Evaluation of Pain Intensity and Oxidative Stress Levels in Patients with Inflammatory and Non-Inflammatory Back Pain

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ABSTRACT

To investigate the relationship between pain threshold and oxidative stress levels in patients with acute and chronic inflammatory or non-inflammatory back pain. A total of 137 patients were recruited for the study, including 33 acut back pain (32 lumbar disk herniation, 1 lumbar spondilosis) (16 men, 17 women), 35 with chronic back pain (33 lumbar disk herniation, 1 lumbar spondilosis, 1 sacralisation) (16 men, 19 women), 34 with ankylosing spondylitis (21 men, 13 women) (AS) and 35 without any back pain (15 men, 20 women). The visual analogue scale (VAS) was used to evaluate pain levels and algometry was used to evaluate the pain threshold in all cases. In addition, serum malondialdehyde (MDA) levels were assessed in all patients. The mean ages for groups 1, 2, 3, and 4 were 40.3±10.3, 39.9±9.7, 40.6±10.4, and 38.5±8.1 years, respectively. There was no significant difference between the ages of the groups (p=0.851) (Table 1). The VAS scores of all groups were significantly higher compared to the control group. Particularly, the acute and chronic back pain groups had significantly higher VAS scores than those of the AS group. All three back pain groups had significantly higher serum MDA levels compared to those of the control group (p<0.01). Moreover, serum MDA levels of acute back pain group were significantly higher than the chronic back pain and AS groups (p=0.004 and p=0.032). Pain threshold levels of the acute and chronic back pain group were significantly lower compared to the control group (p=0.002 and p=0.001). In contrast, the pain threshold levels of the AS group were higher than the control group. Oxidative stress levels in patients with inflammatory and non-inflammatory back pain are higher than in the controls, which suggests that oxidative stress may be involved in the etiopathogenesis of these diseases. Interestingly, the pain threshold levels in AS patients were found to be higher, which indicates an ongoing desensitization process in these patients.

Key words: *Back pain, ankylosing spondylitis, oxidative stress, pain threshold*

İnflamatuar ve Non-inflamatuar Bel Ağrılı Hastalarda Ağrı Yoğunluğu ve Oksidatif Stres Düzeylerinin Değerlendirilmesi

ÖZET

Akut ve kronik inflamatuar veya non-inflamatuar bel ağrılı hastalarda ağrı eşiği ve oksidatif stres düzeyleri arasındaki ilişkiyi değerlendirmek amaçlandı. 33 akut bel ağrılı (16 erkek, 17 kadın), 45 kronik bel ağrılı (16 erkek, 19 kadın), 34 Ankilozan spondilitli (21 erkek, 13 kadın) ve 35 sağlıklı gönüllü (15 erkek, 20 kadın) olmak üzere toplam 137 birey çalışmaya dahil edildi. Bütün bireylerin ağrı düzeyleri VAS ile, ağrı eşikleri ise algometri ile değerlendirildi. İlaveten, tüm bireylerin serum malondialdehyde (MDA) düzeyleri değerlendirildi. 1, 2, 3. ve 4. grupların ortalama yaşları 40.3 ± 10.3, 39.9 ± 9.7, 40.6 ± 10.4 ve 38.5 ± 8.1 yıl idi, Grupların yaşları arasında istatistiksel olarak anlamlı fark yoktu (p=0.851) (Tablo 1). Bel ağrılı grupların herbiri kontrol grubu ile karşılaştırıldığında anlamlı şekilde daha yüksek MDA düzeylerine sahipti (p<0.01), ve serum MDA düzeyleri akut bel ağrılı grupta kronik bel ağrılı ve AS gruplarından anlamlı şekilde daha yüksek idi (p=0.004, p=0.032). Ağrı eşiği düzeyleri akut ve kronik bel ağrılı gruplarda control grubu ile karşılaştırıldığında anlamlı derecede daha düşük idi (p=0.002, p=0.001). Aksine, AS grubunun ağrı eşiği düzeyleri control grubuna göre anlamlı şekilde daha yüksek saptandı (p=0.024). İnflamatuar ve non-inflamatuar bel ağrılı hastalarda oksidatif stres düzeyleri control grubuna göre daha yüksek saptanmış olması oksidatif stresin bu hastalıkların patogenezinde rol oynayabilceğini gösteriyor olabilir. İlginç bir şekilde, AS'li hastaların ağrı eşiği düzeyleri daha yüksek saptandı, bu durum bu hastalarda var olan desensitizasyon sürecinin varlığına işaret ediyor olabilir.

Anahtar kelimeler: *Bel ağrısı, ankilozan spondilit, oksidatif stres, ağrı eşiği*

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Received: 08.10.2012, Accepted: 03.01.2013

INTRODUCTION

The International Association for the Study of Pain described pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain is multidimensional, thus physical as well as non-physical components should be considered when evaluating pain. Pain threshold and response to painful stimuli varies from person to person due to many factors including gender, religion, race, and social-cultural environment (1). Therefore, pain is considered to be a complex interaction of physical, behavioral and cognitive aspects. Back pain, which is a disabling problem with expensive treatment, is a common musculoskeletal disorder that has an increasing incidence in industrialized cultures (2). After the upper respiratory infections back pain is the second most common reason for loss of manpower with a lifetime incidence of 80%, a yearly incidence of 2% and prevalence of 15-39% (3). Although, 70-90% of patients recover without any treatment within six to eight weeks, 38% of them have a recurrence within the first year (4). Factors such as weightlifting, vibration, postural stress, gender and occupational factors increased the risk of back pain (5). In addition, patients with inflammatory diseases such as ankylosing spondylitis may also experience back pain. AS is is mainly characterized by axial involvement and is the prototype of the seronegative spondyloarthropaty (SpA) group of diseases. It is a chronic, progressive, systemic rheumatoid disease with unknown etiology (6). Despite its unclear etiopathogenesis, genetic and environmental factors (7), as well as oxidative stress are thought to be involved. Imbalance between production and secretion of free radicals can cause oxidative stress (8, 9). Recent studies showed that increased free oxygen radicals and lipid peroxidation may play a role in the pathogenesis of a number of chronic inflammatory diseases including rheumatoid arthritis (RA), collagen tissue disorders (CTD), spondyloarthropathies, and osteoarthritis (OA) (6, 10, 11). The aim of the present study is to determine the relationship between pain, pain threshold and oxidative stress levels in acute and chronic inflammatory or non-inflammatory back pain.

MATERIALS AND METHODS

Case Selection

Our study included 102 patients who were admitted to Physical Medicine and Rehabilitation polyclinic between August 2011 and February 2012 and 35 age and gender matched healthy controls. All participants signed an informed consent form approved by the local ethics committee (11-BADK-022). The distribution of patients was as follows: 33 patients diagnosed with acut back pain (5 lumbar sprain, 7 lumbar strain, 4 sacralisation of L5 vertebrae, 3 lumbarisation of S1 vertebra, 7 lumbar disc herniation, 4 spondylosis, 3 spondylolisthesis) (16 men, 17 women) (group 1), 35 with chronic back pain (6 lumbar sprain, 3 lumbar strain, 5 sacralisation of L5 vertebrae, 4 lumbarisation of S1 vertebrae, 8 lumbar disc herniation, 5 spondylosis, 4 spondylolisthesis) (16 men, 19 women) (group 2), 34 with ankylosing spondylitis (21 men, 13 women) (group 3) and 35 healthy volunteers (15 men, 20 women) (group 4). All AS patients met the Modified New York criteria. Back pain that lasted for less than four weeks was considered acute back pain, whereas back pain persisting for more than 3 months was considered chronic back pain. Patients with history of systemic disease, malignancy, infectious disease, history of surgery regarding the lumbar area, and neurologic disease were excluded.

Clinical Measurements

The Visual Analoque Scale (VAS) was used to assess the pain level in all patients during their first visit. VAS is a horizontal or vertical line in which the numbers between 0 and 10 indicate a scale ranging from no pain to unbearable pain, respectively. Pain threshold was assessed by algometry. Pressure algometry (JTECH, CommanderTM), which was used in this study, consisted of a 1 cm diameter rubber disc that is connected to a dial that indicates the pressure in either kilograms (kg) or pounds (Lb). The applier holds the dial and puts pressure on specific points. At the first moment when the patient senses pain, the algometer is removed from the body and the value of the indicator is recorded. Algometric measurements were performed three times at the tenar region of the dominant hand and the mean value was recorded. The Beck depression scale (BDS) was also performed to assess the psychological status of the patients. The BDS includes 21 self-assessment items that consist of depression signs and symptoms that are scored from 0-3. The BDS is used to determine the severity of depression signs and symptoms (12).

Biochemical Analysis

After eight to ten hours of fasting, blood samples of all

patients were taken and centrifuged. A spectrophotometer was used to assess malonildialdehyde (MDA) levels. MDA is an end product of lipid peroxidation that reacts with the chromogen tiobarbituric acid (TBA) at 90°C and generates a pink colored chromogen. MDA levels are assessed by measuring the spectrum of this pink color at 532 nm with spectrophotometry (1). Results were recorded as µmol/L.

Statistical Analysis

The SPSS for Windows version 15.0 software package was used for statistical analyses. Compatibility of the data to a normal distribution was analyzed with Kolmogorov-Smirnov test. Intergroup data comparisons were performed with One-Way ANOVA and Kruskal Wallis H tests followed by Independent samples T and Mann-Whitney U tests. Correlation analysis between parameters was performed with Pearson and Spearmen tests. P<0.05 was considered as statistically significant.

RESULTS

The mean ages for groups 1, 2, 3, and 4 were 40.3±10.3, 39.9±9.7, 40.6±10.4, and 38.5±8.1 years, respectively. There was no significant difference in terms of age and gender between groups (p=0.85) (Table 1). Serum MDA levels for groups 1, 2, 3, and 4 were 1.87±0.26 µmol/L, 1.67±0.16 µmol/L, and 1.69±0.23 µmol/L, 1.38±0.10 µmol/L, respectively. The MDA levels of all three patient groups (groups 1,2, and 3) were significantly higher than those in the control group (p<0.01). In addition, the acute back pain group had significantly higher serum MDA levels than the chronic back pain group and the AS group (p=0.004, p=0.032). The VAS values were 7.81±2.02, 7.45±1.55, 5.77±2.08 and 2.86±1.71 in groups 1,2,3 and 4, respectively. It was determined that the VAS levels of the all patient groups were significantly higher than those in the control group (p<0.01). The acute back pain and chronic back pain groups had comparable VAS values (p=0.276), while both of these groups had VAS levels higher than the AS group (p=0.000, p=0.002). Algometry values were 15.34±3.49, 14.37±2.9, 19.70±3.94 and 18.23±3.37 in groups 1,2,3, and 4, respectively. The acute and chronic pain groups had significantly lower algometry values when compared to those of the control group (p=0.002, p=0.000). In contrast, algometry levels were significantly higher in the AS group than in the control group (p=0.024). Beck depression scores were 9.61±7.01 in group 1, 10.47±6.82 in group 2, 11.80±8.03 in group 3 and 8.90±5.23 in group 4. There was no statistically significant difference in BDS between groups (p=0.715). The clinical and biochemical features of each of the groups are shown in Table 1.

DISCUSSION

Back pain is a common musculoskeletal symptom that often requires expensive therapy and may result in disability (13). It is estimated that 60-90% of the adult population will experience back pain at least once in a lifetime, and acute back pain can become chronic back pain (14). Acute and chronic etiologies of back pain include trauma, lumbar sprain, strain, mechanical causes, lumbar disc herniations, spondylosis, and spondylolisthesis. Inflammatory rheumatoid diseases may also cause back pain and AS is the leading cause among these diseases. AS is a chronic disease characterized by axial as well as peripheral joint involvement and presents with pain, morning stiffness and functional insufficiency (15). The prevalence of AS is 0.2-1.4%, while its incidence is reported as 7.3/100.000 (16).

Nowadays, the oxidative stress is investigated in etiopathogenesis of many diseases, including the diseases causing of back pain (17). Oxidative stress is a pathophysiologic process common in a number of disease

Table 1. *Clinical and biochemical features of the cases*

Group	*Acute back pain (Group 1)(n:33)*	*Chronic back pain (Group 2) (n:35)*	*Ankylosing spondylitis (Group 3) (n:34)*	*Control (Group 4) (n:35)*	*p value*
Men/Women (n)	*16/17*	*16/19*	*19/15*	*15/20*	*0.932*
Age	*40.3±10.3*	*39.9±9.7*	*40.6±10.4*	*38.5±8.1*	*0.851*
VAS	*7.81±2.02*	*7.45±1.55*	*5.77±2.08*	*2.86±1.71*	*0.001*
MDA (µmol/L)	*1.87±0.26*	*1.67±0.16*	*1.69±0.23*	*1.38±0.10*	*0.001*
Pain threshold	*15.34±3.49*	*14.37±2.89*	*19.70±3.94*	*18.23±3.37*	*0.001*
BDI	*9.61±7.01*	*10.47±6.82*	*11.80±8.03*	*8.90±5.23*	*0.715*

Data is presented as mean ± SD. VAS, visual analog scale; MDA, malonedialdehyde; AS, ankylosing spondylitis; BDI, Beck Depression index.

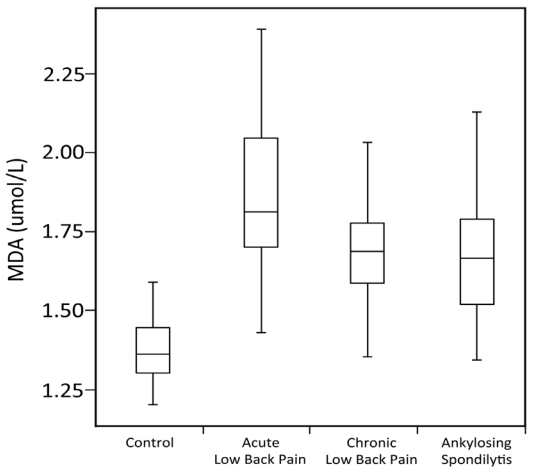

***Figure 1**. Evaluation of MDA levels in acute back pain, chronic back pain, ankylosing spondylitis and control group.*

states, including autoimmune, cardiovascular, and infectious processes, atherosclerosis, cancers, diabetes mellitus, liver damage, rheumatoid arthritis, cataracts, inflammatory bowel disease, and central nervous system disorders (18). MDA is an important indicator of oxidative stress and lipid peroxidation. It interacts with amino groups of proteins, phospholipids and nucleic acids and may have toxic effects (17). These studies have also noted that dyslipidemia is associated with systemic proinflammatory states and increased oxidative stress with lipid peroxidation (19). Oxidative stress is also defined as an imbalance between oxidant and antioxidant mechanisms, in which free oxygen radicals cause damage on carbohydrates, proteins, lipids and DNA. This happens either because of increased production of reactive oxygen species (e.g. hydroxyl radical, superoxide radicals and hydrogen peroxide) or because of decrease in defense mechanisms against them (20). Previous studies have shown that high oxidatıve stress levels as well as increased reactive oxygen substances are related to AS (21, 22). Dysfunction in free radical production and oxydoreduction may alter the expression of various immune and inflammatory molecules and therefore may cause tissue damage (23). MDA is an important end product of lipid peroxidation and is used as a marker of the oxidative stress and free radical damage in lipid molecules (24).

The association between pain and AS is unclear, but recent studies suggest that oxidative stress may cause peripheral and central sensitization. Oxidative stress may also alter nociception, which may cause hyperalgesia with local and spinal oxidant mechanisms (25). Similarly, the reactive oxygen species that occur as a result of oxidative stress due to tissue damage and inflammation might increase the stimulation of sensory neurons that play a role in the transmission of pain (26). In our study, patients with acute and chronic low back pain had significantly higher serum MDA levels than the control group, which may be explained by this aforementioned relationship. Similarly, Karakoc et al. (27) reported increased oxidative stress and lipid peroxidation in patients with AS and showed a correlation between disease activity and oxidative/antioxidative parameters. In another clinical study, Yazici et al. (6) emphasized that in AS inflammation and neutrophil activation may cause and oxidative stress. In addition, Kozaci et al. (28) observed increased NO and MDA levels in patients with AS and these levels were correlated with disease activity. The MDA was studied in terms of its role in the pathogenesis of degenerative inflammatory rheumatic diseases and a study by Dib et al. suggests that MDA can be used as a biologic marker in neurodegenerative disorders (29). In addition, Brisby et al. (30) reported that patients with chronic low back pain due to facet joint arthritis had elevated NO levels, which is a product of ROS. In another study evaluating patients with fibromyalgia, MDA levels were increased, but superoxide dismutase levels were decreased, which was believed to be due to an imbalance in oxidant/antioxidant levels in fibromyalgia patients (31). Yudoh et al. (32) stated that oxidative stress is responsible for the development of osteoarthritis and that this induces dysfunction of the articular cartilage chondrocytes. Poveda et al. conducted immunofluorescence analysis studies on the intervertebral disc and found that reactive oxygen species played a role in disc degeneration. They also suggest that discogenic pain occurs due to increase in pro-inflammatory cytokines and that NF-kB translocation is an important factor in this pathology (33).

The VAS is a commonly used method to detect pain levels. In our study all patient groups had significantly higher VAS scores than the control group. In addition, patients with acute and chronic low back pain had significantly higher VAS scores than AS group. Previous studies reported that patients with AS did not have a

significantly different pain threshold compared to the control group (34), whereas some other studies stated that the pain threshold was higher in AS patients (35). In our study, patients with acute and chronic low back pain had a significantly lower pain threshold than the control group, but interestingly, pain threshold levels were significantly higher in the AS group than in the controls. This may be because of the chronic inflammatory process in AS being different from those in non-inflammatory causes of back pain, which may allow AS patients to develop a tolerance against pain. Lower VAS levels in the AS group in our study support this hypothesis. Absence of correlation between MDA levels, VAS, and algometry scores in investigated diseases suggests that although oxidative stress processes are similar in all of them, different mechanisms of pain and pain perception may be involved in each.

In conclusion, we suggest that oxidative stress plays a role in the etiopathogenesis of non-inflammatory acute and chronic back pain as well as inflammatory back pain. In addition, no relationship between the levels of oxidative stress and pain severity and pain threshold was observed. In this context, there is a need for further randomized studies with a larger number of cases.

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