The Role of Nutrition Therapy in the Management of Chronic Pain

Hatice Tuğçe BERBEROĞLU[*], Muteber Gizem KESER GÜMÜŞ[**]

Abstract

Chronic pain is defined as pain lasting longer than three months or recurring in nature and is considered a major public health problem affecting millions of people worldwide. This condition, which significantly reduces quality of daily life and may lead to physical, psychological, and social problems, can negatively affect individuals' lives over the long term. Although the mechanisms underlying the development of chronic pain have not yet been fully understood, recent scientific studies suggest that certain biological processes may play a role in its development. Among these processes, oxidative stress, inflammation, increased body weight, and imbalance in gut microbiota (dysbiosis) are particularly prominent. Notably, most of these factors are closely associated with nutrition either directly or indirectly. Therefore, investigating the effects of nutrition on the development and severity of chronic pain may enable the development of nutrition-based approaches aimed at reducing pain. This review discusses the possible biological mechanisms involved in the pathogenesis of chronic pain and examines the role and potential contributions of nutrition therapy in this process. Thus, the importance of nutrition as a complementary approach in the prevention and management of chronic pain is emphasized.

Keywords: Chronic pain, oxidative stress, inflammation, dysbiosis, nutrition.

Kronik Ağrı Yönetiminde Beslenme Tedavisinin Rolü

Öz

Kronik ağrı, üç aydan uzun süren veya tekrarlayıcı nitelikte olan ağrı olarak tanımlanmakta ve dünya genelinde milyonlarca insanı etkileyen önemli bir halk sağlığı problemi olarak kabul edilmektedir. Günlük yaşam kalitesini önemli ölçüde düşüren, fiziksel, psikolojik ve sosyal sorunlara yol açabilen bu durum, bireylerin yaşamlarını uzun süreli olarak olumsuz etkileyebilmektedir. Kronik ağrının oluşum mekanizmaları henüz tam olarak aydınlatılamamış olsa da, son yıllarda yapılan bilimsel araştırmalar, bazı biyolojik süreçlerin bu durumun gelişiminde rol oynayabileceğini göstermektedir. Bu süreçler arasında oksidatif stres, inflamasyon, artmış vücut ağırlığı ve bağırsak mikrobiyotasında görülen dengesizlik (disbiyozis) öne çıkmaktadır. Dikkat çekici olan nokta ise bu faktörlerin çoğunun doğrudan ya da dolaylı olarak beslenme ile yakından ilişki içinde olmasıdır. Bu nedenle, beslenmenin kronik ağrının oluşumu ve şiddeti üzerindeki etkilerini araştırmak, ağrıyı azaltmaya yönelik beslenme temelli yaklaşımların geliştirilmesini mümkün kılabilir. Bu derlemede, kronik ağrı patogenezinde rol oynayan olası biyolojik mekanizmalar ele alınmakta ve beslenme tedavisinin bu süreçteki yeri ve potansiyel katkıları

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[*] Res. Asst., Department of Nutrition and Dietetics, Faculty of Health Sciences, KTO Karatay University, Konya, Türkiye. E-mail: tugceaca@gmail.com ORCID https://orcid.org/0000-0002-7098-7344
[**] Asst. Prof. Dr., Department of Nutrition and Dietetics, Nezahat Keleşoğlu Faculty of Health Sciences, Necmettin Erbakan University, Konya, Türkiye. E-mail: mgizemkeser@gmail.com ORCID https://orcid.org/0000-0001-9425-9088

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incelenmektedir. Böylece, kronik ağrının önlenmesi ve yönetiminde tamamlayıcı bir yaklaşım olarak beslenmenin önemi vurgulanmaktadır.

Anahtar Sözcükler: Kronik ağrı, oksidatif stres, inflamasyon, disbiyozis, beslenme.

Introduction

According to the International Association for the Study of Pain (IASP), chronic pain is pain that persists or recurs for longer than three months[1]. Chronic pain affects millions of individuals worldwide and represents a major public health concern as well as one of the leading causes of disability[2]. Although large-scale studies investigating the prevalence of chronic pain remain limited, available evidence indicates that its prevalence varies considerably across populations and societies[3,4]. It is estimated to affect more than one-third of adults globally, including approximately one in five adults in Europe[5], and its prevalence is predicted to increase further in the coming years[6].

The underlying mechanisms involved in the development of chronic pain have not yet been fully elucidated, making it challenging to establish definitive treatment approaches for this widespread health problem. The severity, duration, and impact of chronic pain are influenced by a wide range of social, psychological, physical, and emotional factors. In addition to these factors, nutrition has also been reported to play a role in the development and progression of chronic pain[7-9]. Chronic pain may impair individuals' ability to perform daily activities and engage in physical exercise, while also contributing to poor sleep quality and reduced participation in social activities[10]. Furthermore, it imposes a substantial socioeconomic burden through functional impairment, disability, increased healthcare utilization and costs, absenteeism, and reduced productivity[11].

Current treatment standards emphasize a multifaceted and multidisciplinary approach that acknowledges the complex interactions among biological, psychological, and social factors[7]. These strategies offer an alternative to traditional pain management approaches and may reduce the adverse effects associated with pharmacological interventions while enhancing their therapeutic effectiveness[2]. In this context, nutrition has increasingly emerged as an important lifestyle factor in pain management[2]. Evidence suggests that poor dietary habits, including inadequate and unhealthy nutrition, may substantially influence the onset, progression, and persistence of chronic pain[12]. The relationship between nutrition and chronic pain is highly complex and is thought to involve several underlying mechanisms, including oxidative stress, inflammation, and alterations in the gut microbiota[13].

Although evidence supporting the role of nutrition in chronic pain management is steadily increasing, the mechanisms underlying the interaction between nutrition and chronic pain, as well as the effective implementation of nutritional care in this context, remain incompletely understood. Therefore, this review aims to discuss the biological mechanisms underlying this interaction in individuals experiencing chronic pain and to examine the role of nutritional management in pain prevention and treatment.

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Material and Methods

This article was prepared as a narrative review aiming to summarize the current approaches regarding the role of nutrition therapy in the management of chronic pain. A literature search was conducted in PubMed, Scopus, and Google Scholar databases for studies published between January 2010 and March 2025. Search terms included combinations of "chronic pain", "nutrition", "diet", "Mediterranean diet", "inflammation", "oxidative stress", "gut microbiota", "obesity", "vitamin D", "omega-3 fatty acids", and "micronutrients".

Original research articles, systematic reviews, meta-analyses, and clinical guidelines published in English were considered for inclusion. Studies focusing on acute pain, animal models without clinical relevance, or publications lacking sufficient methodological information were excluded. Relevant articles were selected based on their contribution to understanding the biological mechanisms linking nutrition and chronic pain and the potential role of nutritional interventions in pain management.

Mechanisms Underlying the Relationship between Chronic Pain and Nutrition

The mechanisms through which nutrition contributes to chronic pain have not yet been fully elucidated. Therefore, identifying these mechanisms may improve the effectiveness of nutritional therapy in the management of chronic pain[13]. Several nutrition-related factors have been implicated in the development and persistence of pain, including oxidative stress, inflammation, obesity, and gut dysbiosis.

Oxidative stress is a pathophysiological condition characterized by the excessive intracellular accumulation of reactive oxygen species (ROS), reactive nitrogen species (RNS), and other free radical species[14]. Oxidative stress is considered one of the major pathophysiological mechanisms underlying chronic pain. It can be influenced by dietary factors and plays a significant role in the initiation and progression of inflammation[15]. Oxidative stress may lead to harmful alterations, particularly within the central nervous system. Previous studies have demonstrated an imbalance between pro-oxidant and antioxidant mechanisms in individuals experiencing chronic pain[16-18]. Furthermore, oxidative stress can damage neural tissues, increase pain sensitivity, and contribute to the development of neuropathy[2]. It has been associated with several chronic pain conditions, including osteoarthritis, fibromyalgia, and neuropathic disorders[2]. In contrast, evidence suggests that a high dietary intake of antioxidants and improved endogenous detoxification capacity may help alleviate chronic musculoskeletal pain[19].

Inflammation also plays a central role in the development of chronic pain. It contributes not only to the onset, persistence, and prognosis of chronic pain, but also to the development of various acute and chronic diseases[13]. A nutrient-rich diet is believed to alleviate pain by reducing oxidative stress and systemic inflammation[20]. Previous studies

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have demonstrated that diets high in animal-based foods are associated with increased inflammation and chronic pain[21], whereas dietary patterns rich in refined sugars, saturated fats, trans fats, and artificial additives may promote chronic low-grade inflammation, which has been linked to several chronic pain-related conditions, including arthritis, fibromyalgia, and migraine[2].

In contrast, the consumption of antioxidant-rich foods such as fruits and vegetables, whole grains, fatty fish, nuts, seeds, and olive oil may help reduce inflammation and alleviate pain[2]. In an exploratory pilot case-control study conducted by Jönsson et al., involving patients with chronic peripheral neuropathic pain and healthy controls, participants with neuropathic pain exhibited an altered lipoprotein profile consistent with low-grade chronic inflammation[22]. Although the metabolic mechanisms underlying chronic pain in individuals with diabetes have not yet been fully clarified, chronic pain is thought to arise from a pro-inflammatory state associated with impaired lipid metabolism, ion channel alterations, central and periphera sensitization, and microglial activation[23]. Therefore, the identification and management of impaired glucose metabolism may also play a crucial role in chronic pain management[24].

Gut dysbiosis has emerged as another important mechanism linking nutrition and chronic pain. Evidence from animal models suggests that gut health may play a significant role in modulating pain perception or contributing to the development of various chronic pain conditions[25]. Current evidence also indicates that nutrition may influence the relationship between the gut microbiota and the pathophysiology of both acute and chronic pain[26]. Dietary patterns characterized by high intakes of saturated fats and refined carbohydrates, together with low consumption of vegetables, fruits, and other nutrient-rich foods, may promote intestinal inflammation[27]. In contrast, plant-based dietary patterns such as vegan and vegetarian diets have been shown to exert beneficial effects on the gut microbiota[28].

Reduced microbial diversity has been reported in individuals with chronic pain, suggesting a potential need for nutritional interventions targeting the gut microbiota[29]. The gut microbiota also produces polyamines, which can stimulate N-methyl-D-aspartate (NMDA) receptors[30]. These receptors are known to play a critical role in central sensitization, a mechanism commonly observed in patients with chronic pain[27]. In addition, a reduced abundance of the bacterial family *Lachnospiraceae* has been identified in patients with chronic pain[29].

Several studies have investigated the potential effects of probiotic supplementation on pain-related outcomes. In a clinical intervention study involving 40 patients with Parkinson's disease and constipation, supplementation with *Lactobacillus casei Shirota* for six weeks improved abdominal pain and bowel function[31]. However, in a pilot randomized placebo-controlled trial involving 40 women with fibromyalgia, Roman et al. reported that eight weeks of probiotic supplementation did not significantly improve pain symptoms compared with placebo[32]. Nevertheless, probiotic supplementation containing *Lactobacillus* and *Bifidobacterium* species has been reported to improve decision-making abilities and attentional processes, even in the absence of direct

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reductions in pain intensity. This discrepancy may be explained by the possibility that probiotics contribute to the modulation of neuroinflammation but may be insufficient to reverse long-standing central sensitization within a relatively short intervention period. In contrast, improvements in mood and cognitive function may occur more rapidly through biochemical and neuroimmune pathways. Therefore, although probiotics may not provide acute immediate analgesic effects, they may help prevent the negative consequences of chronic pain on mood, sleep quality, and overall quality of life.

Lastly, maintaining an ideal body weight is important as it protects individuals from numerous diseases and related health complications. Recent studies have demonstrated a bidirectional relationship between obesity and chronic pain[33]. Obesity may contribute to pain through the activation of pro-inflammatory pathways and increased mechanical loading on the musculoskeletal system[34]. It has been associated with several chronic musculoskeletal pain conditions, including osteoarthritis, fibromyalgia, pelvic pain, and chronic low back pain[35].

In a registry-based cross-sectional study conducted by Dong et al. including more than 4,000 patients with chronic pain, over 25% of participants were classified as obese[36]. Similarly, in a cross-sectional study of patients attending a tertiary pain service, obesity was present in approximately 45% of participants[37]. Research focusing on fibromyalgia has further shown that individuals with overweight or obesity tend to experience more severe pain and require greater medication use compared with those with an ideal body weight[38,39]. Moreover, calorie-restricted dietary patterns have been shown to alleviate pain in individuals with chronic musculoskeletal disorders[40].

The relationship between obesity and chronic pain appears to be reciprocal. Chronic pain may alter the sensory and reward-related aspects of eating behavior, potentially reducing satiety regulation and increasing the risk of overconsumption[41]. In addition, chronic pain can impair individuals' ability to prepare healthy meals and maintain healthy eating habits, thereby further contributing to the development and persistence of obesity[34].

Nutrition Therapy for Pain Management

Dietary habits influence overall lifestyle and health status and may therefore affect both the severity of pain and individuals' ability to cope with it. Over the past two decades, increasing attention has been directed towards the role of nutrition in pain management by pain organizations, healthcare professionals, and consumers alike. Interest in nutrition-based approaches has grown substantially as accumulating evidence has highlighted the potential benefits of dietary interventions in alleviating pain and improving quality of life.

In 2020, the International Association for the Study of Pain emphasized the importance of healthy nutrition as a component of pain management. This recommendation was supported by a growing body of evidence demonstrating that dietary factors may contribute to pain reduction and improve pain-related outcomes[42].

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Macro and Micronutrients

The Mediterranean diet represents not only a nutritional model but also a broader cultural and lifestyle pattern. It is characterized by a high intake of olive oil, vegetables, fruits, whole grains, legumes, and nuts; moderate consumption of fish, seafood, eggs, and dairy products; and low consumption of sweets, red meat, and processed meat[43].

This dietary pattern is predominantly plant-based, with meals centered around vegetables, fruits, herbs, nuts, beans, and whole grains. It also includes moderate amounts of dairy products, poultry, eggs, and seafood, whereas red meat is consumed infrequently[43]. The Mediterranean diet is rich in antioxidant-containing foods, including fresh fruits and vegetables, as well as fish that provide omega-3 fatty acids that reduce inflammation. In addition, olive oil contains several bioactive compounds and antioxidants, including vitamin E, oleic acid, and carotenoids[42].

Extra virgin olive oil, in particular, contains oleocanthal, a bioactive compound with anti-inflammatory properties. Oleocanthal has been shown to influence prostaglandin-related inflammatory pathways and has demonstrated effects comparable to those of certain non-steroidal anti-inflammatory drugs used in pain reduction[43]. Furthermore, dietary patterns rich in antioxidants and linolenic acid, such as the Mediterranean diet, may help counteract oxidative damage associated with lipid accumulation and inflammation[43,44]. In a prospective intervention study involving women with fibromyalgia, eight weeks of adherence to the Mediterranean diet was associated with improvements in disability, fatigue, and anxiety scores[44].

Carbohydrates

Carbohydrates serve as a primary and rapid source of energy for the body. Glucose, the fundamental form of carbohydrate, is the main energy substrate for bodily functions, particularly for the nervous system. However, excessive dietary carbohydrate intake and impaired glucose utilization may contribute to increased production of reactive oxygen species and oxidative damage[22]. The World Health Organization (WHO) recommends that added sugars should account for no more than 10% of an individual's total daily energy intake[42].

In addition to the quantity of carbohydrates consumed, the quality and type of carbohydrates are also important in maintaining metabolic health and managing chronic pain. The glycemic index is a classification system that categorizes foods according to the rate at which they are digested, absorbed, and subsequently increase blood glucose levels. Foods with a low glycemic index are digested and absorbed more slowly than foods with a high glycemic index, thereby promoting more stable blood glucose regulation[12].

The consumption of fresh fruits and vegetables of various colors should be encouraged due to their high phytochemical content. Similarly, whole-grain bread and cereal

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products represent healthier carbohydrate sources because they are rich in dietary fiber and B vitamins and generally possess a lower glycemic index. In addition, dietary fiber supports the growth of beneficial gut microbiota by acting as a prebiotic, thereby contributing to the regulation of gut microbial balance. Furthermore, adequate fiber intake may indirectly reduce lipid levels and decrease the risk of inflammation and oxidative stress[12].

Conversely, excessive fructose intake, particularly from sugar-sweetened beverages and ultra-processed foods, may lead to the production of pro-inflammatory cytokines, cholesterol accumulation, endothelial dysfunction, and systemic inflammation[43,44]. Therefore, limiting the consumption of carbonated beverages, sugary drinks, and ultra-processed, energy-dense, nutrient-poor foods may help reduce oxidative stress and alleviate pain-related symptoms[12].

Proteins

Proteins perform a wide range of essential physiological functions in the body and are composed of amino acids. Essential amino acids play a critical role in the regulation of muscle anabolism and protein synthesis. In addition, several neurotransmitters and pain-modulating compounds, including serotonin, gamma-aminobutyric acid (GABA), and endorphins, are synthesized from amino acid precursors[45].

Endorphins are endogenous neuropeptides that exert opioid-like effects within the body and contribute to natural pain relief, in some cases demonstrating analgesic effects comparable to morphine. Adequate protein intake is therefore important not only for maintaining muscle mass but also for supporting neurotransmitter synthesis and neuromuscular function. Research has suggested that a daily protein intake of approximately 90-100 g may help prevent neurotransmitter depletion and significant muscle loss. Furthermore, higher protein intake has been associated with reduced pain severity in individuals with fibromyalgia. Another study reported that insufficient protein intake may contribute to fibromyalgia-related symptoms through disruptions in the tryptophan-serotonin metabolic pathway resulting from inadequate tryptophan availability.[46]

Lipids

Lipids are energy-dense molecules that perform numerous essential physiological functions within the body. However, excessive intake of saturated fats and certain polyunsaturated fatty acids, particularly linoleic acid, has been associated with increased levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and elevated cardiovascular risk[47,48]. Diets high in saturated fat and energy-dense foods may also increase circulating concentrations of inflammatory cytokines, thereby contributing to systemic inflammation. A study involving 605 adults demonstrated that increases in the ratio of omega-6 to omega-3 polyunsaturated fatty acids (n-6/n-3 PUFA ratio) were associated with higher pain level[49].

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Similarly, a meta-analysis of fourteen studies reported a significant association between total body fat levels and widespread pain. Individuals with low back pain and knee pain were found to have higher body fat percentages, suggesting a relationship between adiposity and chronic musculoskeletal pain[50]. In contrast, omega-3 polyunsaturated fatty acids have been reported to exert anti-inflammatory and analgesic effects. In a double-blind randomized placebo-controlled trial involving patients with chronic migraine receiving amitriptyline therapy, omega-3 supplementation for 60 days was associated with a reduction in migraine frequency[51]. These findings provide preliminary evidence supporting a potential role for omega-3 fatty acids in migraine management; however, larger trials are needed to confirm these effects.

Micronutrients

In addition to macronutrients, inadequate dietary intake of micronutrients, particularly vitamins and minerals such as vitamin D, magnesium, zinc, and vitamins B_1, B_6, and B_{12}, has been suggested to be associated with chronic pain[52].

Vitamin D plays an important role in the regulation of several inflammatory pathways involved in the development and persistence of chronic pain. Due to its anti-inflammatory properties, vitamin D may also modulate peripheral pain sensitization[53]. Furthermore, vitamin D deficiency has been associated with increased levels of pro-inflammatory cytokines, which may impair pain signal processing within both the peripheral and central nervous systems[54].

In a randomized study involving 50 vitamin D-deficient women aged 18–30 years, vitamin D supplementation for eight weeks was associated with reduced pain severity. However, the findings are limited by the relatively small sample size and specific study population[55]. Similarly, in a randomized placebo-controlled trial conducted by Zarei et al. involving 85 students aged 18- 32 years, participants were assigned to one of three groups: a calcium plus vitamin D_3 group (1000 mg of calcium and 15,000 IU of vitamin D_3 daily), a calcium-only group (1000 mg calcium daily), or a placebo group[56]. Mean pain intensity decreased in both supplementation groups; however, the reduction reached statistical significance only in the calcium-only group.

Magnesium is an essential macro element with important regulatory functions in both the nervous and muscular systems. The wide range of physiological roles performed by magnesium is reflected in the diverse clinical manifestations associated with its deficiency, which may include irritability, muscle weakness and fatigue, seizures, cardiac arrhythmias, and other neuromuscular disturbances[57]. Magnesium contributes to the stabilization of neuronal cell membranes and has been reported to exert antinociceptive effects, thereby helping to reduce pain associated with tissue injury[58]. In a retrospective cohort study of patients undergoing total knee arthroplasty, perioperative magnesium sulfate administration was associated with a 62% lower incidence of persistent postoperative pain at one-year follow-up[59].

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Zinc is a trace mineral that plays an essential role in DNA synthesis, cell division, and immune system regulation. Within the central nervous system, zinc is also an important micronutrient involved in cognitive function, memory development, glucose homeostasis, and learning processes, in addition to acting as a neuromodulator of synaptic plasticity[60]. The contribution of zinc to pain modulation is thought to occur through its interaction with N-methyl-D-aspartate (NMDA) receptors, which are linked to neuronal nitric oxide synthase (nNOS) activity[61]. In a randomized controlled trial conducted by Teimoori et al., participants aged 18–26 years with primary dysmenorrhea were assigned to receive either 220 mg zinc sulfate once daily combined with 250 mg mefenamic acid three times daily, or placebo. The results showed that the intervention group experienced a greater reduction in pain intensity compared with the control group[62].

Vitamin B_1 is a water-soluble vitamin involved in neural activity, muscle tone regulation, carbohydrate metabolism, blood cell formation, cellular differentiation, and synapse formation. It promotes the synthesis of myelin and several neurotransmitters, including acetylcholine and serotonin. In addition, vitamin B_1 inhibits the activity of acetylcholine esterase, an enzyme responsible for the breakdown of acetylcholine, which is a key neurotransmitter in the central nervous system[63]. Vitamin B_1 may also contribute to pain reduction by enhancing mitochondrial function and reducing oxidative stress[64]. In a randomized placebo-controlled study by Hosseinlou et al., participants were divided into four groups: vitamin B_1 alone, fish oil supplementation, a combination of vitamin B_1 and fish oil, and placebo. All treatment groups showed a significant reduction in pain severity compared with the placebo group[65].

Vitamin B_6 (pyridoxine) exists in nature in three forms: pyridoxine, pyridoxal, and pyridoxamine. The biologically active metabolite derived from these compounds is pyridoxal 5'-phosphate (PLP), which is responsible for the physiological functions of the vitamin. Pyridoxal 5'-phosphate participates in numerous metabolic and biochemical processes, including fatty acid metabolism, neurotransmitter synthesis, immune regulation, gluconeogenesis, folate metabolism, coenzyme Q10 synthesis, and heme synthesis[66].

Vitamin B_6 is thought to exert potential analgesic and neuroprotective effects through several mechanisms, including inhibition of advanced glycation end products, reduction of oxidative stress, modulation of intracellular glutamate concentrations, regulation of calcium channel activity, and antagonist effects on various receptors involved in pain signalling[66].

In a study conducted by Sadeghi et al., daily supplementation with 80 mg of pyridoxine was associated with reductions in both the severity and duration of migraine attacks[67]. In contrast, another study involving both individuals with fibromyalgia and healthy controls reported that vitamin B_6 supplementation was not significantly more effective than placebo[68]. The inconsistent findings regarding the therapeutic effects of Vitamin B_6 may be attributable to several factors. Vitamin B_6 often requires synergistic micronutrients, such as magnesium, to function effectively as a cofactor in

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neurotransmitter synthesis and other metabolic pathways. Thus, deficiencies in these complementary nutrients may limit the clinical efficacy of vitamin B_6 supplementation. Furthermore, the high placebo response commonly observed in fibromyalgia trials may make it difficult to detect the relatively subtle biochemical effects associated with individual vitamin interventions.

Vitamin B_{12} exerts multiple biological effects that may contribute to pain modulation. Its mechanisms of action include antinociceptive effects, promotion of neuronal regeneration, and participation in myelin synthesis, as well as stimulation of axonal growth and differentiation of Schwann cells[69]. Vitamin B_{12} is also involved in DNA methylation and plays an essential role in cell replication and the upregulation of brain-derived neurotrophic factor expression. Several mechanisms have been proposed to explain the neuroprotective effects of vitamin B_{12}. These include reduction of advanced glycation end products, inhibition of the diacylglycerol-protein kinase C (DAG-PKC) pathway, and regulation of the hexosamine and pentose metabolic pathways[70]. In addition, vitamin B_{12} contributes to the regulation of inflammatory mediators and may therefore help alleviate pain-related symptoms. Low serum vitamin B_{12} concentrations, particularly levels below 400 pg/mL, have been suggested to be associated with tension-type headaches, migraine, and other headache disorders[71].

A prospective cohort study involving chronic hemodialysis patients with diabetic polyneuropathy demonstrated improvements in neuropathic pain following six months of intravenous methylcobalamin treatment. In this six-month study, patients undergoing regular hemodialysis treatment for uremia and diabetic polyneuropathy received 500 µg of intravenous methylcobalamin three times weekly. Improvements in neuropathic pain were observed among patients receiving vitamin B_{12} treatment[72].

Similarly, in a randomized placebo-controlled trial involving 71 cancer patients receiving chemotherapy, Schloss et al. evaluated the effectiveness of B-vitamin supplementation in preventing chemotherapy-induced peripheral neuropathy (CIPN). Participants were randomly assigned to receive either placebo or a vitamin formulation containing 50 mg thiamine, 20 mg riboflavin, 100 mg niacin, 163.5 mg pantothenic acid, 30 mg pyridoxine, 500 µg folate (B_9), 500 µg cyanocobalamin, 500 µg biotin, 100 mg choline, and 500 µg inositol twice daily. At the 34-week follow-up assessment, vitamin supplementation did not significantly reduce the incidence of CIPN or pain scores compared with placebo[73]. The functional roles of macro- and micronutrients in the mechanisms underlying chronic pain development are summarized in Table 1.

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Table 1. Functional Roles of Macro- and Micronutrients in the Mechanisms Underlying Chronic Pain.

Nutrient	**Key Mechanisms**	**Pain-Related Outcomes**	**Level of Evidence**
Carbohydrates	High GI → ↑ ROS and inflammation Low GI → glucose stability Fiber → gut microbiota support	Improved pain regulation ↓ inflammatory load	1,3,4,5
Proteins	Amino acids → serotonin, GABA, endorphins Supports muscle synthesis Prevents neurotransmitter depletion	↓ pain sensitivity Improved muscle function	1,4
Fats	Omega-3 fatty acids→ anti-inflammatory cytokines Saturated fat → ↑ inflammation n-6/n-3 imbalance → pain risk	Omega-3 → pain reduction Saturated fat → pain aggravation	1,2,3,5
Vitamin D	↓ Pro-inflammatory cytokines Modulates pain sensitization pathways Immune regulation	↓ pain severity Improved inflammatory control	2,3,5
Magnesium	NMDA receptor inhibition Neuronal stabilization Antinociceptive action	↓ acute & chronic pain Improved neuromuscular balance	3,5
Zinc	NMDA modulation Synaptic plasticity support Immune regulation	↓ pain perception Improved inflammatory pain control	2,5
Vitamin B_1	Neurotransmitter synthesis Mitochondrial support ↓ oxidative stress	↓ pain severity Improved nerve function	2,5
Vitamin B_6	↓ glutamate excitotoxicity Neurotransmitter synthesis (serotonin, GABA) Calcium channel modulation	↓ migraine symptoms (variable) Neuropathic pain modulation	2,5
Vitamin B_{12}	Myelin synthesis & nerve repair ↓ inflammatory mediators Neurotrophic support	↓ neuropathic pain Improved nerve regeneration	2,3,5

GI: Glycemic Index; ROS: Reactive Oxygen Species; GABA: Gamma Aminobutyric Acid; NMDA: N-Methyl-D-Aspartate

Evidence levels were classified as follows: Level 1 = systematic reviews and meta-analyses; Level 2 = randomized controlled trials; Level 3 = cohort and case-control

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studies; Level 4 = cross-sectional and observational studies; Level 5 = mechanistic, experimental, animal, or expert-opinion based evidence.

Conclusion and Recommendations

Chronic pain is a multifactorial clinical condition resulting from the interaction of biological, psychological, and lifestyle-related factors. An increasing body of evidence suggests that nutrition may contribute to the modulation of pain perception through mechanisms involving inflammation, oxidative stress, body weight regulation, and gut microbiota modulation. However, the current literature is heterogeneous, and the level of evidence regarding nutritional interventions varies across different approaches.

In the management of chronic pain, the adoption of a personalized and anti-inflammatory dietary approach is recommended. In particular, dietary patterns such as the Mediterranean diet, which is rich in fruits, vegetables, whole grains, and omega-3 fatty acids, stand out due to their potential anti-inflammatory and antioxidant effects. Conversely, limiting the intake of ultra-processed foods, refined sugars, trans and saturated fatty acids, while ensuring adequate consumption of low-glycemic-index carbohydrates, dietary fiber, and high biological value proteins, is important. In addition, clinical evaluation of deficiencies in vitamin D, magnesium, zinc, and B-complex vitamins should be considered, as they may contribute to pain-related symptoms in some individuals; however, routine high-dose supplementation is not currently recommended as a standard approach due to inconsistent evidence. Prebiotic and probiotic interventions may also contribute to the maintenance of gut microbiota balance and metabolic homeostasis. Nevertheless, the majority of the existing evidence is derived from observational studies, small-scale clinical trials, and selected patient populations. Therefore, although nutritional therapy represents a promising, low-risk, and cost-effective complementary approach in the management of chronic pain, larger-scale randomized controlled trials and high-quality systematic reviews are needed to establish causal relationships in individuals with chronic pain and to develop evidence-based nutritional recommendations.

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