The role of central sensitization in shoulder pain : a systematic literature review

The role of central sensitization in shoulder pain: A systematic literature review

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Abstract

Introduction: Hyperexcitability of the central nervous system has been suggested to play an important role in pain experienced by patients with unilateral shoulder pain. A systematic literature review following the PRISMA guidelines was performed to evaluate the existing evidence related to the presence of central sensitization in patients with unilateral shoulder pain of different etiologies including those with chronic subacromial impingement syndrome. Studies addressing neuropathic pain (e.g. post-stroke shoulder pain) were not considered.

Methods: Electronic databases Pubmed, Ebsco and Web of Science were searched to identify relevant articles using predefined keywords regarding central sensitization and shoulder pain. Articles were included till September 2013. Full text clinical reports addressing studies of central sensitization in human adults with unilateral shoulder complaints including those diagnosed with subacromial impingement syndrome were included and screened for methodological quality by two independent reviewers.

Results: Ten articles were retrieved for quality assessment and data extraction. All studies were cross-sectional (case-control) or longitudinal in nature. Different subjective and objective parameters, considered manifestations of central sensitization, were established in subjects with unilateral shoulder pain of different etiologies, including those receiving a diagnosis of subacromial impingement syndrome. Overall results suggest that, although peripheral mechanisms are involved, hypersensitivity of the central nervous system plays a role in a subgroup within the shoulder pain population.

Conclusions: Although the majority of the literature reviewed provides emerging evidence for the presence of central sensitization in unilateral shoulder pain (including those diagnosed of subacromial impingement syndrome), our understanding of the role

central sensitization plays in the shoulder pain population is still in its infancy. Future studies with high methodical quality are therefore required to investigate this further.

Keywords: shoulder pain, central nervous system sensitization, systematic review, shoulder impingement syndrome.

Introduction

Shoulder pain is the third most common musculoskeletal disorder, with prevalence rates varying from 6.9% to 26% for point prevalence, and up to 66.7% for lifetime prevalence in the general population [1,2]. Although many patients completely recover within a few months after injury, a large patient group reports persisting shoulder pain which contributes to more than 80% of the total economic cost due to shoulder pain [3-5].

Within the unilateral shoulder pain population, subacromial impingement syndrome (SIS) is a common diagnosis. SIS is a disabling and costly disorder affecting the general population, which leads to important expenditures for the public health care system [6,7]. Over the past years, research findings point to the possibility that central sensitization (CS) is present in (some) patients with unilateral shoulder pain (including those with SIS) [8]. CS is defined as an "*amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity*" [9]. CS is a broad term that encompasses distorted sensory processing in the CNS [10], malfunctioning of descending pain inhibitory mechanisms [11], enhanced activity of pain facilitatory mechanisms [12] and long-term potentiation of the neural synapses in the anterior cingulated cortex [13]. Indeed, if the CNS is sensitized, minimal tissue damage or sensory input without tissue damage could be sufficient to trigger pain perception. This may explain the mismatch between the pain experienced by patients and the extent of injury at the subacromial space commonly found in patients with SIS [14].

Different modalities of quantitative sensory testing (QST) have been used to assess central pain dysregulation [15]. QST is based on standardized (painful) stimuli applied to cutaneous and musculoskeletal structures which aim at assessing the sensitivity of

these structures to specific stimuli modalities. Those stimuli can be applied locally (i.e. in the proximity of or at the affected joint or tissue) or at distant sites (i.e. remote from the affected joint or tissue), providing a better understanding of peripheral and central nervous system sensitization, respectively. Various QST responses have been associated with CS in patients with unilateral shoulder pain including alteration of descending pain inhibitory mechanisms [16] or remote areas of hyperalgesia [8,14]. All these changes are considered different pain biomarkers evaluating the same construct (i.e. CS) [15,17,18].

Currently, it remains unclear whether enough consistent evidence is available regarding CS in unilateral shoulder pain, including those patients diagnosed with SIS. Recent systematic literature reviews have demonstrated that CS plays an important role in other chronic pain conditions such as whiplash [19], osteoarthritis [20], chronic fatigue syndrome [21] and (to a much lesser extend) rheumatoid arthritis [22]. In addition, some voices claim for a role of the CNS in pain experienced by people with unilateral shoulder pain such as those with rotator cuff tendinopathy [23], frozen shoulder [24] and chronic hemiplegic shoulder pain [25,26]. The latter group of patients addresses neuropathic pain, as stroke is a typical example of objective evidence of (central) nervous system 'damage', as required for complying with the diagnostic criteria for neuropathic pain [27]. As CS has been well-established as the underlying mechanism of neuropathic pain [17,28,29], neuropathic shoulder pain will not be the focus of the present systematic review. Here we focus on non-neuropathic shoulder pain patients, including those with SIS, for examining whether CS plays a role in these types of shoulder pain.

Although preliminary evidence seems to support the role that CS plays in subjects with unilateral shoulder pain, there is currently no systematic literature review

available regarding CS in these patients. Hence, the aim of this study was to systematically review and evaluate the existing evidence from the literature, in order to establish if there are enough arguments to support or either refute a role for CS in unilateral shoulder pain including those with SIS. Any type of association between CS and unilateral shoulder pain was explored such as the merely presence of CS (i.e. epidemiologic studies), any cause-effect relationship or the effect of treatments focusing on CS in unilateral shoulder pain patients. Studies related to neuropathic shoulder pain (e.g. post-stroke shoulder pain) were not considered.

Methods

Search strategy

To identify relevant articles regarding central pain processing in patients with SIS, a systematic search of the literature using the PRISMA statement guidelines [30] was performed in databases Pubmed (http://www.ncbi.nlm.nih.gov/sites/entrez), Ebsco (http://search.ebscohost.com) and Web of Science (http://apps.isiknowledge.com), until September 2013. The results for every database and combination of keywords and MeSH terms used in the search strategy are represented in Supplementary Table S1. In addition, the reference lists from relevant articles were checked to obtain as complete information as possible.

Study Selection

To be included in this review, an article had to meet all the following inclusion criteria: (I) to be reported in a peer-review academic journal; (II) to study the phenomenon of CS in human adults (18 years or older) with unilateral shoulder pain

including those with SIS; (III) to be a full-text original research report, and (IV) to be written in English. If any of these inclusion criteria were not fulfilled, the article was excluded from the literature search. No limitation regarding year of publication was used and all clinical study designs were eligible. Although review articles were not eligible for inclusion, their reference lists were screened to collect relevant articles, which were not initially retrieved by the systematic search. Articles related to neuropathic shoulder pain (e.g. pain post-stroke shoulder pain) were excluded.

Study process

After performing the literature search, duplicate articles were removed. Eligibility assessment was performed based on title and abstract. Initially, all titles and abstracts of the retrieved articles were screened to identify relevant papers related to CS in unilateral shoulder pain (including those with SIS) using predefined inclusion criteria. In case of uncertainty regarding appropriateness of the paper after reading title and abstract, the full version of the text was retrieved and checked for fulfillment of inclusion criteria. Screening was done independently by two researchers (MNS and MK). A consensus meeting was organized to discuss potential disagreements. When consensus could not be reached, a third opinion was provided by another researcher (ELL).

The full text version of all the articles that met the inclusion criteria were retrieved and methodological quality assessment and data extraction was performed.

Quality assessment

Methodological quality assessment of the full text articles was evaluated using the PEDro scale, which is based on the Delphi list developed by Verhaegen et al. [31]. Inter-rater reliability of the PEDro scale reported a generalized Kappa static ranging between 0.40 and 0.75 [32]. This scale is considered to provide a measure of internal validity and ability to predict bias [33, 34]. The PEDro scale is composed by 11 items, where the first relates to external validity (and it is not considered part of the total score), and the remaining 10 determine the internal quality and indicate whether the trial includes enough data to make it interpretable [35]. The PEDro scale grades articles getting 6/10 or more points from moderate to high quality and it was originally designed to assess the risk of bias Randomized Control Trials (RCT's) [32]. For non-RCT's, the Pedro scale was accommodated to the number of items that were applicable for each experimental design. For instance, criteria number 2,3,6,8 and 9 were not scored for cross-sectional and case-control studies as they are not applicable (see Supplementary Table 2).

The same two independent and blinded researchers who performed the screening of the databases (MNS and MK) assessed the risk of bias of the included studies using the PEDro scale. In order to increase the quality of the risk of bias assessment, a practice trial session for rating scientific papers (not included in this review) was performed prior to assessing the quality of the included papers.

After scoring the selected articles, the results were compared and differences were discussed in a consensus meeting. In the case of disagreement, the article was screened a second time and the point of difference was discussed. Both assessors could argue and convince the other to obtain a consensus. When consensus could not be reached, a third researcher (ELL) was recruited to resolve discrepancy.

Data extraction

Besides evaluating the overall quality, information was extracted for each included study about: (I) study characteristics (subjects, outcome measures, results regarding CS and limitations of the study); (II) study purpose (etiology, treatment, diagnosis), and (III) study design (clinical trial, case-control, cross-sectional). If the studies were focused on patients with SIS, the criteria used for diagnosis were retrieved. Finally, the results were analyzed and the existing evidence regarding CS in SIS was summarized.

Results

Study selection

The selection process of the articles is represented in Figure 1. The initial search resulted in 1902 hits. After removal of duplicates, 755 articles remained. Two additional references were retrieved from the reference lists of selected papers. Titles, abstracts and full text papers, if necessary, were then screened for inclusion criteria fulfillment. After screening, 744 studies were excluded and 10 articles were initially eligible for methodological quality assessment. None of these 10 studies was excluded due to low methodological quality / high risk of bias, because the PEDro scale had to be adjusted to account for the type of study, making the total score difficult to interpret. Ten articles were thus finally retrieved for quality assessment and data extraction.

Study characteristics

Of ten selected studies, most were categorized as case-control (n=7). The other three were cross-sectional studies without control group. Seven articles were classified as etiological studies, one as mixed etiology-treatment and the remaining two were

considered diagnostic studies. Four studies were performed specifically on subjects with SIS while the other six included subjects with unilateral shoulder pain of different etiologies, in particular with rotator cuff tendinopathy, adhesive capsulitis or labral lesion. Of the four studies which studied CS in patients with SIS [8, 14, 18, 36], two [8,36] specified the criteria used for reaching a diagnosis of SIS (Supplementary Table S3).

Risk of bias of individual studies

Initially, there was a 94,5% agreement (104 of 110 items) between the two assessors regarding the risk of bias score of the selected articles. After a second review, the researchers reached consensus in all but three items. A third author was recruited to resolve the discrepancy. The results of the risk of bias assessment are presented in Supplementary Table S2.

Overall, the methodological quality of the studies was good. Only two studies [18,37] did not obtain a score of at least 50% on quality assessment. There were three studies [8,16,38] which reached the maximal scoring (5/5) and consequently had the lowest risk of bias. All the ten studies which were retrieved for methodological assessment were included in this review, and the characteristics and findings of these studies are discussed below.

Evidence for Central Sensitization

The objective of this review was to summarize the current evidence regarding CS in people with unilateral shoulder pain of different etiologies, including those diagnosed with SIS. In the following section, the results of this review will be structured

according to the different aspects of CS which were identified. If study findings were restricted to patients diagnosed with SIS solely, it will be specified. The term "unilateral shoulder pain" will be used to refer to non-neuropathic shoulder pain of different etiologies including rotator cuff pathology, adhesive capsulitis or labral lesion.

Clinical manifestations of CS

Gwilym et al. [14] evaluated QST to detect thresholds for mechanical stimuli (sharp and blunt punctuate stimuli) and heat pain, in a sample of 17 patients with chronic SIS waiting for arthroscopic subacromial decompression and 17 pain-free controls. In addition, referred symptoms were recorded. Patients with chronic SIS, compared to asymptomatic subjects, experienced referred pain radiating down the arm and had significant hyperalgesia to punctuate stimulus of the skin. These findings were interpreted as peripheral manifestations of augmented central pain processing (CS). Interestingly, the presence of either hyperalgesia or referred pain before surgery resulted in a significantly worse outcome 3 months after surgical decompression.

Hidalgo-Lozano et al. [8] explored the presence of myofascial trigger points (MTrPs) in 6 different muscles of the shoulder region in 12 patients with chronic SIS and 10 matched controls. Moreover, they determined if the MTrPs were active or latent in the affected side of patients with SIS and the dominant side in the matched control group. Pressure pain thresholds (PPTs) were assessed at these 6 locations of the shoulder region and at one remote site (tibialis anterior). Subjects with SIS showed a greater number of active and latent MTrPs and significant lower PPTs in all muscles (including tibialis anterior), when compared to matched controls. The presence of widespread pressure hypersensitivity, as observed in their sample of chronic SIS patients, was interpreted as reflective of CS [8].

Two studies gave data regarding prevalence of CS in patients with chronic SIS. Gwilym et al. [14] found that 65% of their patients waiting for subacromial decompression presented features of augmented central pain processing in the form of extended referred pain areas radiating down the arm, significant hyperalgesia to punctuate stimulus of the skin and lower mechanical pain threshold in areas distant of the injured tissue. Hidalgo-Lozano et al. [8] reported a prevalence of more than 90% of CS in their sample of chronic SIS patients. CS was inferred from presence of widespread hyperalgesia and lower PPTs in subjects with chronic SIS as compared to matched controls.

Quantitative Sensory Testing (QST)

All the studies included in this review performed QST as a part of their outcomes measures. Different modalities of QST were used for assessing sensory and pain perception, with the mechanical stimulus being the most common form of external stimulation employed (6/10 studies) [8, 18, 36, 38-40]. Most of the studies performed QST at local (i.e. on or in close proximity to the shoulder) and distant sites (i.e. remote from the affected joint) in order to evaluate peripheral and central sensitization, respectively.

Four studies [8,14,18,40] demonstrated the presence of not only local but also widespread hyperalgesia in patients with unilateral shoulder pain [40] including those with SIS [8,14,18], when compared to controls. Moreover, a higher degree of widespread sensitization was associated to higher pain perception in subjects with unilateral shoulder pain including SIS [8,14, 16,41] and to poor prognosis after surgery intervention in SIS [14].

Descending modulation of pain has been evaluated through the conditioned pain modulation (CPM) paradigm, which assesses the activation of the descending endogenous analgesia system [42,43]. One cohort study studied CPM in subjects with unilateral shoulder pain and healthy controls before and following shoulder surgery [16]. At baseline, CPM did not differ between patients and controls, meaning that both groups had the same absolute baseline capacity for endogenous pain inhibition. In addition, in the unilateral shoulder pain group, CPM remained unchanged after surgery as compared to the pre-surgical assessment. In another study by the same group [41], CPM stability within and between sessions was investigated in subjects with unilateral shoulder pain and it was found that fluctuation of pain intensity did not significantly influence CPM stability.

Suprathreshold Heat Pain Response (SHPR) is a perceptual manifestation of enhanced central excitability, which it is used as a measure of enhanced descending facilitation of pain [16]. Four studies [16, 38, 40, 41] used SHPR within experimental pain sensitivity testing. The 5^{th} pain rating in a series of suprathreshold heat pain stimuli was the QST measure which best predicted shoulder pain intensity in subjects with unilateral shoulder pain, even after psychological factors were considered [38]. One study used SHPR only as the test stimulus for assessing CPM [41]. Coronado et al. [40] found bilateral sensitivity for SHPR in subjects with unilateral shoulder pain as compared to pain-free controls, which was interpreted as suggestive of CS. The severity of central hyperexcitability measured with SHPR was elevated in patients with unilateral shoulder pain and decreased after surgery to values comparable to healthy subjects at baseline [16].

Psychosocial influences

Elevated levels of psychosocial distress, including depression, hypervigilance, catastrophizing, and fear avoidance, have been associated with many chronic musculoskeletal pain disorders. In fact, there is evidence suggesting an association between CS and maladaptive behaviors /thoughts [44-47], often referred to as cognitive-emotional sensitization [46,48]. Only two studies in this review considered psychosocial issues related to unilateral shoulder pain [37, 38].

The influence of pain-related fear and pain catastrophizing on clinical pain intensity and experimental pain sensitivity using a cold pressor task was evaluated by George et al. [37]. They found that pain-related fear contributed to the variance in experimental pain sensitivity, while pain catastrophizing was the only psychological variable influencing clinical pain intensity. Based on those results, the authors recommended consideration of fear-avoidance models when analyzing the pain experience of subjects with unilateral shoulder pain.

The influence of psychological factors (i.e. pain catastrophizing, anxiety, and depression) on ability of QST (using heat and pressure stimuli) to predict clinical pain intensity was examined [38]. SHPR was found to account for a significant amount of variance in clinical pain intensity, even after psychological factors were considered. Subjects with unilateral shoulder pain and elevated pain ratings in QST (suprathreshold heat pain stimuli), pain catastrophizing and depression had higher levels of clinical pain intensity [38].

Supplementary Table S4 summarizes current evidence regarding CS in unilateral shoulder pain including SIS.

Evidence rejecting Central Sensitization in shoulder pain

Two studies retrieved in this review didn't found any evidence regarding the presence of CS in subjects with unilateral shoulder pain [39] or SIS [36]. Alburquerque et al. [36] bilaterally evaluated of the presence of MTrPs over several shoulder muscles and PPTs, including a remote site (tibialis anterior). They found data supporting a role for peripheral sensitization, but refuting the presence of central alterations [36]. Coronado et al. [39] found only peripheral pain processes implicated in patients with unilateral shoulder pain, as reflected by higher experimental pain sensitivity to pressure (i.e. lower PPTs) but not thermal stimuli in the involved side compared to the uninvolved side. In light of their results, the authors concluded that pressure stimuli, such as palpation and mechanical stress testing, can be used to elicit side-to-side differences but not to make determinations about the existence of CS.

Discussion

The aim of this paper was to review and evaluate the existing scientific literature regarding the role of CS in unilateral shoulder pain of different etiologies including those with SIS. Different assessment methodologies were utilized for evaluating the phenomenon of CS, aiming to understand the different changes in pain sensitivity observed in this population. Eight out of the ten papers which were considered in this review seem to support an emerging key role for CS in unilateral shoulder pain including those with SIS. This was confirmed through means of different subjective (e.g. enlarged radiation of pain) and objective parameters (e.g. widespread hyperalgesia). All these findings are considered clinical manifestations of CS [49]. Furthermore, similar findings have been previously demonstrated in other chronic pain

conditions such as whiplash [50] or chronic low back pain [51], suggesting these conditions arise by the same altered mechanism of central pain processing.

CS manifests itself at different degrees over a continuum from none at all to severe. Although prevalent in chronic pain, generalized central hypersensitivity is not present in every patient [52]. For instance, in some populations (e.g. fibromyalgia), CS may be the characteristic feature of the disorder. In others, such in shoulder pain, not all patients have CS, but only a sub-group of them. Although the presence of peripheral sensitization in subjects with unilateral shoulder pain including those with SIS is irrefutable, as was reported by several studies included in this review [8, 18, 36, 39, 40], our review revealed a sub-group of subjects with CS [between 65%-90% of (SIS) pain] [8,14]. However, these prevalence numbers should be interpreted with caution because they are derived from only two studies that used different experimental pain sensitivity protocols. Larger longitudinal studies are needed to provide compelling evidence of the prevalence of CS in subjects with shoulder pain. Nevertheless, the present review supports a role of CS in at least some patients with unilateral shoulder pain, implying that some shoulder pain patients have altered central pain mechanisms contributing (or even dominating) the patient's clinical picture [53]. Interestingly, some of the major classification criteria recently proposed for the classification of CS pain (i.e. presence of diffuse pain distribution and hyperalgesia) [53], were found in this review to be characteristic of this subgroup of patients.

The severity of central hyperexcitability measured with SHPR did change in response to shoulder surgery [16]. This is in line with findings from other studies, where surgical removal of the presumed source of nociception (i.e. total knee or hip replacement) did resolve CS [54,55]. Although not included in this systematic review due to later publication date, a study by Valencia et al [56] found that change in QST-

scores (i.e. difference between pre- and post-surgical assessments in SHPR), but not baseline measures of CS, were predictive of surgical outcome in their sample of SIS patients.

Interventions specifically addressing descending facilitatory (e.g. cognitive-behavioral therapy), or descending inhibitory mechanisms (e.g. exercise therapy) in patients with unilateral shoulder pain including SIS were not identified in this review. Future research should examine the effect of treatment modalities and their influence on outcome measures related to CS in this population. Results from this systematic review should increase clinicians' awareness that CS is an important feature of chronic shoulder pain, and thus that treatments aiming at decreasing the hyperexcitability of the central nervous system in this population [57] are warranted.

Supraspinal descending facilitatory influences are able to modulate central hypersensibility and influence the results of QST [58]. Only two studies [37,38] assessed the impact psychosocial factors could have on psychophysical measures of CS in unilateral shoulder pain. Psychosocial factors were found to contribute to psychophysical measures of CS, suggesting that cognitive-emotional factors contribute to CS in unilateral shoulder pain. Still, the small number of studies investigating these factors, and the cross-sectional nature of the studies preclude drawing firm conclusions. Further experimental and prospective studies are required in order to examine the precise influence of psychological factors on the processing of sensory input in patients with unilateral shoulder pain including those diagnosed with SIS.

To date there is not a gold standard for diagnosis of CS [9]. Different clinical and laboratory methods are employed for detecting potential involvement of CS in musculoskeletal pain conditions (i.e. QST, brain imaging techniques), with no more superior or reliable method than others. All of them assessed the same basic biological

concept (CS), but in its different manifestations related to the different aspects of sensitization [15]. For instance, widespread hyperalgesia, which is a manifestation of CS, can be assessed quantitatively in a standardized way using sensory tests, such as pressure algometry. This review did not retrieve any study evaluating induced referred muscle pain in the context of shoulder pain for evaluating generalized hyperalgesia (CS), as previously done for whiplash [59] or osteoarthritis [60]. The majority of the studies of the current review assessed the presence of CS in laboratory conditions, using costly and inaccessible equipment for most clinicians. Further investigation regarding the assessment of CS in shoulder pain is required in order to provide new assessment methodologies for CS, more accessible and less costly for the clinicians. In this view, the recently proposed clinical classification criteria for CS pain [53] are worthwhile investigating in patients with chronic shoulder pain.

Based on methodological issues raised in this review, future studies should use a sufficient and justified sample size. Indeed, some studies included in this review [8,36] used small sample size. A thorough description of the blinding procedure of measurement is suggested in order to increase the validity of case-control studies. Absence of a (healthy) control group in some studies [37-39] did not allow comparing experimental pain sensitivity between groups to determine if subjects with shoulder pain were more or less sensitive to pain. Finally, many studies were unable to confirm or refute the presence of CS due to insufficient follow-up period. Therefore, future studies should include a longer follow-up period in order to detect the central alterations in this population at long term. In addition, all studies were cross-sectional (case-control) in nature. Hence, experimental studies examining cause-and-effect relationships are essentially lacking. Such studies are required to provide definite proof of the clinical

importance of CS in patients with chronic SIS, and to study potential treatment options for decreasing CS in these patients.

When making conclusions from this systematic literature review it should be noted that only ten articles fulfilled the inclusion criteria and were therefore included. In addition, the modification of the PEDro scale to accommodate those questions pertaining specifically to the experimental designs of the studies should be considered a limitation as well. The methodological quality assessment of the included articles showed huge variations in the scores, which indicates the need of further research on this topic. The majority of the studies with high scores on quality assessment supported a role for CS in unilateral shoulder pain including SIS, although two of them [36,39] failed to provide evidence for CS. The heterogeneous nature of the samples studied may have accounted for these discrepancies. For instance, criteria for defining SIS differed across studies and the term unilateral shoulder pain contained multiple pathologies, including patients with rotator cuff pathology, adhesive capsulitis, and labral lesion (see Supplementary Table 3).

Other limitations need to be also recognized in this review. First, even though the screening databases and study selection was carried out by two independent assessors, some relevant studies may have been missed. However, the fact that the risk of bias of the selected articles was examined by two independents researchers increases the internal validity of the review. In addition, some studies included in this review did not consider confounding factors like analgesic usage, race or menstrual cycle, which may have affected their results. Some of these factors (i.e. race) [61,62] but not others (i.e. menstrual cycle) [63], are known to be significantly associated with pain perception. Finally, the results of this review are not generalizable to all clinical samples but limited to those specific patient population examined with unilateral shoulder pain including

SIS. Hence, this must be taken into account when extrapolating the results of this review to other subjects with different shoulder pathologies.

In conclusion, the majority of the literature reviewed suggested that the CNS becomes hypersensitive in a subgroup of patients with unilateral shoulder pain including patients diagnosed with SIS, and the phenomenon of CS may play a role in the frequent pain complaints reported by these patients. However, the implications of this involvement are just starting to become clear and will be an active topic of further research. More studies with low risk of bias are necessary for providing definite proof of the clinical importance of CS.

There are no conflicts of interest or financial sources to report.

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