Central Sensitization In Chronic Low Back Pain: A Narrative Review

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Abstracts: Objective**:** The aim of this narrative review is to examine the available literature related to central sensitization (CS) and altered central pain processing in chronic low back pain (CLBP) patients. Methodology**:** Literature was searched using many electronic databases. Additionally, reference list of most prominent articles were searched to increase the search accuracy, as much as possible. Studies which are evaluating the concept of CS in conservatively treated CLBP patients were included. Results: Results of studies evaluating the responsiveness to various types of stimuli in CLBP patients are contradictory. Some studies in CLBP patients have showed increased pain responses after sensory stimulation of body parts outside the painful region, when some other studies report no differences between patients and healthy controls. Studies evaluating the integrity of the endogenous pain inhibitory systems describe unchanged activity of this descending inhibitory system. Conversely, studies examining brain structure and function in connection with experimentally induced pain provide initial proof for changed central pain processing in CLBP patients. Also inappropriate beliefs about pain, depression and/or pain catastrophizing, may lead to the development of CS. Conclusion**:** Most of the literatures suggest that the CNS becomes centrally sensitized in a subgroup of patients with CLBP. However, the significance of this involvement is just starting to become clearer. This could be an active topic of future research. More studies are necessary for providing definite evidence for the clinical importance of CS. [Bid D NJIRM 2016; 7(3):114 - 123]

Key Words: Central sensitization, central pain processing, chronic low back pain, hyperalgesia, cortical reorganization, widespread pain, temporal summation.

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Introduction: Low back pain (LBP) is a significant clinical, social, and financial problem frequently observed with prevalence ranging from 8% to 56% in USA and it is estimated that 28% people experience disabling LBP sometime during their lives, 14% experience episodes lasting at least two weeks, 8% of the entire working population will be disabled in any given year [(1)]. Reliable data for CLBP prevalence in Indian population were not found in literature search. According to Rodrigo Dalke Meucci, Anaclaudia Gastal Fassa and Neice Muller Xavier Faria [2] CLBP prevalence was 4.2% in people aged between 24 & 39 years old and 19.6% in those aged between 20 & 59.

Chronic low back pain (CLBP) is sometimes defined as back pain that lasts for more than 7–12 weeks and many others classify frequently repeated back pain as chronic pain since it intermittently affects an individual over a long period [3]. Very little is known about the precise causes despite the high prevalence and high incidence of LBP [4]. Degenerative changes seen in imaging studies in the structures of the lumbar vertebral column and as well in musculoskeletal structures do not explain the symptoms of LBP; as they are also seen in normal healthy subjects[5, 6] and consistently there is a weak association between symptoms of LBP and imaging results [7]. In approximately 85% of the patients with LBP a precise pathoanatomic diagnosis cannot be given, hence these patients are considered having nonspecific LBP [4]. It is observed that only 25% of the variance of back pain intensity can be explained by the combined contribution of pathology and psychosocial factors [8], hence it is imperative to review the literature to find the underlying mechanisms like altered or abnormal central pain processing in CLBP patients.

Abnormal pain processing in the central nervous system (CNS) rather than from actual damage and/or injury to anatomic structures of body may lead to increased neuronal response and central sensitization (CS) [9-11] and this may be responsible for mechanical hyperalgesia, allodynia, and/or referred pain which are frequently seen in chronic pain syndromes [11-15]. CS is described by the International Association for the Study of Pain (IASP) as: *"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input[16].* CS is also defined as "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors"[17].

The outcome of the processes involved in CS is an increased responsiveness to a variety of peripheral stimuli including mechanical pressure, chemical substances, light, sound, heat, cold, and electrical

stimuli. The increased sensitivity to various stimuli results in a large decreased load tolerance of the neuromusculoskeletal system. Although the precise mechanism of CS is not fully understood; several contributing mechanisms have been put forward: It may be an altered sensory processing in the brain [18], malfunctioning of descending anti-nociceptive mechanisms [19], increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up [18, 20], and long-term potentiation of neuronal synapses in the anterior cingulate cortex [21].

Besides the above top-down mechanisms included in the pathophysiology of CS, it is important to understand that there are bottom-up mechanisms as well. For example, peripheral injury and other forms of stressors trigger the release of pro-inflammatory cytokines, with the consequent activation of spinal cord glia with cyclo-oxygenase-2 and prostaglandin E2 expression in the CNS [22-25].

"Wind up" denotes to a central spinal mechanism in which repetitive noxious stimulation results in a slow temporal summation that is experienced in humans as increased pain [26]. It leads to facilitation of ascending pain mechanisms and the literature also describes that there are alterations in the descending inhibitory pathways those arising from the periaqueductal gray matter and the rostral ventral medulla in the brainstem [27]. The work of these descending inhibitory pathways is to "focus" the excitation of the dorsal horn neurons, to generate an urgent, localized, and rapid nociceptive signal to biologically relevant stimuli, thereby suppressing surrounding extraneous neuronal activity [28, 29], and breakdown of one or more components of these inhibitory systems can result in CS [29].

It is recognized that there are facilitatory pathways originating from the brainstem; besides descending inhibitory pathways. Centres in the forebrain are capable of wielding powerful influences on various nuclei of the brainstem [30], including the nuclei recognized as the origin of the descending facilitatory pathway [29].

The activity in descending pathways can be modulated, as it is not constant; for example by the level of alertness, attention, anticipation, and stress [31]. It has been identified that forebrain functions such as cognitions, attention, emotions, motivation, and/or stress as personal factors may regulate the actual pain experience [29]. To name this facilitatory influence, the 'cognitive-emotional sensitization' term has been coined [32]. Functional imaging studies have showed in healthy subjects that pain catastrophizing and anticipations were related to neural processing of nociceptive stimuli; which are psychosocial and cognitive factors [33, 34]. During the last few decades great efforts have been made to untangle how brain processes pain and to decode involved neuronal mechanisms using functional imaging studies [35].

The intent of this narrative review is to search and analyse the available literature regarding CS and altered central pain processing in CLBP patients.

Material and Methods: The first author searched and assessed the literature and it was done by comprehensive computerized search on Science direct, National Library of Medicine (Pubmed), Biomed Central, Google Scholar, CINAHL, Pubmed central and Oxford Press. The key words "chronic low back pain" was used in combination with following terminologies: central sensitization, hyperalgesia, temporal summation, central pain processing, cortical reorganization, pain inhibition, pain facilitation, diffuse noxious inhibitory controls (DNICs) and widespread pain. Additionally, reference lists of most pertinent articles were searched to increase the search accuracy, as much as possible. We have included all the available studies which are evaluating the concept of central sensitization (CS) in conservatively treated CLBP patients.

Second and third author reviewed and revised the manuscript. By searching databases we found 80 records and 4 records were received through other sources. After removing the duplicates we found 26 records. Out of these 26 records, 6 records were not connecting the central sensitization with low back pain, hence discarded. We assessed remaining 20 full-text articles and removed 1 narrative review, 1 case study and 2 pilot studies. At the end, we reviewed 16 full text articles (Figure 1).

<u>Does Segmental and Extrasegmental Sensitization exist in CLBP patients?</u>

Hyperalgesia is showed by "a lowered pain threshold because of sensitization of nociceptive afferents or an increasing pain intensity as a function of graded nociceptive stimulation" in many chronic unexplained

disorders, such as Fibromyalgia, Chronic regional pain syndrome (CRPS), Whiplash Associated Disorders (WADs) to detect CS [36]. In patients with LBP, lower thresholds may be found in areas innervated by spinal segments neighbouring to the spinal segments of the primary source of pain perception. These findings are termed as segmental CS [37]. If pain referral and many areas of hyperalgesia is found away from the site of symptomatic area of back pain than this is termed as widespread or extrasegmental CS[37]. Sixteen studies are found that deals with sensitivity of various types of stimuli in CLBP patients. Details of the study are shown in the Table-1.

Table 1: Summary of the included studies

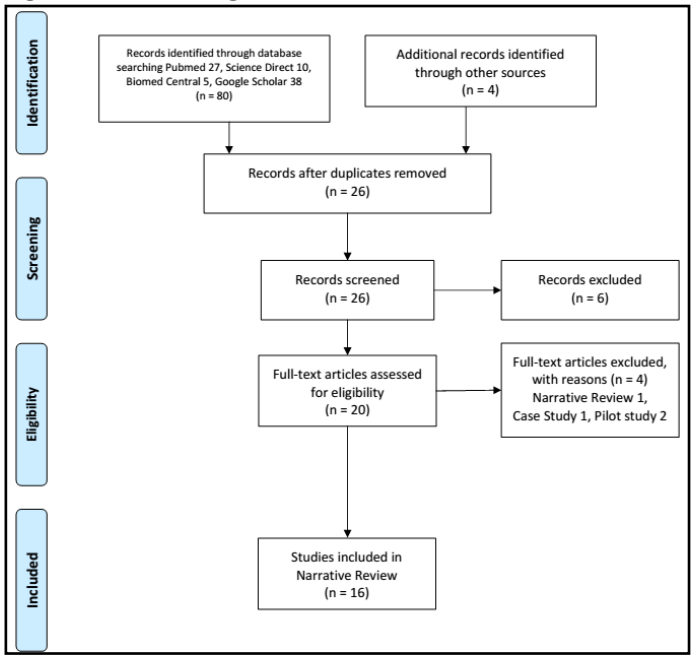
Author/ Publication Year	Design	Population studied	Stimulus used	Outcome measures[including Assessment of CS]	Central sensitization Yes CS+/ No CS-	Results of the study	Level of evidence/Limitations of study
Hyperalgesia (mechanical &/or electrical stimuli)							
Peters and Schmidt(78) (1992)	Case control study	20 CLBP 20 HCs	Electrical pain stimulus, Mechanical pressure	Algometry- Pain perception threshold, & Maximum pain tolerance	No	Higher PPT & MPT in CLBP group. Supports adaptation theory/DNIC	Level IV (85)
Clauw et al (39) (1999)	Cross-sectional pilot study	45 CLBP patients	Mechanical pressure	Algometry, MRI, SF-36, Psychosocial variables	Yes	CLBP patients had more tender points (5.2±5.4) in comparison with 1 to 3.5 in general population.	Level IV
Giesecke et al(38) (2004)	Case control study	11 CLBP 16 Fibro-myalgia 11 HCs	Mechanical Pressure	Pressure pain threshold, fMRI	Yes	Low PPT found in CLBP patients	Level IV Small sample size
Giesbrecht and Battie(40) (2005)	Case control study	30 CLBP females 30 HCs female	Mechanical Pressure	Pressure pain threshold (Electronic Algometry)	Yes	Significantly lower PPT in CLBP patients in comparison with HC	Level IV Only females
Laursen et al (41) (2005)	Case control study	40 female patients - 10FM/whiplash, 10 endometriosis, 10 LBP, 10 Rheumatoid arthritis Compared with 41 female HCs.	Mechanical Pressure	Pressure pain threshold (Electronic Algometry), SF-36	Yes	lower values of PPT in CLBP patients in comparison with HC	Level IV Small sample of CLBP patients; Only female patients.
O'Neill et al (43) (2007)	Case control study	12 CLBP 12 HC	Mechanical pressure, Hypertonic saline injection	Pressure pain threshold; Supra-threshold stimulation; Experimentally induced muscle pain.	Yes	Significant difference between LBP and HC in pain threshold or pain tolerance.	Level IV Small sample size. Selection bias
Meeus et al(42) (2010)	Experimental case control study	26 Chronic Fatigue Syndrome 21 CLBP 31 HC	Mechanical pressure, Aerobic exercises	Pressure pain threshold Venous blood sampling (Nitric Oxide level)	No	No difference between LBP and HC in pain threshold	Level IV Selection bias. Individual difference. Duration of exercise

Hyperalgesia (thermal stimuli)							
Lautenbacher et al (44) (1990)	Cross-sectional study	19 CLBP 19 HC	Thermal stimuli, cold	VAS, Tonic & phasic threshold, Somatosensory perception	No	No difference in threshold between CLBP andHCs but SSP is decreased	Level IV Small sample size
Derbyshire et al(45) 2002	Cross-sectional Case control study	16 CLBP 16 HC	Thermal stimuli	Thermal pain perception; Regional cerebral blood flow (rCBF); VAS rating.	Yes	Patients experienced higher VAS score at higher temperature compared with HCs; Small difference between LBP and HCs in rCBF for thermal stimuli	Level IV Small sample size
Wind up							
Arntz et al (47) (1991)	Pre-post repeated measure design	22 CLBP 21 HC	Electrical pain stimulus	VAS	No	Both the groups showed habituation	Level IV Methodological flaw
Kleinbohl et al (49) (1999)	Case control study	15 CLBP 15 headache patients 23 HCs	Tonic & Phasic heat stimuli	Pain threshold Index of Sensitization	Yes	LBP patients showed stronger & early sensitization	Level IV Selection bias
Flor et al (48) (2002)	Case control study	30 CLBP 30 HCs	Electrical pain stimuli; Repeated stimulation at different intensities	Pain threshold; Pain tolerance threshold; Somatosensory perception	Yes	Elevated pain threshold in CLBP group, Decrease in pain threshold in HC Supports CS+	Level IV
Diers et al (46) (2007)	Cross-sectional Case control study	14 CLBP 11 HCs	Electrical intracutaneous & intramuscular stimulus	Pain threshold Pain tolerance	Yes	Sensitization occurs in all CLBP patients but not in HCs	Level IV Small sample size
DNIC							
Julien et al(56) (2005)	Cross-over trial	30 Fibromyalgia30 CLBP 30 HCs	Immersion in noxious cold water at 12ºC	VAS rating during ascending or descending sessions (spatial summation)	No	Deficit of endogenous pain inhibitory systems found in fibromyalgia but not in chronic low back pain.	Level IV Methodological flaw
Endogenous inhibition during exercise							
Hoffman et al (59) (2005)	Repeated measure design/clinical trial	8 CLBP 10 HCs	Mechanical pressure	PPT	No	Pressure pain perception can be reduced after aerobic exercise in LBP patients and HCs	Level IV Small sample size
Flexion reflex							
Peters et al (63) (1992)	Mixed between-within group design	12 CLBP 12 oral surgery 12 HCs	Electrical pain stimulation	Nociceptive flexion reflex threshold	No	No significant difference between CLBP and HCs; No role of DNIC/supports adaptation theory	Level IV Small sample size

This table 1 describes the results of these studies in relation to the presence or absence of the central sensitization (CS+ or CS-) in CLBP patients.

Presence of Hyperalgesia in CLBP patients: There are four studies, which reported hyperalgesia to pressure to sites unrelated to the lumbo-pelvic area in CLBP patients, indicating generalized or widespread hyperalgesia at least in a subgroup of CLBP patients[38-41]. It was observed that there is a decreased pressure pain threshold (PPT) in a population of CLBP patients with and without radiation distal to the knee, both at sites related to lumbar area(paraspinal lumbar muscles) and unrelated to the lumbar area (extensor muscle of the wrist, finger, etc) [40]. Also contradictory results were reported in the literature suggesting that CLBP patients do not experience sensitization[42].

Figure 1: Flow Diagram of Literature Search



In a study conducted by O'Neill et al, pressure pain thresholds (PPTs) in tibialis anterior muscle were found significantly lower in CLBP patients, whereas PPTs of infraspinatus muscle were not different from healthy controls, suggesting segmental sensitization[(43)]. Lautenbacher et al [(44)] found no differences in pain threshold between patients with CLBP and HC when contact heat was used on the right hand using a Peltier thermode, but in another study by Derbyshire et al[(45)] reported that the patients experienced significant higher pain ratings on Visual Analog Scale (VAS) compared with healthy subjects, suggesting widespread hyperalgesia, but no allodynia (as there were no differences in VAS between patients and control group for the non-painful stimulation).After administering hypertonic saline injection, patients with herniated disk confirmed by MRI exhibited considerably higher pain intensity, duration, and larger areas of pain referral in both infraspinatus and tibialis anterior muscles in comparison with healthy controls, indicating widespread sensitization in these patients with CLBP [43]. In studies, where repeated pain stimulation is applied or continuous stimulation is applied; demonstrates the phenomena of enhanced temporal summation (wind-up) [46-49]. In various studies, to induce temporal summation mechanical, electrical, or thermal stimulation have been used (See Table: 1 Wind up).

The endogenous pain control system whose deficiency is supposed to contribute to chronic musculoskeletal pain is represented by DNIC-like mechanisms [(50, 51)]. The DNIC-like mechanisms originates from the serotonergic dorsoreticular subnucleus in the caudal medulla, is activated by nociceptive afferents and in turn modulates the impending noxious input by the inhibition of wide dynamic range neurons in the dorsal horn [52]. It can be facilitated by serotonergic and opioidergic agents and inhibited by opioid antagonists and serotonin antagonists, respectively [53-55].

The initiation of endogenous pain inhibitory systems by the spatial summation test was assessed [(56)] using immersion of different surfaces of the arm in circulating noxious cold (12ºC) water. Both patients with CLBP and healthy controls perceived their pain in different manner during the ascending and descending sessions. The descending session resulted in smaller pain intensity and unpleasantness, which the authors ascribed to a full recruitment of inhibitory systems at the beginning of the descending session in contrast to a gradual recruitment during the ascending session. During the ascending session pain perception remained static, regardless the stimulated area, whereas a correlation was observed between pain and stimulated area during the descending session. Hence the observations from this study do not support a deficit of this endogenous pain inhibitory system in CLBP. In normal conditions, pain thresholds increase during physical activity because of the release of endogenous opioids, growth factors [57], and other strong inhibitory mechanisms (descending inhibition) engineered by the CNS [58]. However, in patients with CLBP, pain ratings from an experimentally induced pressure pain stimulus increased in response to

submaximal aerobic exercise [59], as they are in healthy controls [60], indicating normal pain processing in response to exercise. Meeus M et al studied pain response in relation to exercise in patients with chronic fatigue syndrome and chronic widespread pain, in patients with CLBP, and in pain-free sedentary controls. The absence of endogenous inhibition during exercise was only seen in patients with chronic fatigue and chronic widespread pain, but not in the group of CLBP patients [42].

Most of the above-mentioned studies are based on the patients' pain assessment, which are actually subjective measurements. Measuring the minimal intensity of transcutaneous electrical stimulation essential to elicit a spinal reflex may provide a better objective measurement of spinal hyperexcitability and CS [61]. The minimal intensity of the stimulus that is sufficient to evoke a reflex at a well-defined latency, known as the reflex threshold, usually represents the minimal stimulus intensity required to elicit a perception of pain [62]. Peters ML et al elicited a nociceptive flexion reflex after noxious stimulation in CLBP patients [63]. There were no differences observed in nociceptive flexion reflex (RIII) threshold between CLBP patients and healthy controls after noxious electrical stimulation of the ankle [63]. Hence, there is no evidence to suggest that spinal reflexes are varied in CLBP patients.

Altered Brain Function in CLBP: Flor et al first showed that cortical hyperactivity and reorganization in CLBP patients [64]. Diers et al [46] used EEG to evaluate brain responses in relation to pain in patients with CLBP. No significant differences were observed in pain threshold, but patients exhibited extrasegmental sensitization when repeated stimulation was applied to evoke temporal summation, but no significant sensitization was seen among healthy controls [(46)]. Evidence for augmented central pain processing has been found in studies using fMRI [38]. In a positron emission tomography study [45] conducted on CLBP patients and HCs with thermal pain stimulation; the regional cerebral blood flow correlated partially well with subjective pain experience in many brain areas, such as the cerebellum, thalamus, midbrain, etc. in both the groups. Hence these data provide some initial evidence for altered central pain processing in CLBP patients [45].

Cognitive Emotional Sensitization: Following characteristics namely, Catastrophizing [65], depressive feelings [66], and fear avoidance [67-69] have been reported to occur in CLBP patients. Inappropriate beliefs have been linked with the development of overstated pain perception [(70, 71)] or other negative effects. All these psychological factors are cited as yellow flags as they are associated with a poor prognosis, may heighten facilitatory pathways in the CNS, leads to sensitization of dorsal horn spinal cord neurons. Initial research findings suggest that cognitive and emotional factors can contribute and/or may sustain the mechanisms of CS in CLBP patients.

Discussion: The purpose of this article was to review and evaluate the existing scientific literature to central sensitization (CS) and altered central pain processing in CLBP patients.

Different assessment methodologies were utilized for evaluating the phenomenon of CS, intending to understand the different changes in pain sensitivity observed in this population. Nine out of the 16 articles that were considered in this narrative review seem to support an emerging key role for CS in CLBP. This was confirmed through by means of different parameters like pain perception threshold, pain tolerance, pain ratings etc. All these findings are considered clinical manifestations of CS [72].

Furthermore, similar findings have been previously seen in some other chronic pain conditions such as whiplash injury [73] or fibromyalgia [38], suggesting these conditions are caused by the same altered central pain processing mechanism. CS demonstrates itself at different degrees over a continuum from no CS at all to severe CS. Although prevalent in chronic pain, generalized central hypersensitivity is not present in every patient [74]. For instance, in some populations (e.g., fibromyalgia), CS may be the characteristic feature of the disorder. In others, such as in CLBP, not all patients have CS, but only a subgroup of them, has it.

There are many studies which suggest that chronic pain should be seen from a "Central" view point. Changes in ascending and descending central modulatory mechanisms for the perception of pain, which is termed as "neuronal plasticity" [28] may be responsible for CS. CS may involve both functional changes and structural changes in the CNS [75, 76].

Though there are many studies that indicate presence of altered central pain mechanisms in CLBP patients but results are ambiguous. Some studies observed reduced pain thresholds suggestive of extra segmental hyperalgesia [38-41], some other studies only observed a segmental hyperalgesia [43], and while some authors did not find hyperalgesia at all [46, 77, 78]. Same results were found when temporal summation was experimentally induced in CLBP patients [46, 77]. Now it is understood that functional organization of the adult brain is not fixed, but plastic changes of the primary cortical areas may happen as a result of injury, stimulation, and training [79]. Continued painful stimulation may result into cortical changes [64, 80]. There is growing evidence that changes in the brain structure, brain function, and brain chemistry may happen in CLBP patients [38, 64, 81, 82]. Functional brain-imaging techniques are especially useful to visualize the brain structures engaged in pain processing during evoked pain and to understand the mysteries of brain circuitry.

So far there is no gold standard available for diagnosis of CS [11]. Different clinical and laboratory methods are used for detecting potential involvement of CS in musculoskeletal pain conditions (i.e., QST [40, 41, 43] and brain imaging techniques [38], without having any comparatively superior or reliable method. All of them evaluated the same basic concept of CS, but in its different expressions related to the different aspects of sensitization [83]. For example, widespread hyperalgesia, which is an expression of CS, can be evaluated quantitatively in a standardized way by using pressure algometry. Most studies of this review assessed the presence of CS in laboratory conditions and used costly and complex equipment; which are not available for most of the clinicians. Further investigation regarding the assessment of CS in CLBP is required in order to provide new assessment methodologies for CS, which is simple and less costly for the clinicians. With this view-point, the recently proposed 'Central Sensitization Inventory' should be investigated in CLBP patients [84].

Conclusion: Most of the literatures reviewed here suggest that the CNS becomes centrally sensitized in a subgroup of patients with CLBP. However, the significance of this involvement is just starting to become clearer. This could be an active topic of future research. More studies are necessary for providing definite evidence for the clinical importance of CS.

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