Araştırma Makalesi
Research Article

An evaluation of central sensitization in medical students: A cross sectional study

TIP FAKÜLTESİ ÖĞRENCİLERİNDE SANTRAL SENSİTİZASYONUN DEĞERLENDİRİLMESİ: KESİTSEL BİR ÇALIŞMA

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ABSTRACT

The objective of this study is to evaluate central sensitization and associated factors in medical students.
Materials and methods: This cross-sectional study included medical students from all grades, aged 18–25 years. Central sensitization was determined based on the Central Sensitization Inventory, based on a Central Sensitization Inventory Part A score of 40 or higher. As associated factors, students were questioned about age, sex, body mass index, education grade, presence of diagnosed chronic disease, regular drug use and the presence of any central sensitization syndrome in first-degree relatives.

Results: 332 students were included with a median age of 21 (range: 18–25) years. A prevalence of central sensitization of 25.9% was identified and was significantly more common in the female respondents than the males (P=0.008). The findings of the Central Sensitization Inventory Part B revealed the most common central sensitization syndrome to be depression, with a rate of 9.0%. There was no significant difference between those with and without central sensitization in terms of age or body mass index (P>0.05). Central sensitization was statistically significantly higher in students who used drugs continuously than those who did not (P=0.021), and was statistically significantly higher in students with a family history of chronic fatigue syndrome, migraine and restless leg syndrome than those without (P=0.001, P<0.001 and P<0.001, respectively). Finally, central sensitization syndrome was statistically significantly more common in those with a family history of the condition.

Conclusion: The prevalence of central sensitization was found to be high in medical students and was associated with sex, family history and continuous drug use.

Keywords: Central sensitization, Central Sensitization Inventory, Medical students

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ÖZ

Amaç: Bu çalışmanın amacı, tıp öğrencilerinde santral sensitizasyon ve ilişkili faktörleri değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel çalışma, 18-25 yaşları arasındaki tüm sınıflardan tıp öğrencilerini içermektedir. Santral sensitizasyon, Santral Sensitizasyon Envanteri'ne göre, Bölüm A'dan 40 veya daha yüksek puan alınmasına göre belirlendi. İlişkili faktörler olarak öğrencilere yaş, cinsiyet, vücut kitle indeksi, eğitim durumu, tanı almış kronik hastalık varlığı, düzenli ilaç kullanımı ve birinci derece akrabalarda herhangi bir santral sensitizasyon sendromu varlığı sorgulandı.

Bulgular: Ortanca yaşı 21 (aralık: 18–25) olan 332 öğrenci dahil edildi. Santral sensitizasyon prevalansı %25,9 olarak saptandı ve kadın katılımcılarda erkeklerden önemli ölçüde daha yaygındı (P=0,008). Santral Sensitizasyon Envanteri Bölüm B bulguları, en sık görülen santral sensitizasyonu sendromunun %9,0 oranıyla depresyon olduğunu ortaya koydu. Santral sensitizasyonu olan ve olmayanlar arasında yaş ve vücut kitle indeksi açısından anlamlı fark yoktu (P>0,05). Santral sensitizasyon, sürekli ilaç kullanan öğrencilerde kullanmayanlara göre istatistiksel olarak anlamlı derecede yüksekti (P=0,021) ve ailesinde kronik yorgunluk sendromu, migren ve huzursuz bacak sendromu öyküsü olan öğrencilerde olmayanlara göre istatistiksel olarak anlamlı derecede daha yüksekti (sırasıyla 0,001, P<0,001 ve P<0,001). Son olarak, santral sensitizasyon sendromu, aile öyküsü olanlarda istatistiksel olarak anlamlı derecede daha yaygındı.

Sonuç: Santral sensitizasyon prevalansının tıp öğrencilerinde yüksek olduğu ve cinsiyet, aile öyküsü ve sürekli ilaç kullanımı ile ilişkili olduğu saptanmıştır.

Anahtar Kelimeler: Santral Sensitizasyon, Santral Sensitizasyon Envanteri, Tıp Fakültesi Öğrencileri

Central sensitization (CS) is a condition caused by neuronal dysregulation and over stimulation of neurons, leading to hypersensitivity to noxious and non-noxious stimuli (1-3). The CS process has been associated with alterations in sensory processing, impaired activity of anti-pain pathways (2), and increased activity in pain-promoting pathways (4). According to the International Association for the Study of Pain, CS is defined as the increased responsiveness of nociceptors to normal or subthreshold afferent inputs that result in pain occurring as a consequence of injury to the somatosensory system or as a direct consequence of injury (5,6).

Central sensitization syndromes (CSSs) are an overlapping group of clinical syndromes without an organic medical cause, with CS being the fundamental characteristic (7,8). In this model, various forms of CSSs can be seen, the root cause of which is CS, although they may have been previously labeled as psychosomatic, functional, individual somatoform disorders and disorders that cannot be explained medically (9,10). CSSs include clinical conditions such as fibromyalgia syndrome (FMS), chronic fatigue syndrome (CFS), temporomandibular joint (TMJ) disorders, migraine/tension headaches, irritable bowel syndrome (IBS) and restless leg syndrome (RLS). These disorders share common clinical characteristics such as fatigue, sleep disorder, paresthesia, increased sensitivity to painful and painless stimuli, anxiety, panic disorder and depression, but pain being the most prominent feature. All of these characteristics indicate the presence of CS (11–13). Other non-CS biological mechanisms, such as disfunction in the stress system, have been associated with CSSs (14). Due to the interaction between psychological and

biological systems, it has been suggested that CSS should be addressed with biopsychosocial models (15).

Medical students are a special group in which stress is often encountered due to the prolonged intense education program and the associated physical and mental exertion (16-18). Psychological constraints (19,20) related to anxiety and depression and sleep disorders (21) have been reported in medical students, and a bidirectional relationship has been found between depression, mental stress, anxiety and fibromyalgia and widespread pain (15). The present study investigates the presence of CS and related factors in medical students.

MATERIALS AND METHOD

This cross-sectional study was granted approval by the local ethics committee of university prior to the initiation of the study, and the trial was registered with the Clinical Trials Network (NCT05495594). A specified number of students, determined based on a power analysis of all grades attending the faculty of medicine in the 2021–2022 academic year, were included in the study. Included in the study were those aged 18–25 years who attended terms 1, 2, 3, 4, 5 and 6 in the medial faculty, while those with a neurological disease, rheumatic disease, uncontrolled hypothyroidism, hyperparathyroidism, diabetes mellitus, infectious disease and malignancy, and those who declined to participate, were excluded from the study. The participants were requested to complete a short form "Central Sensitization Inventory (CSI)" and to provide demographic data and other related information.

The demographic and clinical data included age, sex, body mass index (BMI), educational status, marital status, parental educational status, number of siblings, previous diagnoses of chronic disease, continuous medications, and the presence of one of the CSSs in a first-degree family member. The presence of CS in the participants was evaluated using the CSI – a 25-item index evaluating the key symptoms and determining their grades in those with CS. The CSI is a self-administered questionnaire dealing with the symptoms associated with CS and screening various conditions related to CS. The scale was developed by Mayer et al. (22) in 2012, and the validity and reliability study of the Turkish version of the index was conducted by Düzce Keleş et al. in 2021 (23). The inventory is used to differentiate different types of patients with chronic painful conditions of different degrees, and allows clinicians to identify whether pain is caused by organic causes or CS (22). The CSI contains two parts, A and B. Part A evaluates symptoms that are considered to be related with CS syndromes, while part B reveals any previous specific diagnoses in the respondent. Part A of the CSI covers all symptoms of CSS and helps clinicians identify patients with CSS. It contains 25 items that are rated by the respondent on a scale of 0–100 inquiring the frequency of symptoms observed in CS syndromes. Each symptom is graded as "never" (0 points), "rarely" (1 points), "sometimes" (2 points), "frequently" (3 points) or "always" (4 points) if the patient experienced the given symptom never, rarely, sometimes or all the time, respectively. CS is considered as having developed if the patient scores higher than 40 points on the scale. An increasing CSE score suggests the presence of more symptoms associated with CS. Part B (no scoring), on the other hand, comprises items covering seven different CSSs, inquiring whether the patient has been previously diagnosed with one or more CSSs or related conditions. These CSSs include restless leg syndrome, chronic fatigue syndrome, fibromyalgia syndrome, temporomandibular joint disorder, migraine/tension-type headache, irritable bowel syndrome, multiple chemical sensitivity, whiplash, anxiety/panic attack and/or depression. The scale aids clinicians in better evaluating the symptoms that are considered to be related with CS, and in minimizing or avoiding, where possible, unnecessary diagnostic and therapeutic procedures (22).

A participant is considered to have developed CS if their CSI score is higher than 40 points. Part A of the CSI was divided into five categories according to severity, being subclinical (0–29), mild (30–39), moderate (40–49), severe (50–59) and extreme (60–100) (24).

Clinical and demographic data related to CS was also analyzed, and the CSI scores of students at different grades were compared with each other.

The statistical analyses were performed using IBM SPSS Statistics (Version 24.0. Armonk, NY: IBM Corp.). A

Kolmogorov-Smirnov test was used to determine the normality of data distribution. Parameters without normal distribution were summarized using median and minimum–maximum values. The study data were compared with a t-test or a Mann-Whitney U test, depending on the normality of the distribution of the data. Numerical data were analyzed with a Chi-square test or a Fisher's Exact test. A logistic regression model was created un multivariate analysis. The level of significance was set at a P value of less than 0.05.

A power analysis was carried out using OpenEpi software. From the total 2,038 students, it was planned to reach participation of at least 324 students, with a power of 80% and a confidence interval of 95%, considering a 50% frequency rate for conditions with an unknown frequency and a worst margin of error of 5%. Using a stratified sampling technique, the participants were classified according to the academic terms. The minimum number of students was 59 for term 1, 51 for term 2, 55 for term 3, 54 for term 4, 47 for term 5, and 59 for term 6.

RESULTS

A total of 332 students who met the inclusion criteria completed the survey. The demographic and descriptive data of the students included in this study are summarized in Table 1. The median age of students was 21 (18-25). Of the participants, 59 (17.8%) were term 1 students, 56 (16.9%) were term 2 students, 57 (17.2%) were term 3 students, 55 (16.6%) were term 4 students, 46 (13.9%) were term 5 students and 59 (17.8%) were term 6 students.

Table 1. Demographic and descriptive data of patients

Age (years) mean ±SD [med (min-max)]	 21.48±2.01 21 (18-25)	
Gender (%) Female Male	 51.3 48.7	
BMİ mean ±SD [med (min-max)]	 22.49±3.69 21.83 (9.91-34.87)	
Students' terms [n (%)] 1st year 2nd year 3rd year 4th year 5th year 6th year	 59 (17.8) 56 (16.9) 57 (17.2) 55 (16.6) 46 (13.9) 60 (17.8)	
Marital status (%) Married Single	 0 100	
Diagnosis of a chronic disease (%) Yes No	 13.9 86.1	
Using a medicine regularly (%) Yes No	 12.7 87.3	
Family history for diagnosis of fibromyalgia (%) Yes No	 2.7 97.3	

Family history for diagnosis of chronic fatigue syndrome (%)		
Yes	2.1	
No	97.9	
Family history for diagnosis of Temporomandibular joint disorder (%)		
Yes	2.1	
No	97.9	
Family history for diagnosis of Migraine (%)		
Yes	23.8	
No	76.2	
Family history for diagnosis of irritable bowel syndrome (%)		
Yes	5.7	
No	94.3	
Family history for diagnosis of Restless legs syndrome		
Yes	6.0	
No	94.0	

Of the students, 25.9% scored 40 points and above in part A of the CSI, suggesting the presence of CS. When the CSI Part A score was divided into groups according to the degree of severity, 48.5% of the students had subclinical, 25.6% had mild, 18.4% had moderate, 5.7% had severe and 1.8% had extreme CS.

There was no statistically significant difference when the rates of CS was analyzed according to the terms of the students ($P>0.05$) (Table 2). Although the rate of CS did not differ according to the terms of the students, the highest rate of CS was observed among the term 4 students (36.4%) (Table 2).

Table 2. Central sensitization rates according to the terms of the students

Students' terms	Central sensitization absent (CSI Part A score<40) %	Central sensitization present (CSI Part A score≥40)%
1st year	78.0%	22.0%
2nd year	69.6%	30.4%
3rd year	84.2%	15.8%
4th year	63.6%	36.4%
5th year	73.9%	26.1%
6th year	74.6%	25.4%

Chi-square table, Pearson's Chi Square p=0.2

The mean total CSI part A scores of the students was 29.97±13.77. According to part B of the CSI, 0.3% of the students had restless leg syndrome, 0.6% had chronic fatigue syndrome, 0.3% had fibromyalgia, 0.6% had temporomandibular joint disorder, 2.1% had irritable bowel syndrome, 6.3% had migraine, 0.3% had whiplash syndrome, 5.7% had anxiety/panic disorder and 9.0% had depression. No student had multiple chemical sensitivity. Accordingly, the most common CSS was depression with a rate of 9.0%.

Age and BMI did not significantly differ between the participants with and without CS (P>0.05). CS was significantly more common in females than in males (P=0.008), and also more common in students on continuous medication than in students who did not use regular medications (P=0.021). CS was significantly higher in those with a family history of chronic fatigue syndrome, migraine or restless leg syndrome than those without such a family history (P=0.001, P<0.001 and P<0.001, respectively). (Table 3)

Table 3. Factors Related with Central Sensitization

	Central sensitization absent (CSI Part A score<40)	Central sensitization present (CSI Part A score≥40)	P
Gender			
Female	94 (67.1%)	46 (32.9%)	0.008
Male	108 (81.2%)	25 (18.8%)	
Regular Drug Use			
No	221 (76.2%)	69 (23.8%)	0.021
Yes	25 (59.5%)	17 (40.5%)	
Family History of Chronic Fatigue Syndrome			
No	244 (75.3%)	80 (24.7%)	0.001
Present	1 (14.3%)	6 (85.7%)	
Family History of Migraine			
No	200 (79.1%)	53 (20.9%)	p<0.001
Present	46 (58.2%)	33 (41.8%)	
Family History of Restless Leg Syndrome			
No	239 (76.6%)	73 (23.4%)	p<0.001
Present	7 (35.0%)	13 (65.0%)	

Chi-square table, p<0.05

The rate of CS was not significantly affected by the presence of a chronic disease and parental educational level (P>0.05). The rate of participants with a diagnosis of migraine, anxiety and depression was significantly higher among those diagnosed with a chronic disease than those without a chronic disease (P=0.004, P=0.009 and P=0.022, respectively). Diagnoses of migraine, anxiety and depression were significantly more common among students on continuous medication than those without regular medication use (P=0.036, P=0.022 and P<0.001, respectively).

Diagnoses of fibromyalgia, irritable bowel syndrome and whiplash syndrome were significantly more common among those with a family history of fibromyalgia than those without a family history (P=0.027, P=0.013 and P=0.027, respectively).

Diagnoses of chronic fatigue syndrome, fibromyalgia, temporomandibular joint disorder, whiplash syndrome and depression were significantly more common among those with a family history of chronic fatigue syndrome than in those without a family history (P<0.001, P=0.021, P=0.042, P=0.021 and P=0.018, respectively).

Diagnoses of temporomandibular joint disorder were significantly more common among those with a family history of temporomandibular joint disorder than those without a family history (P=0.042).

Diagnoses of migraine were significantly more common among those with a family history of migraine than those without a family history (P<0.001).

Diagnoses of migraine, irritable bowel syndrome and depression were significantly more common among those with a family history of irritable bowel syndrome than those without a family history (P=0.025, P=0.001 and P=0.020, respectively).

DISCUSSION

The present study investigating the presence of CS and related factors revealed a high rate of CS among medical students. Among the CS syndromes, the most common diagnosis was depression. The rate of CS was significantly higher in female students, in students on regular medication, and in those with a family history of chronic fatigue syndrome, migraine and restless leg syndrome. Diagnoses of migraine, anxiety and depression were significantly more common among students diagnosed with a chronic disease and those on continuous medication. Family history was revealed to be an important determinant for the presence of CSSs.

In a large-scale Japanese study evaluating the prevalence of central sensitization syndrome, the presence of CS was investigated through the application of the CSI on 21,665 participants, and a prevalence rate of 4.2% was reported for CS (25).

A multicenter case-control study evaluating the presence of CS in neurological, psychiatric and pain disorders, reported CS in 20.7% of those with neurological, psychiatric and pain disorders and in 4.7% of the healthy controls (26). In the present study, CS was determined in 25.9% of the medical students based on their CSI scores, which is higher than those reported for the healthy controls. A previous study reported a CSS prevalence of 24.8% in healthy individuals, although the study was limited by its small sample size (24).

A cross-sectional study evaluating the presence of CS, adult hyperactivity and attention deficit disorder in medical students with chronic lumbar pain found a higher rate of CS than in the present study. Chronic lumbar pain was identified in 90 of the 227 student respondents, and CS was determined based on the CSI scores in 78.8% of those without lumbar pain and 97.8% of those with lumbar pain (27).

An analysis of the diagnoses of CSSs in part B of the CSI revealed that 0.3% of the students had restless leg syndrome, 0.6% had chronic fatigue syndrome, 0.3% had fibromyalgia, 0.6% had temporomandibular joint disorder, 2.1% had irritable bowel syndrome, 6.3% had migraine, 0.3% had whiplash syndrome, 5.7% had anxiety/panic

disorder and 9.0% had depression. In an epidemiological Japanese study evaluating the prevalence of CSSs, these rates were reported as 0.01% for restless leg syndrome, chronic fatigue syndrome, fibromyalgia, and whiplash syndrome, 0.08% for migraine, 0.06% for irritable bowel syndrome, 0.24% for anxiety/panic disorder and 0.78% for depression (25). In this regard, it can be suggested based on the findings of the present study that the rates of anxiety/panic disorder, and depression in particular, are higher in medical students. In a review, the rate of depression was reported to be higher in medical students from the Middle East than in those from other countries, and was more prevalent in females than in males [28]. Other studies have reported an overall prevalence of depression and associated symptoms in medical students of 1.4% and 73.5% (29,30).

It has been well established that psychosocial factors are common in those with CSSs, and that these factors contribute to pain, fatigue and poor sleep quality (31). When compared to the students of other faculties, medical students undergo a challenging process and encounter unique difficulties related to the long education period, the intensity of the courses, and the exam stress and anxiety associated with the examinations for specializations in medicine. It has been stated that the psychosocial health status of medical students is affected negatively by the various stress factors they face (32). In a study evaluating the distress experienced by medical students during the six years of medical education, there was no difference between junior medical students and other university students, while medical students in the second and third terms of education recorded higher stress levels, lower life satisfaction and higher rates of depression (33). Although the rates of CS did not differ significantly in the present study, the highest rate was observed in fourth-year students, which can be attributed to the fact that this period coincides with the transition of education to a hospital environment and encounters with real patients.

In the present study, the rate of CS was significantly higher in the female students than in the male students, concurring with the findings of previous studies reporting a difference in CS levels between sexes (25). In a cross-sectional study evaluating the presence of CS in chronic musculoskeletal pain disorders in different populations, the distribution of the patients showed a significant difference between sexes, and consistent with the present findings, the rate of CS was higher in females (34). These differences may be attributed to females are more likely than men to suffer from fibromyalgia, migraine, chronic widespread pain and persistent postoperative pain (35–37).

In the present study, CS was significantly more common in students on continuous medications than in students not on regular medications, which may be related to the significantly higher rate of migraine, anxiety and depression in those on continuous medications than in those without regular drug use. There was no significant difference in the age or BMI values of the participants with and without CS, which can be attributed to the young study population (18–25 years), the mean BMI being within normal ranges, and the low number of obese students with a BMI range of 9.91–34.87.

One of the main findings of the present study is that, concurring with previous studies, family history is an important determinant of CS and central sensitization syndrome in medical students. Patients with a history of pain throughout their lives are known to have a strong familial history. The first-degree relatives of patients with fibromyalgia are more likely to have fibromyalgia than the family members of healthy controls, and high rates of other chronic and painful conditions have been reported in this subpopulation (38). Furthermore, the family members of patients with fibromyalgia have been reported to be more susceptible to the condition than those of control subjects, regardless of whether or not they have chronic pain (39).

The strong susceptibility to fibromyalgia and other painful conditions in families has led researchers to investigate specific genetic polymorphisms. It has been reported that individuals with CS have been previously exposed to stressors and have a strong personal and familial history of pain, and these findings have been confirmed by genetic studies (40). In the present study, the ratio of students diagnosed with fibromyalgia, irritable bowel syndrome and whiplash syndrome was significantly higher in those with a family history of fibromyalgia than those without; the ratio of students diagnosed with chronic

fatigue syndrome, fibromyalgia, temporomandibular joint disorder, whiplash syndrome and depression was significantly higher in those with a family history of chronic fatigue syndrome than those without; the ratio of participants diagnosed with temporomandibular joint disorder was significantly higher among those with a family history of temporomandibular joint disorder than those without; the ratio of participants diagnosed with migraine was significantly higher among those with a family history of migraine than those without; and the ratio of students diagnosed with migraine, irritable bowel syndrome and depression was significantly higher in those with a family history of irritable bowel syndrome than those without. Numerous studies to date have provided strong evidence that these disorders share common comorbidities, including sleep disorders, fatigue and cognitive slowing, all of which are associated with the objective determinants of CS (15, 40–43).

One limitation of the present study is the lack of previous epidemiological studies evaluating the prevalence of CSSs in Turkey for comparison, and so the present data could not be compared with normal population data. As a further limitation, additional factors such as smoking, alcohol use, caffeine consumption, exercise habits, sleep duration and perceived stress were disregarded.

In conclusion, the present study identified a high prevalence rate of CS in medical students, with sex, family history and regular drug use being identified as related factors. Keeping in mind the likely development of central sensitization syndrome in medical students, the consideration of the stress they endure associated with the long and physically and mentally demanding education program is important for early diagnosis and treatment.

REFERENCES

1. .Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013;14(5):438-45
2. Nijs J, Apeldoorn A, Hallegraeff H, Clark J, Smeets R, Malfliet A et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. Pain Phys 2015; 18(3):E333–E346
3. Nijs J, Van Houdenhove B, Oostendorp RA.Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. Man Ther 2010;15(2):135–141
4. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. Pain 2007;129(1-2):130–142
5. L. Arendt-Nielsen, B. Morlion, S. Perrot et al., "Assessment and manifestation of central sensitisation across different chronic pain conditions," European Journal of Pain, vol. 22, no. 2, pp. 216–241, 2018
6. Nijs J, Leysen L, Vanlauwe J, et al. Treatment of central sensitization in patients with chronic pain: time for change? Expert Opin Pharmacother. 2019;20(16):1961-1970.
7. Yunus M. Central sensitivity syndromes: a unified concept for fibromyalgia and other similar maladies. J Indian Rheum Assoc 2000;8(1):27-33).
8. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):339-356.
9. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011 Mar; 152(3 Suppl): S2-15. PubMed PMID: 20961685. Pubmed Central PMCID: 3268359.
10. Ravindran M, Zheng Y, Timbol C, Merck S, Baraniuk J. Migraine headaches in chronic fatigue syndrom (CFS): comparison of two prospective cross-sectional studies. BMC Neurol. 2011; 11:30.
11. Ang D, Chakr R, France C, et al. Association of nociceptive responsivity with clinical and the moderating effect of depression. J Pain. 2011; 12:384–389.
12. Fernandez-de-Las-Penas C, Ortega-Santiago R, Cuadrado M, Lopez-de-Silanes C, Pareja A.

Bilateral widespread mechanical pain hypersensitivity as sign of central sensitization in patients with cluster headache. Headache. 2011;51: 384–391.

13. Bezov D, Ashina S, Jensen R, Bendtsen L. Pain perception studies in tension-type headache. Headache. 2011; 51:262–271.

14. Van Houdenhove B, Luyten P. Central sensitivity syndromes: stress system failure may explain the whole picture. Semin Arthritis Rheum. 2009; 39:218–219.

15. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol. 2007;21: 481–491.

16. Sohail N. Stress and academic performance among medical students. J Coll Physicians Surg Pak 2013;23:67-71

17. Sharifirad G, Marjani A, Abdolrahman C, Mostafa Q, Hossein S. Stress among Isfahan medical sciences students. J Res Med Sci 2012;17:402-6

18. Yusoff MS, Yaacob MJ, Naing NN, Esa AR. Psychometric properties of the Medical Student Well-Being Index among medical students in a Malaysian medical school. Asian J Psychiatr 2013;6:60-5.

19. Rosal MC, Ockene IS, Ockene JK, et al. A longitudinal study of students' depression at one medical school. Academic Medicine : Journal of the Association of American Medical Colleges. 1997 Jun;72(6):542-546. DOI: 10.1097/00001888-199706000-00022. PMID: 9200590.

20. Shapiro, Shauna L. MA; Shapiro, Daniel E. PhD; Schwartz, Gary E. R. PhD. Stress Management in Medical EducationTable 1. A Review of the Literature on Stress Management in Medical Education, 1969 to 1998Table 1. Continued.Table 1. Continued.Table 1. Continued.Table 1. Continued.Table 1. Continued.: A Review of the Literature. Academic Medicine: July 2000 - Volume 75 - Issue 7 - p 748-759

21. Professor P.M. Niemi & P.T. Vainiomäki. Medical students' distress – quality, continuity and gender differences during a six-year medical programme, Medical Teacher, 2006; 28:2, 136-141, DOI: 10.1080/01421590600607088

22. Mayer, T.G., Neblett, R., Cohen, H., Howard, K.J., Choi, Y.H., Williams, M.J., Perez, Y. and Gatchel, R.J. The Development and Psychometric Validation of the Central Sensitization Inventory. Pain Practice, 2012; 12: 276-285. https://doi.org/10.1111/j.1533-2500.2011.00493.x24.

23. Düzce Keleş E, Birtane M, Ekuklu G, Kılınçer C, Çalıyurt O, Taştekin N, et al. Validity and reliability of the Turkish version of the central sensitization inventory. Arch Rheumatol 2021;36(4):518-526.

24. Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ. Establishing clinically relevant severity levels for the central sensitization inventory. Pain Pract. 2017;17(2):166–75.

25. Haruyama, Y., Sairenchi, T., Uchiyama, K. et al. A large-scale population-based epidemiological study on the prevalence of central sensitization syndromes in Japan. Sci Rep 11, 23299 (2021). https://doi.org/10.1038/s41598-021-02678-1)

26. Wang XJ, Ebbert JO, Gilman EA, Rosedahl JK, Ramar P, Philpot LM. Central Sensitization Symptom Severity and Patient-Provider Relationships in a Community Setting. Journal of Primary Care & Community Health. 2021;12. doi:10.1177/21501327211031767

27. Ibrahim ME, Hefny MA. Central sensitization and adult attention deficit hyperactivity disorder in medical students with chronic back pain: a cross-sectional study. Egypt Rheumatol Rehabil. (2022) 49:24. 10.1186/s43166-022-00124-2

28. Mirza AA, Baig M, Beyari GM, Halawani MA, Mirza AA. Depression and Anxiety Among Medical Students: A Brief Overview. Adv Med Educ Pract. 2021 Apr 21;12:393-398. doi: 10.2147/AMEP.S302897. PMID: 33911913; PMCID: PMC8071692.

29. Rotenstein LS, Ramos MA, Torre M, et al. Prevalence of depression, depressive symptoms, and suicidal ideation among medical students a systematic review and meta-analysis. JAMA.

2016;316(21):2214– 2236. Doi:10.1001/jama.2016.17324.

30. Prinz P, Hertrich K, Hirschfelder U, de Zwaan M. Burnout, depression and depersonalisation–psychological factors and coping gies in dental and medical students. GMS Z Med Ausbild. 2012;29(1). doi:10.3205/zma000780

31. Smart KM, Blake C, Staines A, Doody C. The Discriminative validity of "nociceptive," "peripheral neuropathic," and "central sensitization" as mechanisms-based classifications of musculoskeletal pain. The Clinical Journal of Pain. 2011 Oct; 27(8): 655-63. PubMed PMID: 21471812.

32. Kötter T, Pohontsch NJ, oltmer E. Stressors and starting points for health-promoting interventions in medical school from the students' perspective: a qualitative study. Perspect Med Educ. 2015; 4(3):128-35.

33. Niemi PM, ainioma ki PT. Medical students' distress: quality, continuity and gender differences during a six-year medical programme. Med Teach. 2006; 28:136-141.

34. Cristina Roldán-Jiménez, PhD, David Pérez-Cruzado, PhD, Randy Neblett, MA, LPC, BCB, Robert Gatchel, PhD, Antonio Cuesta-Vargas, PhD, Central Sensitization in Chronic Musculoskeletal Pain Disorders in Different Populations: A Cross-Sectional Study, Pain Medicine, Volume 21, Issue 11, November 2020, Pages 2958–2963, https://doi.org/10.1093/pm/pnaa069.

35. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinie`re M. A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: Do biopsychosocial factors alter pain sensitivity differently in women and men? Pain 2012;153(3):619–35.

36. Bartley EJ, Fillingim RB. Sex differences in pain: A brief review of clinical and experimental findings. Br J Anaesth 2013;111 (1):52–8

37. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep 2017;2(6): e 627.

38. Arnold, L. M., Hudson, J. I., Hess, E. V., Ware, A. E., Fritz, D. A., Auchenbach, M. B., Keck Jr, P. E. (2004). Family study of fibromyalgia. Arthritis and Rheumatism, 50(3), 944–952. https://doi.org/10.1002/art.20042

39. Kato, K., Sullivan, P. F., Evengard, B., & Pedersen, N. L. (2009). A population-based twin study of functional somatic syndromes. Psychological Medicine, 39(3), 497–505. https://doi.org/10.1017/S0033291708003784.

40. Harte, S., Harris, R., & Clauw, D. (2018). The neurobiology of central sensitization. Journal of Applied Biobehavioral Research, 23(2), e12137.

41. Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008; 37:339–352.

42. Phillips, K., & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states – Maybe it is all in their head. Best Practice & Research Clinical Rheumatology, 25(2), 141–154. https://doi.org/10.1016/j.berh.2011.02.005

43. Kindler, L. L., Bennett, R. M., & Jones, K. D. (2011). Central sensitivity syndromes: Mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. Pain Management Nursing, 12(1), 15–24. https://doi.org/10.1016/j.pmn.2009.10.003