ORIGINAL ARTICLE



Pain phenotypes in caregivers of children with cerebral palsy

Serebral palsili çocukların bakımını üstlenen bireylerde görülen ağrı fenotipleri

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Summary

Objectives: To determine the phenotypes of chronic pain seen in individuals caring for children with cerebral palsy (CP).

Methods: A current classification system was used to determine the prevalence of predominant pain phenotypes in caregivers of children with CP. To this end, the Visual Analog Scale, Margolis pain diagram, Central Sensitization Inventory, and Short Form-36 questionnaire were administered to the participants. In addition, the participants underwent a quantitative sensory examination.

Results: This study was concluded with 60 individuals. The predominant pain phenotype was nociceptive pain in 30% of the participants, nociplastic pain in 25%, and neuropathic pain in 5%. The pain duration (p=0.365) and quality of life of the individuals did not significantly differ according to the predominant pain phenotypes (p>0.05). However, there was a statistically significant difference between the pain phenotypes in terms of pain severity (p=0.016) and the Central Sensitization Inventory scores (p<0.001).

Conclusion: Nociceptive pain was the most common pain phenotype in caregivers of children with CP. We also concluded that among the pain phenotypes, pain intensity was highest in neuropathic pain. There is a need for further studies in this area to demonstrate the validity and reliability of the evaluated mechanism-based classification system in order for it to be included in clinical guidelines.

Keywords: Caregivers; cerebral palsy; chronic pain; neuropathic pain; nociceptive pain; nociplastic pain.

Özet

Amaç: Serebral palsili (SP) çocukların bakımını üstlenen bireylerde görülen kronik ağrı fenotiplerini belirlemektir.

Gereç ve Yöntem: Bireylerde baskın ağrı tipinin prevalansını belirlemek için güncel bir sınıflandırma sistemi kullanıldı. Bu doğrultuda, bireylere Vizüel Analog Skalası, Margolis Ağrı Diyagramı, Santral Sensitizasyon Ölçeği ve Kısa Form-36 ölçekleri uygulandı. Ayrıca bireylere kantitatif duyu muayenesi yapıldı.

Bulgular: Çalışmamız 60 birey ile tamamlandı. Bireylerin %30'unda nosiseptif ağrı, %25'inde nosiplastik ağrı ve %5'inde nöropatik ağrı baskın ağrı tipi olarak belirlendi. Baskın ağrı tiplerine göre bireylerin ağrı süresi (p=0.365) ve yaşam kaliteleri anlamlı farklılık göstermedi (p>0.05). Ancak ağrı şiddeti (p=0.016) ve Santral Sensitizasyon Ölçeği skorları (p<0.001) açısından ağrı tipleri arasında istatistiksel olarak anlamlı fark bulundu.

Sonuç: SP'li çocukların bakımını üstlenen bireylerde en yaygın görülen ağrı tipi nosiseptif ağrı olarak saptandı. Ayrıca, ağrı fenotipleri arasında ağrı şiddetinin en yüksek olduğu tipin nöropatik ağrı olduğu sonucuna ulaşıldı. Mekanizmaya dayalı sınıflandırma sisteminin klinik kılavuzlarda yer alması için geçerlik ve güvenilirliğin gösterilmesi gerektiğinden bu alanda daha fazla çalışmaya ihtiyaç duyulmaktadır.

Anahtar sözcükler: Bakım verenler; kronik ağrı; nöropatik ağrı; nosiplastik ağrı; nosiseptif ağrı; serebral palsi.

Introduction

Cerebral palsy (CP) is a permanent, non-progressive disorder of posture and movement development that occurs due to a brain lesion in a developing fetal or infant brain and causes movement limitations. ^[1,2] Children with CP need lifelong care due to problems they experience.^[3] This long-term care creates emotional, economic, and physical difficulties for the caregiver. Conditions such as the limitation of social activity, depression, stress, provision of necessary equipment, caring for a child with a disorder for years, and long-term incorrect posture are observed in caregivers of children with CP.^[4–6] In addition to musculoskeletal pain, such as shoulder, waist, back,

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and knee pain, common chronic pain problems; e.g., myofascial pain syndrome and fibromyalgia are also commonly observed in these individuals.^[7]

In the literature, chronic pain is classified in many different ways according to geographical regions, severity, etiology, common clinical disorders, and mechanism of pain.^[8-10] The current, common, and most effective classification system for clinical decision-making recommended by the International Association for the Study of Pain (IASP) is the mechanism-based classification system.^[11-13] According to its mechanisms, pain consists of four types: neuropathic, nociceptive, nociplastic, and mixed type.^[10]

There are studies showing that pain phenotypes affect the severity of pain and quality of life in individuals with chronic pain.^[12,14] In addition, it has been suggested that determining pain phenotypes according to its mechanisms in individuals with chronic musculoskeletal pain will be an important step in creating personalized and effective treatment programs that effectively meet their needs.[11,15] However, to the best of our knowledge, no study has been conducted to investigate musculoskeletal pain experienced by individuals caring for children with CP. Therefore, the current study aimed to determine the phenotypes of chronic musculoskeletal pain among caregivers of individuals with CP and examine the relationship between the quality of life and pain severity according to the identified pain phenotypes.

Material and Methods

This cross-sectional observational multicenter study was carried out between January and June 2021 in special education and rehabilitation centers located in Isparta and Kutahya, Türkiye. The study was approved by the Non-Interventional Ethics Committee of Kutahya Health Sciences University (2020/18-04). In addition, it was registered at ClinicalTrials.gov (NCT04883489). This study was conducted in accordance with the principles set out in the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Individuals aged 21 to 65 years, who were caring for a child diagnosed with CP, had musculoskeletal pain complaints lasting at least six months, and reported a pain intensity of 2 or more according to the Visual Analog Scale (VAS), were included in the study. Individuals with any systemic disease, psychological treatment,

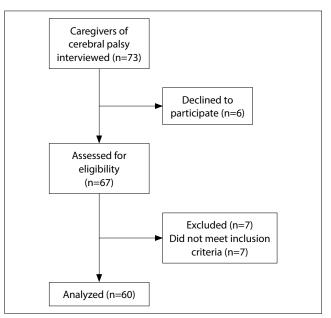


Figure 1. Flow diagram.

and pain lasting less than six months were not included in the sample. Those who did not complete all the evaluations were also excluded from the study (Fig. 1).

Outcome Measures

The primary outcome measure was predominant pain phenotypes obtained using the clinical algorithm presented in Figure 2. Therefore, the demographic data and medical histories of the participants were examined, and the following five outcome measurement methods were applied to use this algorithm. All the evaluations were undertaken faceto-face by the same physiotherapist.

Visual Analog Scale for Pain

The pain intensity of the participants was evaluated using VAS, which is a reliable and valid method for the quantitative assessment of pain intensity. ^[16] This scale presents a 100-mm line with one end representing no pain and the other indicating excruciating pain, and individuals are asked to mark their current pain intensity on this line. The length of the distance from the 'no pain' end of the scale to the marked point indicates the pain intensity of the individual.^[17] In addition to pain intensity, we also recorded the participants' pain durations.

Margolis Pain Diagram

The Margolis pain diagram consists of an anterior and posterior drawing of the body. We asked the participants to mark the body regions where they have pain complaints on this diagram.^[18]

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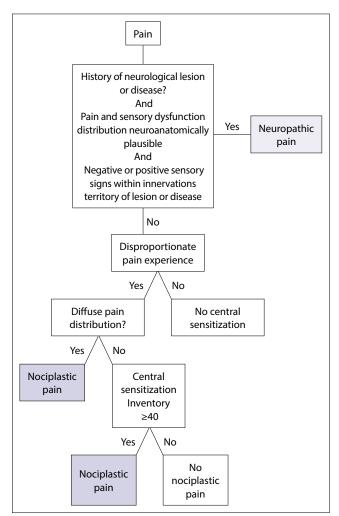


Figure 2. Mechanism-based classification system.

Central Sensitization Inventory

The Central Sensitization Inventory (CSI) was developed by Mayer et al.^[19] to determine central sensitization findings in patients with chronic pain. It consists of a total of 25 items scored as follows: 4 points for always, 3 for often, 2 for sometimes, 1 for rarely, and 0 for never. The total score ranges from 0 to 100 points. The cut-off score is 40. An increase in the total score indicates an increase in the degree of symptoms. In the current study, we used the Turkish version of CSI, for which the validity and reliability studies were undertaken by Duzce Keleş et al.^[20]

Short Form-36 Questionnaire

This instrument consists of 36 items measuring eight domains related to health status: physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, energy/vitality, bodily pain, and general health perceptions. The questionnaire gives a total score for each domain separately. Each domain scores health status from 0 to 100, with an increased score indicating better health. ^[21] Koçyiğit et al.^[22] performed the reliability and validity studies of the Turkish version of the Short Form-36 (SF-36) questionnaire used in the current study.

Quantitative Sensory Examination

This is a psychophysical test method that examines the functional state of the somatosensory system of individuals in terms of the severity of clinical symptoms through calibrated stimuli and subjective perception thresholds.^[23] In the current study, the quantitative sensory examination was performed by applying light touch, pinprick, and vibration sense tests as described below. The results of the examination were recorded as normal, hyposensitive, or hypersensitive response.

Light touch: The dermatome areas associated with the painful area of the individuals were evaluated with a brush while their eyes were closed.^[24,25]

Pinprick: A pointed pin was used to test the participants' ability to sense sharp and dull sensations in the body. While their eyes were closed, the sharp and dull sides of the pin were allowed to touch the painful dermatome areas.^[26]

Vibration sense: A 128 Hz tuning fork was used in the evaluation for neuropathic pain as previously recommended.^[27] Measurements were undertaken with the participants' eyes closed. A trial application was performed over the clavicle or sternum to familiarize the individual with vibration. Then, the vibration perception of individuals was evaluated from the olecranon, lower end of the ulna, and distal joint of the index finger in the upper extremity and cervical region and from the patella, outer malleolus, and distal toe joint in the lower extremity and lumbar region.^[28]

Classification System

In this study, the pain intensity of individuals was classified according to both pain localization and mechanism. A current mechanism-based classification developed by Nijs et al.^[13] was used to determine the pain phenotypes of the participants (nociceptive, neuropathic, nociplastic, and mixed type). This classification system consisted of two steps: (a) diagnosis or exclusion of neuropathic pain and (b) distinction between dominant nociceptive and nociplastic pain (Fig. 2). Individuals with more than one pain phenotype (e.g., both nociplastic and neuropathic) were considered to have mixed-type pain according to the algorithm.



Diagnosis of Neuropathic Pain

For the diagnosis of neuropathic pain, the criteria of (a) history of neurological lesion or disease, (b) neuroanatomically plausible pain distribution, and (c) presence of sensory dysfunction according to the results of quantitative sensory tests should be met.^[9,29] In the current study, if the participants met these three basic criteria, their type of pain was evaluated as neuropathic.

History of Neurological Lesion or Disease

A lesion in the somatosensory system and neurological damage due to an illness or trauma in the past are important signs for neuropathic pain.^[9,29] We questioned the medical history of the participants accordingly and noted whether they had this type of ailment.

Neuroanatomically Plausible Pain Distribution

Dermatomal pain distribution in individuals indicates neuroanatomically plausible pain distribution. Bilateral pain/mirror pain, pain varying by location, large areas with non-segmental distribution, widespread pain, and allodynia/hyperalgesia outside the segmental region of primary nociception suggest the presence of neuroanatomically plausible pain distribution.^[13] In the current study, we evaluated the presence of these conditions in the participants using the Margolis pain diagram.

Quantitative Sensory Test

Hypersensitive or hyposensitive response in one or more of the light touch, pinprick, and vibration sense tests was interpreted as the presence of sensory dysfunction.^[30,31]

Nociceptive vs. Nociplastic Pain

The classification algorithm shown in Figure 1 was used to distinguish nociceptive pain from nociplastic pain. Accordingly, the presence of the following three main classification criteria was questioned: disproportionate/exaggerated pain experience, diffuse pain distribution, and hypersensitivity of nonmusculoskeletal senses.

Disproportionate/Exaggerated Pain Experience

Exaggerated pain experience refers to pain and disability experienced by an individual being contrary to the nature of their injury/pathology. In nociplastic pain, an individual's pain intensity and quality of life are disproportionate to the nature or extent of their injury, whereas nociceptive pain presents with pain intensity and perceived quality of life that are consistent with the nature and extent of tissue damage.^[13] In the current study, the pain severity and quality of life of the participants were evaluated according to their history of injuries or pathologies to determine whether they had disproportionate pain experience.

Presence of Diffuse Pain

According to the results obtained from the Margolis pain diagram, it was determined whether the participants experienced diffuse pain. Diffuse pain was considered when at least one of the following criteria was present:

- Bilateral pain,
- Changes in pain in the anatomical region during palpation,
- · Hemilateral pain,
- Widespread pain,
- Hyperalgesia/allodynia outside the segmental region of primary nociception examined by palpation and sensory testing.^[18]

Hypersensitivity of Senses Unrelated to the Musculoskeletal System

The last criterion examines hypersensitivity to sensations unrelated to the musculoskeletal system, such as light, smell, cold, noise, and medicine. In this study, we used CSI to diagnose hypersensitivity. If individuals obtained a score of 40 or higher on this scale, their pain phenotypes were determined as nociplastic.^[11]

Statistical Analysis

Statistical analyses were performed using SPSS v.20.0 software package. The mean and standard deviation values of the demographic data, pain durations, VAS scores, CSI scores, and SF-36 domain scores were analyzed. The mechanism-based pain distributions of the individuals were given as percentages. The t-test, one of the parametric tests, was used to analyze the differences between the paired groups according to the variables. In order to analyze the differences of individuals in more than two groups according to the variables, the Kruskal-Wallis test was conducted. The differences between the groups in relation to the demographic data, pain durations, VAS scores, CSI scores, and SF-36 domain scores were analyzed using the one-way analysis of variance test. Statistical significance was taken as p<0.05.

	Total (n=60) Mean±SD	Neuropathic pain (n=3) Mean±SD	Nociceptive pain (n=18) Mean±SD	Nociplastic pain (n=15) Mean±SD	Mixed-type pain (n=24) Mean±SD	р
Age (years)	39.32±7.60	32.33±10.60	40.00±7.80	39.13±7.20	39.79±7.50	0.466
Height (m)	1.63±0.08	1.62±0.70	1.63±0.11	1.62±0.70	1.65±0.70	0.314
Weight (kg)	73.36±14.20	70.33±18.50	71.28±12.8	68.40±8.60	78.86±16.70	0.105
BMI (kg/m²)	27.20±5.50	26.60±5.30	26.00±4.40	25.70±4.30	29.10±6.50	0.732
Gender, n (%)						1.000
Female	54 (90%)	3	15	15	21	
Male	6 (10%)	0	3	0	3	
Occupation, n (%)						0.704
Housewife	51 (85%)	2	15	13	21	
Worker	4 (6.7%)	0	2	1	1	
Civil servant	4 (6.7%)	1	0	1	2	
Retired	1 (1.7%)	0	1	0	0	
Educational level, n (%)						0.248
Primary school	35 (58.3%)	1	11	8	15	
Middle school	8 (13.3%)	1	5	0	2	
High school	9 (15%)	0	2	3	4	
University	8 (13.3%)	1	0	4	3	
Number of children with CP						
cared for	2.25±0.97	1.33±1.15	2.11±1.02	2.53±0.91	2.29±0.91	0.463
Duration of care for a child with						
CP (years)	10.3±6.3	14.00±11.30	10.10±5.50	7.80±4.90	11.60±6.70	0.466
Pain duration (years)	6.83±5.60	2.67±1.50	5.50±4.20	6.73±4.60	8.40±6.90	0.365
VAS (mm)	48.96±5.60	67.30±27.73	34.38±17.66	53.00±18.57	55.08±17.25	0.016
CSI	37.12±13.40	35.67±9.00	26.50±12.99	43.00±12.59	41.58±10.04	0.000
SF-36 physical functioning	74.25±16.04	74.25±16.04	81.11±12.31	74.00±16.60	68.54±17.47	0.355
SF-36 physical role limitations	54.16±43.46	33.33±57.03	58.33±45.37	45.00±40.31	59.37±43.49	0.345
SF-36 emotional role limitations	55.00±46.67	11.10±19.22	62.96±45.57	42.22±47.92	62.50±46.43	0.108
SF-36 energy/vitality	46.91±20.62	55.00±8.66	50.83±20.52	43.33±15.19	45.20±24.51	0.742
SF-36 mental health	56.83±16.42	60.00±8.00	60.44±16.11	54.66±13.40	55.08±19.16	0.367
SF-36 social functioning	66.55±25.72	66.66±19.09	74.30±20.77	53.33±24.76	69.00±28.40	0.653
SF-36 bodily pain	54.16±23.07	60.00±22.22	59.44±28.94	51.83±22.29	50.93±18.99	0.175
SF-36 general health perceptions	52.88±15.34	56.66±19.09	56.00±17.68	51.33±14.81	51.04±14.36	0.460
SF-36 health status changes	44.66±14.43	58.33±14.43	51.38±23.43	36.66±15.99	42.91±18.87	0.370

Table 1. Distribution of participants by evaluated variables

n: Number of individuals; SD: Standard deviation; m: Meter; kg: Kilogram; mm: Millimeter; VAS: Visual Analog Scale; CSI: Central Sensitization Inventory; SF-36: Short Form-36; SP: Cerebral palsy; *: P-value <0.05 (one-way analysis of variance).

Results

Sixty individuals who were caring for children with CP were included in the study. The mean age of the participants was 39.32±7.60 years. The gender distribution was 54 (90%) females and six (10%) males. Concerning distribution by educational level, 35 (58.3%) had graduated from primary school, eight

(13.3%) from middle school, nine (15%) from high school, and eight (13.3%) from university. The details of the demographic data of the participants are shown in Table 1. Following the quantitative sensory examination test, it was seen that the majority of participants had hypersensitivity or hyposensitivity in at least one domain of tests (Table 2).

QST	QST Normal response		Hypersensitive response		Hyposensitive response		
	n	%	n	%	n	%	
Light touch	27	45.0	22	36.7	11	18.3	
Pin prick	28	46.7	17	28.3	15	25.0	
Vibration test	34	56.7	18	30.0	8	13.3	

able 2. Quantitative sensory examination results of participants

QST: Quantitative Sensory Test; n: Number of participants; %: Percentage.

Among the 60 individuals included in the study, the predominant pain phenotype was classified as nociceptive in 18 (30%), nociplastic in 15 (25%), and neuropathic in three (5%). More than one type of pain was found to be predominant in the remaining 24 individuals (40%). Mixed nociceptive-nociplastic pain was observed in 11 (18%) individuals, mixed neuropathic-nociceptive pain in seven (12%), and mixed neuropathic-nociplastic pain in five (8%). In addition, one individual (2%) was found to have mixed neuropathic-nociceptive-nociplastic pain. In brief, 61.6% (n=37) of the participants had a nociceptive pain component, 53.3% (n=32) had a nociplastic pain component, and 26.6% (n=16) had a neuropathic pain component.

The neuropathic (n=3), nociceptive (n=18), nociplastic (n=15), and mixed-type (n=24) pain groups did not significantly differ in terms of age (p=0.466), body mass index (p=0.732), gender (p=1.000), occupation (p=0.704), and educational level (p=0.248). Similarly, there was no significant difference between the groups in relation to the number of children with CP they took care of (p=0.463), duration of care for a child with CP (p=0.466), and pain durations (p=0.365). However, a statistically significant difference was detected between the VAS scores of the groups (p=0.016), with the highest pain intensity being observed in the neuropathic pain group. There was also a statistically significant difference between the groups concerning the CSI scores (p=0.000), with the highest score being obtained from the nociplastic pain group. Lastly, when the SF-36 quality of life questionnaire scores were compared according to the predominant pain phenotypes, the differences between the groups were not statistically significant (p>0.05).

Discussion

In this cross-sectional study examining the pain phenotypes of 60 individuals who were caring for children diagnosed with CP and had chronic musculoskeletal pain complaints, the most common predominant pain phenotype was determined as nociceptive pain. In addition, it was observed that 40% of the individuals had mixed-type pain, indicating the presence of more than one pain phenotype. Among the pain phenotype groups, the neuropathic pain group had the highest pain intensity, but there was no significant difference between the groups in terms of pain duration and quality of life.

We found no similar study in the literature that classified the chronic pain phenotypes of the caregivers of children with CP according to the mechanisms of pain. However, there are studies that performed mechanism-based pain classification in different populations. Liu et al.^[32] found that 7% of individuals with chronic neck pain had primarily neuropathic pain and 57% had possible neuropathic pain, while the remaining 43% had non-neuropathic pain. However, in that study, a detailed classification was not made for individuals who did not have the neuropathic pain phenotype. Takahashi et al.^[33] reported the pain phenotypes of patients with lumbar spinal stenosis as nociceptive in 57.9%, neuropathic in 17.6%, and unclear in 24.5%. Beith et al.,[34] evaluating patients with chronic low back pain, determined that 59% had possible nociceptive pain, 25% had an unclear pain phenotype, and 16% had possible neuropathic pain. However, none of these studies took into account all the pain phenotypes defined by IASP (nociceptive, neuropathic, nociplastic, and mixed type),^[35,36] which led to the classification of an unclear pain phenotype in some individuals. Our study revealed that the most common type of mus-

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culoskeletal pain in caregivers of children with CP was nociceptive pain (30%). In addition, our results showed that 40% of the individuals had mixed-type pain, exhibiting more than one pain phenotype rather than a single predominant pain phenotype. Different results reported in the literature may be due to the differences in the classification systems used to determine pain phenotypes.

Caring for a child with CP is a long and challenging process. Especially individuals who take care of children with CP that cannot walk independently face more physical workload, limitations due to low back and neck pain, upper and lower extremity dysfunction, musculoskeletal pain in multiple regions, and depressive symptoms, and have lower health quality compared to caregivers of children with CP that can walk independently.^[37] Previous studies suggest that musculoskeletal problems are frequently seen in caregivers of children with CP.^[7,38] In the current study, nociceptive pain being the most common type among the three predominant pain phenotypes in individuals who take care of children with CP may be related to the micro and macro traumas they experienced during the caring process.

It is known that family relatives generally undertake the care of a child with cerebral palsy, and that women play a greater role than men in the family, and especially mothers undertake care.[39] Similarly, this study showed that 94% of the participants were women and 76.7% were mothers of children with CP. According to these findings, it can be said that mothers of children with CP are at greater risk of chronic pain compared to other parents. Besides, a previous study^[40] reported that the majority of mothers of children with CP had a low education level. Similarly, it was observed that the majority of participants (58.3%) in the current study had low education levels. Therefore, individuals with low education levels among caregivers might be a significant factor for chronic pain. Future studies might further investigate the factors of chronic pain among caregivers of CP.

Limitations

There are some limitations to our study. First, the validity and reliability of the classification system used in this study have not yet been established.

Second, the participants of this study formed a heterogeneous sample in terms of musculoskeletal pain. Besides, the authors did not evaluate the depression status of the participants, which does not enable them to consider the potential effects of depression on the pain phenotypes, especially on nociplastic pain. Lastly, the types and/ or functional status of children with CP could be an important factor in determining the pain phenotypes of caregivers, although the author did not report this data. Future studies can examine the validity and reliability of the evaluated mechanism-based pain classification and the potential effects of depression status on caregivers and the functional status of children with CP. In addition, similar studies can be planned in a more homogeneous population, such as individuals with chronic low back pain or chronic neck pain.

Conclusion

In this study, we also found that 40% of individuals had more than one type of pain (mixed type), and the most common combination was nociceptivenociplastic pain (18%). In addition, nociplastic pain was the most common type of pain after nociceptive pain among the predominant pain phenotypes. Previous studies have demonstrated the importance of central sensitization and psychosocial factors in the etiology of nociplastic pain.^[41,42] When we consider the social, economic, and mental problems seen in caregivers of children with CP, it can be better understood why the nociplastic pain phenotype is so common in these individuals.

We detected no significant difference between the pain phenotypes in terms of pain duration and quality of life parameters, but we observed that individuals with neuropathic pain had the highest reported pain severity among all the participants. However, there was no significant difference between the pain phenotype groups in terms of the participants' quality of life, which is consistent with their pain intensity. Similarly, Leysen et al.^[12] showed that the quality of life of cancer survivors did not differ according to pain phenotypes. These results are not surprising considering that the quality of life of individuals in these two populations can also be affected by many factors.



Ethics Committee Approval: The Kutahya Health Sciences University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 22.12.2020, number: 2020/18-04).

Authorship Contributions: Concept – TC; Design – TC; Supervision – İS; Resource – TC, İS; Materials – TC; Data collection and/or processing – TC; Analysis and/or interpretation – İS; Literature review – TC; Writing – TC; Critical review – İS.

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