International Journal of Orthopaedics Research
www.orthopaedicsjournal.in
E-ISSN: 2663-0923, P-ISSN: 2663-0915
Received: 12-08-2022, Accepted: 29-08-2022, Published: 15-09-2022
Volume 4, Issue 2, 2022, Page No. 50-59

The frequency of central sensitization among patients with chronic musculoskeletal pain disorders– A cross sectional study

Hingarajia Dharti
Lecturer, SPB Physiotherapy College, Surat, Gujarat, India

Abstract
Background: Chronic musculoskeletal pain disorders (CMPDs) are among the leading causes of disabilities across populations, resulting in high social and financial burden. This persistent pain condition may include the central sensitization (CS) phenomenon, which implies a wide range of symptoms and that may be taken into account in CMPD treatment. CS symptoms can be measured by the Central Sensitization Inventory (CSI).
Objective: The aims of the study were to know the frequency of CS symptoms in patients suffering from different CMPDs.
Methods: In present cross-sectional study total of 185 gujarati participants aged 18-75, suffering from several CMPDs were included. CS symptoms were measured with the Gujarati Version of the CSI. The Demographic Data and CSI Score were analyzed by mean, median and standard deviation. The level of significance was set at $\alpha = 0.05$.
Results: The mean CSI total score for the whole sample was 24.73±15.28 points. CSI total score had subclinical values in the whole sample, whereas participants with scores ≥40 were found across different CMPDs, such as low back pain (36.73%) and neck pain (31.71%); 28.44% of females and 10.53% of males presented CSI scores ≥40. Patients showed significant differences in CSI total score by gender (P = 0.096).
Conclusion: Present study conclude that although participants showed mean subclinical values in CSI total score, participants with scores ≥40 were found across different CMPDs, ages, BMI and duration subgroups. In particular, females, LBP and neck pain participants were the subgroups most affected by high CSI scores.

Keywords: central sensitization, CMPDs, frequency, CSI

Introduction

Musculoskeletal disorders (MSDs) are a diverse group of complex regional syndromes leading to acute or chronic pain, impaired physical function, and disability. The prevalence of musculoskeletal disorders increases with age, obesity, and physical inactivity [1]. Musculoskeletal disorders are a major cause of morbidity, influence health and quality of life and impose an enormous burden on our healthcare system. The burden of musculoskeletal disorders is global, and looking at the gravity of the situation the World Health Organization (WHO) had declared 2000-2010 as the Bone and Joint decade. India is no exception to this situation [1]. WHO estimates that approximately 40% of people over 70 years suffer from osteoarthritis (OA) knee and 80% of individuals experience low back pain (LBP) pain during their lives [2]. A prevalence study conducted by the Indian Council of Medical Research reported an overall prevalence of musculoskeletal disorders to be 7.08%–11.5% [1]. High prevalence of OA and spinal pain is associated with lifestyle factors, level of physical activity, occupation, and psychosocial factors [3].

Twenty per cent of the general population experiences prolonged or recurrent pain for at least 3 months, such pain is then considered to be chronic [4]. Musculoskeletal disorders commonly known as chronic musculoskeletal pain disorders (CMPDs), these conditions lead to increased risk of developing other chronic health conditions, as well as decline in mental health [5]. CMPDs account for the greatest proportion of persistent pain across geographies and ages, and prevalence increases with aging and obesity [5]. The economic consequences of chronic pain include direct costs of medical care and pain management treatments, as well as indirect costs of decreased work productivity and sick leave, and of disability and sickness retirement [6].

The Global Burden of Disease study shows that CMPDs such as low back pain (LBP), headache disorders, neck pain, and others are within the top leading causes of years lived with disability and disability- adjusted life-years (DALY) worldwide [7]. Specifically, in the European Union, musculoskeletal disorders account for 10.3% of the total DALY [8]. CMPDs are therefore responsible for disability and high social and financial burden [9].

Chronic pain is a multi-factorial condition which has an impact on physical or body structures and functions, on psychological processes and on daily activities and quality of life of individuals [10]. Limited functioning or capacity to perform everyday tasks (essential for an independent living) affects individuals with chronic pain in their mobility and self-care, social relationships, work and leisure [11]. Individuals' functioning is composed of

body functions (body level)—described by impairments they experience, and of activities and participation (personal and social levels, respectively) described by capacity and performance tests [10].

Under musculoskeletal conditions, some symptoms such as pain cannot be explained by a specific organic cause [12]. This has led to a growing interest in central sensitization (CS) to explain some cases of "nonorganic" symptoms. This neuro-physiological phenomenon is defined as an amplification of neural signaling within the central nervous system, which provokes an abnormal increase in pain [13]. In the past decennia, a relevant subsample of patients with chronic pain, including individuals with chronic low back pain (CLBP), have shown an increased responsiveness to noxious and non-noxious stimuli, described as CS [14]. CS is a result of an imbalance in the nociceptive pathways ('pain pathways') and supraspinal structures due to an amplified facilitation and/or reduced inhibition [13]. The phenomenon, CS, is manifested by an amplified pain perception regarding its intensity (hyperalgesia and allodynia), duration (aftersensations and temporal summation) and distribution (expansion of the receptive field), as well as a reduced conditioned pain modulation (CPM) [15]. CS can explain why patients with musculoskeletal disorders suffer from pain, disability, and other symptoms in the absence of a clear nociceptive input or tissue damage [16].

Because patients with CS are more reactive to stimuli and their pain experience is enhanced, the presence of CS and/or higher levels of CS could plausibly be associated with lower physical functioning and participation in patients with CMPD, and vice versa. More severe symptomatology of CS, decreased parasympathetic/vagal activity or altered somatosensory responses have been associated with greater self-reported pain-related disability [17].

Given the need to transfer the CS concept to clinical management of persistent pain [13], the Central Sensitization Inventory (CSI) was designed as a screening instrument to help identify if a patient's symptoms may be related to CS [18]. This tool has shown strong psychometric properties and that it is a clinically useful outcome measure [19]. Scored from 0 to 100 [20], a cutoff score of 40 is considered to identify >82% of central sensitization pain patients [21]. This cutoff score was integrated as part of an algorithm to classify patient pain as neuropathic pain, nociceptive pain, or CS pain [22]. Moreover, five severity levels have been proposed to help in the clinical interpretation of CSI score [23]. Since the CSI was developed, there has been growing evidence of the presence of CS phenomena under CMPD, such as LBP [24], shoulder pain [25], chronic whiplash [26], knee pain [27], and tendinopathies [28]. Indeed, there is evidence that suggests that treatment for patients with predominant CS symptoms should be different from that of patients suffering from persistent painful conditions without CS [29].

Although the increase in the frequency of CS in patients with chronic pain is known, data on the incidence of this condition in various diseases with chronic pain is limited. There is close relationship of CS with many musculoskeletal diseases with chronic pain has been demonstrated in several studies. In the study conducted by Roldan-Jimenez *et al*., the frequency of CS was mostly reported in patients with low back (37.8%) and neck pain (32.4%) [30]. Tanaka *et al*. reported higher rates of disability in patients with high CSI scores [31]. However the exact frequency of CS in these patients is not fully understood.

Hence there was a need to study the frequency of CS symptoms among the patients with CMPDs. Thus the aim of the present study was to determine the frequency experience CS-related symptoms among patients suffering from different CMPDs.

Aims and Objectives of the Study

The aim and objective of the present study was to determine the frequency of CS-related symptoms among patients suffering from different CMPDs.

Methodology

Study Design: Cross sectional study.

Study Population: Patients with any of chronic musculoskeletal pain disorder.

Sampling Technique: Convenient sampling

Study Duration: 8 months

Sample Size: Sample size for present study was calculated by considering the proportion of chronic musculoskeletal pain disorder patients among OPD of S.S. Agrawal institute of Physiotherapy and Medical Care Education, Navsari (i.e. 14% of total OPD) i.e. $N = Z^2\ pq/d^2 = (1.96)^2\ (0.14)\ (1\text{-}0.14) / (0.05)^2 = 184.93 = 185$ with different CMPDs was included in this study. Where, Z = Level of significance i.e. 95% = 1.96, p = Proportion of CMPDs by one-month pilot survey i.e. 14%, q = 1-p, d = allowable error = 5%

Study Setting: S.S. Agrawal institute of Physiotherapy and Medical Care Education, Navsari.

Inclusion Criteria [32]

- Subjects with any chronic musculoskeletal pain disorder.
- Subjects suffering from MPD for at least 3 months duration.
- Both male and female with age group 18 to 75 years.
- Subjects who can read and write Gujarati language.
- Subjects willing to participate.

Exclusion Criteria [32]

- Subjects consuming analgesics or non-steroidal anti-inflammatory drugs (NSAIDs).
- Subjects underwent any surgical intervention in the last three months.
- Subjects diagnosed of specific medical conditions that can negatively affect the central nervous system, including cancer, brain or spinal cord injury, neurological disease or injury,
- Subjects with rheumatoid arthritis, fibromyalgia, polyarthralgia or any other systemic wide spread pain disease.
- Subjects with primary diagnosis of neuropathic pain and
- Subjects experiencing pain as a result of infection.
- Subjects with known psychiatric disorders.

Outcome Measure

The Central Sensitization Inventory Gujarati (CSI-G) version was used in present study to identify symptoms of CS [33]. The CSI is a measure that is used to identify symptoms related to CS and to ascertain the degree of symptoms represented in a 100-point scale. The CSI is the first instrument developed to identify key symptom manifestations of CS, rather than focus on those found in each separate disorder [18]. There are 25 questions that ask about variables related to CS, each a Likert scale of 0–4, where 0 corresponds to the respondent experiencing the event "never" and 4 to "always." A score ≥40/100 is consistent with a larger degree of CS symptomatology. Recently, five severity levels (subclinical = 0–29; mild = 30–39; moderate = 40–49; severe = 50–59; and extreme = 60–100) have been developed to help in the clinical interpretation of the CSI [23]. The CSI has very acceptable internal consistency with Cronbach's alpha at 0.88 and stability with test-retest reliability of r = 0.82 [21]. The study by D. Bid *et al* provided us with the evidence that the CSI-G is a reliable and valid measure to assess CS in Gujarati-speaking patients [33].

Procedure

The study was approved by Institutional ethics committee of Sarvajanik College of Physiotherapy, Surat. The subjects were screened on the basis of inclusion and exclusion criteria and their demographic data were taken by an assessment Performa. Prior to the commencement of the study, detailed procedure of the study was explained to the participants and a signed written informed consent form was taken from them. All the participants then assessed for all the outcome measures described in outcome measures section.

Statistical Analysis

The data was entered using Microsoft Excel 2017 and it was analyzed using SPSS 15 version. Demographic Data and CSI Score were analyzed by mean, median and standard deviation. The level of significance was set at $\alpha = 0.05$.

Results

A total of 228 patients with different CMPDs were screened for this study out of that 185 participants were included in the study and 43 patients were excluded for not meeting selection criteria. The mean age was 50.66 (SD=14.96) years, mean BMI was 26.18 (SD=4.81) kg/m^2 and Mean duration of symptoms was 21.54 (SD=27.30) months of all participants. The mean total CSI score was 24.73 (SD=15.28) points. More details of demographics and outcome measure data of sample are given in Table 1.

Among total 185 participants 76 (41.1%) were males and 109 (58.92%) were females. The frequency of CS was higher for females 28.44% (N=31) than males 10.53% (N=8). The CSI mean total score was 27.40±16.15 points for females and 20.89±13.11 (17.5) for males. Significant differences were also found in average CSI total score by gender (P = 0.0096). Gender distribution is showed in Table 2.

The most frequent diagnoses were LBP 26.49% (N=49) and Shoulder pain 26.49% (N=49), followed by knee pain 24.86% (N=46) and Neck pain 22.16% (N=41). From the total sample, 146 (78.92%) subjects had a CSI score <40 points (cutoff score), whereas the remaining 39 (21.08%) subjects had CSI score ≥40. The frequency of CS among various CMPDs is ranging from most frequent in low back pain 36.73% followed by 31.73% in Neck Pain, 10.20% in shoulder pain and least frequent 6.52% in knee pain. The mean CSI total score, ranging from 19.09 (SD=10.86) points in knee pain to 31.04 (SD=16.60) points for participants suffering from low back pain. Table 3 shows this distribution by CMPDs.

Participants from different age subgroups showed different frequency of CS, ranging from most frequent 33.33% (10) in those aged 18-34 to 8.33% (3) in those aged 55-65 years. CSI total score mean ranging 19.69±13.02 points in those aged 55-64 to 27.63±16.16 in those aged 65-75 years (Table 4). The kruskal wallis test showed no significant differences in CSI total score between age subgroups (P=0.2475).

Regarding BMI, the highest mean CSI total score, 25.88 (SD=10.27) points was found in underweight participants, although this subgroup was made up of eight participants followed by 25.16±17.17 in obese, 24.96±16.19 in overweight and 24.09±13.89 in normal weight. The majority had a CSI score <40 (Table 5). The kruskal wallis test showed that there were no significant differences in CSI total score by BMI subgroup (P=0.9378).

On the base of Duration of symptoms participants showed different frequency of CS, ranging from most frequent 61.54% (N=8) in those with duration of 61-120 months to only 13.11% (N=8) in those with duration of 3-6

months. CSI total score mean ranging 36.85±20.38 points in those with duration of 61-120 months to 22.15±12.76 in those with duration of 3-6 months. (Table 6). The kruskal wallis test showed no significant differences in CSI total score between different duration of symptoms subgroups (P=0.125).

Study Layout

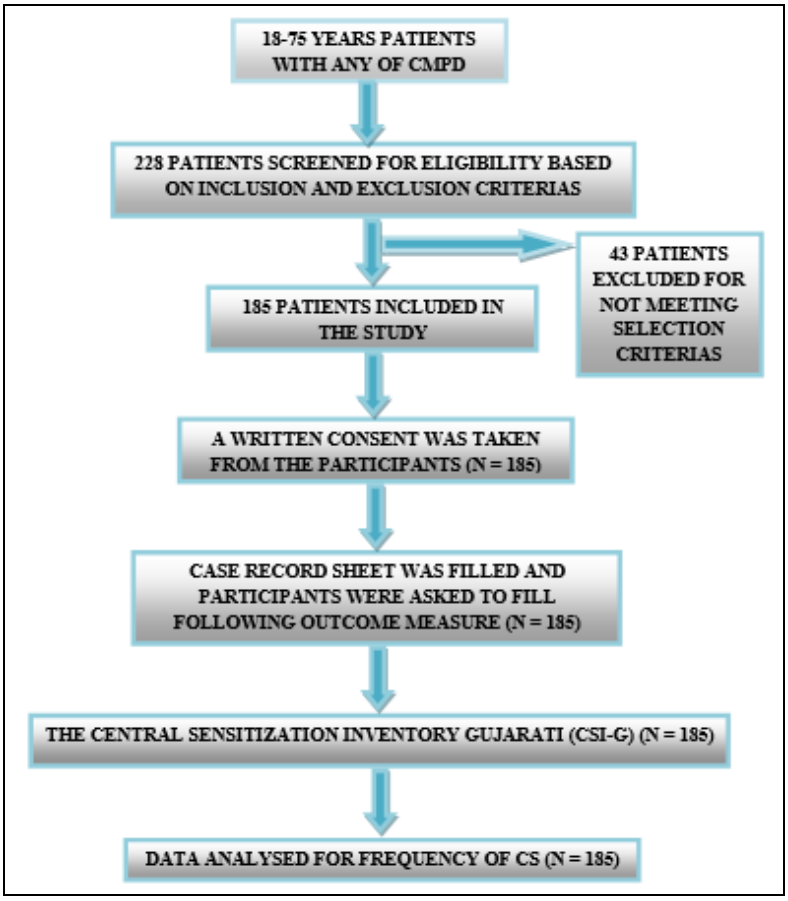


Fig 1

Table 1: Patient's Demographic Variables. (N=185)

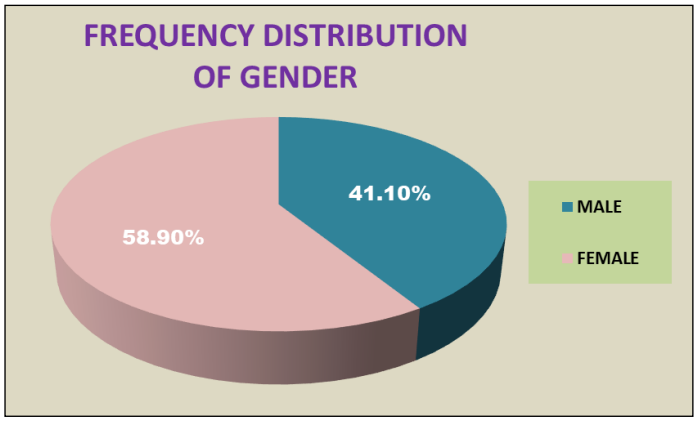
Variables	Mean ± SD	Median	Min	Max
Age (years)	50.66 ± 14.96	52	18	76
BMI (kg/m^2)	26.18 ± 4.81	25.83	16	41.54
Duration (months)	21.54 ± 27.30	12	3	120
Total CSI score	24.73±15.28	22	0	66

Table 2: CSI score divided by <40 or ≥40 points and scores in each gender group

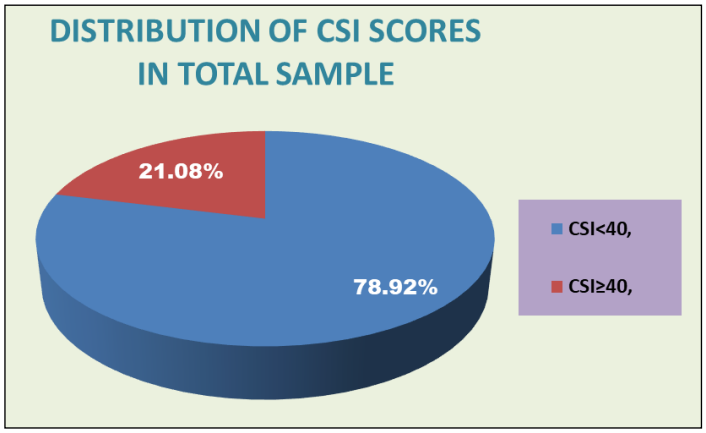
Gender	Total % (No.)	CSI<40, % (No.)	CSI≥40, % (No.)	CSI Total Score, Mean ± SD (Median)	P Value
Male	41.1% (76)	89.47% (68)	10.53% (8)	20.89±13.11(17.5)	0.0096
Female	58.92% (109)	71.56% (78)	28.44% (31)	27.40±16.15(23)	

Table 3: CSI score divided by <40 or ≥40 points and total score in each CMPD

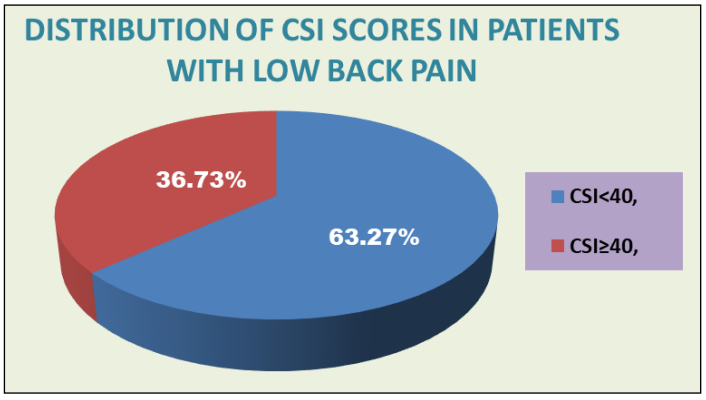
CMPDs	Total % (No.)	CSI<40, % (No.)	CSI≥40, % (No.)	CSI Total Score, Mean ± SD (Median)
Total Sample	100% (185)	78.92% (146)	21.08% (39)	24.73±15.28(22)
Low back pain	26.49% (49)	63.27% (31)	36.73% (18)	31.04±16.60(28)
Neck pain	22.16% (41)	68.29% (28)	31.71% (13)	26.71±15.94(25)
Shoulder pain	26.49% (49)	89.80 (44)	10.20% (5)	22.06±14.68(22)
Knee pain	24.86% (46)	93.48% (43)	6.52% (3)	19.09±10.86(17.5)



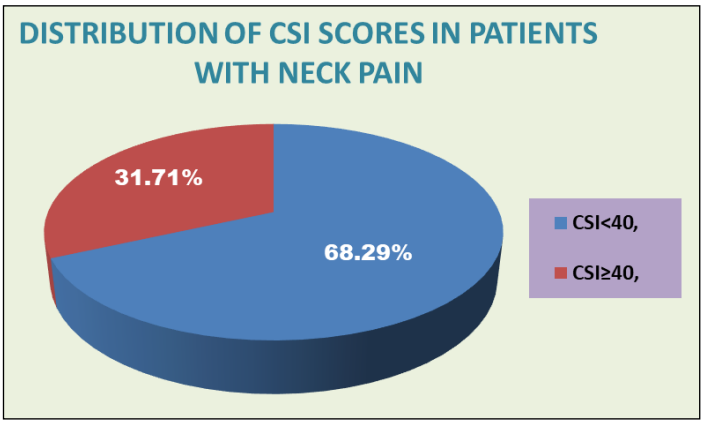
Graph 1: Pie-chart representing the frequency distribution of gender



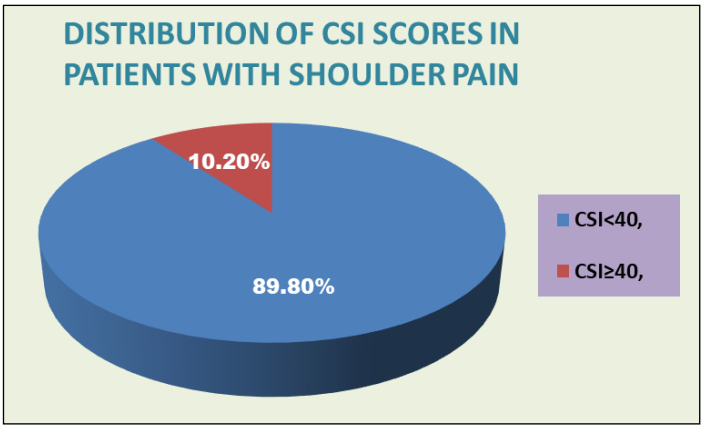
Graph 2: Pie-chart representing the distribution of CSI scores in total sample



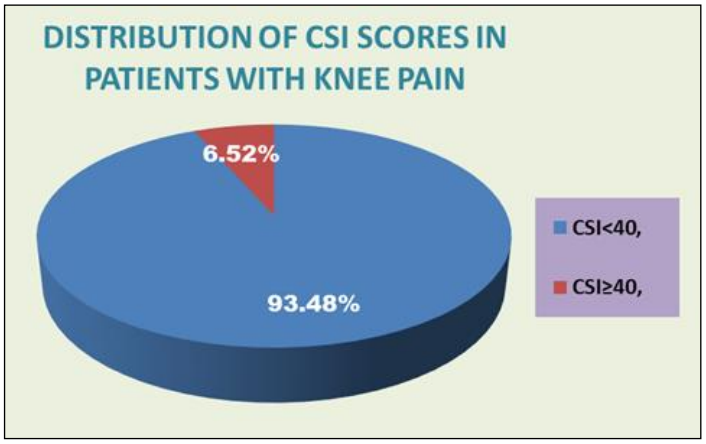
Graph 3: Pie-chart representing the distribution of CSI scores in patients with Low Back Pain



Graph 4: Pie-chart representing the distribution of CSI scores in patients with Neck Pain



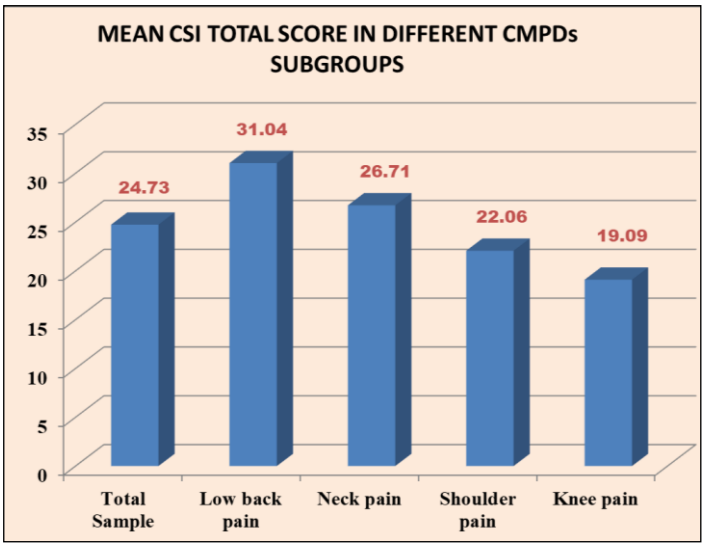
Graph 5: Pie-chart representing the distribution of CSI scores in patients with Shoulder Pain



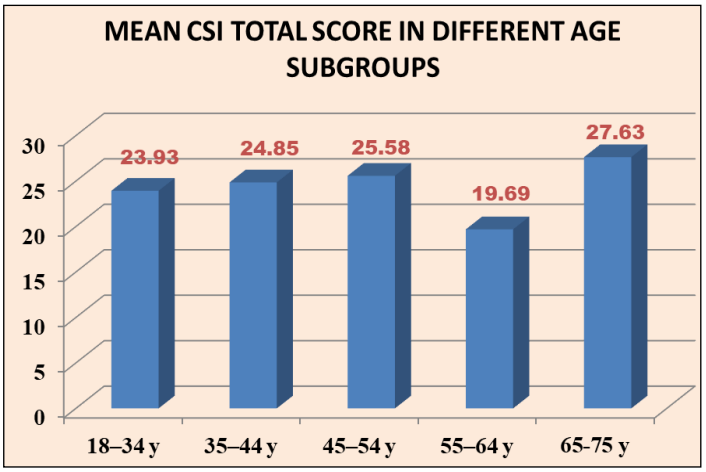
Graph 6: Pie-chart representing the distribution of CSI scores in patients with knee Pain

Table 4: CSI score divided by <40 or ≥40 points and scores divided by age subgroup

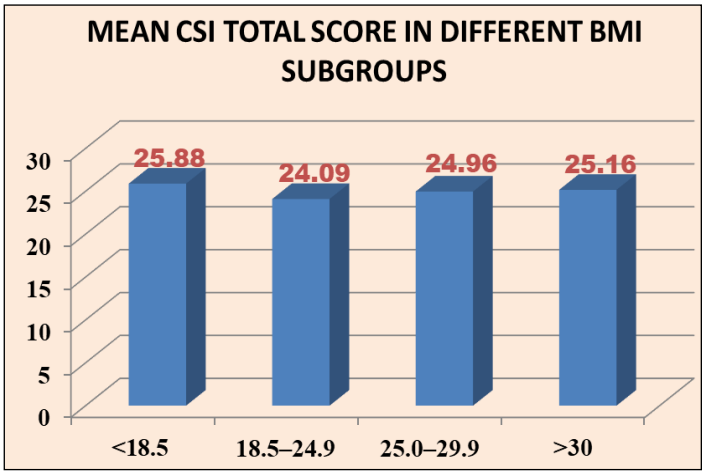
Age Subgroup	Total % (No.)	CSI <40, % (No.)	CSI ≥40, % (No.)	CSI Total Score, Mean ± SD(Median)	P Value
18–34 years	16.22% (30)	66.67% (20)	33.33% (10)	23.93±15.40 (22.5)	0.2475
35–44 years	17.84% (33)	78.79% (26)	21.21% (7)	24.85±15.66 (21)	
45–54 years	20.54% (38)	84.21% (32)	15.79% (6)	25.58±15.34 (22)	
55–64 years	19.46% (36)	91.67% (33)	8.33% (3)	19.69±13.02 (17)	
65-75 years	25.94% (48)	72.92% (35)	27.08% (13)	27.63±16.16 (27)	



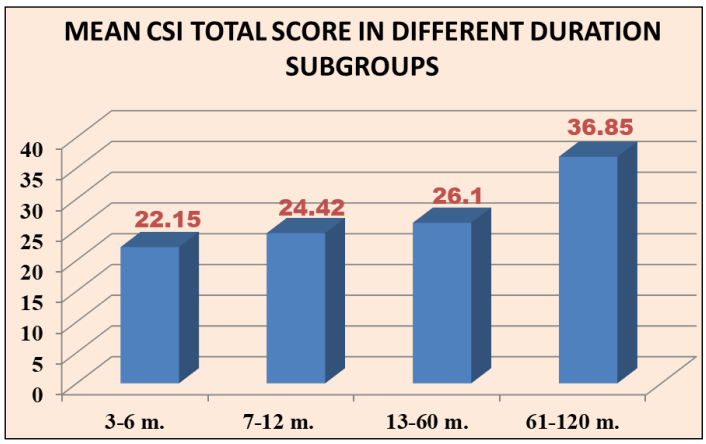
Graph 7: Bar diagram representing the mean CSI total score in different CMPDs



Graph 8: Bar diagram representing the mean CSI total score in different age subgroups



Graph 9: Bar diagram representing the mean CSI total score in different BMI subgroups



Graph 10: Bar diagram representing the mean CSI total score in different duration subgroups.

Table 5: CSI score divided by <40 or ≥40 points and scores in each BMI subgroup

BMI Subgroup	Total % (No.)	CSI <40, % (No.)	CSI ≥40, % (No.)	CSI Total Score, Mean ± SD (Median)	P Value
Underweight (<18.5 kg/m^2)	4.32% (8)	100% (8)	0% (0)	25.88±10.27(28.5)	**0.9378**
Normal weight (18.5–24.9 kg/m^2)	35.14% (65)	80% (52)	20% (13)	24.09±13.89(22)	
Overweight (25.0–29.9 kg/m^2)	43.24% (80)	76.25% (61)	23.75% (19)	24.96±16.19(22)	
Obese (>30 kg/m^2)	17.30% (32)	78.12% (25)	21.88% (7)	25.16±17.17(20.5)	

Table 6: CSI score divided by <40 or ≥40 points and scores divided by Duration of Symptoms subgroup

Duration of Symptoms (Months)	Total % (No.)	CSI <40, % (No.)	CSI ≥40, % (No.)	CSI Total Score, Mean ± SD (Median)	P Value
3-6 m.	32.97% (61)	86.89% (53)	13.11% (8)	22.15±12.76 (18)	0.125
7-12 m.	32.43% (60)	83.33% (50)	16.67% (10)	24.42±14.75 (22.5)	
13-60 m.	27.57% (51)	74.51% (38)	25.49 (13)	26.10±16.16 (21)	
61-120 m.	7.03% (13)	38.46% (5)	61.54% (8)	36.85±20.38 (40)	

Disscussion

This study showed CSI total scores and their distributions based on a 40-point cutoff in different gender, age, and BMI classified populations across a sample suffering from CMPD. The main finding was that CSI total score had subclinical mean values in the whole sample, whereas participants with scores ≥40 were found across different CMPDs; LBP and neck pain participants, especially, were the subgroups most affected by high CSI scores. High CSI scores were also found across different age and BMI subgroups. These differences were not significant in terms of CSI total score point by age, BMI and duration of symptoms but the difference of CSI total score was significant by gender.

There is evidence of CS in the diagnoses included in the present study [25, 26, 27] Although CSI scores <25 points in the sample indicated subclinical values according to previously established severity levels [23], it should be noted that a percentage of participants from the present sample had CSI values ≥40. In this regard, 36.73% were participants suffering from LBP. In light of these results, there are subgroups of participants with and without significant CS symptoms within participants with the same musculoskeletal diagnosis (i.e., LBP). Patients with significant CS symptoms are likely to have poorer response to local treatment in cases of LBP [24], chronic whiplash [34] or shoulder pain [35]. This is in line with research proposing diagnoses based on CS phenotype instead of, or in addition to, the musculoskeletal condition itself. (36) Regarding LBP, symptoms of CS have been proposed as a possible moderator of therapeutic effects [24].

For these reasons, CS has recently been proposed as a new diagnosis label that allows patient treatment to be redirected from traditional local therapies (such as electrotherapy, exercise, or surgery) to targeting lifestyle factors (including illness beliefs, stress, sleep, physical activity, and diet) [29]. For example, interventions such as pain neuroscience education (PNE) are effective in patients with chronic diseases such as spinal pain, regardless of CS [37]. However, PNE combined with cognition targeted motor control training has significantly superior effects, lowering CS symptoms compared with current best-evidence physiotherapy for individuals with chronic spinal pain [38]. Moreover, a "McKenzie exercise program" has been shown to be more effective in reducing CS than conventional physiotherapy in patients with chronic nonspecific LBP [39]. Therefore, under the same diagnoses as LBP, patients may be stratified clinically as experiencing predominantly CS pain or not in order to direct treatment [40].

When analyzing differences, a higher percentage of females (28.44%) had significant CS symptoms than men (10.53%). This finding concurs with previous literature suggesting that there are gender differences in chronic pain risk [41] and in the association between brain structure alterations and pain-related psychosocial characteristics [42]. These differences may be related to CS in terms of higher prevalence of fibromyalgia, migraine, chronic widespread pain, and persistent postoperative pain in females than males [41]. Overall, the prevalence of persistent pain is greater among females [43]. Although further research is needed related to CS.

In the present sample, the most frequent diagnoses were LBP 26.49% (N=49) and Shoulder pain 26.49% (N=49), followed by knee pain 24.86% (N=46) and Neck pain 22.16% (N=41). These diagnoses imply the main causes of global YLD, were causes between the low back pain and the anxiety [7]. The high prevalence rates of anxiety and depression, along with CMPD, are in line with research suggesting that psychiatric factors play an important role in both chronic pain [44] and the prevalence of comorbid psychiatric disorders in CMPD [9]. Specifically, psychological factors such as somatization and poor self-expectation of recovery are predictors of CS in CMPD, and psychological distress contributes to the variance of CSI in chronic pain patients [45].

Given the complexity of CMPD, current musculoskeletal models of care highlight the importance of behavior change assessments and interventions for success in treatment [46], as well as targeting other lifestyle variables such as sleep disturbance under chronic pain including patients with CS [47]. CSI provides a valid, economical tool to measure CS related symptoms. It is important for clinicians to assess the significance of CS-related symptoms under persistent pain conditions [48]. Given the high prevalence of CMPD and its high related cost, it is essential for clinicians to supplement their assessment with CSI for better decision-making during treatment, which may include targeting lifestyle factors [29] such as sleep disturbance [47] and pain education [49]. CSI may also be a useful predictor tool. For example, a CSI cutoff point of 40 has been shown to be a predictor of quality of life and increased length of stay after spinal fusions [50].

Limitations and Suggestions

- In this study only four, more prevalent non-traumatic and non-operative musculoskeletal disorders were included because of the conveniences and availability of the patients. Future study can be carried out including other MSDs i.e. traumatic, operative, arthropathies etc.
- CSI is a patient-reported outcome, as used to assess a patient's symptoms or functional status at a specific time. However, this information is subjective. Future research should supplement CSI data with objective measures.

- Further research based on a wider sample would allow analysis of differences between BMI and age subgroups.

Conclusion

Present study conclude that although participants showed mean subclinical values in CSI total score, participants with scores ≥40 were found across different CMPDs, ages, BMI and duration subgroups. In particular, females, LBP and neck pain participants were the subgroups most affected by high CSI scores.

References

1. Sharma R. Epidemiology of Musculoskeletal Conditions in India. New Delhi, India: Indian Council of Medical Research, 2012.
2. Andersson GB. Epidemiological features of chronic low-back pain. Lancet.,1999:354:581-5.
3. Chang DG, Holt JA, Sklar M, Groessl EJ. Yoga as a treatment for chronic low back pain: A systematic review of the literature. J Orthop Rheumatol.,2016:3:1-8.
4. The Joint Task Force (JTF). ICD-11 Beta Draft - Mortality and Morbidity Statistics.
5. Briggs AM, Cross MJ, Hoy DG, *et al*. Musculoskeletal health conditions represent a global threat to healthy aging: A report for the 2015 World Health Organization world report on ageing and health. Gerontologist,2016:56(Suppl 2):S243-55.
6. Boonen A, van den Heuvel R, van Tubergen A, *et al*. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. Ann Rheum Dis,2005:64:396-402.
7. James SL, Abate D, Abate KH, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet,2018:392(10159):1789-858.
8. World Health Organization. Prevention and Control of Noncommunicable Diseases in the European Region: A Progress Report. Geneva: World Health Organization, 2014.
9. Vargas C, Bilbeny N, Balmaceda C, *et al*. Costs and consequences of chronic pain due to musculoskeletal disorders from a health system perspective in Chile. Pain Rep,2018:3(5):e656.
10. Nugraha B, Gutenbrunner C, Barke A, *et al*. The IASP classification of chronic pain for ICD-11. Pain,2019:160:88-94.
11. Cieza A, Stucki G, Weigl M, *et al*. Icf core sets for low back pain. J Rehabil Med,2004:44:69-74.
12. Rief W, Hessel A, Braehler E. Somatization symptoms and hypochondriacal features in the general population. Psychosom Med,2001:63(4):595-602.
13. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain,2011:152(Suppl):S2-15.
14. Giesecke T, Gracely RH, Grant MAB, *et al*. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum,2004:50:613-23.
15. Den Boer C, Dries L, Terluin B, *et al*. Central sensitization in chronic pain and medically unexplained symptom research: a systematic review of definitions, operationalizations and measurement instruments. J Psychosom Res,2019:117:32-40.
16. Nijs J, Van Houdenhove B, Oostendorp R. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. Man Ther,2010:15(2):135-41.
17. Kregel J, Schumacher C, Dolphens M, *et al*. Convergent validity of the Dutch central sensitization inventory: associations with psychophysical pain measures, quality of life, disability, and pain cognitions in patients with chronic spinal pain. Pain Pract,2018:18:777-87.
18. Mayer TG, Neblett R, Cohen H, *et al*. The development and psychometric validation of the central sensitization inventory. Pain Pract,2012:12(4):276-85.
19. Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C. Measurement properties of the central sensitization inventory: A systematic review. Pain Pract,2018:18(4):544-54.
20. Neblett R, Hartzell MM, Cohen H, *et al*. Ability of the central sensitization inventory to identify central sensitivity syndromes in an outpatient chronic pain sample. Clin J Pain,2015:31(4):323-32.
21. Neblett R, Cohen H, Choi Y, *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.
22. Nijs J, Torres-Cueco R, van Wilgen CP, *et al*. Applying modern pain neuroscience in clinical practice: Criteria for the classification of central sensitization pain. Pain Physician,2014:17(5):447-57.
23. 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.
24. Aguilar Ferr_andiz ME, Nijs J, Gidron Y, *et al*. Auto-targeted neurostimulation is not superior to placebo in chronic low back pain: A fourfold blind randomized clinical trial. Pain Physician,2016:19(5):E707-19.
25. Noten S, Struyf F, Lluch E, D'Hoore M, Van Looveren E, Meeus M. Central pain processing in patients with shoulder pain: A review of the literature. Pain Pract,2017:17(2):267-80.

26. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: A systematic literature review. Eur J Pain,2013:17(3):299-312. Central Sensitization in Musculoskeletal Pain Disorders 5 Downloaded from
27. Lluch E, Nijs J, Courtney CA, Rebbeck T, Wylde V, Baert I. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. Disabil Rehabil,2018:40(23):2836-45.
28. Plinsinga ML, Brink MS, Vicenzino B, van Wilgen CP. Evidence of nervous system sensitization in commonly presenting and persistent painful tendinopathies: A systematic review. J Orthop Sports Phys Ther,2015:45(11):864-75.
29. Nijs J, Polli A, Willaert W, Malfliet A, Huysmans E, Coppieters I. Central sensitisation: Another label or useful diagnosis? Drug Ther Bull,2019:57(4):60-3.
30. Tanaka K, Nishigami T, Mibu A, Imai R, Manfuku M, Tanabe A. Combination of Pain Location and Pain Duration is Associated with Central Sensitization-Related Symptoms in Patients with Musculoskeletal Disorders: A Cross-Sectional Study. Pain Pract.,2021:21(6):646-652.
31. Suzuki K, Haruyama Y, Kobashi G, Sairenchi T, Uchiyama K, Yamaguchi S, *et al*. Central Sensitization in Neurological, Psychiatric, and Pain Disorders: A Multicenter Case-Controlled Study. Pain Res Manag.,2021:2021:6656917.
32. Cristina Roldán-Jiménez, David Pérez-Cruzado, Randy Neblett, Robert Gatchel, Antonio Cuesta-Vargas; Central sensitization in chronic musculoskeletal pain disorders in different populations: A cross-sectional study. Pain med.,2020:21(11):2958-2963.
33. Bid Dibyendunarayan D, Soni Neela C, Rathod Priyanshu V, Thangamani Ramalingam A. Content validity and test retest reliability of the Gujarati version of the Central Sensitization Inventory. Natl J Integr Res Med,2016:7(5):18-24.
34. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash?—A preliminary RCT. Pain,2007:129(1):28-34.
35. Valencia C, Fillingim RB, Bishop M, *et al*. Investigation of central pain processing in postoperative shoulder pain and disability. Clin J Pain,2014:30(9):775-86.
36. Williams DA. Phenotypic Features of Central Sensitization. J Appl Biobehav Res.,2018:23(2):e12135.
37. Malfliet A, Kregel J, Meeus M, *et al*. Patients with chronic spinal pain benefit from pain neuroscience education regardless the self-reported signs of central sensitization: Secondary analysis of a randomized controlled multicenter trial. PM R,2018:10(12):1330-43.e1.
38. Malfliet A, Kregel J, Coppieters I, *et al*. Effect of pain neuroscience education combined with cognition-targeted motor control training on chronic spinal pain: A randomized clinical trial. JAMA Neurol,2018:75(7):808-17.
39. Bid, D Dibyendunarayan, C Neela Soni, S Abhishek Yadav, V Priyanshu Rathod. "A Study on Central Sensitization in Chronic Non-specific Low Back Pain." Indian Journal of Physiotherapy and Occupational Therapy—An International Journal,2017:11:165-175.
40. Nijs J, Clark J, Malfliet A, *et al*. In the spine or in the brain? Recent advances in pain neuroscience applied in the intervention for low back pain. Clin Exp Rheumatol,2017:35(Suppl 107)(5):108-15.
41. 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.
42. Malfliet A, De Pauw R, Kregel J, *et al*. Gender differences in the association of brain gray matter and pain-related psychosocial characteristics. Pain Physician,2019:22(3):E191-203.
43. Tsang A, Von Korff M, Lee S, *et al*. Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. J Pain,2008:9(10):883-91.
44. Workman EA, Hubbard JR, Felker BL. Comorbid psychiatric disorders and predictors of pain management program success in patients with chronic pain. Prim Care Companion J Clin Psychiatry,2002:04(04):137-40.
45. Van Wilgen CP, Vuijk PJ, Kregel J, *et al*. Psychological distress and widespread pain contribute to the variance of the central sensitization inventory: A cross-sectional study in patients with chronic pain. Pain Pract,2018:18(2):239-46.
46. Briggs AM, Jordan JE, Jennings M, *et al*. Supporting the evaluation and implementation of musculoskeletal models of care: A globally informed framework for judging readiness and success. Arthritis Care Res,2017:69(4):567-77.
47. Nijs J, Loggia ML, Polli A, *et al*. Sleep disturbances and severe stress as glial activators: Key targets for treating central sensitization in chronic pain patients? Expert Opin Ther Targets,2017:21(8):817-26.
48. Nijs J, Leysen L, Adriaenssens N, *et al*. Pain following cancer treatment: Guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. Acta Oncol,2016:55(6):659-63.
49. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: Practice guidelines. Man Ther,2011:16(5):413-8.
50. Bennett EE, Walsh KM, Thompson NR, Krishnaney AA. Central Sensitization Inventory as a predictor of worse quality of life measures and increased length of stay following spinal fusion. World Neurosurg,2017:104:594-600.