ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2025.3.02

CHARACTERISTICS OF ADRENAL INSUFFICIENCY IN PATIENTS UNDERGOING HEMODIALYSIS FOR END-STAGE KIDNEY FAILURE*

M. Polat[1], S. E. Basmaz[2]

[1] Karabuk Training and Research Hospital, Karabuk, Turkey;
[2] Kocaeli City Hospital, Kocaeli, Turkey
drmehmetpolat@gmail.com

Chronic kidney disease is a progressive disease characterized by structural and functional changes in the kidney due to various causes, especially diabetes mellitus and hypertension. Chronic kidney disease is diagnosed with a glomerular filtration rate below 60 mL/min/1.73 m² for at least 3 months. Chronic renal failure, which has a prevalence of 11-13% in the general population, is divided into 5 stages and the majority of patients are in stage 1 [1–4]. Many physiological pathways may change as renal function decreases. For example, there may be changes in erythropoietin, growth hormone, parathyroid hormone, cortisol, thyroid hormones or sex hormones. Chronic kidney disease (CKD) is a recognized public health problem, with mortality rates exceeding rates in the general population. The annual mortality rate for dialysis patients is 21.2% [5]. The end-stage renal failure stage is the period in which the glomerular filtration rate is ≤ 14 mL/min/1.73 m² and patients are followed closely in terms of initiation of renal replacement therapy. Symptoms and signs such as hypotension, nausea and dizziness are frequently detected in patients undergoing hemodialysis as renal replacement therapy and these symptoms are also frequently observed in case of adrenal insufficiency [6, 7]. Treatment of adrenal insufficiency in hemodialysis patients and reduction or disappearance of these symptoms and signs will provide an increase in the quality of life of patients during hemodialysis sessions and in the interdialytic period.

The adrenal glands are an endocrine organ consisting of cortex and medulla located at the upper pole of both kidneys. The cortex secretes androgens, cortisol, aldosterone and estrogen, while the medulla secretes dopamine, adrenaline and noradrenaline. Overactive or underactive adrenal glands cause various symptoms. A hyperplasia or adenoma of the adrenal glands

* The study was initiated by the authors.

The authors declared that this study received no financial support.

The authors guarantee full responsibility for all the information published herein.

The authors guarantee absence of competing interests and their own financial interest when carrying out the research and writing the article.

The manuscript was received by the editorial staff 24.04.2025.

This work is licensed under a Creative Commons Attribution 4.0 International License. OPEN ACCESS

can cause excessive secretion of the hormone cortisol, while sometimes the adrenal glands can secrete hormones at low levels or not at all due to primary or secondary causes. In case of adrenal insufficiency (AI), symptoms and signs such as fatigue, diffuse weakness, abdominal, muscle and joint pains, craving for salty food, dizziness, nausea-vomiting, decreased appetite, weight loss, darkening of the skin, low blood pressure, decreased axillary and pubic hair growth in the women, and decreased libido [8, 9].

Hypotension is a frequently observed clinical manifestation in patients with adrenal insufficiency, with a subset presenting with orthostatic hypotension. In such cases, the underlying etiology is primarily attributed to sodium and intravascular volume depletion resulting from aldosterone deficiency, secondary to impaired secretion by the zona glomerulosa of the adrenal cortex. In physiologically intact individuals, hypotensive episodes elicit a compensatory adrenal response aimed at restoring arterial pressure to homeostatic levels. Conversely, in individuals with inadequate adrenal reserve, this compensatory mechanism is blunted, thereby necessitating pharmacological intervention to achieve hemodynamic stability. Early identification of this patient group, followed by appropriate corticosteroid replacement therapy such as hydrocortisone, which exerts both glucocorticoid and mineralocorticoid effects may lead to significant improvements in symptom burden, intradialytic blood pressure control, and overall dialysis adequacy [10].

This study was performed to clarify the characteristics of adrenal insufficiency in patients undergoing hemodialysis.

MATERIALS AND METHODS

In this retrospective, single-center study, patients aged ≥18 years who received regular hemodialysis treatment at Karabuk Training and Research Hospital between January and June 2020 were evaluated. The study was approved by Karabuk University Non-Interventional Clinical Research Ethics Committee Decision No: 2021/562. Written informed consent was taken from all the participants.

Patients with symptoms such as general fatigue and loss of appetite, unexplained systolic blood pressure (BP) below 100 mmHg, blood glucose levels below 70 mg/dL, showing signs of adrenal insufficiency and sent to the endocrine outpatient clinic with a pre-diagnosis of possible AI were included in the study.

Patient demographic data, cortisol levels, ACTH stimulation test results, BMI, CKD etiology, Dialysis duration, Current smoker, Alcohol Use, TSH level, Parathyroid hormone level, Ca×P, Kt/V were obtained from the electronic database of Karabuk Training and Research Hospital.

Patients who were evaluated in the endocrine clinic were divided into two categories according to basal cortisol levels:

High Basal Cortisol Levels (> 15 µg/dL): The diagnosis of AI was not considered in patients with cortisol levels > 15 µg/dL. Therefore, these patients were excluded from the study.

Intermediate Basal Cortisol Levels (5–15 µg/dL): Patients with cortisol levels of 5–15 µg/dL were subjected to the low-dose 1 µg ACTH stimulation test and cortisol levels at 30 and 60 minutes after intravenous (iv) administration of low-dose 1 µg ACTH. Patients with cortisol levels > 18 µg/dL were excluded from the study because AI was excluded. Patients cortisol levels < 18 µg/dL were considered to have AI and these patients were included in the study.

Statistical Analysis. Demographic data were analyzed according to the distribution of the data and divided into two as parametric and non-parametric data.

Parametric data among the groups were compared with Student T-test and non-parametric data were compared with Mann-Whitney U-test. Chi-square test was used to compare categorical data between both groups. Which independent predictor was for adrenal insufficiency was examined including the data with significant differences among the groups and the results close to significance in the multivariate logistic regression analysis. IBM SPSS Software v22 software was used to analysis the statistical data and as a result of the analyses values $P < 0.05$ were considered statistically significant.

Table 1

Baseline demographic and clinical characteristics of patients with and without adrenal insufficiency

Variables	Adrenal Insufficiency		P
	Yes (n = 8)	No (n = 129)	
Gender, n (%) Female Male	 1 (12.5) 7 (87.5)	 52 (40.3) 77 (59.7)	0.151
Age (years), median (range)	65 (48–77)	64 (38–86)	0.938
Dialysis duration (months), median (range)	78 (12–194)	65 (7–240)	0.285
BMI (kg/m^2), median (range)	28.3 (18.2–37.6)	25.7 (19.3–35.3)	0.139
Ca × P, n (%) > 55 < 55	 1 (12.5) 7 (87.5)	 30 (23.3) 99 (76.7)	0.683

Table 2

Kt/V levels among patients with and without adrenal insufficiency

Variables	Adrenal insufficiency		P
	Yes (n = 8)	No (n = 129)	
Kt/V, n (%) < 1.2 > 1.2	 3 (37.5) 5 (62.5)	 22 (17.1) 107 (82.9)	0.160
Kt/V, median (range)	1.35 (1.10–1.40)	1.5 (1–2.5)	0.018

RESULTS AND THEIR DISCUSSION

Between January-June 2020, 243 patients aged ≥18 years who underwent hemodialysis treatment in Karabuk Training and Research Hospital were evaluated. Among these patients, 137 patients who were sent to the endocrine outpatient clinic with a pre-diagnosis of possible AI were included in the study. According to the basal cortisol value, the diagnosis of AI was excluded in 92 patients and the low-dose 1 μg ACTH stimulation test was performed in 45 patients with suspected AI and 8 of these patients were diagnosed with AI.

Of the 8 patients diagnosed with AI, the demographic characteristics of the patients are presented in Table 1. The mean duration of dialysis was 65 (7-240) months (see Table 1).

No statistically significant difference was found between age, gender, BMI, hemodialysis duration, Ca × P in the group with and without AI (P > 0.05) (Table 2).

When the Kt/V value of 1.2 was taken as the cut off between patients with and without AI, although the patient ratios between the two groups were similar, in terms of Kt/V value, the median Kt/V value was significantly lower in the group with AI compared to those without (see Table 2).

The Kt/V value of patients with AI was determined as 1.35 according to ROC analysis (73% sensitivity, 69.2% specificity, area 0.749 (95% CI 0.636-0.862). A Kt/V value below 1.35 was found to be an independent predictor for AI (OR;59.5 95%CI: 1.402–2524, P = 0.033) (see Table 2).

No statistically significant differences were observed between patients with and without AI in terms of thyroid function, smoking or alcohol use, CKD etiology, or parathyroid hormone levels. However, the small sample size in the AI group may limit the power of these comparisons (Table 3).

Adrenal insufficiency commonly presents with symptoms such as nausea, vomiting, fatigue, weight loss, and hypotension. Although rare in patients undergoing hemodialysis (HD), these symptoms may overlap significantly with those observed in this population, leading to underdiagnosis of the condition [11].

Table 3

Thyroid function, lifestyle factors, and chronic kidney disease etiology in patients with and without adrenal insufficiency

Variables	Adrenal Insufficiency		P
	Yes (n = 8)	**No (n = 129)**	
TSH level, n (%) Upper normal Normal	 1 (12.5) 7 (87.5)	 13 (10.1) 115 (89.9)	0.591
Current smoker, n (%) Yes No	 0 (0) 8 (100)	 18 (14) 111 (86)	0.597
Alcohol Use, n (%) Yes No	 0 (0) 8 (100)	 7 (5.4) 122 (94.6)	1
CKD etiology, n (%) HT DM	 0 (0) 8 (100)	 11 (8.5) 118 (91.5)	1
Parathyroid hormone level (pg/mL), median(range)	517 (4–1065)	599 (191–2000)	0.982

Studies evaluating the hypothalamic-pituitary-adrenal (HPA) axis in CKD remain limited. In one study, 100 HD patients were screened. After excluding those receiving corticosteroid therapy or with morning cortisol levels > 18 µg/dL, 68 patients were evaluated. Of these, 17 with symptoms suggestive of AI and low cortisol levels were further assessed with corticotropin-releasing hormone (CRH) and ACTH stimulation tests. AI was ultimately diagnosed in 7 patients [11].

Another study demonstrated that relying solely on subjective symptoms, clinical findings, or adrenal imaging is insufficient for diagnosing AI in HD patients. In this cohort, a morning serum cortisol cut-off of 8.45 µg/dL provided the highest sensitivity and specificity for diagnosis [11].

An autopsy-based study examined 30 adrenal glands from 15 HD patients and found amyloid deposition in 26 glands [12]. Similarly, β2-microglobulin deposition has been documented in the myocardium, tendons, and joint cartilage of long-term HD patients. However, significant amyloid deposition in adrenal vasculature remains rare, and thus, the direct relationship between amyloid accumulation and adrenal insufficiency remains unclear [13].

Several case reports have described AI in HD patients, particularly in that undergoing home dialysis, receiving immunosuppressive therapy, or presenting with unexplained hypotension [14]. For instance, in 2003, a patient with hypercalcemia (calcium: 14.9 mg/dL) and normal PTH and bone turnover markers was diagnosed with isolated ACTH deficiency. Cortisol levels normalized following ACTH stimulation, despite normal pituitary imaging findings [15].

Another case described AI in a patient on HD for four years, who developed the condition after fluconazole treatment for presumed fungal meningitis. This suggests that AI may be unmasked by drugs that interfere with cortisol synthesis in susceptible individuals [16].

In our study, AI was confirmed in 8 of 45 patients who underwent ACTH stimulation testing. A Kt/V value below 1.35 was found to be an independent predictor of AI among HD patients. Based on these findings, we recommend that adrenal function should be evaluated via morning cortisol measurements and dynamic testing when necessary in patients with unexplained hypotension, anorexia, or weight loss despite adequate dialysis.

This study has several limitations. First, it is retrospective in nature. However, it may serve as a basis for future prospective randomized controlled trials. Second, the low-dose 1 µg ACTH stimulation test was used to diagnose AI. Although this test has been shown to be

more sensitive in some studies, concerns over dilution accuracy have prevented it from fully replacing the 250 µg ACTH test [17]. Therefore, we acknowledge that a 250 µg ACTH test may be warranted in cases where AI is suspected but the low-dose 1 µg ACTH stimulation test yields inconclusive results.

In conclusion, adrenal insufficiency should be considered in HD patients presenting with symptoms such as nausea, vomiting, and hypotension, especially when dialysis adequacy is compromised. The Kt/V value may serve as a practical and independent predictor to guide further endocrine evaluation.

CONCLUSION

In hemodialysis patients, a Kt/V value below 1.35 should be considered as an independent predictor of adrenal insufficiency and the relationship between Kt/V and adrenal insufficiency should be clarified with studies including a larger number of patients.

REFERENCES

1. Meuwese CL, Carrero JJ. *Arch Med Res* 2013;44(8): 591-600. https://doi.org/10.1016/j.arcmed.2013.10.009
2. Jha V, Garcia-Garcia G, Iseki K, et al. *Lancet* 2013;382: 260-272. https://doi.org/10.1016/S0140-6736(13)60687-X
3. Suleymanlar G, Utas C, Arinsoy T, et al. *Nephrol Dial Transplant* 2011;26: 1862-1871. https://doi.org/10.1093/ndt/gfq656
4. Hill NR, Fatoba ST, Oke JL, et al. *PLoS ONE* 2016;11: e0158765. https://doi.org/10.1371/journal.pone.0158765
5. Sari Oznur, Ahmed Muhammad Bashir. *Int J Clin Pract* 2022;1: 1503227. https://doi.org/10.1155/2022/1503227
6. Bakan A, Köstek O, Ecder SA, et al. *Turkiye Klin J Nephrol-Special Topics* 2015;8(2): 40-47, *available at: https://www.turkiyeklinikleri.com/article/en-hemodiyalizin-komplikasyonlari-72286.html*
7. Özdemir Başer Ö. *Adrenal Diseases and Surgical Treatment* 2021: 12-17, *available at: https://www.turkiyeklinikleri. com/article/en-adrenal-yetmezlik-94349.html*
8. Bornstein SR, Allolio B, Arlt W, et al. *J Clin Endocrinol Metab* 2016;101(2): 364-389. https://doi.org/10.1210/jc.2015-1710
9. Gurnell M, Heaney LG, Price D, Menzies-Gow A. *J Internal Med* 2021; 290(2): 240-256. https://doi.org/10.1111/joim.13273
10. Pamuk BÖ, Polat S, Pamuk G. F Ü Sağ Bil Tıp Derg 2013;27 (1): 33-37, available *at: https://tip.fusabil.org/pdf/pdf_FUSABIL_905.pdf*
11. Ohashi N, et al. *Renal Repl Ther* 2021;17(7): 1-11, *available at: https://rrtjournal.biomedcentral.com/articles/10.1186/s41100-021-00337-9*
12. Barton CH, Vaziri ND, Gordon S, Eltorai I. *Paraplegia* 1984;22(1): 7-16. https://doi.org/10.1038/sc.1984.4
13. Mazanec K, McClure J, Bartley CJ, et al. *J Clin Pathol* 1992;45(9): 832-833. https://doi.org/10.1136/jcp.45.9.832
14. Kam Koh TJ, Chan CT. *Hemodial Int* 2016;20(3): E10-E3. https://doi.org/10.1111/hdi.12412
15. Kato A, Shinozaki S, Goga T, Hishida A. *Am J Kidney Dis* 2003;42(2): E32-E36. https://doi.org/10.1016/s0272-6386(03)00672-3
16. Suzuki R, Morita H, Nishiwaki H, Yoshimura A. *NDT Plus* 2010;3(1): 99-100. https://doi.org/10.1093/ndtplus/sfp143
17. Kim SY. *Endocrinol Metab (Seoul)* 2015;30(4): 443-455. https://doi.org/10.3803/EnM.2015.30.4.443

CHARACTERISTICS OF ADRENAL INSUFFICIENCY IN PATIENTS UNDERGOING HEMODIALYSIS FOR END-STAGE KIDNEY FAILURE

M. Polat[1], S. E. Basmaz[2]

[1] *Karabuk Training and Research Hospital, Karabuk, Turkey;*
[2] *Kocaeli City Hospital, Kocaeli, Turkey*
drmehmetpolat@gmail.com

Background. Adrenal insufficiency causes nonspecific symptoms such as general fatigue, signs such as hypotension, and abnormalities such as hypoglycemia and leads to a poor prognosis. However, all these are also observed in hemodialysis (HD) patients without adrenal insufficiency. This study aims to investigate the prevalence and clinical characteristics of adrenal insufficiency in patients undergoing hemodialysis due to end-stage kidney failure.

Aims. This study was performed to clarify the characteristics of adrenal insufficiency in hemodialysis patients.

Methods. Between January-June 2020, 243 patients aged ≥ 18 years who underwent hemodialysis treatment in Karabuk Training and Research Hospital were evaluated. Among these patients, 137 patients who were sent to the endocrine outpatient clinic with a pre-diagnosis of possible adrenal insufficiency were included in the study. Based on baseline cortisol levels and results of the low-dose 1 μg ACTH stimulation test, patients were categorized as having or not having adrenal insufficiency. Parametric data among the groups were compared with Student T-test and non-parametric data were compared with Mann-Whitney U-test. Chi-square test was used to compare categorical data between both groups. Multivariate logistic regression analysis was also used.

Results. Eight HD patients were diagnosed with adrenal insufficiency. There was no significant difference between groups in age, gender, BMI, dialysis duration, or Ca × P. However, patients with adrenal insufficiency had significantly lower Kt/V values (median 1.35 vs. 1.5, p = 0.018). A Kt/V value below 1.35 can be considered an independent predictor of adrenal insufficiency (OR: 59.5, 95% CI: 1.402–2524, p = 0.033).

Conclusions. Adrenal insufficiency should be considered in hemodialysis patients presenting with nonspecific symptoms such as nausea, vomiting, hypotension, and fatigue. A Kt/V value below 1.35 may serve as an independent predictor of adrenal insufficiency in this population.

Keywords: adrenal insufficiency, cortisol, end-stage kidney failure, hemodialysis.

ХАРАКТЕРИСТИКА НАДНИРНИКОВОЇ НЕДОСТАТНОСТІ У ПАЦІЄНТІВ, ЩО ПРОХОДЯТЬ ГЕМОДІАЛІЗ З ПРИВОДУ ТЕРМІНАЛЬНОЇ СТАДІЇ НИРКОВОЇ НЕДОСТАТНОСТІ

Полат М.[1], Басмаз С. Е.[2]

[1] *Навчально-дослідна лікарня Карабюк, м. Карабюк, Туреччина;*
[2] *Міська лікарня Коджаелі, м. Коджаелі, Туреччина*
drmehmetpolat@gmail.com

Недостатність надниркових залоз викликає неспецифічні симптоми, такі як загальна втома, такі ознаки, як гіпотензія, і такі відхилення, як гіпоглікемія, і призводить до поганого прогнозу. Проте все це також спостерігається у хворих на гемодіалізі без надниркової недостатності. Це дослідження спрямоване на вивчення поширеності та клінічних характеристик надниркової недостатності у пацієнтів, які проходять гемодіаліз через термінальну стадію ниркової недостатності.

Дослідження було проведено з метою уточнення особливостей надниркової недостатності у хворих на гемодіалізі.

Матеріали та методи. У період з січня по червень 2020 року було оцінено 243 пацієнтів віком ≥ 18 років, які проходили лікування гемодіалізом у навчально-дослідній лікарні Karabuk. Серед цих пацієнтів у дослідження було включено 137 пацієнтів, які були направлені в ендокринологічний диспансер з попереднім діагнозом можливої надниркової недостатності. На підставі базового рівня кортизолу та результатів низькодозового тесту на стимуляцію з 1 мкг АКТГ пацієнти були класифіковані як такі, що мають або не мають надниркової недостатності. Параметричні дані між групами порівнювали за допомогою t-критерію Стьюдента, а непараметричні дані — за допомогою U-критерію Манна-Вітні. Для порівняння категоріальних даних між обома групами використовували критерій хі-квадрат. Також використовували багатовимірний логістичний регресійний аналіз.

Результати. У восьми пацієнтів на гемодіалізі діагностовано надниркову недостатність. Не було істотної різниці між групами за віком, статтю, ІМТ, тривалістю діалізу або показником Ca×P.

Проте пацієнти з наднирковою недостатністю мали значно нижчі значення Kt/V (медіана 1,35 проти 1,5, p = 0,018). Значення Kt/V нижче 1,35 можна вважати незалежним предиктором надниркової недостатності (OR: 59,5, 95% ДІ: 1,402–2524, p = 0,033).

Висновки. У пацієнтів на гемодіалізі, які мають неспецифічні симптоми, такі як нудота, блювання, артеріальна гіпотензія та втомлюваність, слід враховувати недостатність надниркових залоз. Значення Kt/V нижче 1,35 може служити незалежним предиктором надниркової недостатності в цій популяції.

Ключові слова: надниркова недостатність, кортизол, термінальна стадія ниркової недостатності, гемодіаліз.