

Pain in patients with chronic kidney disease, including those undergoing renal replacement therapy – current state of knowledge

Ból u pacjentów z przewlekłą chorobą nerek w tym poddanych leczeniu nerkozastępczemu – aktualny stan wiedzy

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STRESZCZENIE

BÓL U PACJENTÓW Z PRZEWLEKŁĄ CHOROBAŁ NEREK W TYM PODDANYCH LECZENIU NERKOZASTĘPCZEMU – AKTUALNY STAN WIEDZY

Wprowadzenie. Przewlekła choroba nerek to wielopłaszczyznowe schorzenie, które przyczynia się do rozwoju wielu zaburzeń biochemicznych, metabolicznych i patologii wielonarządowej. Pacjenci doświadczają także różnego rodzaju dolegliwości bólowych, w tym często o natężeniu od umiarkowanego do silnego. Pacjenci leczeni zachowawczo w stadium trzecim lub czwartym choroby są tak samo narażeni na ból, jak pacjenci w stadium piątym.

Cel pracy. Przedstawienie oraz scharakteryzowanie problematyki występowania bólu u pacjentów z PChN, w tym pacjentów poddanych leczeniu nerkozastępczemu.

Metoda. Przegląd i analiza piśmiennictwa dotyczącego problematyki bólu u pacjentów z PChN, w tym pacjentów poddawanych leczeniu nerkozastępczemu.

Podsumowanie. Ból mięśniowo-szkieletowy wymieniany jest jako najczęstszy objaw bólowy zarówno przez pacjentów leczonych zachowawczo jak i dializowanych. Przeszczepienie nerki przyczynia się do zmniejszenia częstości dolegliwości bólowych. Wysoki odsetek chorych cierpiących z powodu bólu o natężeniu od umiarkowanego do silnego sugeruje, że ból jest pomijany lub nieskutecznie leczony. Zadaniem lekarzy i pielęgniarek jest zwrócenie szczególnej uwagi na ten objaw niepożądany podczas leczenia ambulatoryjnego jak również po rozpoczęciu leczenia nerkozastępczego.

Słowa kluczowe:

ból, przewlekła choroba nerek, natężenie bólu

ABSTRACT

PAIN IN PATIENTS WITH CHRONIC KIDNEY DISEASE, INCLUDING THOSE UNDERGOING RENAL REPLACEMENT THERAPY – CURRENT STATE OF KNOWLEDGE

Introduction. Chronic kidney disease is a multifaceted condition that contributes to the development of many biochemical, metabolic disorders and multi-organ pathology. Patients also experience various types of pain, often with moderate to severe intensity. Patients treated conservatively in the third or fourth stage of the disease are just as susceptible to pain as patients in the fifth stage.

Aim. The aim of the study was present and characterize the problem of pain among patients with CKD, including patients undergoing renal replacement therapy.

Method. Review and analysis of the literature on the issue of pain among patients with PChN, including patients undergoing renal replacement therapy.

Conclusions. Musculoskeletal pain is mentioned as the most common pain symptom by both conservatively treated and dialysis patients. Kidney transplantation helps reduce the frequency of pain. The high percentage of patients suffering from moderate to severe pain suggests that pain is ignored or ineffectively treated. The task of doctors and nurses is to pay special attention to this adverse symptom during outpatient treatment as well as after starting renal replacement therapy.

Key words:

pain, chronic kidney disease, pain intensity

INTRODUCTION

According to the Kidney Disease Initiative Global Outcome (KDIGO) guidelines, chronic kidney disease (CKD) is defined as a structural or functional impairment of the kidneys lasting more than 3 months and affecting health status. CKD is classified based on the estimated glomerular filtration rate (eGFR, 5 stages „G” – glomerular) and on the basis of the level of albuminuria (3 categories „A” – albuminuria) perceived as the most significant risk factor for CKD progression, which helps physicians to accurately assess the severity of the disease (Table 1) and – after taking into account comorbidities and the risk of occurrence and progression of organ complications – facilitates decision-making related to the treatment and monitoring of patients [1]. It is worth noting that CKD is a global public health priority due to its prevalence and the very high costs of treating people affected by it, regardless of their place of residence. More than 800 million adults worldwide (i.e. more than 10% of the population) suffer from CKD [2], while in Poland this figure is approximately 4.7 million [3]. It has been calculated that the progression from stages 1-2 of CKD to stages 3a.-3b. and then to stages 4-5 is associated with a 1.1-1.7-fold and 1.3-4.2-fold increase in average annual healthcare costs per patient, respectively [4].

■ Tab. 1. Classification of chronic kidney disease according to KDIGO (2012) based on the estimated value of glomerular filtration

Classification according to eGFR (G, ml/min/1.73 m ²) and degree of filtration impairment (glomerular filtration)		
G1	≥90	Normal or increased
G2	89-60	Slightly reduced
G3a	59-45	Slightly to moderately reduced
G3b	44-30	Moderately to significantly reduced
G4	29-15	Significantly reduced
G5	<15	Renal failure
Classification according to the extent of albuminuria (A)		
A1	<30 mg/g (<3 mg/mmol)	Normal or slightly increased
A2	30–300 mg/g (3–30 mg/mmol)	Moderately increased
A3	>300 mg/g (>30 mg/mmol)	Greatly increased

The treatment of choice for patients with end-stage renal disease (ESRD) classified as stage 5 (Tab. 1) is renal replacement therapy: hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (KTx). Hemodialysis is the most common form of renal replacement therapy in the world, used by approximately 80% of all patients with ESRD. This fact is also confirmed by Polish data: the number of patients dialyzed with ESRD in December 2023 was 20,536, of which 19,770 (96%) were subjected to HD procedures [5]. KTx is considered the optimal and perceived as the target therapy. Dialysis therapy (HD, PD) allows patients to move from stage 5 to stage 4 of CKD. Kidney transplantation allows them to return to stage 2 of CKD with comorbidity (if diagnosed) depending on the duration of CKD, including dialysis therapy. Many publications emphasize that organ transplantation, including

KTx, improves the quality of life and significantly prolongs it [6]. Five-year comparative analyses of the survival period of patients on dialysis and after KTx from deceased donors indicate, that there are almost twice as many of the latter (45% vs. 82%) and the results are even better with KTx from a living donor (92%) [7]. In the course of CKD, in addition to many biochemical, metabolic disorders and multi-organ pathology, patients also experience pain of various types and intensity. In addition to procedural pain accompanying HD procedures [8], chronic pain occurs, resulting from both the primary disease damaging the kidneys and the accompanying multi-organ comorbidity that increases with the decrease in GFR (e.g. advanced ischemic heart disease, degenerative joint disease, osteoporosis peripheral neuropathy) [9]. It should be noted that pain in patients with CKD is diagnosed more often than in the general population [6], and its treatment requires the selection of analgesics in such a way as to ensure both safety and pain relief allowing for a satisfactory quality of life [10]. Untreated or insufficiently treated pain adversely affects daily functioning (the ability to walk, mood, relationships with other people, sleep and work) [11], reduces health-related quality of life, impedes access to public health care, may lead to shorter treatment duration or even abandonment of treatment, and increases mortality [12].

AIM

The aim of the study was to present and characterize the problem of pain among patients with CKD, including patients undergoing renal replacement therapy.

Definition and classification of pain

The International Association for the Study of Pain (IASP) has defined pain as an unpleasant sensory and emotional experience associated with or resembling an event associated with actual or potential tissue damage. According to the new definition, the occurrence of pain cannot be assumed solely on the basis of the activity of sensory neurons. Pain is a personal experience that is influenced to varying degrees by biological, psychological, and social factors. Therefore, pain should be recognized when an examined patient reports it [13]. Today, there are several ways of classifying pain. The division taking into account the time perspective distinguishes acute pain (lasting up to 3 months) and chronic pain (experienced more than 3 months), while the division based on the pathophysiological mechanism includes nociceptive, neuropathic, and mixed pain. Nociceptive pain is caused by direct activation of nociceptors (tissue damage, somatic and visceral pain), while neuropathic pain is caused by damage or disease of the somatic nervous system. It is most often described as burning, stinging, stabbing, dull, or pressing [14].

General characteristics of pain as an adverse symptom accompanying patients with CKD and renal replacement therapies

Frequency of pain

Patients with stage 3 or 4 CKD treated conservatively are at the same risk of pain as patients with stage 5, which results from a meta-analysis conducted by Lambourg et al. on data obtained from 1879 patients not treated in palliative units. The results obtained in the study group confirmed the experience of pain, respectively on average: in stage 3 CKD – 70%, CKD 4 – 60% and CKD 5 – 70% [8]. Fletcher et al. identified pain among the adverse effects in >45% of patients with CKD treated conservatively and on dialysis (poor sleep, sexual dysfunction, heartburn, muscle cramps, itching/dry skin) [6]. In the studies by Lambourg et al. and Davison et al., pain was present in 60.5%-65% of patients undergoing HD procedures and 35.9%-58% of patients treated chronically with PD [8,15]. Interestingly, the frequency of pain in patients after renal KTx was on average 46% [8].

Type of pain

Acute and chronic pain are common complaints in patients with chronic hemodialysis with ESRD. Brkovic et al. estimated that among 2377 patients undergoing HD, the incidence of acute pain (current pain, intradialytic pain, pain in the last 4 weeks) ranged from 21% to 92%, while chronic pain ranged from 33% to 82% [16]. Dos Santos et al., after analyzing data from 98,162 patients undergoing HD, determined the incidence of chronic pain in the study group at 57% to 77%. The incidence of neuropathic pain ranged from 2% to 62%, while nociceptive pain reached as much as 90% [11].

Pain intensity

In the study by Viderman et al., which assessed pain intensity on a scale of 0-10, the majority of hemodialysis patients indicated values of 4-6 for the moderate pain category and 7-10 for the severe pain category [17]. Davison et al., based on data from 16,558 hemodialysis patients, reported that an average of 43.6% of them reported chronic pain of moderate or severe intensity [15]. The dominance of moderate (13.1%-100%) and severe (5%-60.5%) pain was also visible in the study published by Santos et al. Mild pain was reported by 15.6%-36.8% of the study participants [11]. In turn, the results of a single-center study conducted among 463 Chinese PD patients (median dialysis duration 37.7 months) suggested that these patients experienced less pain intensity than HD patients (33.1% of patients with pain; median VAS = 20/100 points) [18].

Pain localization

In patients with CKD undergoing HD, the most frequently reported pain was related to vascular access, headache/backache/abdominal pain/chest pain/upper and lower limb pain/musculoskeletal pain [11, 16]. It should also be added that musculoskeletal pain was the most common pain symptom in patients with CKD treated conservatively (42%) or on dialysis (45%), while abdominal pain was the most common symptom in kidney transplant

recipients (41%) [8]. In the case of PD patients, the most frequently reported pain was in the limbs (80.4%) and in the thorax area (34%) [18].

Characteristics of selected types of pain accompanying renal replacement therapy

Pain associated with arteriovenous fistula (HD)

Vascular access is necessary for the HD procedure. The incidence of pain associated with cannulation of the arteriovenous fistula ranges from 12% to 80% [19]. Some patients experience acute pain of severe intensity (24.4% to 27.4%) [20], which may result in early termination of the dialysis session in as many as one in nine patients [20]. It is worth mentioning that the presence of an arteriovenous fistula may also be a source of severe chronic pain (3.2%) [20,21].

Headache

Headache is one of the common neurological symptoms during HD procedures, but in PD patients it is not a clinical problem [21]. Its incidence depends on the selection of diagnostic criteria and in HD patients ranges from 4% to 76.1% [11]. It is usually a tension-type or migraine headache that begins in the third or fourth hour of HD [22]. The pathophysiology of pain is not fully understood, but factors that may trigger pain have been identified, such as: fluctuations in sodium/urea/magnesium concentration in systemic circulation, blood pressure fluctuations, weight loss, fluctuations in nitric oxide/calcitonin gene-related peptide/substance P concentration. A special situation is the first, initial period of HD initiation, when too rapid removal of urea is associated with clinical symptoms resembling cerebral edema (high urea concentrations in the central nervous system lead to the transfer of water from the extracellular to the intracellular space), which translates into increased intracranial pressure (headache, nausea, vomiting) [22].

Abdominal pain

A meta-analysis conducted by Lambourg et al. showed that the frequency of abdominal pain in CKD patients on dialysis (16%) and not on dialysis (15%) was lower than after KTx (41%) [8]. Fletcher et al. reported that over 50% of patients after KTx reported abdominal pain, which was classified as one of the most common side effects, including dyspepsia, constipation, muscle weakness, and muscle cramps [6]. The probable cause responsible for such a high frequency of this undesirable symptom was postoperative pain and side effects of immunosuppressive therapy necessary after KTx [8]. It is worth adding that in patients treated with PD, abdominal pain may occur both during the inflow and outflow of dialysate, especially in the period after starting dialysis therapy. The pain accompanying the inflow subsides over time and is mainly related to the acidic pH of the dialysate. The pain accompanying the outflow at the end of peritoneal drainage is associated with the suction of the viscera or peritoneum by the catheter tip. This type of pain usually subsides or decreases in tidal dialysis (TDI), during which a certain volume of dialysate is left in the peritoneum (the peritoneum is not completely drained) and during

subsequent exchanges the peritoneal cavity is "filled up" to the planned inflow volume [22]. In turn, severe, acute and most often diffuse abdominal pain (80% of cases) accompanies the most common complication of PD, which is dialysis peritonitis (PDP) [23]. In patients on chronic PD for >5 years, a decrease in ultrafiltration and abdominal pain may indicate the so-called sclerosing peritonitis, which is an urgent indication for changing the dialysis method to HD [24].

Chest pain

The incidence of chest pain during HD is 2.6%-25%, while chronic pain ranges from 5.9% to 9.3% [16]. Chest pain occurring during HD may have a diverse etiology and pathogenesis (including: first-time dialyzer use syndrome, acute coronary event, hemolysis, uremic pericarditis, uremic pleurisy, gastroesophageal reflux, air embolism, depression). Given the diverse etiology of pain, coexisting symptoms and past diseases play an important role in directing the treatment. If the symptoms appear in the first minutes of the procedure and are accompanied by dyspnea and anxiety, their cause is most likely first-time dialyzer use syndrome or, occasionally, air embolism or hemolysis [25].

Bone and joint pain

Bone and joint pain is reported by both HD patients (45.8%) and PD patients (50%). A typical example of bone and joint pain is dialysis-related amyloidosis, which occurs as a complication of long-term conventional (diffusion) dialysis associated with the deposition of β_2 -amyloid that is not effectively removed by the dialyzer. The accumulation of this compound in the periarticular and joint spaces causes typical symptoms of carpal tunnel syndrome, shoulder pain and destructive arthropathy, leading to chronic pain in patients [26].

Musculoskeletal pain

Musculoskeletal pain according to Molsted and Eidemak is not reported more frequently by patients with CKD stages 4 and 5 (without mobility problems, on and off dialysis) than in the general population. In the Molsted and Eidemak study, neck/arm pain was reported by 45% of patients, back/lower back pain was reported by 57% of patients, and limb pain was reported by 64% of patients treated with repeated HD [27]. The results of the study by Hsu et al. showed that chronic musculoskeletal pain occurred with similar frequency regardless of the stage of CKD (stage 1–2 vs. stage 3–4 vs. stage 5, respectively: 49.4% vs. 58.2% vs. 52.2%). Almost 60% of patients complained of severe pain, and about 30% experienced moderate pain [28]. Chronic musculoskeletal pain was probably caused by electrolyte and acid-base imbalances (chronic hypocalcemia, hyperphosphatemia, chronic decompensated metabolic acidosis, hypo/hypermagnesemia, hyperuricemia). Renal replacement therapies do not always effectively correct these disorders or, as in the case of HD, do not guarantee the stability of ion or organic compound concentrations, on the concentrations of which these symptoms depend [29]. The source of pain in 33–85%

of HD patients may include sudden, recurrent, tonic or clonic, painful, involuntary muscle contractions. The contractions may affect the muscles of the lower limbs, abdomen, arms, hands and occur even several times a week, which may be the reason for early termination of dialysis in up to 18% of patients. This situation, if repeated, leads to underdialysis (and increased pain) [30]. Similar symptoms were observed in 73% of patients undergoing peritoneal dialysis for ≥ 3 months. The causes of spasms include: reduced effective plasma volume, hypotension, hyponatremia, hypocalcemia/metabolic alkalosis, hypomagnesemia, and carnitine deficiency [31].

Neuropathic pain

The main cause of painful neuropathies and ischemic ulcers in patients with CKD/ESRD is concomitant diabetes. Pain of this type affected over 50% of patients with long-term metabolic disorders resulting from diabetes, especially uncontrolled diabetes. In addition, peripheral uremic neuropathy occurs in > 90% of patients with ESRD in the form of paresthesia, burning, itching and motor disorders (restless legs syndrome). These polyneuropathies have similar clinical features: they are usually symmetrical and progressive, with symptoms appearing primarily in the lower limbs. Neurophysiological studies have shown a key role of impaired conduction and dysfunction of the Na⁺/K⁺ pump in diabetic neuropathy and axonal dysfunction in uremic neuropathy [32]. Peripheral neuropathies together with concomitant diabetes, peripheral arterial disease and coronary artery disease increase the risk of foot ulcers and lower limb amputations in patients treated with HD [33], and preparation of such patients for surgery requires effective control of diabetes, which results from the increased risk of failure and complications of most medical procedures in dialysis patients with diabetes [34].

Ischemic Pain

Ischemic pain is common in HD patients and is usually associated with peripheral vascular disease (atherosclerosis, arteriosclerosis, inflammation). Ischemic pain may not be related to arterial occlusion but may result from spontaneous necrosis (rhabdomyolysis) of skeletal muscle in diabetic patients with end-stage renal disease [35].

Pain resulting from calciphylaxis

Pain resulting from calciphylaxis is a consequence of ischemic necrosis of the skin and subcutaneous tissue of a given area of the body resulting from the deposition of calcium salts in the walls of blood vessels, thrombosis and occlusion of small blood vessels, and also metastatic calcifications in striated muscles. The pain accompanying this rare but life-threatening condition in dialysis patients falls into the category of acute pain. They are nociceptive, neuropathic, and inflammatory in nature [36].

Pain management in patients with CKD

The results of a meta-analysis of studies published between 1996 and 2020 and covering 2,307,797 patients with CKD showed that 41% of these patients regularly

used painkillers – every fifth person took opioids chronically, and 7% of patients used NSAID therapy chronically [37]. The prevalence of painkiller use was particularly high among patients undergoing dialysis, which is also confirmed by the Polish study – the prevalence of over-the-counter analgesic use was 26% for dialysis, 20% for stages 1–5, and 10% for KTR [38]. More than almost 37% of CKD Polish patients had never consulted their doctor before taking NSAIDs or paracetamol, which was chosen the most often [39]. High levels of opioid use generated serious adverse events such as death, hospitalization or fractures [37]. The above results emphasize the need for an individualized approach to the selection and dosing of analgesics, taking into account the impact of reduced renal function, drug interactions, and comorbidities on analgesic efficacy and the risk of adverse events. It may be helpful to use the adapted World Health Organization analgesic ladder for pain management in patients with renal disease and optimize the use of non-opioid drugs (e.g., paracetamol, NSAIDs, gabapentinoids, topical agents) before and after initiating opioid therapy. It is worth noting that opioids such as hydromorphone, fentanyl, methadone, buprenorphine are preferred in chronic kidney disease and end-stage renal failure, while morphine, hydrocodone, codeine should be avoided, and oxycodone, tramadol should be used with caution [40].

CONCLUSIONS

Pain occurs with similar frequency in patients with CKD, regardless of the stage of the disease and the method of treatment (conservative, HD, PD). The frequency of pain complaints is significantly reduced by kidney transplantation. Musculoskeletal pain is most often mentioned by patients treated conservatively and on dialysis, while abdominal pain is most often mentioned by patients after kidney transplantation. The high percentage of acute and chronic pain of moderate to severe intensity suggests that despite the common use of analgesics, including opioids, the treatment is ineffective and generates serious adverse events. Therefore, an individualized approach to the selection and dosing of analgesics is necessary, which should take into account the altered pharmacokinetics of drugs, reduced renal clearance and the possibility of drug accumulation. Education of physicians, nurses and patients on the assessment and treatment of pain is essential.

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