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Pain Management and Nutritional Medicine

Benjamin I. Brown

Chronic pain is one of the most widespread health problems, with up to 43% of people in the UK reporting that they experience chronic pain, of which 10–14% report moderate to severely disabling chronic pain.[1] Chronic pain is typically defined as pain persisting longer than 3 months, and generally refers to pain that has become a disease entity of itself and distinct from pain associated with acute injury or disease.[2] As a unique disease state, chronic pain, like other chronic diseases, has unique biological features, clinical symptoms and long-term consequences.

Chronic pain can be divided into primary or secondary classifications. Secondary chronic pain is divided into several sub-categories, including cancer-related pain; postsurgical or posttraumatic pain; secondary headache or orofacial pain; secondary visceral pain; and secondary musculoskeletal pain.[3] Primary chronic pain, also termed nociplastic pain, is used to broadly classify conditions in which pain itself has become the primary disease, and includes presentations such as fibromyalgia and non-specific low-back pain.[4] Primary chronic pain syndromes frequently overlap, and patients often present with a mosaic of conditions that include temporomandibular joint disorders, fibromyalgia, irritable bowel syndrome, chronic headaches, interstitial cystitis, chronic pelvic pain, chronic tinnitus, whiplash-associated disorders and vulvar vestibulitis.[5] The consequences of chronic pain are significant and impact psychological and physical health, including an adverse impact on sleep, cognitive processes and brain function, mood, mental health, cardiovascular health, sexual

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Affiliation: B. Brown is with the Nutritional Medicine Institute, London, UK, and the British College of Nutrition and Health (BCNH), London, UK.
Corresponding author: Benjamin I. Brown (email: **ben@nmi.health**)
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function, appetite and nutrition, medication dependence, social connection, and overall quality of life.[6,7]

The biology and pathophysiology of chronic pain is diverse and highly individual; however, there may be important sharded mechanisms across seemingly disparate clinical conditions that could help identify mechanism-based as opposed to symptom-based treatments.[8] A key feature of chronic pain is central sensitisation, which is characterised by increased activity in neurons and circuits involved in processing pain in the central nervous system coupled with reduced inhibition and ineffective endogenous pain control.[9] A 25-item Central Sensitisation Inventory (CSI) has been used as a screening tool for chronic pain, and CSI score reliably predicts pain intensity among patients with different types of chronic pain.[10] Central sensitisation may be more important than local tissue changes and provide a more unified explanation for chronic pain shared by different disorders, in this sense pain syndromes such as fibromyalgia, irritable bowel syndrome and chronic headaches are different manifestations of the same underlying aetiology.[11]

Although by definition primary chronic pain syndromes have no apparent functional cause, there are in fact several factors implicated in the pathogenesis of central sensitisation and chronic pain that may also, in some cases, be modifiable treatment targets. Pro-inflammatory mediators, although not consistently detectable in the periphery of people with chronic pain, may be active in the central nervous system and play an important role in the development of central sensitisation.[12] Inflammatory mediators sensitise pain-sensing neurons and enhance pain transmission.[13]

Mitochondria are implicated in the development of chronic pain, with dysfunction of mitochondrial metabolism and related adenosine triphosphate (ATP) deficiency, excessive reactive oxygen species, and impaired calcium buffering amongst several potential mechanisms that may be involved in pain sensitisation.[14] Preclinical studies indicate that mitochondrially targeted treatments may improve mitochondrial function and have important analgesic effects.[15]

Oxidative stress could contribute to the development and maintenance of chronic pain. In the central nervous system, reactive oxygen species can produce central sensitisation and hyperalgesia in the absence of nerve damage or tissue inflammation.[16] Furthermore, elevated biomarkers of oxidative stress have been observed in patients with a wide range of chronic pain syndromes, including chronic and recurrent neck pain,[17] low-back pain,[18] tension-type headache,[19] migraine headache,[20] fibromyalgia,[21] irritable bowel syndrome[22] and interstitial cystitis.[23]

Nutritional neuropathies are an important but often overlooked cause of chronic pain, with deficiencies in vitamins B1, B3, B6, B12 vitamin E and copper of particular importance.[24] Due to the multifaceted roles of nutrients in regulating nervous system function, inflammation, mitochondrial energy metabolism and oxidative stress, many other nutrients can play an important role in the development and therapy of chronic pain.[25] Several nutrients have been shown to modulate pain, including amino acids (tryptophan, phenylalanine and carnitine), fatty acids (omega 3 fatty acids, resolvins and N-palmitoylethanolamide), minerals (selenium, magnesium, iron and manganese) and vitamins (vitamins B, C, D, E and K).[26] Screening patients with chronic pain for underlying contributory nutritional deficiencies could help identify personalised nutritional interventions and improve clinical management.

In a retrospective observational study of 17 834 patients receiving opioids for chronic pain, a biomarker assay that determines possible modifiable nutritional drivers of pain suggested that 86% of patients had at least one abnormal biomarker.[27] In a randomised-controlled trial of this biomarker assay in clinical practice, it was found that clinicians using that assay were more likely to identify a micronutrient deficiency

(41.5%), treatable metabolic dysfunction (29.4%) and underlying oxidative stress (26.1%), and less likely to prescribe opioids, order unnecessary imaging or order an unnecessary pain referral.[28] This suggests that assessment of nutritional biomarkers relevant to pain could improve clinical management; however, patient pain outcomes were not measured in this study so more research is needed to determine if there is any impact on pain severity or medication use. Nevertheless, this work does support a role of nutrition in pain management.

Dietary therapy is a cornerstone of chronic pain management.[29] Important mechanisms for the benefit of dietary changes include modulation of inflammation,[30] reduction of oxidative stress,[31] direct analgesic effects[32] and reduced exposure to dietary factors that provoke pain.[33] A range of dietary interventions across different clinical pain syndromes have been studied. A review of 37 clinical trials including patients with generalised chronic musculoskeletal pain, low-back pain, neck pain, osteoarthritis, fibromyalgia, chronic headache or migraine, generalised chronic musculoskeletal pain and abdominal pain found that dietary interventions such as caloric restriction and fasting, enriched polyunsaturated fatty acid diets, low-fat plant-based diets, high-protein diets and elimination diets all generally revealed positive results.[34]

Dietary recommendations for patients with chronic pain can be based on anti-inflammatory and antioxidant foods and food components. Guidelines and a food pyramid have been developed, and broadly include advice to consume carbohydrates with a low glycaemic index, fruits and vegetables, yogurt and extra virgin olive oil daily; legumes and fish, white meat, eggs and fresh cheese weekly; and red or processed meats once per week, in addition to personalised nutritional supplementation.[35]

In this issue of the *Nutritional Medicine Journal,* one of the most frequent and debilitating pain disorders, migraine, is reviewed in the article *Migraine Headaches: Opportunities for Management with Precision Nutrition.* However, opportunities for pain management with precision nutrition are clearly not limited to migraine, and represent an underappreciated clinical strategy that has potential to improve management and reduce suffering for an untold number of people living with chronic pain.

Benjamin I. Brown
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