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**HEADACHE ASSOCIATED WITH  
HEMODIALYSIS**

**ГЛАВОБОЉА ПОВЕЗАНА СА  
ХЕМОДИЈАЛИЗОМ**

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**Abstract**

Headache is the most common neurological complication in patients undergoing chronic hemodialysis, with a frequency of 6.6% to 70%. According to the criteria of the third edition of the International Headache Society, hemodialysis-associated headache begins within the first 2 hours of dialysis, lasts 4 hours, resolves within 72 hours of the end of the dialysis session, and ceases after successful transplantation. Clinically, it manifests as a mild, bifrontal pain, often developing into a more severe, throbbing headache that is usually worse in the supine position. It is multifactorial, with an insufficiently clear etiopathogenesis. Factors that may predispose to headache include female gender, diabetes mellitus, type of dialysis solution, variations in urea, sodium, magnesium, arterial blood pressure, calcitonin gene-related peptide, and substance P levels during dialysis, water intoxication syndrome, and nitric oxide. Other factors may also contribute to the development of dialysis headache, including hypertension, weight changes during hemodialysis, dehydration, smoking, use of nonsteroidal anti-inflammatory drugs, antibiotics, and immunosuppressants, and caffeine withdrawal. Treatment is complex and requires a balanced and individualized approach that includes nonpharmacological interventions such as cognitive behavioral therapy and physical modalities, along with cautious pharmacological strategies. Treatment may include the use of oxygen therapy, hemodiafiltration as a form of hemodialysis, and, as prophylaxis, angiotensin-converting enzyme inhibitors, amitriptyline, magnesium substitution, chlorpromazine, and botulinum toxin. It is recommended to control interdialysis yield, electrolytes and blood pressure, as well as avoid excessive caffeine use. Paracetamol, dihydroergotamine and ergotamine tartrate are analgesics used to stop dialysis headache. Dialysis headache is highly prevalent among the dialysis population, with no clear pathophysiology and no standardized diagnostic criteria, or clear treatment strategies. Therefore, better organized research is needed to understand its etiopathogenesis and improve therapeutic protocols.

**Definition of hemodialysis-induced headache**

One of the most common neurological symptoms in patients on hemodialysis is headache. Its diagnosis is based on the characteristics of clinical presentation, time of onset, frequency and duration, as well as location, quality and intensity. Dialysis headache lasts on average less than 4 hours, is located bilaterally in the frontotemporal lobe and is of moderate intensity<sup>(1)</sup>.

The International Headache Society-3, sets parameters that define hemodialysis-associated headache, it begins during hemodialysis and resolves within 72 hours of the end of

the dialysis session and disappears after successful kidney transplantation<sup>(2)</sup>, Box 1<sup>(3)</sup>.

**Characteristics and dilemmas regarding the diagnosis of dialysis headaches**

Dialysis headache has determinants of bifrontal, pulsating headache in 50% of patients, mild in intensity in more than two-thirds, but often progresses in severity and lasts less than four hours<sup>(4)</sup>.

Dialysis headache is most often of a migraine nature and the most recent diagnostic criteria are presented in the

International Classification of Headache Disorders-3 beta, and it is recognized under the subtitle of headaches attributed to disturbances of homeostasis, Box 1.

Patients diagnosed with primary headache are at higher risk for dialysis headache. However, it is still controversial whether it can be a predictor for the development of dialysis headache (5).

All International Headache Classifications have undergone several revisions, which, individually, have refined the definition of dialysis headache. It is most likely that these differences in the definition of dialysis headache are the reason for their different prevalence rates in different studies. Unfortunately, the dilemma persists because the existing guidelines for the diagnosis of dialysis headaches do not provide precise guidance on whether a headache that occurs before chronic renal failure, i.e., before the start of hemodialysis, can be characterized as a dialysis headache (6).

Regardless of the existing guidelines regarding the definition of criteria for dialysis headaches, it often happens that patients do not meet all the criteria that would speak in favor of the existence of dialysis headaches. Even when all the criteria are met, it is difficult to exclude secondary headaches, which poses a difficulty for the definitive diagnosis of dialysis headaches, until the underlying cause of the secondary headache is resolved or cured or it is significantly improved with therapy (7).

Therefore, general diagnostic criteria have been proposed that could contribute to resolving these dilemmas. They imply that the headache occurred within a time interval from the onset of the presumed causative disorder, that the headache occurred or worsened significantly in accordance with the presumed cause, that the headache improved in parallel with the improvement of the presumed causative disorder, and that the headache has characteristics that are typical of the underlying cause. Dialysis headaches can be classified as headaches that do not meet the criteria for hemodialysis-related headaches, those headaches that were present before hemodialysis and that meet the criteria for dialysis headaches, and headaches that meet the criteria for dialysis headaches without a previous headache (true dialysis headache) (7).

It should be noted that hypertensive patients also experience headaches, especially when blood pressure drops rapidly from very high to low levels, which may trigger a mechanism similar to that caused by some antihypertensive drugs, resulting in headaches due to cerebral vasodilation (5).

Thus, there are several types of hemodialysis headaches, those that occur with the start of dialysis, without previous headaches, existing primary headaches that worsen during dialysis, and headaches that begin during dialysis, without previous headaches, but with headaches that occur between sessions (8).

### ***Pathophysiology of dialysis headaches***

The interaction between the kidney and the body is realized through various relationships, which include the regulation of water and sodium balance and blood pressure, which is mediated by the activity of the sympathetic nervous system and the synthesis of hormones, which are considered essential for homeostasis in the body. Secondary electrolyte

imbalance, due to renal failure, accumulation of neurotoxins and endothelial changes, can contribute to neurological damage. Unfortunately, there is not much adequate information in the literature on the correlation of kidney disease and headache, which is sometimes described as a complication of chronic renal failure associated with other chronic pain conditions, such as low back pain and fibromyalgia (9).

There is no consensus on the etiopathophysiological mechanisms that trigger or cause dialysis headache. These mechanisms are controversial, poorly understood and multifactorial. The presumed reasons that could be predictors of dialysis headaches are dialysis solutions (acetate solutions carry a higher risk of dialysis headaches), changes in urea concentrations and electrolytes sodium and magnesium, arterial blood pressure, as well as substance P and the concentration of calcitonin gene-related peptide. The blood-brain barrier may also play an important role in the occurrence of dialysis headaches. Namely, the disequilibrium, as a result of the concentration gradient between the brain and blood during dialysis, due to the passage of free water across the blood-brain barrier, can lead to cerebral edema, which causes the occurrence of dialysis headaches. Nitric oxide, as a vasodilator, may be involved in the pathophysiology of dialysis headaches, as it is assumed that the compensatory mechanisms of cerebral self-regulation fail when there is a loss of vasoreactivity, similar to the condition seen in patients with intracranial atherosclerotic disease (1, 2). The sudden drop in blood urea during hemodialysis does not have the same effect on lowering the urea concentration in the brain, which is why an osmotic gradient is created when water crosses the blood-brain barrier, increasing intracranial pressure and causing cerebral edema and headache symptoms, an effect known as the "reverse urea effect". Hypertension is a rare etiological entity for headache and these two entities can coexist in the same patient, creating a feeling of tension-type headache, which can also occur as a result of anxiety associated with hypertension (10).

Potential triggers for dialysis headache include body weight changes during hemodialysis, higher sodium levels before dialysis, and lower magnesium levels before and after dialysis. Dialysis headache may be caused by low magnesium levels, through various mechanisms, such as a decrease in the free energy released by ATP hydrolysis in brain mitochondria, the release of substance P, tumor necrosis factor, prostanoids and free radicals, interleukin-1, interleukin-6, or modulation of the glutamate N-methyl-D-aspartate receptor, which is involved in nociceptive transmission. Low magnesium concentrations have been studied in vasospasm due to subarachnoid hemorrhage, suggesting that there may be a vascular origin to the pathophysiology of dialysis headache (4). Headaches can be exacerbated by dehydration, which is a common occurrence in hemodialysis patients, similar to headaches at high altitudes. Migraine can be triggered by electrolyte imbalances, especially magnesium, sodium, and potassium, during hemodialysis, and they play a key role in the pathogenesis of migraine, especially through their effects on neural and vascular function. Smoking also increases the intensity of dialysis headaches in the back of the head or face, because nicotine has a vasoconstrictive effect, reducing blood flow to the brain and meninges, which

is a significant prerequisite for the development of migraine. Also, some medications, such as nonsteroidal anti-inflammatory drugs, antibiotics, and immunosuppressants, can be stimulants for the development of headaches after dialysis. Headaches caused by excessive use of nonsteroidal anti-inflammatory drugs occur when the drug is used for more than 15 days per month for 3 months. Dysbiosis resulting from previous antibiotic therapy causes changes in the composition of the intestinal flora and may be a trigger for behavioral disorders and migraines. Immunosuppressive agents, such as tacrolimus (Prograf), muromonab CD3 (OKT3), and cyclosporine, are often associated with headaches, exacerbating pre-existing headaches and may also predispose to encephalopathy with subsequent headache (11, 12).

The trigeminal vascular system may be active during migraine attacks. Substance P and calcitonin gene-related peptide are released after stimulation of the trigeminal ganglia in experimental animals. During spontaneous migraine attacks, an increase in calcitonin gene-related peptide has been observed, which may have a causal role in the onset of migraine. Basal serum concentrations of calcitonin gene-related peptide were significantly reduced after dialysis in patients with dialysis headaches. Caffeine withdrawal headache may occur in excessive caffeine users, exceeding 200 mg of caffeine per day for more than 2 weeks. Such patients have throbbing and bilateral headaches 24 hours after the last caffeine intake and resolve within 1 hour of 100 mg of caffeine (7).

### ***Prevalence of dialysis headaches***

There are no consistent data on the prevalence of headaches associated with hemodialysis, most likely due to uneven stratification of the patient samples studied. The estimated prevalence of headaches on dialysis ranges from 6.6% to 70%, with some studies reporting a slightly lower prevalence of dialysis headaches, between 35.4–44%. These differences may be explained by improvements in the quality of hemodialysis, as well as different diagnostic criteria for defining dialysis headaches. Some studies have suggested that headaches on dialysis are more common in women, while other studies have found that headaches are more common in men. The gender difference may be due to different studies using different methods, which may have included more male patients undergoing hemodialysis. Another possible explanation is that women have a lower pain threshold and that fluctuations in sex hormones, especially estrogen and progesterone, may cause changes in the frequency or intensity of headaches (3, 13).

A lower rate of dialysis headaches has been observed in patients on hemodialysis for less than a year, but after the first year of dialysis treatment, there is a significant increase in prevalence, which stabilizes after 5 years of dialysis (8).

Also, differences in the prevalence of dialysis headaches have been observed in relation to the dialyzers used, and these differences range from 46% to 70%. Dialysis solutions may influence the differences in the prevalence of dialysis headaches, with more frequent and more severe headaches occurring in patients using acetate, as opposed to bicarbonate dialysis. In patients with chronic renal failure, the inci-

dence of headache in patients with chronic renal failure is similar to the incidence of headache in the general population, indicating that headache in patients on hemodialysis is not associated with renal failure but with the hemodialysis process itself (7).

An interesting conclusion is the conclusion of Biscetti et al. (14) who state that the prevalence of dialysis headaches is significantly influenced by the underlying cause of end-stage renal failure, especially in people with autoimmune conditions and diabetes (12).

### ***Headache and kidney transplantation***

One of the typical features of dialysis headaches is their resolution after kidney transplantation. However, although successful kidney transplantation and cessation of hemodialysis lead to the cessation of dialysis headaches, they can persist after transplantation, and in some cases may be associated with transplantation or its treatment with immunosuppressive drugs, which themselves can contribute to the occurrence of headaches (7, 15).

Although kidney transplantation is the best therapeutic option for patients with end-stage renal failure, which leads to the recovery of osmotic functions and can cause a complete reorganization of metabolic pathways, some studies show that several neurological complications, including headache, occur after transplantation. According to the established criteria of the International Headache Society, dialysis headache should resolve after transplantation and cessation of hemodialysis, and these results were unexpected for many authors. A close relationship between headache and kidney transplantation has also emerged from the effects of specific pharmacological treatments, primarily steroids, which have improved headache symptoms. This observation is explained by the effect of steroids on reducing neurogenic inflammation, which occurs during migraine attacks, as well as a positive effect that may be associated with a decrease in the systemic proinflammatory state. Also, the use of calcium channel blockers, which are used for migraine prophylaxis, is considered a chronic therapy in kidney transplant patients, which affects the improvement of headaches after several months of therapy (9).

### ***Impact of dialysis headaches on quality of life***

Pain is a pervasive and debilitating symptom in dialysis patients, significantly affecting daily functioning and quality of life. The burden of pain remains constant regardless of the duration of treatment, indicating the chronic and persistent nature of pain in end-stage renal disease, highlighting the need for effective treatment strategies. In addition, the physiological and psychological impact of end-stage renal disease exacerbates the intensity and perception of pain and further complicates its treatment (16).

The unresolved nature of pain disrupts sleep and mood, reduces life satisfaction, and patients highlight its role not only as a physical symptom but also as a major contributor to psychosocial distress. Therefore, comprehensive pain management is necessary, requiring integration into the broader scope of dialysis care, with the joint contribution of nephrologists, pain specialists, and mental health professionals (16).

Women, younger people, people with higher levels of education and longer dialysis experience have significantly more frequent dialysis headaches, which were significantly associated with high negative impact on patients' lives, with significant negative impact on the perception of their health and pain that interfered with quality of life to a greater extent (1, 11).

The increased incidence of depression, in correlation with the increased incidence of pain throughout the body in hemodialysis patients, also leads to a reduced quality of life, probably related to complaints such as fatigue and apathy. Assessment of sleep disorders, determined using the „Pittsburgh Sleep Quality Index”, showed that 45.6% of patients had sleep disorders. It was also found that hemodialysis patients with chronic pain have a more severe form of depression, defined by the Beck Depression Inventory. In the final analysis, the frequency and severity of sleep disturbances and depression increased as pain occurred during dialysis; that is, pain in dialysis patients was closely associated with depression and sleep disturbances. Anxiety about dialysis, the obligation to go to the dialysis center, fear of needles, problems observed in other patients during dialysis, and concerns about their experience trigger sleep disturbances and increase the frequency and severity of depression in these patients. On the other hand, dialysis headaches also increase the severity of depression, so that the problem continues as a vicious cycle (7).

### ***Treatment of Dialysis Headaches***

Due to the complex interplay between analgesic pharmacokinetics, reduced renal clearance, and potential drug interactions unique to this population, current approaches to pain management in dialysis patients are often inadequate. Therefore, a balanced and individualized approach that includes nonpharmacological interventions such as cognitive behavioral therapy and physical modalities, along with cautious pharmacological strategies, is necessary. The complex nature of pain in this population requires continued attention and innovative treatment approaches, with the ultimate goal of improving quality of life (16). Hemodiafiltration is a form of dialysis modality and has superior results in reducing the incidence of dialysis headaches. Prophylactic drug treatments include amitriptyline, magnesium replacement, chlorpromazine, angiotensin-converting enzyme inhibitors, and botulinum toxin (5).

There are almost no controlled studies on abortive or prophylactic treatment of dialysis headaches. There are only isolated reports of responses to the use of chlorpromazine before dialysis and angiotensin-converting enzyme inhibitors, nortriptyline, and magnesium oxide as prophylactic treatments. Paracetamol, ergotamine tartrate, and dihydroergotamine can also be used as part of the therapeutic options for the cessation of dialysis headaches. Ergot alkaloids should be used with caution because of the possibility of arteriovenous fistula thrombosis. Caffeine is also used in treatment, when the headache resolves after administration of 100 mg of caffeine within 1 hour; amitriptyline/chlorpromazine is also used; magnesium supplements (in patients with hypomagnesemia); onabotulinum toxin is used for the treatment of migraine in the general population, but has not yet been tested in dialysis patients. Bicarbonate dialysis is a good way to prevent dialysis headaches. A similar effect can

be achieved by slow dialysis, with a lower blood flow rate, controlled ultrafiltration, and sodium concentration, to prevent sudden changes in blood pressure and serum sodium levels (4). Dialysis headaches may be caused by excessive cerebral vasodilation in response to the decrease in oxygen during dialysis through autoregulation or hormonal abnormalities, and the vasoconstrictive effect of oxygen may have a beneficial effect on headaches, as indicated by positive experiences with 2 liters of 100% oxygen via nasal catheter. However, therapeutic guidelines in this regard remain elusive. There are clinical experiences that have established the preventive benefits of oxygen therapy, when administered before the start of dialysis, reducing the intensity of headaches, and the patient maintained headache remission for 12 months (17).

### ***CONCLUSION***

Dialysis headache is of moderate intensity in the bilateral frontotemporal lobe region, with an average duration of less than 4 hours, and disappears 72 hours after the end of dialysis. There is no single opinion on the physiopathology of dialysis headache, dialysis solutions, variations in urea and electrolytes, arterial blood pressure, calcitonin gene-related peptide, and substance P are mentioned. The most common is a disequilibrium due to the concentration gradient between the brain and blood and the consequent passage of free water through the blood-brain barrier, as well as many other factors. The prevalence of dialysis headache ranges from 6.6% to 70% and may be lower. Some studies claim that dialysis headaches occur in women and in patients who have been on dialysis for a longer period. Treatment of dialysis headache requires a balanced and individualized approach that includes nonpharmacological interventions along with cautious pharmacological treatments.

### ***Declaration of conflicting interests***

The authors declared no conflicts of interest concerning the authorship and/or publication of this article.

#### **Box 1. 10.2 Diagnostic criteria for headache during dialysis based on the International Headache Society,**

##### **3rd edition (3)**

A headache without specific features that occurs during dialysis and is caused by hemodialysis. It resolves spontaneously within 72 hours after the end of the hemodialysis session.

- A. At least three episodes of acute headache that meet criterion C
- B. The patient is on hemodialysis
- C. Evidence of causation is demonstrated by at least two of the following:
  1. Each headache developed during the hemodialysis session
  2. One or both of the following:
    - a) Each headache worsened during the dialysis session
    - b) Each headache resolved within 72 hours after the end of the dialysis session
  3. The headache episodes completely resolved after successful kidney transplantation and cessation of hemodialysis
- D. Not better explained by another International Headache Society-3 diagnosis.

Caffeine is rapidly removed by dialysis: 8.3.1 Caffeine withdrawal headache should be considered in patients who consume large amounts of caffeine.

## Сажетак

Главобоља је најчешћа неуролошка компликација код пацијената на хроничној хемодијализи, са учесталошћу од 6,6% до 70%. Према критеријумима трећег издања Међународног удружења за главобољу, дијализна главобоља започиње у прва 2 сата дијализе, траје 4 сата, повлачи се у року од 72 сата од завршетка дијализе и престаје након успешне трансплантације.

Клинички се манифестује као благ, бифронтални бол, који се често развија у јачу, пулсирајућу главобољу.

Мултифакторске је етиопатогенезе. Фактори који могу предиспонирати главобољу укључују женски пол, дијабетес мелитус, врсту раствора за дијализу, варијације у уреји, натријуму, магнезијуму, артеријском крвном притиску, пептиду повезаном са геном калцитонина и нивоима супстанце П током дијализе, синдром интоксикације водом и азотни оксид. Други фактори такође могу допринети развоју дијализне главобоље, укључују хипертензију, варијацију тежине током хемодијализе, дехидрацију, пушење, употребу нестероидних антиинфламаторних лекова, антибиотика и имunosупресива, као и апстиненцију од кофеина.

Лечење је сложено и захтева уравнотежен и индивидуализован приступ који укључује нефармаколошке интервенције као што су когнитивно-бихејвиорална терапија, заједно са опрезним фармаколошким стратегијама. Лечење може укључивати употребу терапије кисеоником, хемодијализацију као облик хемодијализе, као профилаксу, инхибиторе ангиотензин-конвертујућег ензима, амитриптилин, супституцију магнезијума, хлорпромазин и ботулинум токсин. Препоручује се контрола интердијализног приноса, електролита и крвног притиска, као и избегавање прекомерне употребе кофеина. Парацетамол, дихидроерготамин и ерготамин тартарат су аналгетици који се користе за заустављање дијализних главобоља.

Дијализна главобоља је веома распрострањена међу популацијом на дијализи, без јасне патофизиологије и стандардизованих дијагностичких критеријума, или јасних стратегија лечења. Стога је потребно боље организовано истраживање како би се разумела њена етиопатогенеза и побољшали терапијски протоколи.

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