



High Prevalence of Chronic Musculoskeletal Pain and Analgesics Use Habits in the Geriatric Population with Chronic Kidney Disease

Kronik Böbrek Hastalığı Olan Geriyatrik Popülasyonda Kronik Muskuloskeletal Ağrının ve Analjezik Kullanım Alışkanlıklarının Yüksek Prevalansı

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Abstract

Objective: Individuals with chronic kidney disease (CKD) are at a risk of unsuccessful pain management and kidney injury using analgesics inappropriately. In this study, the prevalence of chronic musculoskeletal pain (CMP) and analgesics use habits was investigated in a geriatric population with non-dialysis dependent CKD, as well as the frequency of non-steroidal anti-inflammatory drugs (NSAIDs) and/or paracetamol use.

Method: This single-center cross-sectional study recruited patients over 65 years under follow-up for non-dialysis dependent CKD in nephrology clinic at least 1 year. Frequency of chronic pain was evaluated by Cornell musculoskeletal discomfort questionnaire. Pain was assessed using visual analogue scale (VAS).

Results: A hundred forty-two (52.8%) of 269 CKD patients had CMP. Patients with CMP were older than individuals without CMP ($p=0.042$). A hundred twenty-nine male patients and 140 female patients were present. Patients with CMP had a substantially higher ratio of females and mean body mass index than patients without CMP ($p=0.0001$). 9.7% of patients used paracetamol overall, while 42.8% utilized NSAIDs. 10.2% of non-CMP patients and 71.8% of CMP patients were reported to use NSAIDs ($p=0.0001$). Mean VAS score for patients with CMP was 5.01 ± 2.07 , and 48.6% of them reported moderate to severe pain. VAS score and estimated glomerular filtration rate level was similar regardless of analgesic type. Family physicians prescribed NSAIDs in 57.8% of cases, emergency medicine physicians in 9.0%, orthopedist in 17.5%, and others in 15.7% ($p<0.0001$).

Öz

Amaç: Kronik böbrek hastalığı (KBH) olan bireyler, analjeziklerin uygun olmayan kullanımına bağlı olarak başarısız ağrı yönetimi ve böbrek hasarı riski altındadır. Bu çalışmada diyalize bağımlı olmayan KBH'si olan geriyatrik bir popülasyonda kronik musculoskeletal ağrı (KMA) prevalansının ve analjezik kullanım alışkanlıklarının yanı sıra steroidal olmayan anti-enflamatuvar ilaçların (NSAİİ) ve/veya parasetamol kullanım sıklığının araştırılması amaçlanmıştır.

Yöntem: Bu tek merkezli kesitsel çalışma, nefroloji kliniğinde en az 1 yıldır diyalize bağımlı olmayan KBH nedeniyle takip edilen 65 yaş üstü hastaları içermektedir. Kronik ağrı, Cornell kas-iskelet rahatsızlık anketi ile değerlendirildi. Ağrı şiddeti, görsel analog skala (VAS) kullanılarak değerlendirildi.

Bulgular: İki yüz altmış dokuz KBH hastasının 142'sinde (%52,8) KMA olduğu belirlendi. KMA olan hastalar, olmayan bireylerden daha yaşlıydı ($p=0,042$). Yüz yirmi dokuz erkek hasta ve 140 kadın hasta mevcuttu. KMA olan hastalarda kadın oranı ve ortalama vücut kitle indeksi, KMA olmayan hastalara göre önemli ölçüde daha yüksekti ($p=0,0001$). Hastaların %9,7'si genel olarak parasetamol kullanırken, %42,8'i NSAİİ kullanmıştı. KMA olmayan hastaların %10,2'sinde ve olan hastalarının %71,8'inde NSAİİ kullanımı mevcuttu ($p=0,0001$). KMA'lı hastalarda ortalama VAS skoru $5,01\pm 2,07$ idi ve bunların %48,6'sı orta ila şiddetli ağrı bildirdi. Analjezik tipinden bağımsız olarak VAS skoru ve tahmini glomerüler filtrasyon hızı düzeyi benzerdi. Olguların %57,8'ine aile hekimlerinin, %9,0'ına acil servis hekimlerinin, %17,5'ine ortopedi hekimlerinin ve %15,7'sine başka uzmanların NSAİİ reçete ettiği belirlendi ($p<0,0001$).



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Cite this article as: Gülçiçek S. High Prevalence of Chronic Musculoskeletal Pain and Analgesics Use Habits in the Geriatric Population with Chronic Kidney Disease. Bagcilar Med Bull 2023;8(3):248-258

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Abstract

Conclusion: Based on high frequency of CMP, NSAIDs usage and prescriptions in elderly patients with CKD, an accurate risk assessment must be individualized in these patients based on CKD stage, age, comorbid conditions, and concomitant medication use.

Keywords: Analgesics, chronic kidney disease, chronic musculoskeletal pain, geriatric population

Öz

Sonuç: KBH'li yaşlı hastalarda KMA sıklığı, NSAİİ kullanımı ve reçetelenmesinin sıklığının yüksek olmasından ötürü, bu hastalarda doğru bir risk değerlendirmesi KBH evresi, yaş, komorbid durumlar ve eşzamanlı ilaç kullanımına göre bireyselleştirilmelidir.

Anahtar kelimeler: Analjezikler, kronik böbrek hastalığı, kronik muskuloskeletal ağrı, geriyatrik popülasyon

Introduction

The prevalence of chronic kidney disease (CKD), which is age-dependent, is high in the general population (1). Acute and chronic pains are predominant complaints among the adults and geriatric patients (2,3) and drug-related side effects dependent on all analgesic classes place restrictions on the management of disease (4). Due to distorted metabolism and excretion, as well as elevated accumulation of analgesic and their metabolites, the patients with lower glomerular filtration rate (GFR) are more susceptible to drug-related toxicity. As patients proceed to more severe stages of CKD, more medications that have side effects particular to their use in CKD are prescribed (5). Moreover, decreased life quality, a heavy burden of symptoms, and an increased risk of renal disease development, progression, and mortality have all been linked to the pain (6). In order to provide optimal health care for patients with CKD, the pain management is therefore essential (7).

It is well-known that non-steroidal anti-inflammatory drugs (NSAIDs) have been potentially dangerous pharmaceuticals for patients with CKD (8,9). Nephrotoxicity, fluid and electrolyte imbalances, hypertension, and other problems may occur when NSAIDs are used by CKD patients (10-12). To the current knowledge, a limited number of studies have examined the relationship between the analgesics use habits and prescriptions in the geriatric population with CKD, particularly in terms of NSAIDs or paracetamol usage (7,10). The present study investigated the prevalence of chronic musculoskeletal pain (CMP) and analgesics use habits in a Turkish geriatric population with non-dialysis dependent CKD and then aimed to explore factors associated with NSAIDs and/or paracetamol use, as well as short-term outcomes associated with using these analgesics.

Materials and Methods

Patients Selection

This single-center cross-sectional study recruited 320 patients over the age of 65 with a diagnosis of CKD at

different stages, who applied to the nephrology clinic of a tertiary hospital between February 2022-May 2022 and who were not yet on hemodialysis. Only the patients who have been under follow-up in the nephrology outpatient clinic for at least 1 year with CKD, who were over 65 years and who want to participate in the survey were selected for the study. The exclusion criteria were to having kidney transplant have a diagnosis of cancer not in remission, not volunteer to participate in the survey, to use of opioid analgesics and not followed up at least one year. According to the exclusion criteria, 51 patients were excluded. The study protocol was approved by the Local Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (number: 2022-40, date: 01/28/2022), in accordance with the Committee on Publication Ethics guidelines and with the Helsinki Declaration of in 2000. Written informed consent was taken from the patients before participating in the study.

Data Collection

All eligible patients (n=269) were carefully interviewed to identify primary disease and current medications. At the time of the visit, the demographic features and the findings of laboratory tests were also recorded. The frequency of chronic pain was evaluated by the Cornell musculoskeletal discomfort questionnaire (CMDQ) in the Turkish language, validated by Erdinc et al. (13). CMDQ involves self-rating of the frequency, severity and work interference of the musculoskeletal discomfort on three scales across 20 body parts. The responses given on the frequency, severity and work interference scales were used in computations as percentages. On the frequency scale, the frequency of experiencing CMP in the past work week is rated across the following anchors: "Never", "1-2 times last week", "3-4 times last week", "Once every day" and "Several times every day" with weights of 0, 1.5, 3.5, 5, and 10, respectively. On the severity scale, the severity of the experienced MSD is rated across the following anchors: "Slightly uncomfortable", "Moderately uncomfortable" and "Very uncomfortable" with weights of 1, 2, and 3, respectively. On the work

interference scale, the interference of the experienced MSD with ability to work is rated across the following anchors: "Not at all", "Slightly interfered" and "Substantially interfered" with weights of 1, 2 and 3, respectively (13).

For patients with chronic pain, the score of pain was assessed using a visual analogue scale (VAS), a scale for pain assessment the pharmacological treatment of musculoskeletal pain proposed by the World Health Organization in 1996 (14). VAS consists of a scale range between 0 mm (no pain) to 100 mm (very painful), after which the patients were examined by a rheumatologist to confirm the information and characterize CMP symptoms. For the calculation of prevalence and for all other analyses, CMP was defined as non-traumatic CMP for over 3 months with a VAS score of >1 (14).

Fasting blood samples were collected from all patients during examination and centrifugated. Whole blood count, blood urea nitrogen, creatinine, uric acid, total protein, albumin, parathormone (PTH), C-reactive protein (CRP), calcium (Ca), phosphorus (P) was analyzed by using a Roche, Cobas 8000 e602 analyzers (Roche Diagnostics, Mannheim, Germany). The levels of urea, urine creatinine, albumin, Ca, P, bicarbonate and hemoglobin were measured by a photometric method while the levels of urine protein and CRP were measured by a turbidimetric method. Electrochemiluminescence assay was used to measure 25(OH)D and PTH.

The demographic features and laboratory data recorded at the time of VAS scoring assessment were compared between groups which were determined according to the presence of chronic pain and to the type of analgesics used and the frequency of analgesic use. The eGFR was calculated according to the equations determined by chronic kidney disease epidemiological collaboration (CKD-EPI) (15,16). CKD was defined as the presence of persistent proteinuria, or a decreased estimated glomerular filtration rate (eGFR) of <90 mL/min per 1.73 m² determined by the CKD-EPI creatinine equation, in two separate measurements within an interval of 3 months. The CKD-EPI equation, expressed as a single equation, is $GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993 \text{ age} \times 1.018$ (if female), where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. Only eGFR values were compared according to the changes and a decline in eGFR of $\geq 30\%$ in a 1-year baseline period (17).

NSAIDs usage may cause acute renal impairment but no patient was hospitalized due to this disorder during drug use. In terms of renal diseases, the acute renal changes during NSAIDs usage were analyzed annually. The number and type of analgesics prescribed and the physicians to whom the patients consulted to prescribe these analgesics in the last 1 year with the complaint of pain were screened from the system of national Social Security Agency.

Follow-up

All geriatric patients who were diagnosed with CKD were followed up at 3-month intervals and they were informed not to use NSAIDs regularly in each physical examination.

Statistical Analysis

As a pilot study, eGFR levels were measured in patients with and without chronic pain and were found as 47.16 ± 18.21 mL/min/1.73 m² in chronic pain group and as 52.49 ± 8.00 mL/min/1.73 m² in no chronic pain group. The effect power calculated based on these mean eGFR levels was found to be 0.3789. As a result of the Power analysis performed with the GPower 3.1.9.4 program, the design of the comparison of eGFR levels of two groups with a margin of error of 0.05 gave a power level of 80% in case of minimum of 222 patients included in the study.

All statistical analysis was performed by using SPSS 23 (Statistical Package for the Social Sciences). Continuous quantitative variables were given as mean \pm standard deviation or median (minimum-maximum) and categorical variables were given as frequency and percentages. The Kolmogorov-Smirnov test was used to test the normality of continuous variables. The continuous variables of two groups were analyzed by Mann-Whitney U test. The categorical variables were compared by chi-square test and by Fisher's Exact and Fisher-Freeman-Halton test where appropriate. All analysis was tested at 95% confidence interval and p-value <0.05 considered as statistically significant.

Results

A total of 269 patients with a diagnosis of CKD and a mean of age of 72.48 ± 5.88 year was included in the study (Table 1). Of those, 142 patients (52.8%) had a CMP while 127 patients (47.2%) had none. The mean age of patients with a chronic pain was significantly higher than that of patients without pain (71.76 ± 5.74 vs. 73.11 ± 5.96 ; $p=0.042$). The ratio of female patients (40.2% vs. 62.7%) and the mean body mass index (BMI) (30.29 ± 4.81 kg/m² vs. 32.2 ± 5.46 kg/m²) were significantly higher in

patients with chronic pain than that in patients without pain ($p=0.0001$ and 0.007 , respectively). There was no significant difference in the distribution of patients according to the education levels, comorbidities and usage of antidepressants between two groups ($p>0.05$). 71.8% of the patients with chronic pain have used NSAIDs while only 10.2% of patients without pain have used these drugs ($p=0.0001$).

The mean VAS score of patients with CMP was 5.01 ± 2.07 (median: 4; range: 0-10) (Table 1). The severity of

pain was slightly uncomfortable among 37 patients (26.1%), moderate among 69 patients (48.6%) and very uncomfortable among 36 patients (25.4%). Of the patients having CMP, 67 patients declared a knee pain (47.18%), 62 had a lumbar pain (43.66%), 18 had a back pain (12.68%), 4 had a neck pain (2.82%), 12 had a shoulder pain (8.45%), 10 had an arm pain (7.04%), 18 had a hip pain (12.68%). The number of patients who had a pain only at one part of the body was 96 (67.61%), those at two parts was 34 (23.94%), and those at three parts was 7 (4.93%). The number of patients whose pain frequency was 1-2 times for last week

Table 1. Baseline characteristics of patients classified according to the presence of chronic MS pain

Characteristics	Total n=269	No chronic pain n=127	Chronic pain n=142	p-value
Age (y), X ± SD	72.48±5.88	71.76±5.74	73.11±5.96	0.042
Gender (n, %)				0.0001
Male	129 (52.04)	76 (59.8)	53 (37.3)	
Female	140 (47.96)	51 (40.2)	89 (62.7)	
BMI, kg/m²	31.31±5.25	30.29±4.81	32.2±5.46	0.007
Education (n, %)				0.482
Non-literate	74 (27.5)	30 (23.6)	44 (31.0)	
Primary school	155 (57.6)	75 (59.1)	80 (56.4)	
High school	19 (7.1)	10 (7.9)	9 (6.3)	
Undergraduate	21 (7.8)	12 (9.4)	9 (6.3)	
Comorbidities (n, %)				
DM	144 (53.5)	65 (51.8)	79 (55.6)	0.465
HT	261 (97)	121 (95.3)	140 (98.6)	0.154
CHD	55 (20.5)	26 (79.5)	29 (20.4)	0.992
Cancer	21 (7.8)	11 (8.7)	10 (7.0)	0.621
Others	39 (14.5)	22 (17.3)	17 (11.9)	0.213
# ≥3	41 (15.2)	16 (12.6)	25 (17.6)	0.254
NSAIDs (n, %)	115 (42.8)	13 (10.2)	102 (71.8)	0.0001
Paracetamol (n, %)	26 (9.7)	0 (0)	26 (18.3)	
Antidepressants (n, %)	24 (8.9)	10 (7.9)	14 (9.9)	0.569
VAS score, X ± SD	5.01±2.07	-	5.01±2.07	-
Median (range)	4 (0-10)	-	4 (0-10)	-
Severity of pain (n, %)				
Slightly uncomfortable	-	-	37 (26.1)	-
Moderately	-	-	69 (48.6)	-
Very uncomfortable	-	-	36 (25.4)	-
Pain location (n, %)				
Knee	-	-	67 (47.18)	-
Lumbar	-	-	62 (43.66)	-
Back	-	-	18 (12.68)	-
Neck	-	-	4 (2.82)	-
Shoulder	-	-	12 (8.45)	-
Arm	-	-	10 (7.04)	-
Hip	-	-	18 (12.68)	-
Frequency (n, %)				
1-2 times a week	-	-	50 (35.21)	-
3-4 times a week	-	-	14 (9.86)	-
Each day of 3 weeks	-	-	58 (40.85)	-
More than once in a day	-	-	20 (14.08)	-

X ± SD: Mean ± standard deviation, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CHD: Coronary heart disease, NSAIDs: Non-steroidal anti-inflammatory drugs, VAS: Visual analogue scale, MS: Musculoskeletal

was 50 (35.21%), those whose frequency was 3-4 times for last week was 14 (9.86%), those who had pain in each day of three weeks was 58 (40.85%), and those who had pain for more than once in a day was 20 (14.08%) (Table 1). Seventy-three patients (51.41%) stated that the pain they experienced interfered slightly with their ability to work, but 19 patients (13.38%) stated that it interfered substantially.

Comparison of laboratory findings of the patients according to the presence of CMP was presented in Table 2. No significant changes in the laboratory parameters were detected according to the presence of chronic pain ($p>0.05$) except a significant difference found in the mean hemoglobin level between two groups. The mean hemoglobin level of the patients with chronic pain (12.52 ± 1.6) was significantly lower than that of patients without pain (12.89 ± 1.59) ($p=0.04$).

Baseline characteristics and laboratory findings of patients classified according to type of analgesics used are presented in Table 3. Overall, 9.7% of all patients ($n=26$) were using paracetamols and 42.8% ($n=115$) were using NSAIDs. All these analgesics users had CMP but one of the patients with chronic pain declared not use any analgesic. No significant difference was observed in the distribution of patients according to the age, education, comorbidities, usage of antidepressants, ACE/ARB, and the mean BMI ($p>0.05$), while the distribution of gender showed a borderline of statistical significance ($p=0.052$). The most common location of pain was lumbar region in paracetamol group (46.2%) while it was the knee region in NSAIDs group (45.2%). The median VAS score and mean eGFR did not differ significantly according to

the type of analgesics used ($p>0.05$). 18.3% of patients using NSAIDs stated that they used more than 6 boxes of NSAIDs (each box contains 20 tablets) per year. The median VAS score (median: 6; range: 2-10) was significantly higher among patients who used NSAIDs intensively (more than 6 boxes per year) compared to those who did not use NSAIDs intensively (median: 4; range 0-10) ($p=0.022$).

The number of patients with a decrease in eGFR value over 30% was 4 (36.4%) among the patients using paracetamol and 7 (63.6%) among the patients using NSAIDs ($p=0.120$) (Table 3). The median eGFR value of the patients using paracetamol was 53.4 (range: 11.3-82) one year ago, while the value at the time of recording VAS score decreased to a median 51.65 mL/min/1.73 m² (range: 6-80.2 mL/min/1.73 m²). The median eGFR value of patients using NSAIDs was 48.7 mL/min/1.73 m² (range: 11.6-105 mL/min/1.73 m²) one year ago, while the current value decreased to a median 48.12 mL/min/1.73 m² (range: 9.9-100.7 mL/min/1.73 m²). The median decrease in eGFR level at the end of one-year follow-up was 2.5 (range: -19.7-20.9) among the patients using NSAIDs while it was 3 (range: -12.9-41.4) among the patients using paracetamol ($p=0.801$) (Table 3).

The frequency of analgesic use among the patients was compared according to the presence of CMP and CKD stage and presented in Table 4. 16.5%, 66.1% and 17.3% of 127 patients without CMP was at stage 1-2, stage 3 and stage 4 of CKD, respectively. 23.2%, 60.6% and 16.2% of 142 patients with CMP was at stage 1-2, stage 3 and stage 4 of CKD, respectively. No significant difference was found

Table 2. Comparison of laboratory findings of the patients according to the presence of chronic musculoskeletal pain

Parameter	No chronic pain n=127	Chronic pain n=142	p-value
Urea (mg/dL)	48 (21-140)	47.9 (24.6-180)	0.751
eGFR (mL/min/1.73 m ²)	48.22±16.17	49.26±16.64	0.605
Urine P/C ratio (mg/gr)	135 (1-6031)	127 (5-7483)	0.817
Albumin (g/L)	4.49±0.44	4.45±0.31	0.856
Ca (mg/dL)	9.4±0.95	9.44±0.48	0.810
P (mmol/L)	3.76±3.2	3.66±0.63	0.092
Ca × P (mg ₂ /mL ₂)	32.82 (0.37-368.6)	34.78 (22.31-56)	0.092
PTH (ng/L)	55.1 (3.5-244)	55 (9.5-458)	0.630
25(OH)D (µg/L)	19.45 (3-55.7)	20.4 (4.14-99)	0.490
HCO ₃ ⁻ (mmol/L)	25.7 (18.8-31.1)	26 (17.6-37.5)	0.717
Hb (g/dL)	12.89±1.59	12.52±1.6	0.04
CRP (mg/dL)	3.3 (0.1-59.7)	3.62 (0.33-61.4)	0.478

All values are presented as mean ± standard deviation or median (minimum-maximum), P: Phosphorus, PTH: Parathyroid hormone, Hb: Hemoglobin, 25(OH)D: 25 hydroxy vitamin D, HCO₃⁻: Bicarbonate, CRP: C-reactive protein, P/C: Protein/creatinine ratio in spot urine, eGFR: Estimated glomerular filtration rate

in distribution of patients according to CKD stages and presence of CMP ($p>0.05$). Among patients at chronic pain group, 75.8% of 33 patients at stage 1-2, 42.9% of 86 patients at stage 3 and 69.6% of 23 patients at stage 4 were NSAIDs users, all of which were significantly higher than those at no chronic pain group ($p<0.0001$, $p<0.0001$ and $p=0.0015$, respectively). Moreover, the frequency of heavy NSAIDs users (more than 6 boxes per year) was significantly higher in patients with CMP and CKD at stage 3 compared to corresponding patients without CMP (42.9% vs. 5.5%, respectively, $p=0.0021$). Additionally, the ratio of paracetamol users was significantly higher in patients with CMP and CKD at stage 3 compared to corresponding patients without CMP (11.3% vs. 0%, respectively, $p<0.0001$). No such significance was found in heavy NSAIDs or paracetamol users among patients at CKD stage 1-2 or stage 4 ($p>0.05$).

As shown in Figure 1, there was a significant difference between the prescription numbers of NSAIDs by the family physician (57.9%), emergency medicine physicians (9.0%), orthopedists (17.5%), and other physician groups (15.7%) ($p<0.0001$). As a result of the paired comparisons, it was determined that family physicians prescribed NSAID drugs the most ($p<0.0001$). There was a significant difference between the prescription numbers of paracetamols by the family physicians (71.4%), emergency medicine physicians (14.3%), orthopedist (5.4%), and other physician groups (8.9%) ($p<0.0001$). Also, the number of paracetamol prescriptions by the family physicians was higher than those by other physicians ($p<0.0001$). There was no significant difference between the prescribing numbers of the emergency medicine physicians, orthopedists, and other physician groups ($p>0.05$).

Table 3. Baseline characteristics and laboratory findings of patients classified according to type of analgesics used

Characteristics	Paracetamol n=26	NSAIDs n=115	p-value
Age (n, %)			0.206
65-75 years	16 (61.5)	85 (73.9)	
≥76 years	10 (38.5)	30 (26.1)	
Gender (n, %)			0.052
Male	7 (26.9)	55 (47.8)	
Female	19 (73.1)	60 (52.2)	
BMI, kg/m² (X ± SD)	32.28±5.34	31.74±5.24	0.730
Education (n, %)			0.959
Non-literate	8 (30.8)	35 (30.4)	
Primary school	15 (57.7)	64 (55.6)	
High school	2 (7.7)	8 (7.0)	
Undergraduate	1 (3.8)	8 (7.0)	
Comorbidities (n, %)			
DM	12 (46.2)	68 (59.1)	0.228
HT	26 (100)	112 (97.4)	0.405
CHD	2 (7.7)	26 (22.6)	0.85
Cancer	3 (11.5)	9 (7.8)	0.540
# ≥3	4 (15.4)	20 (17.4)	0.806
Antidepressants	1 (3.8)	14 (12.2)	0.214
ACE/ARB	19 (73.1)	80 (69.6)	0.724
Pain location			
Knee	9 (34.6)	52 (45.2)	0.324
Lumbar	12 (46.2)	43 (37.4)	0.408
Back	6 (23.1)	10 (8.7)	0.081
Neck	2 (7.7)	2 (1.7)	0.099
Shoulder	1 (3.8)	8 (7.0)	0.558
Arm	2 (7.7)	7 (6.1)	0.762
Hip	2 (7.7)	14 (12.2)	0.515
VAS score			0.782
Median (range)	4 (3-8)	4.5 (0-10)	
eGFR (mL/min/1.73 m ²) (X ± SD)	48.62±15.34	49.35±16.82	0.827
Decrease above 30% (n, %)	4 (36.4)	7 (63.6)	0.120

X ± SD: Mean ± standard deviation, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CHD: Coronary heart disease, NSAIDs: Non-steroidal anti-inflammatory drugs, ACE: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, VAS: Visual analogue scale, eGFR: Estimated glomerular filtration rate

Discussion

The present study showed that the rate of presence of CMP was 52.8% in the geriatric sample including 269 patients with non-dialysis dependent CKD and the mean age, the ratio of females, the mean BMI and rate of using NSAIDs among the patients with CMP was significantly higher than those without pain. VAS score and eGFR level were comparable between the groups of analgesic type (NSAIDs vs paracetamol). A significant higher ratio of NSAID drugs (57.8%) was prescribed by family physicians compared to other physicians for the patients using NSAIDs. A similar higher ratio was also observed for paracetamol prescriptions by family physicians (71.4%) for patients using paracetamols. Most of patients with CMP were NSAIDs users at all stages 1-4 of CKD but the ratio of heavy

NSAIDs users decreased at higher stages. These findings showed that a high frequency of CMP, NSAIDs usage and prescriptions in elderly patients with CKD, suggesting the unnecessary prescriptions and use of analgesics should be avoided in these patients due to the risk of nephropathy emerged by NSAIDs use.

Patients with kidney diseases frequently suffer chronic pain as one of the important symptoms of disease. Pain in patients with early-stage CKD is associated with lower quality of life and CKD has severe impact on quality of life (18). In patients with CKD, chronic pain was reported by more than 70% of patients (7). A study reported that more than 50% of CKD patients but less than 10% of non-CKD patients experienced a chronic pain (19). CMP is the most common type of pain in CKD and a high number of CKD

Table 4. Comparison of frequency of analgesic use among the patients according to the presence of chronic musculoskeletal pain and CKD stage

CKD stage		No chronic pain n=127	Chronic pain n=142	p-value
Stage 1-2	Total number, n (%)	21 (16.5)	33 (23.2)	0.223
	NSAIDs user, n (%)	2 (9.5)	25 (75.8)	<0.0001
	Heavy NSAIDs user, n (%)	0 (0)	4 (16)	0.261
	Paracetamol, n (%)	0 (0)	5 (20)	0.164
Stage 3	Total number, n (%)	84 (66.1)	86 (60.6)	0.412
	NSAIDs user, n (%)	7 (5.5)	61 (42.9)	<0.0001
	Heavy NSAIDs user, n (%)	0 (0)	11 (7.7)	0.0021
	Paracetamol, n (%)	0 (0)	16 (11.3)	<0.0001
Stage 4	Total number, n (%)	22 (17.3)	23 (16.2)	0.934
	NSAIDs user, n (%)	4 (18.2)	16 (69.6)	0.0015
	Heavy NSAIDs user, n (%)	0 (0)	2 (8.7)	0.489
	Paracetamol, n (%)	0 (0)	5 (21.7)	0.065

NSAIDs: Non-steroidal anti-inflammatory drugs, CKD: Chronic kidney disease

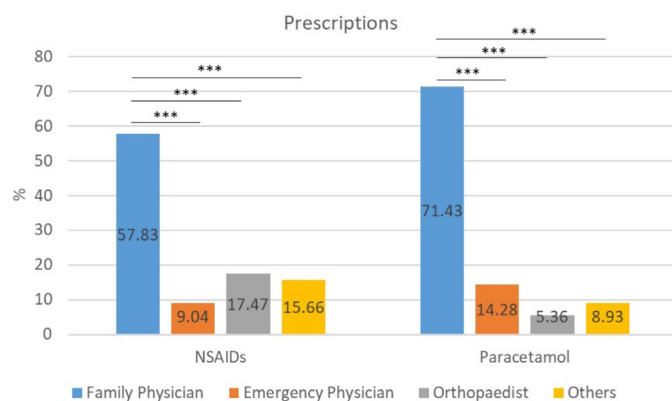


Figure 1. Distribution of prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol among the physicians

patients have experienced moderate-to-severe pain (20). There are studies claiming that CKD patients with CMP showed independently higher rates of all-cause mortality than those without chronic pain. However, long-term follow-up of CKD patients indicated that patients with CMP had similar risk of CKD progression as those without pain (21). As with the general population, elderly age, female gender, obesity and some comorbid conditions are the best determinants of CMP (22). In the present study, among 269 geriatric patients with non-dialysis dependent CKD, 142 patients (52.8%) had CMP. This relatively high prevalence rates in patients with CKD in its earlier stages may be due to the fact that the burden of comorbidity accounts for a large portion of the pain in CKD. Another reason is that a number

of medical professionals lack the knowledge and confidence to pursue appropriate chronic pain treatment options. Some of them are reluctant to administer and supervise analgesics since they believe it is not their obligation to address symptoms that are not specifically linked to CKD. I noticed that the use of analgesics in the patients was mostly due to CMP and mostly as a result of referral to the family physician. In order to reduce the unnecessary use of NSAIDs and limit their prescribing, we recommend that the family physicians be provided with detailed continuous medical education on the damages of NSAIDs use in CKD patients, especially in advance stages.

To manage the CMP in CKD patients, more analgesics have been prescribed especially in the elderly. The anatomical and physiopathological changes seen with aging alter the responses to neuraxial and peripheral neural blockade and affect the pharmacokinetic and pharmacodynamic properties of the individual agents used. Due to these changes, elderly patients have an increased sensitivity to both therapeutic and adverse effects of many drugs used for pain management (23,24). In this study, the frequency of NSAIDs usage among CKD patients was 42.8% and this frequency increased to 71.8% among CKD patients with CMP. This may be related to lower levels of hemoglobin CKD patients with CMP who may have a gastrointestinal occult bleeding as a complication of NSAIDs usage, although the difference between the groups with and without CMP showed statistically borderline significance. This finding is consistent with the literature suggesting that NSAIDs can cause mucosal injury in the upper, mid- and lower GI tract resulting in bleeding which can be overt (with melaena) or occult (iron deficiency) (25). NSAIDs inhibit platelet cyclooxygenase, thereby blocking the formation of thromboxane A₂. These drugs produce a tendency toward systemic bleeding by impairing thromboxane-dependent platelet aggregation and consequently prolonging bleeding time (26). Therefore, a lower level of hemoglobin among CKD patients with CMP is an expected finding.

Female patients tend to use NSAIDs and painkillers more frequently than male patients, which may be due to the fact that women are typically more susceptible to developing chronic and autoimmune diseases and conditions like arthritis (27). In the literature, NSAIDs prescribing and utilization has been associated with the female gender among elderly patients (28). In a study conducted in Italy, the use of NSAIDs was more common in the elderly and women (29). In a study from UK, the rate of NSAIDs usage was 12.3% among female and 9.4% among male

patients with CKD (30). The present study showed that the frequencies of NSAIDs usage were more common among female patients with CMP, showing a borderline significance difference with compared to male patients.

The present study revealed that there was no significant difference in the mean eGFR value and the decrease in eGFR over 30% in CKD patients using NSAIDs and paracetamol, which showed that the drug choice did not cause a significant change in kidney function. The use of NSAIDs should be questioned in every patient with a decrease in eGFR, although it is recommended not to use it, over-the-counter use can be seen frequently. The reason for this is the inadequacy of chronic pain management. Epidemiologic studies examining analgesics and kidney failure have revealed controversial findings about the risk of NSAIDs usage (10,31). There are studies reporting no risk of decreased GFR among moderate users of NSAIDs (32,33). On the other hand, several case-control studies found substantial consumption of NSAIDs was associated with an increased risk of kidney failure (34). Prolonged use of NSAIDs was related to reduction of eGFR in CKD patients (31). A study of patients with CKD using opioids and NSAIDs demonstrated that NSAIDs usage was associated with a lower risk of kidney failure with kidney replacement therapy in patients with eGFR <45 mL/min/1.73 m² (34). This finding may also be related to the frequency of analgesic use which was restricted to self-report, hence did not necessarily reflect actual use of all prescribed drugs. Opioid use is relatively low in this country compared to other analgesics because there is a restriction on opioid analgesics. It is available with a special prescription. The data of NSAIDs usage was collected by the patient interviews; obviously this approach is prone to recall bias.

Use of prescription analgesics, both paracetamols and NSAID, has been reported to increase in time especially in patients with CKD (10). There are several evidence-based reports suggesting not to prescribe NSAIDs for geriatric patients with CKD due to common comorbidities including cardiovascular or renal diseases, however, it has been demonstrated that the prescription and use of NSAIDs is widespread among these patients (35-38). The use of NSAIDs is associated with increased gastrointestinal and cardiovascular risks and renal function disorders, particularly in elderly patients (37). The use of NSAIDs was reported to be associated with a two-fold increased risk of CKD, especially in patients aged >65 years. In one study, the ratios of individuals with hypertension, heart failure, or CKD used prescribed NSAIDs for musculoskeletal pain

management were between 14.4% and 16.2% (38). Ndlovu et al. (39) reported that 5.7% of people with moderate to severe CKD reported using NSAIDs; however, the majority of these people used over-the-counter drugs, and many of them were not aware that they had CKD. In a large cohort study of primary care visits involving older adults with a musculoskeletal disorder and history of hypertension, heart failure, or CKD, almost 10% of patients were found to prescribed and use NSAIDs despite the high risk for cardiovascular and renal complications. They also reported that widespread prescription of NSAIDs among primary care practices and physicians while the use of prescribed NSAIDs was not associated with significantly higher (or lower) risk of cardiovascular or renal outcomes (35). The present study contributes to these earlier studies by showing that a high frequency of NSAIDs and paracetamols use among the geriatric patients with CKD and high rates of comorbidities, such as hypertension (97%), diabetes mellitus (53.5%), and cardiovascular disease (20.5%).

The variations in analgesic use among different countries that have been documented in the literature may be related to obstacles to receiving medical care and varying cultural views of how to manage pain. In a study conducted in 835 Turkish patients aged over 65 years (mean age 74.2±6.6 years), the mean number of drugs used was 6.8±3.2, total number of inappropriate drugs used was 688 and the number of patients using inappropriate drugs was 431 (51.6%) (37). The reports from Europe declared a NSAIDs prescription rate of 73% and 20% among elderly patients (30,40). A recent population-based study evaluating >9 million Canadian residents found that individuals aged 66 years or older formed the majority (93.4%) of those who had received one or more NSAIDs for ≥14 days (41). We found that 9.7% of all patients were using paracetamols and 42.8% were using NSAIDs. The frequency of NSAIDs usage in older CKD patients with CMP (115 of 142 patients) is also consistent with the literature. In every country, different national regulations of the health systems affect these prescription rates of NSAIDs. For example, in USA, there are mainly over-the-counter drugs but in Turkey, all drugs are sold in pharmacies. Therefore, the non-prescribed drugs are in control of the pharmacists. This can be an additional safety measure.

Several drugs with potential toxicity are prescribed to patients with advanced CKD (42). In fact, NSAIDs are considered a class of drugs that should be avoided in patients with CKD, particularly those with advanced CKD (9). This approach has led to increased opioid

administration and use of adjuvant therapies to manage pain. Importantly, opioid use poses many risks and data regarding the safety of even commonly used agents in patients with CKD are markedly limited (43). Baker et al. (44) reported that NSAIDs were safer than opioids in this group of patients (34). In view of this, a tighter approach to CKD stage and other risk-enhancing comorbidities should be used in which the management of pain becomes challenging in advanced CKD stages. In the present study, the patients with CMP continued to use NSAIDs regardless of CKD stage, and the frequency of NSAIDs users was significantly higher compared to patients without CMP for all CKD stages, but the patients at CKD stage 4 avoided heavy NSAIDs use, which was different from the data on the paracetamol users compared according to CKD stage and presence of CMP. This finding shows that patients with advanced CKD stage do not completely stop using NSAIDs, but they try to avoid intensive use and we can say that these patients use NSAIDs a little more consciously or carefully. Therefore, correct use of NSAID in patients with CKD should be on the basis of an individualized examination for the type of pain, expected dose and duration, patient risk profile including stage of CKD, availability of alternative therapies, and care targets.

The present study evaluated the prescriptions of NSAIDs and paracetamols in CKD patients. In a study by Arakawa et al. (45), the prescription of NSAIDs within East Asia was examined by means of a questionnaire survey for physicians and most physicians prescribed nonselective NSAIDs, cyclooxygenase-2 inhibitors or aspirin for more than 5 patients per week. In another study, widespread prescribing of NSAIDs were identified among primary care practices and physicians and prescription NSAIDs usage was not associated with the varied risk of cardiovascular or renal safety-related outcomes (35). In a recent study conducted in Turkey, the most common analgesics ordered by physicians were NSAIDs (n=505, 67.9%) in the emergency departments (ED) and physicians prescribed an analgesic at discharge from the ED in 55.6% of the patients and acute pain was present in 7.5% of the patients (46). Here, the frequency of prescriptions for NSAIDs was highest by the family physicians compared to other physicians. One of the reasons why family physicians prescribed NSAIDs more often to patients with CMP depends on the high rate of application to family physicians in Turkey. At this point, it is understood that physicians should continue medical education. The primary care physician should be well aware of the characteristics of the analgesics to be used as

well as the characteristics of the patient in order to be able to effectively manage pain.

Study Limitations

The present cross-sectional study has the limitations that were related with the design such as information bias. Another limitation of this study that non-prescribed medications was probably missed out due to the collection of data of prescriptions by screening the national social security agency. As another limitation, the present study did not assess the independent effect of CKD and not compare the outcomes with a control group or the patients with other diseases. Also, one cannot rule out the possibility analgesic choice may have change in years by the regulations of health authorities on the prescription of NSAIDs.

Conclusion

Based on the high frequency of CMP, NSAIDs usage and prescriptions in patients with CKD, an accurate risk assessment must be highly individualized based on CKD stage, age, comorbid conditions, and concomitant medication use. It is crucial to educate the physicians to consider potentially life-threatening NSAID-related complications before NSAIDs therapy initiation and to avoid prescriptions of NSAIDs in geriatric patients with CKD. Optimizing pain management in a complex condition such as kidney disease should remain a priority for clinicians and researchers. Given the difficulty in pain management in the elderly population, more evidences are required to support NSAIDs usage in CKD patients by a more detailed strategy considering CKD stage and other risk-promoting comorbidities.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (number: 2022-40, date: 01/28/2022), in accordance with the Committee on Publication Ethics guidelines and with the Helsinki Declaration of in 2000.

Informed Consent: Written informed consent was taken from the patients before participating in the study.

Peer-review: Internally and externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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