p = 0.048$). The β-endorphin to dynorphin ratio showed a positive correlation with both the 4IIQ ($r = 0.272$, $p = 0.047$) and the ItchyQoL score ($r = 0.288$, $p = 0.034$) (Figure 1).

4. Discussion

CKD–aP is a prevalent and distressing symptom among patients with ESRD, with its severity typically escalating along with the duration of dialysis and the progressive decline in renal function [19]. While CKD–aP has been extensively studied in hemodialysis patients, pruritus in RTRs remains underexplored. Notably, most RTRs who experience CP report significant relief or a reduction in itch severity following successful transplantation [13, 20, 21]. Intriguingly, our study identified that pruritus developed *de novo* in 42.86% of RTRs, suggesting a potentially distinct pathophysiological mechanism compared to CKD–aP in patients on hemodialysis [13].

The endogenous opioid system, known for its critical role in modulating pain, also appears to be a key player in the pathogenesis of pruritus. There are three primary opioid receptors, MOR, KOR, and DOR, each differing in their ligand-binding affinities and physiological effects [11]. Activation of KOR, predominantly by dynorphins, has been shown to suppress itching, whereas MOR activation by endorphins tends to exacerbate pruritus [11]. Recent studies have demonstrated a significant correlation between reduced KOR expression and increased MOR activity with the severity of pruritus in CKD patients [7, 12].

Opioid receptors play diverse roles in itch sensation. Opioid-induced pruritus is a common adverse effect associated with MOR agonists. Conversely, MOR antagonists have been found to alleviate itch in various conditions. Peer et al. [22] reported that naltrexone, a MOR antagonist, significantly reduced pruritus in patients with CKD–aP [22]. Similarly, Monroe [23] demonstrated that nalmefene could reduce itch in patients with chronic urticaria and AD [23]. Another MOR antagonist, nalbuphine, has been shown to be both safe and effective in diminishing itch intensity in hemodialysis patients [24]. In addition, KOR agonists such as nalfurafine and difelikefalin have shown promise in managing CKD–aP, further supporting the hypothesis that opioid receptor dysregulation contributes to CKD–aP development [25, 26].

The study from 2023 by Wala-Zielinska et al. [27] revealed that hemodialysis patients with CP had significantly lower β-endorphin levels, as well as a reduced β-endorphin to dynorphin ratio [27]. Interestingly, while pruritic RTRs exhibited statistically lower β-endorphin concentrations compared to their nonpruritic counterparts, there was no significant difference between the pruritic RTR group and the control group [27]. Moreover, dynorphin A concentrations did not differ significantly among the groups studied, consistent with our previous findings [27].

Enkephalins, another class of endogenous opioids, have been found to have elevated levels in patients receiving hemodialysis [27, 28]. However, the relationship between enkephalin levels and pruritus is still unclear. Our research indicated that met-enkephalin levels were significantly higher in pruritic hemodialysis patients compared to those without pruritus [27]. In contrast, Danno, Nishiura, and Tanaka. [28] did not observe such an association. Furthermore, evidence supporting the role of leu-enkephalin in itch development remains insufficient [27, 29]. The findings of this study did not support the involvement of met-enkephalin and leu-enkephalin in pruritus pathogenesis. The suggested pathway of involvement of endogenous opioids in the pathogenesis of pruritus is illustrated in Figure 2.

The observed correlations between β-endorphin levels, itch severity, and IL-31 suggest a complex interplay between the opioid and immune systems in modulating pruritus among RTRs. The reduced β-endorphin levels in pruritic RTRs may reflect an increased sensitivity of the MOR

Table 1: Serum levels of endogenous opioids in renal transplant recipients.

Characteristics	Nonpruritic RTRs No pruritus in last 3 days ($n = 75$)	Pruritic RTRs Pruritus in last 3 days ($n = 54$)	Control ($n = 47$)	p	Post hoc
Met-enkephalin (ng/mL, mean ± SD)	271.0 ± 96.5	269.9 ± 117.9	260.4 ± 99.4	NS	NA
Leu-enkephalin (ng/mL, mean ± SD)	5.3 ± 3.8	5.5 ± 3.5	7.2 ± 5.4	NS	NA
β-endorphin (pg/mL, mean ± SD)	253.2 ± 78.0	211.6 ± 56.6	244.6 ± 79.5	0.008	Nonpruritic vs. pruritic $p = 0.008$ Nonpruritic vs control NS Pruritic vs. control NS
Dynorphin A (ng/mL, mean ± SD)	164.1 ± 68.5	152.0 ± 83.6	164.1 ± 94.3	NS	NA
β-endorphin to dynorphin A ratio (mean ± SD)	1.8 ± 1.0 (0.002 ± 0.001 adjusted)	1.9 ± 1.2 (0.002 ± 0.001 adjusted)	1.8 ± 0.8 (0.002 ± 0.001)	NS (NS adjusted)	NA

Note: n, number of patients; NS, not statistically significant.
Abbreviation: RTRs, renal transplant recipient.

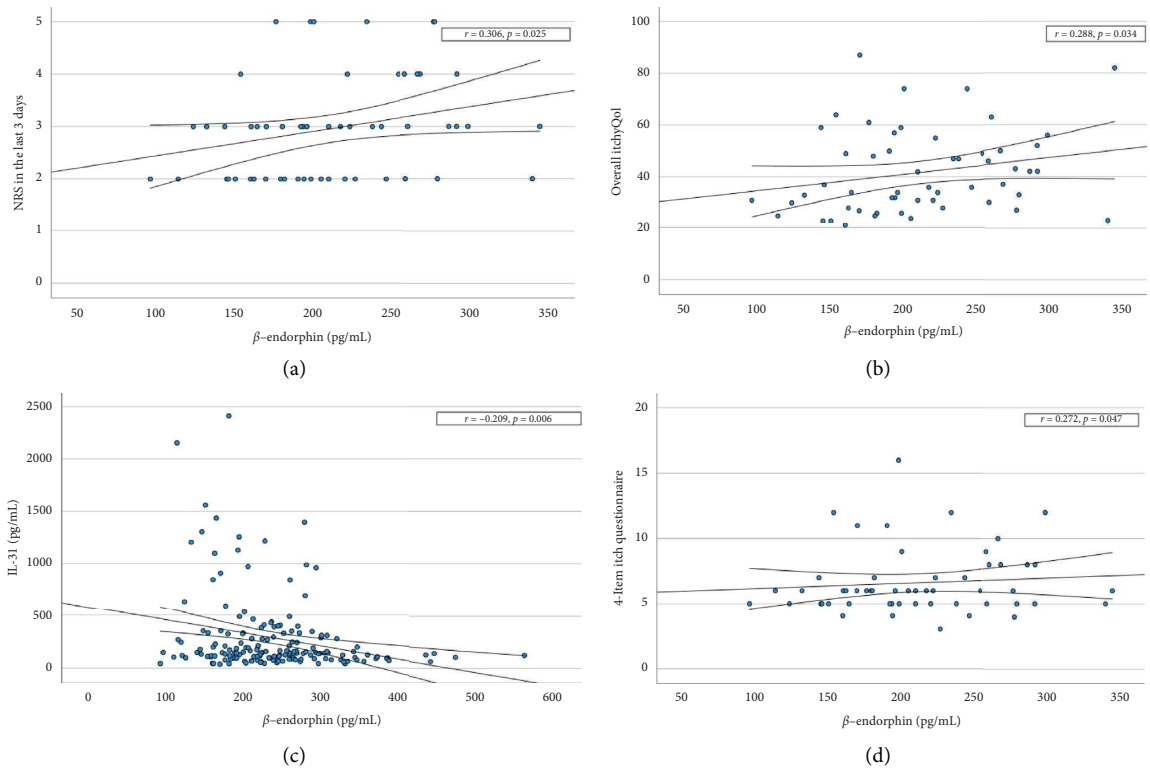

FIGURE 1: Correlations between β-endorphin concentrations and NRS in the last 3 days (a), overall ItchyQoL score (b), IL-31 concentration (c), and 4-item itch questionnaire score (d).

pathway, potentially heightening itch responses even at low β-endorphin concentrations. Concurrently, the negative correlation with IL-31 implies that elevated IL-31 levels might further disrupt β-endorphin availability or activity, amplifying pruritus through neuroimmune pathways. Lastly, the positive association between β-endorphin levels and itch severity within the pruritic group could indicate a compensatory response aimed at moderating the itch, though likely inadequate due to opioid system dysregulation. Furthermore, the absence of significant β-endorphin differences between pruritic RTRs and HCs may suggest a unique alteration in β-endorphin dynamics specific to the RTR population, potentially arising from transplantation-related changes in opioid receptor regulation. Collectively, these findings underscore the intertwined roles of opioid and immune dysregulation in pruritus among RTRs, with IL-31 exacerbating the condition in the presence of impaired β-endorphin-mediated inhibition.

The role of endogenous opioids in pruritus appears significant across various pruritic conditions, with studies indicating that pathways involving neuroimmune interactions may underlie itch in both AD and psoriasis (Pso) [30]. For instance, IL-31, often elevated in AD, stimulates β-endorphin production via keratinocytes, which can transmit itch through the MOR pathway, contributing to the intense pruritus typical of AD [30]. Similarly, in Pso, β-endorphin and MOR dynamics may also modulate itch, though with notable differences: Pso-associated itch is generally tied to visible lesions, while AD-related itch can occur without apparent skin changes, suggesting divergent mechanisms [30]. Exploring these common opioid-mediated and neuroimmune pathways in chronic kidney disease–associated pruritus could reveal overlapping pruritic mechanisms while highlighting CKD–specific pathways, thus advancing therapeutic strategies tailored to each condition.

This study, while offering valuable insights, has some limitations that should be considered when interpreting the results. First, the cross-sectional design restricts our ability to determine causality between opioid levels and pruritus. However, the findings provide a crucial foundation for future longitudinal studies that could explore these relationships more deeply. Second, although our cohort is one of the largest to date in studying pruritus among RTRs, it may only partially capture the diversity of the RTR population. Nonetheless, the study's rigorous selection criteria and exclusion of confounding conditions help ensure that the findings are robust and relevant to the specific population of interest. In addition, while self-reported measures of pruritus are inherently subjective, the use of validated and widely accepted scales minimizes bias and enhances the reliability of the results. Lastly, although our focus was on the opioid system, which is a key player in pruritus, other potential contributing factors were

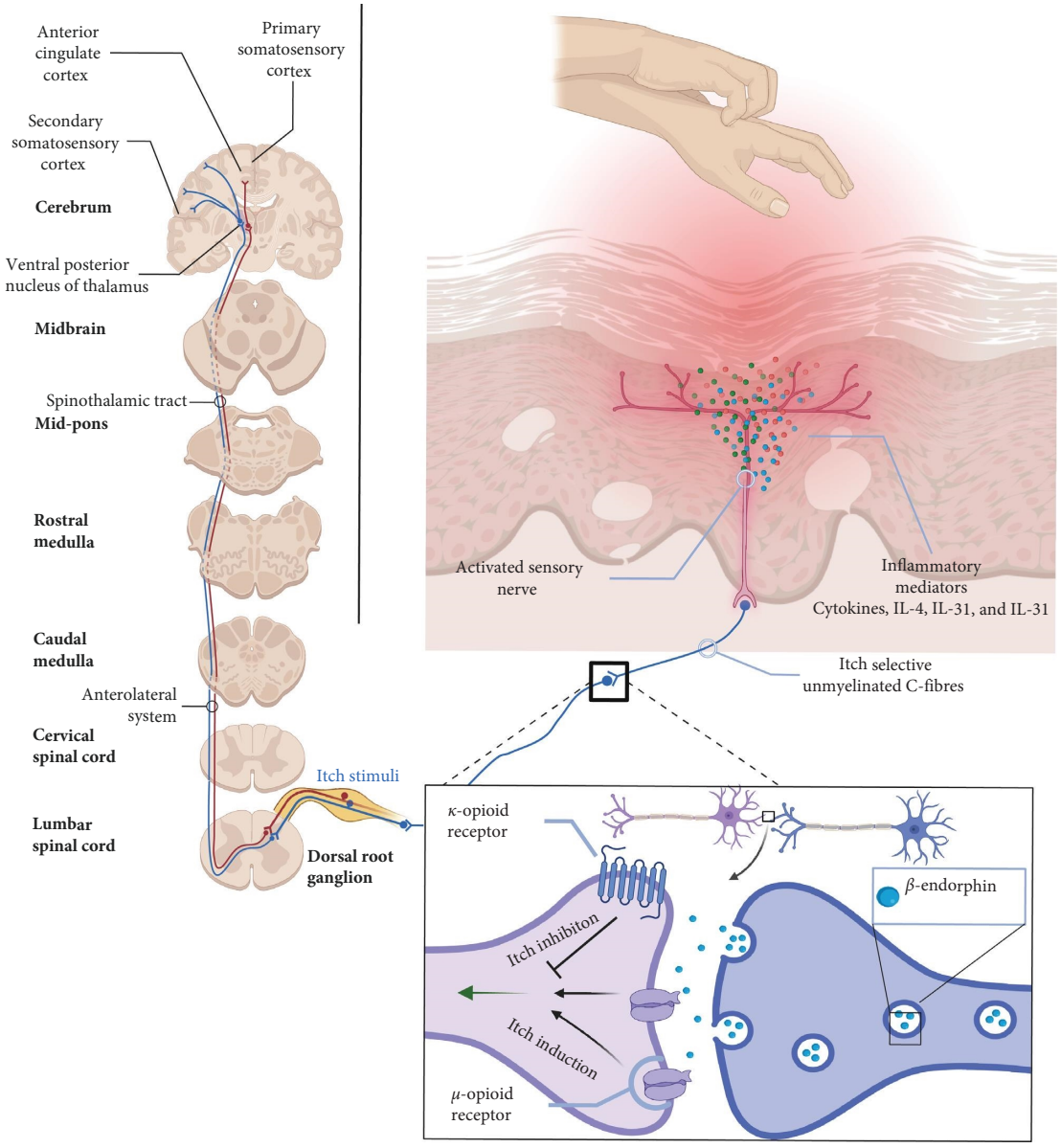

Figure 2: Graphical presentation of endogenous opioid implication in the pathomechanism of pruritus in renal transplant recipients.

not explored in this study. Future research could build on these findings by examining additional biochemical pathways to provide a more comprehensive understanding of pruritus in RTRs.

5. Conclusions

Our study suggests that disturbances in the endogenous opioid system, particularly involving β-endorphin and its interaction with dynorphin A, may contribute to the pathogenesis of pruritus in RTRs. The findings indicate that pruritic RTRs have lower levels of β-endorphin compared to nonpruritic RTRs, although this difference does not extend to HCs. Despite these insights, the precise mechanisms remain elusive, necessitating further research. Understanding these pathways could lead to the development of targeted therapies to manage pruritus in this vulnerable patient population better.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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References

[1] E. Weisshaar, J. C. Szepietowski, F. J. Dalgard, et al., "European S2k Guideline on Chronic Pruritus," *Acta Dermato-Venereologica* 99, no. 5 (2019): 469–506, https://doi.org/10.2340/00015555-3164.

[2] U. Matterne, C. J. Apfelbacher, A. Loerbroks, et al., "Prevalence, Correlates and Characteristics of Chronic Pruritus: A Population-Based Cross-Sectional Study," *Acta Dermato-Venereologica* 91, no. 6 (2011): 674–679, https://doi.org/10.2340/00015555-1159.

[3] A. Reich, S. Ständer, and J. C. Szepietowski, "Drug-Induced Pruritus: A Review," *Acta Dermato-Venereologica* 89, no. 3 (2009): 236–244, https://doi.org/10.2340/00015555-0650.

[4] C. F. Wahlgren, "Pathophysiology of Itching in Urticaria and Atopic Dermatitis," *Allergy* 47, no. 12 (1992): 65–75, https://doi.org/10.1111/j.1398-9995.1992.tb05091.x.

[5] K. Welz-Kubiak, R. Reszke, and J. C. Szepietowski, "Pruritus as a Sign of Systemic Disease," *Clinics in Dermatology* 37, no. 6 (2019): 644–656, https://doi.org/10.1016/j.clindermatol.2019.07.031.

[6] P. K. Krajewski, K. Tyczyńska, K. Bardowska, P. Olczyk, M. Krajewska, and J. C. Szepietowski, "Psychosocial Burden of Itch Among Renal Transplant Recipients," *Toxins* 14, no. 5 (2022): 320, https://doi.org/10.3390/toxins14050320.

[7] A. Wieczorek, P. Krajewski, M. Kozioł-Gałczyńska, and J. C. Szepietowski, "Opioid Receptors Expression in the Skin of Haemodialysis Patients Suffering From Uraemic Pruritus," *Journal of the European Academy of Dermatology and Venereology* 34, no. 10 (2020): 2368–2372, https://doi.org/10.1111/jdv.16360.

[8] B. Wikström, R. Gellert, S. D. Ladefoged, et al., "Kappa-Opioid System in Uremic Pruritus: Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Studies," *Journal of the American Society of Nephrology* 16, no. 12 (2005): 3742–3747, https://doi.org/10.1681/ASN.2005020152.

[9] A. Reich and J. C. Szepietowski, "Opioid-Induced Pruritus: An Update," *Clinical and Experimental Dermatology* 35, no. 1 (2010): 2–6, https://doi.org/10.1111/j.1365-2230.2009.03463.x.

[10] B. S. Kim, S. Inan, S. Ständer, T. Sciascia, J. C. Szepietowski, and G. Yosipovitch, "Role of Kappa-Opioid and Mu-Opioid Receptors in Pruritus: Peripheral and Central Itch Circuits," *Experimental Dermatology* 31, no. 12 (2022): 1900–1907, https://doi.org/10.1111/exd.14669.

[11] C. Stein, "Opioid Receptors," *Annual Review of Medicine* 67, no. 1 (2016): 433–451, https://doi.org/10.1146/annurev-med-062613-093100.

[12] Y. S. Roh, J. Choi, N. Sutaria, and S. G. Kwatra, "Itch: Epidemiology, Clinical Presentation, and Diagnostic Workup," *Journal of the American Academy of Dermatology* 86, no. 1 (2022): 1–14, https://doi.org/10.1016/j.jaad.2021.07.076.

[13] P. K. Krajewski, P. Olczyk, M. Krajewska, W. Krajewski, and J. C. Szepietowski, "Clinical Characteristics of Itch in Renal Transplant Recipients," *Frontiers of Medicine* 7 (2020): 615334, https://doi.org/10.3389/fmed.2020.615334.

[14] P. K. Krajewski, K. Tyczyńska, K Bardowska, et al., "High Serum IL-31 Concentration is Associated With Itch Among Renal Transplant Recipients," *Journal of Clinical Medicine* 11, no. 15 (2022): 4309, https://doi.org/10.3390/jcm11154309.

[15] K. Tyczyńska, P. K. Krajewski, D. Nowicka-Suszko, et al., "Neurotrophin-4 and Brain-Derived Neurotrophic Factor Serum Levels in Renal Transplant Recipients With Chronic Pruritus," *Dermatologic Therapy* 13, no. 11 (2023): 2785–2796, https://doi.org/10.1007/s13555-023-01029-4.

[16] A. Reich, E. Chatzigeorkidis, C. Zeidler, et al., "Tailoring the Cut-Off Values of the Visual Analogue Scale and Numeric Rating Scale in Itch Assessment," *Acta Dermato-Venereologica* 97, no. 6 (2017): 759–760, https://doi.org/10.2340/00015555-2642.

[17] A. Reich, K. Mędrek, and J. Szepietowski, "Czteropunktowy Kwestionariusz Oceny Świądu-Walidacja Kwestionariusza," *Dermatology Review/Przegląd Dermatologiczny* 99, no. 5 (2012): 600–604.

[18] N. S. Desai, G. B. Poindexter, Y. M. Monthrope, S. E. Bendeck, R. A. Swerlick, and S. C. Chen, "A Pilot Quality-of-Life Instrument for Pruritus," *Journal of the American Academy of Dermatology* 59, no. 2 (2008): 234–244, https://doi.org/10.1016/j.jaad.2008.04.006.

[19] X. Hu, Y. Sang, M. Yang, X. Chen, and W. Tang, "Prevalence of Chronic Kidney Disease-Associated Pruritus Among Adult Dialysis Patients: A Meta-Analysis of Cross-Sectional Studies," *Medicine (Baltimore)* 97, no. 21 (2018): e10633, https://doi.org/10.1097/md.0000000000010633.

[20] S. Schricker, E. Weisshaar, J. Kupfer, and T. Mettang, "Prevalence of Pruritus in a Single Cohort of Long-Term Kidney Transplant Recipients," *Acta Dermato-Venereologica* 100, no. 4 (2020): 1–2, https://doi.org/10.2340/00015555-3421.

[21] V. Panuccio, R. Tripepi, M. Bellantoni, et al., "Pruritus and Quality of Life in Renal Transplant Patients," *Clinical Transplantation* 31, no. 3 (2017): https://doi.org/10.1111/ctr.12893.

[22] G. Peer, S. Kivity, O. Agami, et al., "Randomised Crossover Trial of Naltrexone in Uraemic Pruritus," *The Lancet* 348, no. 9041 (1996): 1552–1554, https://doi.org/10.1016/s0140-6736(96)04176-1.

[23] E. W. Monroe, "Efficacy and Safety of Nalmefene in Patients With Severe Pruritus Caused by Chronic Urticaria and Atopic Dermatitis," *Journal of the American Academy of Dermatology* 21, no. 1 (1989): 135–136, https://doi.org/10.1016/s0190-9622(89)80353-6.

[24] V. S. Mathur, J. Kumar, P. W. Crawford, H. Hait, T. Sciascia, and T. R. S. Investigators, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Nalbuphine ER Tablets for Uremic Pruritus," *American Journal of Nephrology* 46, no. 6 (2017): 450–458, https://doi.org/10.1159/000484573.

[25] S. Fishbane, A. Jamal, C. Munera, W. Wen, F. Menzaghi, and K.-T. Investigators, "A Phase 3 Trial of Difelikefalin in Hemodialysis Patients With Pruritus," *New England Journal of Medicine* 382, no. 3 (2020): 222–232, https://doi.org/10.1056/nejmoa1912770.

[26] B. Wikstrom, R. Gellert, S. D. Ladefoged, et al., "Kappa-Opioid System in Uremic Pruritus: Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Studies," *Journal of the American Society of Nephrology* 16, no. 12 (2005): 3742–3747, https://doi.org/10.1681/ASN.2005020152.

[27] K. Wala-Zielinska, K. Swierczynska-Mroz, P. K. Krajewski, D. Nowicka-Suszko, M. Krajewska, and J. C. Szepietowski, "Endogenous Opioid Imbalance as a Potential Factor Involved in the Pathogenesis of Chronic Kidney Disease-Associated Pruritus in Dialysis Patients," *Journal of Clinical*

Medicine 12, no. 7 (2023): 2474, https://doi.org/10.3390/jcm12072474.

[28] K. Danno, K. Nishiura, and M. Tanaka, "Increased Met-Enkephalin Plasma Levels in Hemodialysis Patients With or Without Pruritus," *Journal of Dermatological Science* 10, no. 3 (1995): 238–240, https://doi.org/10.1016/0923-1811(95)00451-w.

[29] M. M. Dull, K. Wolf, M. Vetter, P. Dietrich, M. F. Neurath, and A. E. Kremer, "Endogenous Opioid Levels do Not Correlate With Itch Intensity and Therapeutic Interventions in Hepatic Pruritus," *Frontiers of Medicine* 8 (2021): 641163, https://doi.org/10.3389/fmed.2021.641163.

[30] S. Yu, Y. Li, Y. Zhou, T. Follansbee, and S. T. Hwang, "Immune Mediators and Therapies for Pruritus in Atopic Dermatitis and Psoriasis," *Journal of Cutaneous Immunology and Allergy* 2, no. 1 (2019): 4–14, https://doi.org/10.1002/cia2.12049.