The Role of Quantitative Sensory Testing in the Evaluation of Musculoskeletal Pain Conditions

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Abstract Quantitative sensory testing (QST) is a noninvasive method of assessing sensory and pain perception that has been used in the past 30 years primarily for analysis of cutaneous and mucosal perception. In recent years, several published studies have demonstrated that QST may be useful in the analysis of painful musculoskeletal disorders as well. Based on the results of these studies, it can be postulated that QST may be useful in the analysis of the pathogenesis, classification, and differential diagnosis of musculoskeletal disorders. However, due to the diverse ethiopathogenetic basis of these disorders, a broad range of QST test batteries may be necessary to analyze the various musculoskeletal disease entities. This review analyzes published studies on this subject and summarizes current information on altered sensory and pain perception available for some of the most common musculoskeletal disorders. At present, QST remains primarily a research tool but may be useful in differential diagnosis in indicating the presence of central sensitization and for clinical monitoring of disease progression or treatment response.

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Introduction

Quantitative sensory testing (QST) is a term used to describe different forms of psychophysical testing of skin, mucosa, or muscle tissue that assess sensory and pain perception pathways. Various forms of QST test batteries have been introduced that encompass various methods of sensory and pain detection threshold determination, as well as suprathreshold and pain tolerance threshold determination under different testing paradigms [1•, 2]. They typically include warm and cold perception threshold testing, heat pain, and cold pain detection threshold testing using a thermotesting device such as TSA-II (Medoc Ltd., Ramat Yishai, Israel), CASE IV (WR Medical Electronics Co., Stillwater, MN) or MSA Thermotest (Somedic, Mörby, Sweden); mechanical detection threshold determination using von Frey filaments and a pressure algometer; vibration detection threshold determination using a tuning fork or any of the several commercially available vibration threshold testers; allodynia testing using a cotton swab or paintbrush; and dynamic wind-up testing using repeated skin stimulation with a predefined force and tip size. Several additional invasive tests for the quantification of muscular pain perception using electrical stimulation or intramuscular injection of hypertonic saline also have been described [3•]. This testing is rather expensive and time consuming but provides comprehensive information on the state of peripheral sensory and pain perception as well as central sensitization.

To exclude the influence of the state of peripheral nociceptors and solely test neuronal transduction of peripheral sensory input, its processing, and its perception in the spinal cord and central nervous system, one can test the neurophysiologic response to peripheral electrical stimulation of the skin using a peripheral nerve stimulator routinely used in regional anesthesia or commercially available experimental devices (Neurometer; Neurotron, Baltimore, MD). Similar testing has been applied successfully to test muscle tissue sensitivity to electrical stimulation [4]. Specific testing of pain fibers (A-δ and C fibers) is possible using laser-evoked potentials by means of inducing heat pain without actual skin contact [5]. To test a mechanism of endogenous analgesia, also known as *diffuse noxious inhibitory control* (DNIC), it is possible to test local or referred pain perception while providing a conditioning stimulus at the same time, based on the principle of pain inhibiting pain [6•]. Although many variations of this test have been described, the most commonly used are the induction of DNIC by immersion in ice water (so-called cold pressor test), or hot water on a different/distant body part than the one on which the pain perception testing is being performed.

All these different methods of QST can be used to do the following:

1. Study the anatomic and physiologic basis of normal and pathological sensory and pain perception
2. Discern different pain syndromes clinically presenting with similar symptomatic paradigms
3. Allow for a qualitative and semiquantitative assessment of those illnesses that show poor correlation of patients' symptoms and signs with respective pathological changes, or have no obvious changes
4. Evaluate patients' response to pharmacologic or non-pharmacologic therapeutic approaches under experimental and clinical conditions.

QST is considered to be semi-objective because it is dependent on the patient's perception and reporting and relies on his or her cooperation and attentiveness during the testing procedure [1•]. As discussed in the review articles by Rolke et al. [2] and Backonja et al. [1•], standardization of the experimental protocol and environmental conditions under which the testing is being performed is essential for obtaining reproducible results comparable to normative data and data from different testing laboratories/centers.

Rationale for Quantitative Sensory Testing in Musculoskeletal Pain Disorders

Musculoskeletal pain is one of the most common reasons for seeking physicians' help. The term encompasses a wide range of disease states, ranging from well-defined illnesses such as osteoarthritis, rheumatoid arthritis (RA), and gout to more unspecific regional and generalized pain syndromes such as epicondylalgia, fibromyalgia, and finally pain related to the spine such as neck and low back pain. The pathophysiology of many painful conditions is unspecific and/or unclear, whereas different etiologic/pathogenetic mechanisms causing pathological changes in muscles, bones, joints, and ligaments have been identified in great detail in others. However, in most cases, the exact etiologic/pathogenetic mechanism for a given pain problem is seldom obvious or known. This broad etiologic basis for pain development in musculoskeletal disorders is further complicated by the pathophysiologic relevance of various psychological and social factors, as well as the potential for central sensitization of sensory and nociceptive pathways, which may lead to further increases in the perceived intensity and distribution of pain. Central sensitization represents an augmentation of pain signaling in neurons and neuronal circuits in pathways related to nociception. It is caused by increases in membrane excitability and synaptic efficacy; loss of neuronal inhibition, including descending pain inhibition; and potentially by a dysfunction in the top-down regulation within the central nervous system. Objective findings for abnormal central pain processing range from muscle hyperalgesia to generalized and polymodal hyperalgesia, as well as referred pain. These features in turn share many common characteristics with neuropathic pain, all of which can be detected using QST.

For that reason, various methods of QST were applied in recent years to investigate the pathophysiologic mechanisms of musculoskeletal pain, primarily using experimental muscle pain paradigms [7]. However, many studies also have been conducted and published in which QST has been used to analyze pain pathways and mechanisms involved in musculoskeletal disease states in humans [3•]. For some of these conditions, such as fibromyalgia and myofascial pain, certain tests (eg, pressure algometry of tender or trigger points) may contribute to the illness classification and/or diagnosis [8]. In other diseases, the testing has been used primarily to try to elucidate potential underlying pathogenetic mechanisms, as in the case of low back pain, primary and secondary restless legs syndrome associated with small-fiber neuropathy [9•, 10], or temporomandibular joint pain [11]. It is noteworthy that such testing can be performed not only locally at the site of musculoskeletal pain but also at the site of referred pain. However, a comprehensive analysis of peripheral sensory perception and nociception in patients with various musculoskeletal disorders, such as the one performed for neuropathic pain disorders in Germany [2], has not been undertaken thus far.

Quantitative Sensory Testing Findings in Musculoskeletal Disorders

Osteoarthritis

Osteoarthritic pain has been classically attributed to joint damage. This simplistic view has been questioned in view of poor correlations between objective markers and symptomatology in this condition [12]. Findings from QST studies in patients with osteoarthritis also support an additional role for abnormal central pain and sensory processing in the maintenance and development of chronic pain in osteoarthritis.

Deficits in proprioception have been shown not only in the osteoarthritic joint(s) but also in distal body areas [13]. Furthermore, several studies reported lower and upper extremity deficits in vibration perception in individuals with knee or hip osteoarthritis [14, 15]. This suggests an extensive effect of a local ostheoarthritic process on the sensory system. Experimental animal studies demonstrated increased expression of the neuromodulatory peptide substance P in peripheral tissue affected by osteoarthritis and an increased expression of calcitonin gene-related peptide in the dorsal root ganglia in a rat model of chronic knee inflammation, which may suggest increased susceptibility to central sensitization of neuronal pathways.

Further QST studies provide additional evidence for altered pain processing in osteoarthritic patients. As early as 1981, painful electrical stimulation in patients with osteoarthritis of the knee indicated decreased pain thresholds on the affected side [16]. An intramuscular injection of hypertonic saline into the anterior tibialis muscle demonstrated increased sensitivity to painful stimulation in patients with osteoarthritis of the lower extremity as compared with healthy controls. In a recent study, patients with osteoarthritis were found to have significantly lower perception threshold for punctate stimuli and hyperalgesia to noxious punctate stimuli in areas of referred pain [17]. This finding correlates well with increased brainstem activity induced by stimulation of areas of referred pain, as demonstrated by using functional brain imaging in patients with osteoarthritis, thus further supporting the role of central sensitization in osteoarthritis. On the other hand, pressure pain thresholds measured with pressure algometry at various body areas independent from the osteoarthritic site were statistically significantly higher in patients with osteoarthritis compared with healthy individuals [18]. Furthermore, patients with osteoarthritis demonstrated a lack of analgesic effects of DNIC on pressure-induced pain [19], which normalized after successful hip replacement (i.e., the cessation of ongoing nociceptive input). These complex and somewhat contradictory results suggest that different underlying etiopathogenetic mechanisms may contribute to symptom expression in a common clinical syndrome such as osteoarthritis-related pain. Moreover, they emphasize the need for further systematic investigation of the peripheral and central sensory and nociceptive processing in chronic pain conditions.

Rheumatoid Arthritis

A mild symmetric sensory or sensorimotor axonal polyneuropathy has been detected in RA patients, mostly expressing itself as a subclinical entity associated with axonal pathology [20]. Vibration perception was altered in one third of the patients, suggesting involvement of A-β fibers, but the condition of smaller fibers (C fibers) was not analyzed in this study. In another study of patients with RA, it was determined that pressure pain thresholds in nonaffected body parts were significantly lower than they were in healthy individuals, suggesting that the function of A-δ fibers might also be negatively affected by RA [18]. An admittedly small study on RA patients carried out by Lanzillo et al. [21] in 1998 ($n=28$) showed a subclinical peripheral nerve dysfunction. A total of 65% of patients exhibited electrophysiologic findings consistent with sensorimotor neuropathy. In addition, there was a moderate loss of myelinated fibers in 75% of nerve biopsy samples, and all biopsied patients showed an increased number of endoneural and perineural vessels and some signs of axonal degeneration [21]. Furthermore, capsaicin-induced axonal reflex vasodilatation in patients with RA was significantly greater over the affected wrists, but not the forearms, compared with age-matched healthy controls [22]. This phenomenon was associated with a slight increase in pain perception measured on a visual analogue scale in RA patients. One reason for the development of this polyneuropathy could be a disease-induced dysfunction of the hypothalamic-hypophyseal axis and its influence on the balance between inflammation-stimulating sensory nerve endings and inflammation-suppressing symphathetic nerve endings. The evaluation of the somatosensory dysfunction in RA is further complicated by its potential to develop a drug-induced secondary peripheral neuropathy. An example of this confounding component is a sensorimotor dysfunction reported in RA patients treated with etanercept [23].

Assessment of pain sensitivity in RA should also take into consideration its frequent comorbidity with conditions such as fibromyalgia syndrome, which can lead to increased clinical and spontaneous pain and can result in a generalized hyperalgesia [24]. In contrast, an imaging study using positron emission tomography showed a dampened brain response to painful heat stimulation in patients with RA alone compared with healthy controls and with patients with fibromyalgia syndrome–like pain, with RA patients being the least sensitive to nociceptive stimuli [25].

Ankylosing Spondylitis

Response to painful stimuli was analyzed in two studies of patients with ankylosing spondylitis, one of which found an increased threshold to pressure pain measured with a pressure algometer compared with healthy controls [18]. The other found no difference in pain sensitivity to blunt pressure in comparison with healthy controls [26]. Although response to additional sensory or painful stimuli was not investigated, these limited results suggest that in ankylosing spondylitis, neuronal pathways involved in pressure pain perception are neither peripherally nor centrally sensitized.

Fibromyalgia

Fibromyalgia has been classified by chronic widespread pain and at least 11 of 18 painful tender points on palpation, although a new classification based on symptom load was suggested recently [27]. Using QST paradigms, fibromyalgia patients also show an increased pain response to painful mechanical stimuli [28, 29]. Decreased heat pain thresholds of fibromyalgia patients compared with controls also have been shown by multiple groups [30, 31], as have reduced cold pain thresholds [31] and reduced tolerance to the cold pressor test and the tourniquet ischemia test [8]. Sensitivity to innocuous warmth and cold stimuli and nonpainful electrical stimulation seems unaffected [32]. This pattern of hyper-responsiveness to sensory stimuli has also been shown for auditory stimulation.

Importantly, fibromyalgia-associated hyperalgesia is not limited to the so-called tender points and mechanical stimulation but is widespread and present for multiple sensory domains, as demonstrated independently by Staud et al. [33] and Carli et al. [8]. They and other authors suggested central sensitization as a contributing pathophysiologic factor [30, 32]. Accordingly, wind-up as an experimental correlate for central sensitization can be evoked in controls and in patients with fibromyalgia syndrome, but clear differences between controls and patients can be observed. The magnitude of the sensory response to the first stimulus within a series is greater in fibromyalgia, as is the amount of temporal summation within a series [34].

Hyperalgesia in fibromyalgia patients also has been shown to be independent of the stimulation paradigm (ascending stimulation vs random stimulation) [30], and thresholds to elicit the potentially more "objective" nociceptive flexion reflex in patients with fibromyalgia are decreased. These findings indicate that one can assume that hyperalgesia and thus central sensitization in fibromyalgia do not primarily result from psychological factors but rather from a hyperexcitable nociceptive environment, although

there is also some evidence for the modulatory influence of psychological factors such as catastrophizing [35].

Several mechanisms have been implicated in the development of this phenomenon. An active involvement of excitatory amino acid neurotransmitter systems in this hyperexcitability is suggested by the finding that ketamine, an N-methyl-D-aspartate receptor antagonist, reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients [36]. The relevance of ongoing peripheral input to maintain generalized sensitization was recently shown by Staud et al. [37••]. Efferent DNIC, also referred to as *heterotopic noxious conditioning stimulation*, is also suppressed in fibromyalgia patients. Such diminished DNIC response has been documented under various DNIC-inducing paradigms, such as ice and hot water noxious stimulation and electrical noxious stimulation, and is further supported by recent functional imaging findings [38, 39].

Epicondylalgia

Fernandez-Carnero et al. [40] have analyzed local and general skin sensitivity to pressure stimuli in patients with clinical or experimental lateral epicondylalgia. Patients with epicondylalgia showed significantly lower pressure pain thresholds and larger referred pain areas upon stimulation of active trigger points in the forearm extensor muscles when compared with controls. Furthermore, not only do active trigger points with a typical referred pain pattern show an increased sensitivity to pressure, but so-called latent trigger points on both the ipsilateral and contralateral side (which are not painful per se but may cause pathological muscle dysfunction upon activation) also demonstrate increased sensitivity to painful pressure stimuli. Interestingly, this hyperalgesia was confined to pressure stimuli, with normal reactions to vibration or thermal stimuli [41]. However, upon painful stimulation (weightlifting), pain intensity in the local and referred pain areas was significantly increased [42]. Repeated muscle contractions resulted in altered somatosensory functions in the affected arm and unaffected arm. Tactile perception thresholds, which were initially not altered in the areas of primary and referred pain, increased significantly following pain provocation in the referred pain area only and normalized following injection of a local anesthetic, indicating that the sensitivity to light touch was altered by nociceptive input from the affected arm.

Temporomandibular Disorders

Compared with controls, patients with temporomandibular disorders (TMDs) have significantly lower thermal pain threshold, ischemic pain threshold, and ischemic pain

tolerance values, not only in the jaw but also in distal extremities [43]. Thermal pain tolerance also tends to be lower. Furthermore, TMD patients show increased thermal C-fiber–mediated temporal summation compared with pain-free individuals and report higher pain levels compared with controls in response to sustained noxious heat pulses applied to the face or the forearm. Interestingly, individuals with TMDs and those who are pain free are equally able to distinguish and detect small increments of heat applied to existing painful thermal stimulation [44]. A general hyperalgesia in female patients with TMDs was also confirmed by another independent group [45]. Interestingly, a recent study using the German standardized QST protocol found two different QST profile patterns among TMD patients that correlated with their number of tender points, suggesting an overlap in pathophysiology with fibromyalgia [46•].

Chronic Neck Pain

Analysis of the sensory and deep muscle perception in chronic neck pain revealed an interesting finding. Pressure pain threshold levels were significantly decreased bilaterally over the masseter, temporalis, and upper trapezius muscles, and in the C5-C6 zygapophyseal joints in patients with mechanical chronic neck pain compared with controls [47]. However, the testing performed over the anterior tibialis muscle showed no increased sensitivity to nonpainful or painful stimuli. This finding suggests a spinal level rather than a supraspinal sensitization in chronic neck pain.

Low Back Pain

The term *low back pain* encompasses an array of etiologic entities that all symptomatically converge as pain in the lower dorsal segment of the trunk with or without radicular or pseudoradicular radiation to the lower extremity. This pain can originate from compressed dorsal nerve roots as a consequence of prolapsed intervertebral disc material and/or degenerative narrowing of the intervertebral foramina but may have predominantly muscular or joint origin and remain clinically unspecific in most patients. Poor correlation between radiologic imaging and clinical symptoms, as well as the lack of specificity of neurophysiologic testing further preclude a definitive etiopathogenetic diagnosis in many cases.

Thus, clinically, chronic low back pain (CLBP) shows similarities to conditions such as fibromyalgia (only localized and not generalized) and has common characteristics with neuropathic pain in cases of established radicular pain. A clear distinction between a (predominantly) neuropathic (radicular) or referred (nondermato-

mal) pain radiation in the leg or the identification of markers for generalized central sensitization using QST would be of great value in the classification of this type of pain.

Several QST studies have addressed this interesting question. In a study published in 1999, Clauw et al. [48] assessed whether pressure pain sensitivity at thumbnail and various psychological and imaging factors correlated well with clinical pain and functional status in CLBP. The pressure pain sensitivity, as a measure of local tenderness to blunt stimuli, was found to be a significant predictor of a clinically relevant pain magnitude. In an imaging study using functional MRI, a small and selected sample of patients with nonspecific CLBP showed similar overall tenderness as patients with fibromyalgia, and a similarly augmented response in brain activity to painful stimulation as patients with fibromyalgia when compared with healthy controls [49]. Another study demonstrated a correlation between increasing heat pain sensitivity, female sex, and increased psychological burden in a cohort of tertiary care patients with CLBP (unfortunately without a control group) [50]. Taken together, one could conclude that in at least a subgroup of patients with CLBP, central sensitization may be a relevant pathophysiologic factor.

In a pilot trial of QST of patients with CLBP conducted by Freynhagen et al. [9•], the authors reported a distinction in vibration detection thresholds among the "radicular" and "nonradicular" patients. However, they also reported a considerable rate of sensory loss in the "nonradicular" group (>40%). Furthermore, the overall number of participants was again small. These findings led to a constructive discussion focusing on a putative initial distinction and later confluence of mechanogenic, neuropathic, and psychogenic learned pain, further influenced by mechanisms of central sensitization, as the probable main components of the underlying pathophysiologic mechanisms leading to a clinically relevant lower back pain syndrome.

Conclusions

Most of the studies of invasive or noninvasive sensory testing of the skin or deep tissues in patients with musculoskeletal disorders have been performed primarily in an attempt to analyze the pathogenesis of the underlying illness. This is also the reason for the diverse methodology applied in these studies, thus making comparison of results difficult. Whether an approach to QST similar to that of the German Network on Neuropathic Pain also makes sense for musculoskeletal pain remains an open question and challenge. One could argue that this approach to neuropathic pain already yielded its first success in the case of

small-fiber neuropathy, for which classical neurophysiologic testing cannot provide a final diagnosis. The best example is a recent publication of differential warmth and cold perception in patients with secondary restless legs syndrome associated with small-fiber neuropathy as compared with primary restless legs syndrome patients [10], thus making an invasive diagnostic skin biopsy unnecessary. However, this structured approach seems to be only a first step toward development of a mechanism-based algorithm to diagnose and treat neuropathic pain.

In musculoskeletal pain, the current data on QST show central sensitization to be a potential common theme for different clinical conditions. This varies from localized to generalized presentations but may be caused by similar mechanisms. The role of peripheral input and/or peripheral sensitization in the development and maintenance of central sensitization and chronic pain is far from unequivocal, but there is evidence for the role of ongoing (nociceptive) stimulation, at least in some of these conditions.

It is tempting to suggest a standardized approach to QST in musculoskeletal pain that would require a broad agreement on the set of tests and stimulus modalities that would be routinely performed. Such a QST test battery for musculoskeletal disorders should focus on detecting central sensitization of sensory and pain perception in the affected body parts, as well as on the assessment of descending inhibitory antinociceptive pathway activity. In addition, the effects of potential ongoing peripheral sensory and nociceptive stimulation should be assessed. The development of easy-to-use, validated, and simple test paradigms controlling for psychological comorbidity remains another challenge.

Finally, the use of current QST procedures could be clinically very useful as a monitoring tool in patients taking medications that typically and frequently affect the peripheral nervous system, as these neuropathic changes could be detected easily in the early stages of their pathogenetic development using QST testing. Patients with comorbid musculoskeletal conditions may also benefit from QST by shifting the diagnostic and therapeutic focus from local pathology to generalized changes in pain perception in these disease states.

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