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Somatosensory Temporal Discrimination and Neutrophil/Lymphocyte Ratio in Patients with Chronic Low Back Pain

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ABSTRACT

Objective: Central sensitization is known in the pathogenesis of chronic low back pain. We aimed at this study considering that somatosensory temporal discrimination (STD) may also be impaired in this process. We also looked at the neutrophil-lymphocyte ratio in terms of its contribution to inflammation suggested in the pathogenesis. **Materials and Methods:** A total of 52 participants have been enrolled in this study. They were divided into two groups, 27 patients with chronic low back pain (pain caused by facet, sacroiliac joint arthropathy and intervertebral disc degeneration) and 25 healthy volunteers. STDT (somatosensory temporal discrimination threshold) stimulus intensity and STD measurements were obtained in the dorsum of the hands and foot in four extremities of both groups, and neutrophil-lymphocyte ratio was evaluated. **Results:** STD thresholds in patients with chronic low back pain were found significantly prolonged in all four extremities compared to the control group. Neutrophil-lymphocyte ratio was also found to be statistically significantly higher in the low back pain group compared to the control group. **Conclusion:** Prolonged STD thresholds indicate that pain perception of patients with chronic low back pain is disrupted. In addition, the high rate of neutrophils-lymphocytes indicates that the inflammatory process continues even if low back pain becomes chronic.

Keywords: Low Back Pain, Somatosensorial Temporal Discrimination, Neutrophil-Lymphocyte Ratio.

Kronik Bel Ağrılı Hastalarda Somatosensoryel Temporal Diskriminasyon ve Nötrofil / Lenfosit Oranı

ÖZ

Amaç: Kronik bel ağrısının patogenezinde santral duyarlılaşma bilindiğinden, somatosensoriyel temporal diskriminasyonun (STD) da bu süreçte bozulabileceğini düşünerek bu çalışmayı amaçladık. Nötrofil lenfosit oranına da patogenezde ileri sürülen inflamasyona katkısı açısından baktık. **Gereç ve Yöntem:** Bu çalışmaya toplam 52 katılımcı katılmıştır. Kronik bel ağrılı (faset, sakroiliak eklem artropatisi ve intervertebral disk dejenerasyonu kaynaklı ağrı) 27 hasta ve 25 sağlıklı gönüllü olmak üzere iki gruba ayrıldı. Her iki grubun dört ekstremitesinde el ve ayak dorsumundan somatosensoriyel temporal diskriminasyon eşik (STDT) uyarı şiddeti ve STD ölçümleri yapıldı ve nötrofil/lenfosit oranı değerlendirildi. **Bulgular:** Kronik bel ağrısı olan hastalarda STD eşikleri, kontrol grubuna kıyasla dört ekstremitede önemli ölçüde uzamış bulundu. Nötrofil/lenfosit oranı da bel ağrısı grubunda kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek bulundu. **Sonuç:** Uzamış STD eşikleri, kronik bel ağrılı hastaların ağrı algısının bozulduğuna işaret etmektedir. Ayrıca nötrofil/lenfosit oranının yüksek olması da bel ağrısı kronikleşse bile inflamatuar sürecin devam ettiğini gösterir.

Anahtar Kelimeler: Bel Ağrısı, İki Nokta Diskriminasyonu, Nötrofil/Lenfosit Oranı.

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INTRODUCTION

Low back pain is a significant public health problem due to its high prevalence, economic burden, chronicity, and associated disability. Its peak incidence occurs between 35 and 55 years of age. The reported lifetime prevalence of non-specific low back pain in developed countries is estimated to be in the range of 84%, and best estimates suggest that the prevalence of chronic low back pain is about 23% (Airaksinen et al., 2006). Low back pain is non-specific (85%) and usually caused by mechanical. Mechanical low back pain originates in the spine, intervertebral discs, or surrounding soft tissues. Specific causes are uncommon (<15% of all back pain, e.g., infection, tumor, osteoporosis, fracture, structural deformity, inflammatory disorder, radicular syndrome, or cauda equine syndrome). Clinical clues or red flags can help identify non-mechanical low back pain cases. Performing a good examination or imaging helps make an accurate diagnosis (Giesecke et al., 2004; Will et al., 2018). Somatosensory temporal discrimination (STD) is the ability to perceive as temporally separate two successive somatosensory stimuli applied to the same or different parts of the body (Hoshiyama et al., 2004). A normal STD requires the presence of intact peripheral and central pathways and the proper functioning of the primary somatosensory cortex. The threshold for the somatosensory temporal discrimination provides information on the cortical functioning of the sensory stimuli.

Individuals with chronic low back pain have been found to have several neurochemicals, structural, and functional cortical alterations in many brain areas, including the somatosensory cortex. In patients with complex regional pain syndrome and low back pain, cortical re-organization has been found to correlate with impairments in tactile discrimination, increased pain intensity and decreased tactile accuracy (Wand et al., 2011). The neutrophil/lymphocyte ratio (NLR) is an inflammation marker used for prognostic estimations regarding the systemic inflammatory responses. NLR is a widely available and inexpensive test (Aktürk and Büyükavcı 2017). Several systemic cytokines and biomarkers have been previously tested in terms of their ability to gauge the efficacy of different treatment modalities. In this regard, diagnostic biomarkers may offer a potential benefit in guiding individualized therapeutic plans in patients with low back pain. (Khan et al., 2017).

This study was primarily undertaken to determine whether the STD test may be utilized as a novel adjunctive diagnostic test allowing quantitative measurements in patients with chronic low back pain (pain caused by facet, sacroiliac joint arthropathy and intervertebral disc degeneration); to provide initial data for its validity, and to discuss its potential clinical utility. The secondary objective was to examine the role of NLR as a diagnostic and therapeutic biomarker in patients with low back pain.

MATERIALS AND METHODS

Patient Selection

This study was carried out by including 27 patients diagnosed with chronic low back pain at the algology outpatient clinic. 25 healthy volunteers were recruited. The overall study population consisted of 52 males and females aged between 18 and 65 years. The inclusion criteria were as follows: Absence of pregnancy and space-occupying cranial lesions, absence of known systemic disorders or regular use of medications; lack of hepatic or kidney dysfunction, low vitamin B12, hypothyroidism, or anemia in laboratory tests performed within the past six months; adequate patient cooperation for study tests; pain caused by facet, sacroiliac joint arthropathy and intervertebral disc degeneration with ongoing degenerative changes. The exclusion criteria were as follows: Patients with radiculopathy were not included in the study. Patients with red flags were not included in the study. Red flags include progressive motor or sensory loss, recent urinary retention and incontinence, invasive spinal procedure, significant trauma, cauda equina syndrome, malignancy, fracture, or infection. Imaging methods were requested from all patients (MRI or CT) for exclusion criteria. STDT (somatosensory temporal discrimination threshold) measurements were made from four extremities by the same investigator in the patient and control groups. Also, NLR was measured in all participants. VAS (Visual analogue scale) was measured in the patient group.

STD procedure

STDT measurements were performed by previous descriptions (Hoshiyama et al., 2004). STDT was measured at four different sites, at the dorsum of both hands and feet. Superficial Ag-AgCl electrodes of 10 mm diameter were used for this purpose. A distance of approximately 1 cm was allowed between the anode and cathode. A constant current stimulator (Medtronic, Keypoint) was used for tactile stimulation. The required current intensity for the minimum sensory threshold level was determined by stimuli of 0.2 msec. Again, to determine the minimal sensory threshold, the current intensity was increased with increments of 0.2 mA starting from 1 mA with three stimuli applied at a time. The intensity at which the patient perceived all three stimuli was accepted as the minimum sensory threshold. Initial interstimulus interval (ISI) between the paired stimuli was 5 ms and it was increased with of steps 5 ms. A paired stimuli was given every 10 s. The first of three consecutive ISIs where the subjects discriminated two discrete stimuli, was recorded as the ascending STDT (aSTDT). Then ISI was decreased with steps of 5 ms until the patient could not discriminate a paired stimuli and the first of three consecutive ISIs where the subject reported paired stimuli as one stimulus was recorded as descending STDT (dSTDT). Similarly, the procedure was repeated at 1.5 folds of the minimal threshold level. The arithmetic mean of two aSTDT and dSTDT values was calculated as the STDT value for the dorsum hand/foot. In addition, when each participant was given

a single stimulus before the test and asked whether they were pair or single, those who gave a double answer were not included in the study.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, Release 22.0. The normal distribution was tested using the Skewness and Kurtosis values for each group. The significance of the difference between the groups was tested with Sample t-test. The results of the variables after normalization were taken as the mean and standard deviation. Statistical significance level was set at ≤ 0.05.

Ethical considerations

Prior to study procedures, the study protocol was approved by the Ethics Committee for Clinical Research with the number 2019/50. Also, all participants provided written informed consent before the study.

RESULTS

The patient and control groups were comparable in terms of demographic characteristics. The mean age among patients with low back pain and controls was 45.4±10.6 years (19 female, 8 male) and 29.1±8.5 years (21 female, 4 male). Since STDT results are not affected under the age of 65, the difference in the average age of the control and low back pain groups does not affect our results (Hoshiyama et al., 2004).

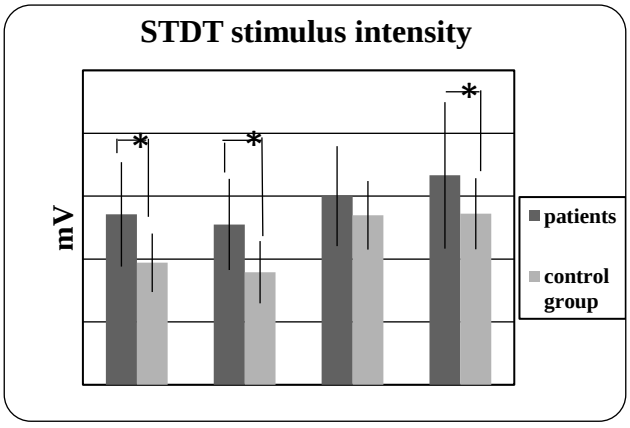

Figure 1. In the patient group, STDT stimulus intensity were higher in both hands and left foot. *p≤ 0.05

The stimulus intensity of STDT was significantly higher in three extremities as compared to controls shown in Figure 1 and Table 1. The STDT from four extremities were significantly prolonged among patients compared to controls, shown in Figure 2 ($p \leq 0.05$) and Table 2. Also, NLR was significantly higher in those with low back pain as compared to controls, shown in Figure 3.

Table 1. STDT stimulus intensity between patient and control groups.

	Patient group	Control group	p
	Mean± SD (mV)	Mean± SD (mV)	
Right hand	5.42±1.66	3.88±0.93	0.000**
Left hand	5.10±1.45	3.58±0.99	0.000**
Right foot	6±1.59	5.39±1.09	0.111
Left foot	6.66±2.33	5.44±1.13	0.020*

***** p<0.05, ******p<0.001, **SD:** Standard deviation.

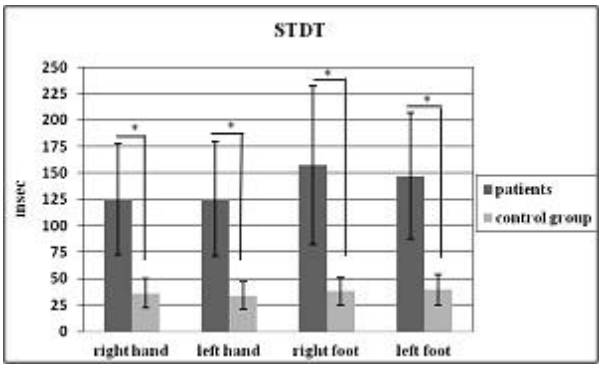

Figure 2. STDT was significantly prolonged in all extremities in the patient group compared to the control group. STDT: Somatosensory temporal discrimination thresholds. * p≤ 0.05

Table 2. STDT between patient and control groups.

	Patient group	control group	
	Mean±SD(msec)	Mean±SD(msec)	p
Right hand	125±52.6	36.1± 13.8	0.000*
Left hand	125.5±54.2	34.0± 12.9	0.000*
Right foot	157.3±75.0	38.0± 13.0	0.000*
Left foot	147.15 ± 59.40	39.6± 14.5	0.000*

*****p<0.001, **SD:** Standard deviation.

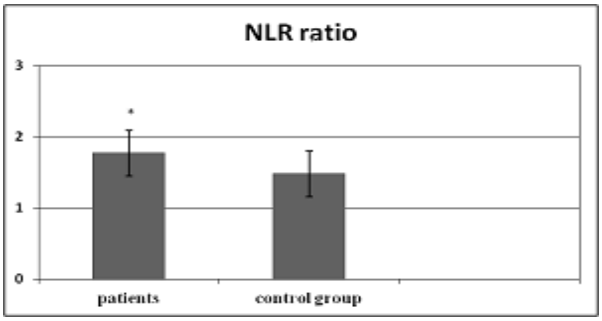

Figure 3. NLR rate was statistically significant in the patient group. NLR ratio: neutrophil-lymphocyte ratio. * p≤ 0.05

DISCUSSION

Chronic low back pain is a common condition associated with high economic burden and reduced quality of life. The lack of treatment options that provide long-term remission in patients with chronic low back pain indicates that there is a need for new studies on the pathogenesis. Central sensitization has recently been recognized as a potential pathophysiological mechanism underlying a group of chronic pain disorders including chronic low back pain (Nijs et al., 2015). In parallel with this information, we wanted to examine the potential contributions of STDT and NLR measurement to the etiopathogenesis of chronic low back pain in patients with chronic low back pain due to facet, sacroiliac joint arthropathy and intervertebral disc degeneration. STDT measured from four extremities was prolonged among patients with chronic low back pain than controls, suggesting an impaired perception of non-painful stimuli in chronic low back pain patients. Furthermore, higher NLR in the patient group than in controls supports ongoing inflammation in these subjects.

Low back pain usually is muscle tension or stiffness localized below the costal margin and above the inferior gluteal folds. Many spinal structures have sensory innervation, e.g., muscles, tendons, ligaments, fascia, facet joints, sacroiliac joint, vertebrae, the outer ring of the intervertebral disc, vascular tissue, dura, nerve roots, and dorsal root ganglia. However, all of these structures can cause widespread low back pain (Vlaeyen et al., 2018). Pain originating from the facet joint and sacroiliac joints can be accurately diagnosed with a combination of physical examination and image guidance (magnetic resonance (MR) or computed tomography (CT)) (Jeffrey and Walter 2009). Although most intervertebral disc lacks sensory innervation, this structure has a nociceptive contribution to back pain, especially in relation to disc degeneration (Brinjikji et al., 2015; Endea et al., 2011).

Chronic low back pain is a prevalent condition associated with a high economic burden and significantly reduced quality of life. The lack of treatment options that provide long-term remission in chronic low back pain patients indicates a need for new studies on pathogenesis. Central sensitization has recently been recognized as a potential pathophysiological mechanism underlying a group of chronic pain disorders, including chronic low back pain (Nijs et al., 2015). Moreover, patients with chronic low back pain experience generalized deep-tissue hyperalgesia when exposed to quantitative nociceptive stimuli (O'Neill et al., 2007).

Examination of both spatial and temporal aspects of the two-point discrimination test using functional magnetic resonance imaging showed activation at the cortical level in areas such as the inferior parietal lobule, middle and inferior frontal gyri, anterior part of the right insula, and right anterior cingulate gyrus. In subcortical areas, basal ganglia were found to be activated, particularly at both caudate heads, substantia nigra, and the subthalamic nucleus. In addition, significant activity was found in the cerebellum (Pastor et al., 2004). Chronic low back pain has been associated with neurochemical, structural, and functional cortical alterations in many brain areas, including the somatosensory cortex. Cortical re-organization leads to increased pain intensity, in addition to hampering successful treatment. However, plasticity, which is the basis for cortical re-organization, is also an indication of the ability of the brain to respond to targeted therapy (Moseley and Flor, 2012). While prolonged STD values may represent an electrophysiological indicator of altered intra-cortical inhibition, they may also be associated with increased pain intensity and clinical signs of reduced functionality (Lim et al., 2015). STD measured at four extremities was significantly impaired in patients with chronic low back pain compared to controls, suggesting alterations in cognitive-sensory processing in these patients. This finding may suggest that our therapeutic and diagnostic approach may be re-evaluated in this disorder. Our literature search has not revealed any studies similar to ours, which, to the best of our knowledge, has evaluated the potential diagnostic and therapeutic role of these practical clinical measurements for the first time.

Patients with chronic low back pain suffer from pain due to various spinal disorders, including intervertebral disc degeneration, disc herniation, spinal stenosis, and arthritis of the facets. In recent years, inflammatory markers have been the subject of important studies with the thought that inflammation may play a role in the pathogenesis of disc degeneration and related pain mechanisms. Furthermore, increasingly more studies have revealed that presence of inflammatory markers in the blood may be shown systematically and may be utilized as a novel tool to guide patient management. Although surgical treatments may offer anatomical correction and pain reduction, they are also invasive and costly procedures, in addition to difficulties associated with the estimation of response and recurrence. Diagnostic biomarkers of spinal degeneration have the potential to trigger an era of personalized spine medicine in the treatment of chronic low back pain. Increased levels of inflammatory biomarkers such as TNF-alpha, IL-6, and IL-1B were found to increase inflammation and neuropathic pain (Sommer and Kress, 2004). Also, NLR has been studied in systemic disorders with increased neutrophil and decreased lymphocyte counts during inflammation. NLR (increased neutrophil and reduced lymphocyte counts) is associated with increased disease activity in many systemic, rheumatologic, neurologic, and neoplastic conditions (Proctor et al., 2012; Torun et al., 2012). Furthermore, NLR has been reported to be a prognostic marker for determining systemic inflammatory responses (Uslu et al., 2013). For example, in a study, patients with lumbar disc herniation had elevated NLR compared to controls (Yılmaz et al., 2019). It has even been suggested that role of antibiotic therapy should be re-evaluated in patients with chronic low back pain (Kjersti et al., 2017).

Similarly, our patients with chronic low back pain had increased NLR compared to control subjects, indicating persistent inflammation despite the chronicity of pain in these patients. One potential limitation of the NLR rate is the lack of sensitivity of MRI imaging modalities early in the disease process.

Our study limitations firstly, our patient and control groups were small. Secondly, STD measurements require proper attention and cooperation of the patient, they should be carried out in individuals with good cognitive functions. Therefore, lack of STD testing among patients with low level of education is also a disadvantage, indicating the need for improved test procedures. Thirdly, we could compare non-specific low back pain and specific low back pain groups. Fourthly, patients could be sub grouped, but could not be done due to the small number of patients.

CONCLUSION

Although impaired STD appears to be a potential measurement tool for patients with chronic low back pain, further studies are required to confirm these observations as well as to assess its role in the follow-up of patients. Elevated NLR indicates that the inflammatory process persists in these patients, despite the chronic course of the disease. We believe that future studies could better define the association between biomarkers and clinical outcomes in patients with chronic low back pain. These results might change the classic biomarkers for patient follow-up. This study showed us that when planning the diagnosis and treatment of chronic low back pain, both a change in cognitive, sensory processing and the continuation of the inflammatory process should be considered. We suggest that alternative approaches and additional assessments may be required for more effective utilization of existing treatments and reducing their side effects.

Conflicts of Interest

The author declares no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions

Plan, design: O.F. T, NT; **Material, methods and data collection:** O.F. T, NT; **Data analysis and comments:** O.F. T, NT; **Writing and corrections:** O.F. T, NT.

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