DERLEME REVIEW

DOI: 10.5336/jtracom.2022-91401

The Vagus Nerve and the Microbiota May Play a Reciprocal Role in the Chronicity of Pain: Traditional Review

Vagus Siniri ve Mikrobiyota Ağrının Kronikleşmesinde Karşılıklı Rol Oynayabilir: Geleneksel Derleme

Ali Veysel ÖZDEN[a], Gizem ZORLU GÖRGÜLÜGİL[b], Cihan AKSOY[c]

[a]Department of Physiotherapy and Rehabilitation, Bahçeşehir University Faculty of Health Sciences, İstanbul, Türkiye
[b]Clinic of Internal Medicine, Antalya Atatürk State Hospital, Antalya, Türkiye
[c]Private, İstanbul, Türkiye

ABSTRACT Chronic pain is defined by continuous nociceptive hypersensitivity and for more than 3 and/or 6 months duration, it is classified as longstanding pain. Most of the suffered pain is caused by musculoskeletal pathologies. Multiple anomalies in genetic structure, autonomic nervous system dysregulation, dysbiosis, oxidative stress, central and peripheral sensitization, the drawing reduction or inhibition of inhibitory control, altered muscular structure and changes in neurotransmitters, hypothalamic-hypophyseal-adrenal axe hormones, and pain modulation centers may occur in chronic musculoskeletal conditions but chronicity still remains not fully explained. Inadequate function of the vagus nerve may alter the microbiota and may be involved in the pathophysiology of pain with bidirectional interaction. In chronic pain syndromes, patterns of incorrect adaptation to ongoing pain have been developed; subjective pain persists after objective tissue damage or without tissue damage. In the literature, it is stated that dysbiosis can cause the pain to become chronic, but possible problems in the vagus nerve are not mentioned enough. We propose that vagus nerve function irregularity may cause or contribute to the dysbiosis in the gut and eventually may give rise to chronicity of the pain. In this review, we aimed to point out the possible crosstalking between the vagus nerve and microbiota accompanied by vagus nerve dysfunction and dysbiosis in chronic pain syndromes related to the musculoskeletal system.

Keywords: Autonomic nervous system; chronic pain; microbiota; vagus nerve

ÖZET Kronik ağrı, sürekli nosiseptif aşırı duyarlılık ile tanımlanır ve 3 ve/veya 6 aydan uzun süredir devam eden ağrı olarak sınıflandırılır. Yaşanan ağrıların çoğu kas-iskelet sistemi patolojilerinden kaynaklanır. Genetik yapıda çok sayıda anomali, otonom sinir sistemi düzensizliği, disbiyozis, oksidatif stres, merkezi ve periferik duyarlılaşma, inhibitör kontrolün çekilmesi veya inhibisyonu, bozulmuş kas yapısı ve nörotransmitterlerdeki hipotalamik-hipofiz-adrenal aks, hormonlarındaki ve ağrı modülasyon merkezlerindeki değişiklikler kronik kas-iskelet sistemi rahatsızlıklarında ortaya çıkabilir, ancak kronikleşme hâlâ tam olarak açıklanamamıştır. Vagus sinirinin yetersiz işlevi mikrobiyotayı değiştirebilir ve çift yönlü etkileşim ile beraberce ağrının patofizyolojisinde rol oynayabilirler. Kronik ağrı sendromlarında, devamlılık gösteren ağrıya yanlış adaptasyon kalıpları gelişmiştir; subjektif ağrı, objektif doku hasarından sonra veya doku hasarı olmadan devam eder. Literatürde, disbiyozisin ağrının kronikleşmesine neden olabileceği belirtilmektedir, ancak vagus sinirinde olası sorunlardan yeterince bahsedilmemektedir. Vagus siniri, fonksiyonel düzensizliğinin bağırsaktaki disbiyozise neden olabileceğini veya katkıda bulunabileceğini ve nihayetinde ağrının kronikleşmesine yol açabileceğini öne sürüyoruz. Bu derlemede, kas-iskelet sistemi ile ilişkili kronik ağrı sendromlarında vagus siniri disfonksiyonu ve disbiyozisin eşlik ettiği, vagus siniri ve mikrobiyota arasındaki karşılıklı ilişkiye dikkat çekmeyi amaçladık.

Anahtar Kelimeler: Otonom sinir sistemi; kronik ağrı; mikrobiyota; vagus siniri

Humankind struggle with pain for centuries. Regarding the pain, that human beings encountered in the first in utero at 26 weeks, the Hippocrates said "Sedare Dolorem Opis Divinum Artem" (Relieving pain is a divine art).[1] Pain is a kind of feeling that makes patient uncomfortable, varies between individuals, says something is going wrong on body and affects the quality of life seriously. Also its underlying pathology for chronic pain still remains doubtful. International Association for the Study of Pain describes the pain as follow; an unpleasant sensation or emotional experience by accompanying existing or potential tissue damage.[2]

Correspondence: Ali Veysel ÖZDEN
Department of Physiotherapy and Rehabilitation, Bahçeşehir University Faculty of Health Sciences, İstanbul, Türkiye
E-mail: aliveysel.ozden@hes.bau.edu.tr

Peer review under responsibility of Journal of Traditional Medical Complementary Therapies.

Received: 19 May 2022 ***Received in revised form:*** 05 Oct 2022 ***Accepted:*** 24 Oct 2022 ***Available online:*** 28 Oct 2022

There are many publications about the ways by which pain occurs and becomes chronic but exact mechanism has not been fully clarified. The process of the formation and chronicity of pain in these syndromes still remains a mystery. Central sensitization, peripheral sensitization, autonomic nervous system (ANS) dysfunction or dysregulation, hypothalamic-hypophyseal-adrenal axis (HPA) distortion, peripheric nociceptive and cognitive processes, dysbiosis are explained in many papers but not fully reveal mechanism of pain.[3,4] Dysfunction of the neuroendocrine immune network guard of the ANS; vagus nerve, may change microbiota and participate in pain pathophysiology with bidirectional interaction.[5] Well, the pathophysiology that makes the acute pain chronic may be the vagus nerve itself.

In this review, we aimed to point out the possible interactions-crosstalks between chronicity of pain in chronic pain syndromes expecially in musculoskeletal pain disorders and dysbiosis caused by vagus nerve dysfunction.

CHRONIC PAIN AND RELATED MUSCULOSKELETAL DISEASES

Chronic pain is defined by continuous nociceptive hypersensitivity and for more than 3 and/or 6 months duration, it is classified as longstanding pain. In chronic pain syndromes, pain is the most common reason for patients to admit to clinics and real challange to clinicians because of unexplained etiology, little or no response to treatment. Most of the suffered pain is caused by musculoskeletal pathologies. Chronic musculoskeletal pain is a major clinical problem and has a significant socio-economic impact with only a few current effective pain management strategies. Chronic musculoskeletal pain disorders consist of interaction between psychologic, physiologic, biologic, social and genetic factors and these disorders require a multidisciplinary approach of the clinician. The teories about the etiology of pain first started with Decartes and cannot be explained only by biomedical mechanisms.[2] In addition to the musculoskeletal system, you can find the other chronic pain syndromes in different regions of the body in Table 1.

Multiple anomalies in genetic structure, ANS dysregulation, dysbiosis, oxidative stress, central and peripheral sensitization, the drawing reduction or inhibition of inhibitory control, altered muscular structure and changes in neurotransmitters, HPA axis hormones, and pain modulation centers occur in chronic musculoskeletal conditions but chronicity still remains not fully explained.[6] Beyond this biomedical mechanisms patient related factors such as sex, environmental, behavioral, emotional, cognitive are also relevant with chronic pain.[2] It is known that one of the mechanisms of muscoloskeletal pain disorders is due to peripheral and central sensitization.[7] Nociceptive signals from the periphery cause the opening of voltage-gated calcium channels in the nerve terminations in the posterior horn. Calcium entry into the presynaptic nerve end causes neuro-

TABLE 1: Chronic pain related diseases/disorders.

Musculoskeletal	Neurological	Gastrointestinal	Gynecological	Urological	Others
Fibromyalgia	Neuropathic pain, neuralgias	Chronic visceral pain syndrome	Endometriosis	Chronic, recurrent urinary tract infections	Cardiovascular diseases
Myofascial pain syndrome	Nerve entrapment syndromes	Gastroesophageal reflux	Ovulation pain	Chronic pelvic pain syndromes	Peripheral vascular diseases
Temporomandibular disorder	Polyneuropathies	Inflammatory bowel diseases	Adhesions	Chronic Prostatitis	Surgical complications
Osteoarthritis	Migraine, headaches	Irritable bowel syndrome	Pelvic inflammatory disease	Chronic urethral syndrome	Chemotherapy complications
Rheumatoid arthritis	Central pain syndome	Chronic constipation	Adnexal cyst		Radiotherapy complications
Polymyalgia Rheumatica	Causalgia	Chronic Pancreatitis	Chronic endometritis		
Chronic spinal pain		Diverticulitis			

transmitters such as substance P (SP) and glutamate to discharge into the synaptic space. Substance-P binds to neurokinin-1 receptors on the postsynaptic membrane, and glutamate to alpha amino-3-hydroxy-5 methyl-4-isoxazolepropionate (AMPA) and metabotropic glutamate receptors, especially to N-methyl-D aspartic acid. They enable the activation of the pathways at the nerve end. This synaptic interaction is under the influence of gamma-aminobutyric acid-ergic (GABAergic) inhibitory neurons. If the nociceptive signal from the periphery becomes chronic, plastic changes occur, like the appearance of receptors on the postsynaptic membrane. Even if the signal from the periphery ceases due to apoptosis of GABAergic inhibitory neurons, the postsynaptic nerve end continues to send signals perceived as pain in the center.[8] Increased excitation or reduced inhibition of the central nervous system due to central sensitization can cause pain hypersensitivity, temporal summation, tactile allodynia, and secondary hyperalgesia, thereby increasing the perception of pain.[9] Heightened sensitivity resulting from central sensitization produce intolerable discomfort like myalgias, artralgias, headaches etc.[10] Central sensitization manifests as hypersensitivity to various detrimental (eg, pressure and heat) and nondetrimental (eg, touch) stimuli. It is one of the possible mechanisms involved in the transition from acute pain to chronic pain. Sympathetic hyperactivity may be related to central sensitization and cause of diffuse pain, poor sleep, fatigue etc.[11] Central sensitivity syndromes such as fibromyalgia (FM), complex regional pain syndrome, myofascial pain syndrome, migraine, chronic fatigue, low back pain, irritable bowel syndrome, chronic tension type headache, temporomandibular joint disease, restless leg syndrome, multiple chemical sensitivity, primary dysmenorrhea, female urethral syndrome, major depression, panic attacks and post-traumatic stress disorder have no clear etiological factor. HPA axis distortion together with ANS dysfunction may contribute to the process or besides central sensitization, ANS dysfunction may play a pivot role in etiopathogenesis of musculoskeletal pain or in pain survival.[11-13] Chronic stress plays a role in the development of chronic musculoskeletal disorders and sympathetic nervous system (SNS) activity predominance exists. These syndromes can be viewed as an unsuccessful attempt or overreaction of our main complex adaptive system, ANS to stress.[14]

ANS is the main network responsible for maintaining the overall homeostasis and allostasis of the body. The ANS is made up of 2 branches: the sympathetic system, associated with energy mobilization (fight or flight response) and the parasympathetic system, associated with vegetative and restorative functions, (rest and digest). There is one addition in some sources, the *enteric nervous system.* Normally, the activities of these branches are in a dynamic balance. When this turns into a chronic imbalance, for example, under internal and external challenges or stress, the organism becomes vulnerable to this disorder and the predisposing condition it creates.[15] The intensity of ANS function is determined in part by genetics, and a chronic "hyperadrenergic state" is often associated with hypersensitivity to pain, although pain itself can increase sympathetic activity. ANS modulates and integrates afferent and efferent nerve activities related to physiological processes such as pain, fever, and hunger, to provide homeostasis, thanks to its extensions in the central and peripheral nervous system. The role of ANS in pain response can vary according to personality, experience and situation. Visceral and somatic pain doesn't differ in ANS function and may overlap in clinical painful conditions.[16] Gockel and collegues say that autonomic nervous function is associated with disability, not pain in chronic low back pain patients. They found decreased parasympathetic and increased sympathetic activity by heart rate variability (HRV) analysis.[17]

Precise assessment of ANS function and level in clinical practice is difficult. Changes in mental stress, breathing pattern, or even posture, can immediately affect the sympathetic/parasympathetic activity levels. Therefore, this dynamic system cannot be clearly evaluated by 'static' tests such as the levels of circulating neurotransmitters or their urinary catabolites. HRV analysis, tilt table test can be used to detect cardiovascular autonomic function and the sympathetic skin response for sudomotor function but these tests also give clues.[18] The vagus nerve provides the brain-gut connection and communicates with the micro-

biota through the enteric nervous system. As a result of subdiaphragmatic vagotomy, it creates sensitization in afferent nociceptors with the release of catecholamines.[19] Based on these, we think that both dysbiosis and vagus dysfunction may be responsible for the development of chronic pain, and the effect of the vagus nerve may be greater than previously thought. We should consider that an unexplained part of all these chronic pain mechanisms may be the impaired microbiota caused by the sick vagus nerve, and we can resolve the clinician's dilemma in chronic pain with the regulation of the vagus nerve and the ANS. Therefore, dysfunctional condition in vagus nerve should be noticed together with dysbiosis.

FM

FM is a chronic, diffuse muscle tenderness syndrome with central sensitization. Sleep disturbance, fatigue, headache, morning stiffness, irritable bowel syndrome, interstitial cystitis, dyspareunia, and mood disturbance can accompany to FM. Sleep disturbance has been reported in FM with alpha activity entering delta wave sleep, and patients complain of non-restorative, non-regenerative sleep.[20,21] In contrast, Chervin and colleagues found no sleep difference between FM patients and healthy controls but found sympathetic hyperactivity in FM by HRV analysis.[22] Altered neuroendocrine and ANS function also may play a role in etiopathogenesis of FM. Persistent hyperactive SNS activity most apparent at night can be seen.[13] Patients may have excessive amounts of norepinephrine in their body and this may prevent receptors in the brain from being activated when necessary. So, a large increement in the SNS activity can be needed to affect the brain.[23] HPA axis and ANS show hyporeactivity to subsequent stressful situations (because already hyperactivated). This altered neuroendocrine response appears to result from functional changes in central centers of the ANS, such as the hypothalamus. It is unknown whether these neuroendocrine changes are involved in the pathophysiology of FM and contribute to its ongoing symptomatology or whether they are the result of pain and associated symptoms (eg, fatigue, low physical fitness, sleep and mood disorder), or both.[13]

Eisinger says that ANS dysfunction exists in FM but it is not same in all patients.[24] It is a bit controversy because there are also studies saying ANS dysfunction doesn't exist in FM. In one study like this, however, it is found that resting systolic and diastolic blood pressure is significantly higher in the patients with FM as compared to the healthy controls. Patients with FM have higher vascular sympathetic tones.[25] In FM, sympathetic tone elevation may occur in vascular bed not in the heart.[26] It is proposed by Katz et al. and collegues that prominent cause of the FM is muscle hypoperfusion and low-grade ischemia induced by vasomotor dysregulation in separate vascular beds. Chronic sympathetic activity can induce beta adrenergic receptor desensitization and as a result hypoperfusion.[21] Kulshreshtha and Deepak further suggest that HRV changes in FM may not represent increased cardiac sympathetic tone. Normal muscle sympathetic nerve activity and normal autonomic reactivity tests can be seen in FM patients with defective vascular end organ.[25] Exercise intolerance is a common problem in patients with FM. Hypoactive sympatho-adrenal system and the hyporeactive HPA-axis during exercise is seen in FM.[27] This condition may be because of chronic muscle hypoperfusion in FM and/or due to SNS which is already hyperactive, so can not respond suitably to exercise in a normal physiologic manner.

FM is characterized by heightened somatic pain sensitivity and there are deficits in descending pain inhibition. FM patients have hyperalgesic responses to painful stimuli. Thus, sympathetic hyperactivity may be related to pain inhibitory pathways. Functional pain conditions (FM, irritabl bowel syndrome etc.) may present common, but graded, pain processing and autonomic dysfunctions.[28] Increased arryhtmia prevelance is found in FM. This might be as a consequence of decreased parasympathetic and increased sympathetic activity.[29] HRV analysis diagnostic property vary among studies but it can be used to estimate FM severity and/or responses to therapies. Sympathetic hyperactivity, which is correlated with HRV parameters, could be the cause of FM symptoms.[30]

When we look at the treatment in terms of ANS, FM can be considered as a sympathetically main-

tained neuropathic pain syndrome.[18,30] So medically some anticonvulsants (gabapentin, pregabalin) and some antidepressants (amitriptyline, duloxetine, milnacipran) can be used, but it is now recognized that drug treatment alone provides only limited benefit. Studies show that regular exercise, stress reduction interventions such as relaxation and stress management training cause decreasing of the high sympathetic activity and increasing of the low parasympathetic activity.[13,31] Some studies suggest sympatholytic drugs (daily doses of Pindolol, beta adrenergic receptor blocker) can reduce symptoms of muscle pain, muscle stiffness and sleep disorders.[23] 0.1 mg/kg intravenous propranolol treatment diminishes the clinical pain severity by 40% in both FM and temporomandibular disorder (TMD) patients. Patients who show greater adrenergic dysregulation have greater pain decrement after propranolol infusion.[32]

ANS/vagus nerve dysfunction (low parasympathetic and/or high sympathetic) is associated with higher pain intensity in FM or chronic widespread pain but there isn't enough evidence to prove the role of ANS in the development of the disease.[33] Afferent vagal stimulation has a key role on descending serotonergic and noradrenergic neurons to relieve the pain.[34] Vagus nerve stimulation (VNS) is applied to 14 women in a study by Lange G et al. and it was shown that VNS could reduce musculoskeletal pain in FM via effect on nociceptive system and lower the pathophysiological processes.[35] Pain pathways originate from the cortical structures, hypothalamus, brainstem, and modulate sensory input from primary afferent fibers and projection neurons within the dorsal horn of the spinal cord. Serotonin, norepinephrine and endogenous opioids launch from that pathway, which inhibit the release of excitatory neurotransmitters including glutamate. Any disorder in these pathways including vagus nerve could reason persistent ache syndromes. The foremost hassle of these pathways might be approximately vagus nerve dysfunction and dysbiosis which may lead to chronic pain.[36,37] Dysbiosis appears to prevail in FM patients, indicated by using disrupted microbiota metabolites, helping the model that microbiota may additionally modify mind feature thru the gut-mind axis, with the gut being a gateway to generalized ache.[19]

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome (MPS) is a muscle pain syndrome with central sensitization that results from a primary dysfunction in the muscle and is associated with a segmental spread leading to the phenomenon of referred pain.[20] MPS and FM can be considered as distinct syndromes, but there are overlapping points and some findings are similar. Local muscle ischemia and autonomic hyperactivity is also seen in MPS.[38] Patients with chronic neck-shoulder pain (trapezius myalgia) have sedantary life style according to healthy people. Their diminished parasympathetic and elevated sympathetic activity is an important element in maintenance of pain.[39]

In one study Takamoto et al. found that compression of trigger points by means of massage therapy increases parasympathetic activity and induces reduction of fatigue. Parasympathetic activity increment may be one way of the pain relief in trigger point compression.[40] Ge et al. declare sympathetic facilitation in local and referred pain reactions and mechanical sensitization in MPS. Elevated sympathetic efferent activity can enable both mechanical hyperalgesia and allodynia.[41]

Consequently MPS can be thought as a localized form of FM. Possible dysfunction of the ANS (similar to FM) is peripheral, more truely segmental.

TMD

TMD includes persistent pain in the musculature of the jaw, neck, and head and has the highest prevalence of all chronic orofacial pain conditions worldwide, estimated at 10%.[32] TMD has close relationship with adrenergic dysregulation and FM.[42,43] Disease process in masticatory muscles and TMD has similar properties as FM and other chronic musculoskeletal pain disorders have. An increase in SNS output produces general arteriolar vasoconstriction, which increases systemic arterial blood pressure and causes a redistribution of blood flow to organs. In working muscles, adequate blood flow is usually guaranteed, as sympathetic vasoconstriction is antagonized by the potent local vasodilator effect of metabolites released by the contracting muscles. If sympathetic vasoconstriction overbears or inadequate relaxation occurs,

then it leads chronic hypoxia and pain. In addition, sympathetic activation via a direct effect on muscle spindle receptors can potentially affect different aspects of proprioception and motor control, eventually leading to TMD.[44]

People with sleep bruxism have predisposition to TMD. Sleep bruxism is defined as a stereotypical movement disorder characterized by grinding and/or clenching of the teeth during sleep. Increase in the activity of sympathetic-cardiac and motor neuronal networks preceeds sleep bruxism onset.[45-47] The increased sympathetic tone suggests increased stress and may be associated with occlusal disharmonies.[48] Stress may exacerbate bruxism but stress condition may not affect all muscles in the same way. For example, in healthy subjects during the increase in sympathetic outflow caused by mental stress, masseter muscle seems to be more affected than the temporalis muscle.[44] Low dose beta-blocker agents can decrease pain intensity and normalize adrenergic dysregulation in TMD.[32,48,49] Propranolol and prazosin show promise in preventing progression from jaw clenching and teeth grinding to chronic muscle-facial pain.[47]

TMD, like MPS, may be a local or regional form of ANS dysfunction. These pathologies mostly coexist with other diseases, not only seen alone. Holistic or integrative approach seems more appropriate while considering ANS dysfunction and related disorders because they might be members of a disease spectrum.

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is characterized by spontaneous or stimulus-induced pain, motion limitation that is disproportionate to the triggering event and accompanied by a wide variety of autonomic and motor symptoms in highly variable combinations. CRPS I is intended to cover reflex sympathetic dystrophy and similar disorders that occur without any nerve damage, while CRPS II is equivalent to causalgia, i.e. develops after a peripheral nerve injury.[50] In the acute stages the skin is often red and hot; in later chronic stages, the skin becomes bluish and cold.[51] In early CRPS basal sympathetic function decreases rather than an increment.[50] However sympatholytics are beneficial in the acute phase of the condition but not so in chronic cases.[52] These conflicting evidences may be due to central nervous system predominance in the acute phase or etiopathogenetic variability. Another probability is, interventions done after the disease process started may have little effect. In other words, there are many factors (inflammation, psychological state, immobilization, neuropeptides, cytokines, neuropathy, SNS dysfunction, central nervous system changes) at the root of CRPS.

The increased vasoconstriction in patients with “cold” CRPS may actually be due to vascular hypersensitivity to circulating catecholamines rather than a hyperactive SNS. Additionally, hypersensitivity of vascular structures in the affected limb due to the relative low level of initial sympathetic activity may play a role in the etiopathogenesis.[50,53] A group of patients report pain relief after sympathetic blockade but nowadays not advised and thought to have no effect on disease process. Sympathetic innervation of deep somatic tissue; including muscle, bone, tendons, and joints, contributes to the pain together with the cutaneous sympathetic activity. Nevertheless, it is also likely to involve a central pathway of sympathetically induced pain exacerbation in some patients. Increased sympathetic activity might contribute to excitation of nociceptive fibers and thus to the development of pain, correspondingly neurogenic inflammation may have additive effects in augmented vasodilation, high local skin temperature, red skin color and possibly edema.[51,53] Further impaired sensation and non-dermatomal sensory symptoms are mostly centrally mediated and result form brain plasticity.[54]

Shortly, CRPS is a very complicated disease. SNS dysfunction (particularly sympathetic hyperactivity) occurs in CRPS and is strongly associated with disease morbidity but its role in the disease and the question where or when it occurs still waits an answer. Additionally, SNS dysfunction doesn’t seem to go in the same way in all disease duration. However, vagus nerve dysfunction and dysbiosis should also be brought to mind as they might play a role in the onset of the disorder or affect the disease process.

VAGUS NERVE FUNCTION

Vagus nerve, the basic element of the ANS, has great importance in maintaining the homeostasis of the organism. The vagus, the 10th cranial nerve, has widespread projection with myelinated and non myelinated fibersin the whole body. 80% of the vagus nerve consists of afferent fibers which means that carrying information to brain is much more important. It provides a remarkable connection between brain and the body parts like neck, thorax and abdomen.[55] Treatment strategies targeting a shift from sympathetic dominance to equivalance or parasympathetic dominance like yoga, acupuncture, massage therapy, thermal or hydrotherapies, relaxation techniques like breathing exercises or cognitive behavioral therapies prove their potential unlike medical treatments that temporarily change ANS activity. These are the treatment methods which have been shown in various studies that the mechanism of action is through parasympathetic activity via vagus function.[56,57] Beyond the vegetative function and anti-inflammatory effect of the vagus, the number of publications showing its relationship with brain pain centers is increasing. Vagus nerve is related to pain modulation in the spinal cord and the brain, with effects on nociception, implicate the involvement of descending 5-HT and noradrenergic systems which displays analgesic properties.[58]

A study designed by Koopman et al, in which the cervical vagus nerve in rheumatoid arthritis (RA) patients was electrically stimulated, showed that RA symptoms such as pain decreased, and the production of inflammatory cytokines was inhibited.[59] Vagus nerve is known as having a pain inhibitor action. Gastric vagal afferents have been shown to have an inhibitory effect on somatic pain perception in humans.[60] Failure or dysfunction of vagus nerve coping with the pain can make the pain chronic but the possibility of vagus nerve dysfunction being a preliminary condition in pain production still has to be debated. We propose that vagus nerve dysfunction may play a larger-than-anticipated role in the pathophysiology of musculoskeletal and chronic pain. It is probably mediated both centrally and peripherally, under the influence of diysbiosis, has neural-muscular-hormonal-social and phsycologic components. Genetic and environmental factors also affect the disease process, of course.

In chronic pain syndromes, patterns of incorrect adaptation to ongoing pain have been developed; subjective pain persists after objective tissue damage or without tissue damage. We think that vagus nerve dysregulation, that is, dysbiosis caused by the sickness of the vagus nerve itself, causes the patient to feel pain in chronic pain syndromes. So we have a blurred vision in evaluation of vagus nerve but if the evidences are put on together, vagus nerve dysfunction becomes clear. It is frequently diffucult to find preliminary condition in these “complex” diseases, solve the interconnections and choose the appropriate treament.

MICROBIOTA

Microbiota plus dysbiosis, which is caused by the deterioration of microbiota and balance, which has recently become a favorite of science, plays a role in the pathophysiology and treatment of many diseases, and many studies are still being conducted on it. It is known that the human microbiota, dominated by bifidobacteria and stabilized during the first 2-3 years, plays a key role in various metabolic, nutritional, physiological and immunological processes.[61] During life, the microbiota increases and reaches its highest form in the adult human, dominated by Bacteroidetes and Firmicutes.[62]

Gut-brain axis is a bidirectional communication between the gut and the central nervous system, that integrates immunological, neural, and hormonal signals. It is increasingly noticed that gut dysbiosis, has a role in pathophysiology of many diseases, especially the disease with an inflammatory component like; obesity, diabetes mellitus, asthma, heart failure, cancer, inflammatory bowel disease (IBD), non-alcoholic fatty liver, major depressive disorders, musculoskeletal pain disorders, cardiovascular diseases and rheumatological diseases.[63] Fecal bacteriotherapy, or fecal transplantation, is the inoculation of liquid filtrate feces from a healthy donor into a patient’s gut to treat diseases such as *Clostridium difficile* infection, IBD, obesity, and insulin resistance. Ac-

cording to a publication by Thurm et al.; a patient with FM was fully recovered from pain after faecal microbiota transplantation.[64]

VAGUS NERVE DYSREGULATION, DYSBIOSIS AND CHRONICITY OF PAIN (CROSS TALKING)

The vagus nerve extends to the gut mucosa and provides the primary bidirectional connection between the gut microbiome and the brain.[65] VNS appears as an efficient procedure to decrease inflammation so it can be said that dysfunction of the vagus nerve can play a role in inflammation rise and as a result pain becomes evident and chronic.[66] Dysbiosis can trigger processes that occur in the chronicity of pain via vagus nerve dysfunction. We can expect an increase in proinflammatory cytokines when any pathology occurs in the vagus which will eventually disrupt crosstalk in this communication pathway. Increases in proinflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-6, IL-1β contribute to the sensitization of the nerve fibres in the central nervous system that causes enhanced pain transmission.[67] Interaction between organs by cytokines, hormones, bioelectricity of nerves etc. are important for integration. The homeostatic property is maintained using a complex biological device of reciprocal communication between organs, but these organ interactions can contribute to adverse consequences in the functional state of distant organs. Interplay of organs has been described in some diseases, and linking the nervous and immune systems to modulate end-organ inflammation is an example of communication between systems. Interaction between vagus nerve function and intestinal microbiota could be another crosstalk model in terms of their interplay. Because the vagus nerve has such a large distribution and connectivity throughout the body, manipulations such as VNS are very likely to benefit multiple organs and affect organ crosstalks.[68] The point we want to reach is that the vagus dysregulation affects the gut microbiota or vice versa, the impaired microbiota disrupts the effective functioning of the vagus; consequently the result is that the neuroinflammation may cause pain to become evident and chronic.

CONCLUSION

When pain becomes chronic, it is likely that there is a clinical or subclinical disorder in many parts of the body. The body should be approached holistically and the source of the problem and other accompanying problems should be evaluated together. The treatment program should also be organized in a multidisciplinary manner and include the whole body. ANS regulation; the role of the ANS in homestasis, its relationship with many functions in the body and its widespread distribution should be included in the treatment.

Chronic musculoskeletal painful conditions most probably have vagus dysfunction or dysregulation. It is a cause or a result is still under debate and investigation. Mostly sympathetic predominance and dysbiosis exists in these disorders. Centrally, peripherally, neurotransmitter and/or receptor mediated dysregulations may give rise to these pathologies. Variability in the origin possibly makes the difference between the patients and the diseases. Environmental factors may determine and emerge underlying genetic susceptibility in different ways. It seems to us that vagus nerve dysfunction and impared microbiota role in human illness is needed to be revealed more detailed in the future. We hope that this article could insight into how the vagus nerve works with taking the microbiome behind and give a new point of view about pain. Considering that the brain can also affect the intestines, the underlying cause of dysbiosis may be a malfunction of the vagus nerve. Both dysbiosis and vagal dysfunction may contribute to chronic pain and they may be crosstalking about it.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

REFERENCES

1. Lee SJ, Ralston HJ, Drey EA, Partridge JC, Rosen MA. Fetal pain: a systematic multidisciplinary review of the evidence. JAMA. 2005;294(8):947-54. [Crossref] [PubMed]
2. Demir H. Ağrının anatomisi ve fizyolojisi [Anatomy and physiology of pain]. Turkiye Klinikleri J PM&R- Special Topics. 2011;4(3):1-5. [Link]
3. Galland L. The gut microbiome and the brain. J Med Food. 2014;17(12):1261-72. [Crossref] [PubMed] [PMC]
4. Akkuş S. Ağrı ve fizik tedavi ajanları [Pain and physical therapy modalities]. Turkiye Klinikleri J PM&R-Special Topics. 2011;4(3):25-8. [Link]
5. Dworsky-Fried Z, Kerr BJ, Taylor AMW. Microbes, microglia, and pain. Neurobiol Pain. 2020;7:100045. [Crossref] [PubMed] [PMC]
6. Kingsley JD. Autonomic dysfunction in women with fibromyalgia. Arthritis Res Ther. 2012;14(1):103. [Crossref] [PubMed] [PMC]
7. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26(12):696-705. [Crossref] [PubMed]
8. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-S15. [Crossref] [PubMed] [PMC]
9. Fleming KC, Volcheck MM. Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. Rambam Maimonides Med J. 2015;6(2):e0020. [Crossref] [PubMed] [PMC]
10. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):339-56. [Crossref] [PubMed]
11. Arendt-Nielsen L, Fernández-de-Las-Pe-as C, Graven-Nielsen T. Basic aspects of musculoskeletal pain: from acute to chronic pain. J Man Manip Ther. 2011;19(4):186-93. [Crossref] [PubMed] [PMC]
12. Crofford LJ. Chronic pain: where the body meets the brain. Trans Am Clin Climatol Assoc. 2015;126:167-83. [PubMed] [PMC]
13. Adler GK, Geenen R. Hypothalamic-pituitary-adrenal and autonomic nervous system functioning in fibromyalgia. Rheum Dis Clin North Am. 2005;31(1):187-202. [Crossref] [PubMed]
14. Martínez-Martínez LA, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol. 2014;20(3):146-50. [Crossref] [PubMed]
15. Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. Ann N Y Acad Sci. 2006;1088:361-72. [Crossref] [PubMed]
16. Paine P, Kishor J, Worthen SF, Gregory LJ, Aziz Q. Exploring relationships for visceral and somatic pain with autonomic control and personality. Pain. 2009;144(3):236-44. [Crossref] [PubMed]
17. Gockel M, Lindholm H, Niemistö L, Hurri H. Perceived disability but not pain is connected with autonomic nervous function among patients with chronic low back pain. J Rehabil Med. 2008;40(5):355-8. [Crossref] [PubMed]
18. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther. 2007;9(4):216. [Crossref] [PubMed] [PMC]
19. Malatji BG, Mason S, Mienie LJ, Wevers RA, Meyer H, van Reenen M, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. Metabolomics. 2019;15(4):54. [Crossref] [PubMed]
20. Gerwin RD. A review of myofascial pain and fibromyalgia--factors that promote their persistence. Acupunct Med. 2005;23(3):121-34. [Crossref] [PubMed]
21. Katz DL, Greene L, Ali A, Faridi Z. The pain of fibromyalgia syndrome is due to muscle hypoperfusion induced by regional vasomotor dysregulation. Med Hypotheses. 2007;69(3):517-25. [Crossref] [PubMed]
22. Chervin RD, Teodorescu M, Kushwaha R, Deline AM, Brucksch CB, Ribbens-Grimm C, et al. Objective measures of disordered sleep in fibromyalgia. J Rheumatol. 2009;36(9):2009-16. [Crossref] [PubMed] [PMC]
23. Gur A, Oktayoglu P. Central nervous system abnormalities in fibromyalgia and chronic fatigue syndrome: new concepts in treatment. Curr Pharm Des. 2008;14(13):1274-94. [Crossref] [PubMed]
24. Eisinger J. Dysautonomia, fibromyalgia and reflex dystrophy. Arthritis Res Ther. 2007;9(4):105. [Crossref] [PubMed] [PMC]
25. Kulshreshtha P, Deepak KK. Autonomic nervous system profile in fibromyalgia patients and its modulation by exercise: a mini review. Clin Physiol Funct Imaging. 2013;33(2):83-91. [Crossref] [PubMed]
26. Kulshreshtha P, Gupta R, Yadav RK, Bijlani RL, Deepak KK. A comprehensive study of autonomic dysfunction in the fibromyalgia patients. Clin Auton Res. 2012;22(3):117-22. [Crossref] [PubMed]
27. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. 2010;42(8):765-72. [Crossref] [PubMed]
28. Chalaye P, Goffaux P, Bourgault P, Lafrenaye S, Devroede G, Watier A, et al. Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients. Clin J Pain. 2012;28(6):519-26. [Crossref] [PubMed]
29. Doğru MT, Aydin G, Tosun A, Keleş I, Güneri M, Arslan A, et al. Correlations between autonomic dysfunction and circadian changes and arrhythmia prevalence in women with fibromyalgia syndrome. Anadolu Kardiyol Derg. 2009;9(2):110-7. [PubMed]
30. Lerma C, Martinez A, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. Arthritis Res Ther. 2011;13(6):R185. [Crossref] [PubMed] [PMC]
31. Ablin J, Fitzcharles MA, Buskila D, Shir Y, Sommer C, Häuser W. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. Evid Based Complement Alternat Med. 2013;2013:485272. [Crossref] [PubMed] [PMC]
32. Light KC, Bragdon EE, Grewen KM, Brownley KA, Girdler SS, Maixner W. Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder. J Pain. 2009;10(5):542-52. [Crossref] [PubMed] [PMC]
33. Barakat A, Vogelzangs N, Licht CM, Geenen R, MacFarlane GJ, de Geus EJ, et al. Dysregulation of the autonomic nervous system and its association with the presence and intensity of chronic widespread pain. Arthritis Care Res (Hoboken). 2012;64(8):1209-16. [Crossref] [PubMed]
34. Randich A, Gebhart GF. Vagal afferent modulation of nociception. Brain Res Brain Res Rev. 1992;17(2):77-99. [Crossref] [PubMed]
35. Lange G, Janal MN, Maniker A, Fitzgibbons J, Fobler M, Cook D, et al. Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. Pain Med. 2011;12(9):1406-13. [Crossref] [PubMed] [PMC]
36. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther. 2011;13(2):211. [Crossref] [PubMed] [PMC]
37. Levine JD, Reichling DB. Fibromyalgia: the nerve of that disease. J Rheumatol Suppl. 2005;75:29-37. [PubMed]
38. Staud R. Future perspectives: pathogenesis of chronic muscle pain. Best Pract Res Clin Rheumatol. 2007;21(3):581-96. [Crossref] [PubMed]
39. Hallman DM, Lyskov E. Autonomic regulation, physical activity and perceived stress in subjects with musculoskeletal pain: 24-hour ambulatory monitoring. Int J Psychophysiol. 2012;86(3):276-82. [Crossref] [PubMed]

40. Takamoto K, Sakai S, Hori E, Urakawa S, Umeno K, Ono T, et al. Compression on trigger points in the leg muscle increases parasympathetic nervous activity based on heart rate variability. J Physiol Sci. 2009;59(3):191-7. [Crossref] [PubMed]
41. Ge HY, Fernández-de-las-Pe-as C, Arendt-Nielsen L. Sympathetic facilitation of hyperalgesia evoked from myofascial tender and trigger points in patients with unilateral shoulder pain. Clin Neurophysiol. 2006;117(7):1545-50. [Crossref] [PubMed]
42. Monaco A, Cattaneo R, Mesin L, Ciarrocchi I, Sgolastra F, Pietropaoli D. Dysregulation of the autonomous nervous system in patients with temporomandibular disorder: a pupillometric study. PLoS One. 2012;7(9):e45424. [Crossref] [PubMed] [PMC]
43. Balasubramaniam R, de Leeuw R, Zhu H, Nickerson RB, Okeson JP, Carlson CR. Prevalence of temporomandibular disorders in fibromyalgia and failed back syndrome patients: a blinded prospective comparison study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104(2):204-16. [Crossref] [PubMed]
44. Passatore M, Roatta S. Modulation operated by the sympathetic nervous system on jaw reflexes and masticatory movement. Arch Oral Biol. 2007;52(4):343-6. [Crossref] [PubMed]
45. Lavigne GJ, Huynh N, Kato T, Okura K, Adachi K, Yao D, et al. Genesis of sleep bruxism: motor and autonomic-cardiac interactions. Arch Oral Biol. 2007;52(4):381-4. [Crossref] [PubMed]
46. Huynh N, Kato T, Rompré PH, Okura K, Saber M, Lanfranchi PA, et al. Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity. J Sleep Res. 2006;15(3):339-46. [Crossref] [PubMed]
47. Bracha HS, Lenze SM, Shelton JM. Bruxism and autonomic activity. Clin Auton Res. 2007;17(1):50; author reply 51. [Crossref] [PubMed]
48. Marthol H, Reich S, Jacke J, Lechner KH, Wichmann M, Hilz MJ. Enhanced sympathetic cardiac modulation in bruxism patients. Clin Auton Res. 2006;16(4):276-80. [Crossref] [PubMed]
49. Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V, et al. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011;12(11 Suppl):T75-91. [Crossref] [PubMed] [PMC]
50. Borchers AT, Gershwin ME. Complex regional pain syndrome: a comprehensive and critical review. Autoimmun Rev. 2014;13(3):242-65. [Crossref] [PubMed]
51. Birklein F. Complex regional pain syndrome. J Neurol. 2005;252(2):131-8. [Crossref] [PubMed]
52. Field J. Complex regional pain syndrome: a review. J Hand Surg Eur Vol. 2013;38(6):616-26. [Crossref] [PubMed]
53. Maihöfner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. Eur J Neurol. 2010;17(5):649-60. [Crossref] [PubMed]
54. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology. 2010;113(3):713-25. [Crossref] [PubMed]
55. Kaniusas E, Kampusch S, Tittgemeyer M, Panetsos F, Gines RF, Papa M, et al. Current directions in the auricular vagus nerve stimulation I-a physiological perspective. Front Neurosci. 2019;13:854. [Crossref] [PubMed] [PMC]
56. Uchida C, Waki H, Minakawa Y, Tamai H, Miyazaki S, Hisajima T, et al. Effects of acupuncture sensations on transient heart rate reduction and autonomic nervous system function during acupuncture stimulation. Med Acupunct. 2019;31(3):176-84. [Crossref] [PubMed] [PMC]
57. Eda N, Ito H, Akama T. Beneficial effects of yoga stretching on salivary stress hormones and parasympathetic nerve activity. J Sports Sci Med. 2020;19(4):695-702. [PubMed] [PMC]
58. Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. Joint Bone Spine. 2021;88(3):105149. [Crossref] [PubMed]
59. Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2016;113(29):8284-9. [Crossref] [PubMed] [PMC]
60. Sedan O, Sprecher E, Yarnitsky D. Vagal stomach afferents inhibit somatic pain perception. Pain. 2005;113(3):354-9. [Crossref] [PubMed]
61. Ottman N, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what do they do? Front Cell Infect Microbiol. 2012;2:104. [Crossref] [PubMed] [PMC]
62. Rajilić-Stojanović M, Heilig HG, Molenaar D, Kajander K, Surakka A, Smidt H, et al. Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. Environ Microbiol. 2009;11(7):1736-51. [Crossref] [PubMed] [PMC]
63. Guo R, Chen LH, Xing C, Liu T. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. Br J Anaesth. 2019;123(5):637-54. [Crossref] [PubMed]
64. Thurm T, Ablin J, Buskila D, Maharshak N. Faecal microbiota transplantation for fibromyalgia: a case report and review of the literature. Open J Gastroenterol 2017;7(4):131. [Crossref]
65. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. Adv Exp Med Biol. 2014;817:115-33. [Crossref] [PubMed]
66. Pereira MR, Leite PE. The involvement of parasympathetic and sympathetic nerve in the inflammatory reflex. J Cell Physiol. 2016;231(9):1862-9. [Crossref] [PubMed]
67. Watkins LR, Maier SF. Glia: a novel drug discovery target for clinical pain. Nat Rev Drug Discov. 2003;2(12):973-85. [Crossref] [PubMed]
68. Tanaka S, Hammond B, Rosin DL, Okusa MD. Neuroimmunomodulation of tissue injury and disease: an expanding view of the inflammatory reflex pathway. Bioelectron Med. 2019;5:13. [Crossref] [PubMed] [PMC]