

# **Diet as a Potential Therapeutic Target in the Management of Chronic Pain: A Review**

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# Diet as a Potential Therapeutic Target in the Management of Chronic Pain: A Review

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## Abstract

**Introduction:** Chronic pain affects millions in the UK, with those affected more likely to suffer with diabetes, cardiovascular disease and obesity, all intrinsically linked to diet. Due to growing concerns around the dangers of opioid prescription, there has been an increased effort to adopt a more holistic approach when treating chronic pain. Despite this, diet has yet to be addressed as a possible therapeutic target. This review aims to investigate how diet can influence pain and if dietary advice can be used in the management of chronic pain patients.

**Methods:** A literature review was performed using the PubMed database to identify relevant literature, with the following keywords “chronic pain”, “diet”, “gut microbiome” and “omega-3”. The research papers found were critically appraised and only those of high quality and relevance were selected.

**Results:** Research has shown that inflammation in the gut microbiome plays a key role in chronic pain. This is thought to be modulated by the effect of endotoxins leaving the gut and causing peripheral and central sensitization, resulting in chronic pain. Many studies have demonstrated the pro-inflammatory effects of Omega-6 and a high Omega-6 to Omega-3 ratio, as well as the anti-inflammatory benefits of Omega-3. Systematic reviews have shown that nutritional interventions promoting a healthy eating diet, as opposed to the use of individual supplements only, have significantly reduced pain scores by -1.415 ( $P=0.030$ ) in those with chronic pain.

**Conclusion:** The gut microbiome plays an important role in pain regulation, primarily through inflammation, which can be mediated by a high Omega-6 to Omega-3 ratio. Systematic reviews have shown that a healthy balanced diet provides important pain relief in those suffering with chronic pain. More research is needed in this area; however it would seem appropriate for nutritional advice to be included in the management of chronic pain.

## Key Words

Diet; Chronic Pain; Gut Microbiome

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## Introduction

Chronic pain can be defined as pain lasting beyond the typical healing time of three months and has been shown to be the leading cause of disability in the world.<sup>1</sup> Research suggests that it affects between 35% to 51.3% of the UK population, with up to 14.3% of the population reporting this pain as severely disabling.<sup>2</sup> This has an impact on both the mental and physical wellbeing of the population as well as on our NHS, with back pain alone costing £10 billion pounds and accounting for 40% of sickness absence in the NHS.<sup>3</sup> Furthermore, many nutrition-related comorbidities such as type 2 diabetes, obesity and cardiovascular disease are associated with chronic pain.<sup>4</sup> Many of these are considered to be both cause and effect, whereby pain increases the risk of that condition, whilst that condition can exacerbate pain, shown by the higher

rates of overweight and obese individuals (80%) in those suffering with chronic pain.<sup>4</sup>

As incidence of chronic pain has increased, there has also been a rise in opioids, with prescriptions doubling between 1998 and 2018.<sup>5</sup>

In order to combat this, there has been an increased effort in offering lifestyle advice and providing a more holistic approach to pain management.<sup>6</sup> Pain management programmes now offer body reprogramming which offers a range of lifestyle advice around exercise and mindfulness; however they fail to target the potential therapeutic benefits of providing dietary advice. When 31 patients on the Cornwall pain management waiting list were surveyed, 87% said they would be interested in diet as a way of managing their pain,

with professionals involved in the pain management programme also expressing interest.

The aim of this review is to establish how diet can affect chronic pain, with the hope of creating an educational resource for patients, enabling them to manage their pain through diet. This could be of particular benefit to those on the pain management waiting lists. The efficacy of this intervention could be assessed using a chronic pain assessment tool such as the brief pain inventory.<sup>7</sup>

## Methods

An initial search about diet and chronic pain was conducted on PubMed using the following focused terms: “chronic pain”, “diet”, “gut microbiome” and “omega-3”. Abstracts were then read and if deemed suitable, the whole paper was then analysed. In order to establish suitability, the papers needed to be published in English and no earlier than 2002, with the majority of sources included having been published in 2015 or later. Where possible, high quality papers were selected such as qualitative and systematic reviews as well as randomised control trials. One cross-sectional study was also included.

## Discussion

### 3.1 Pain regulation via the gut microbiome

The gut microbiome (GM) is made up of trillions of bacteria, with no two persons' being the same. Its composition can be influenced by delivery mode at birth, where we live, how we were fed as babies and what we eat now as adults as well as physical and psychological stress.<sup>8</sup> The GM has seen a massive surge in interest in recent years, as clinicians and researchers try and identify the GM's role in health and disease, and how we can influence this through diet.

One aspect that has been identified is that the GM plays a crucial role in pain and inflammation through several different factors.<sup>9-12</sup> The GM produces many endotoxins such as lipopolysaccharides (LPS), which can cross through the intestinal wall, especially when this barrier is damaged or destroyed.<sup>10</sup> A narrative review has shown that pathogen-associated molecular pattern molecules (PAMPs) such as LPS have been shown to bind to CD14 cells, promoting the release of pro-inflammatory cytokines which can lead to peripheral sensitisation.<sup>9</sup> LPS from the GM binds to toll-like receptors (TLR), present on immune cells, hence indirectly regulating the neuronal excitability of primary sensory neurones in the dorsal root ganglia via the release of pro-inflammatory cytokines into the systemic circulation. LPS can also directly regulate the primary sensory neurones in the dorsal root ganglia, “through activation or sensitisation of the pain-related receptors [and] ion channels”.<sup>9</sup> Pro-inflammatory cytokines also increase the release of

cyclooxygenase-2 and prostaglandins in the central nervous system, by activating neuronal and glial cells.<sup>13</sup>

If this inflammatory response persists beyond normal healing time, this can lead to prolonged peripheral sensitisation as well as changes in peripheral and central neuronal structure, resulting in chronic pain.<sup>12</sup> This chronic inflammation is associated with conditions such as rheumatoid arthritis, osteoarthritis, chronic lower back pain, nociceptive pain and fibromyalgia.<sup>13</sup>

As the majority of pain syndromes are related to inflammation, it is important to note that the GM has been shown to play a key role in the development of pain and inflammation, contributing to systemic inflammation as well as inflammation in the central nervous system.<sup>11,12</sup> It is therefore of interest to identify how diet can contribute to inflammation mediated by the GM.

### 3.2 The impact of Omega-6 and Omega-6/3 ratio on the gut microbiome

Many people in the UK follow a Western diet, characterised by a high intake in saturated fats, and Omega-6, with low levels of Omega-3, as well as excessive consumption of salt and refined sugar.<sup>14</sup> Whilst it is well established that this type of diet can lead to conditions such as cardiovascular disease and diabetes, research has shown that it also contributes to inflammation.<sup>14,15</sup>

One of the key contributors to inflammation is high levels of Omega-6 and subsequent high Omega-6 to Omega-3 ratio.<sup>13</sup> A Western diet has been shown to have a ratio of around 15/1, despite the recommended ratio between 1/1 and 4/1.<sup>15</sup> Omega-6 polyunsaturated fatty acids (PUFA) have been shown to be pro-inflammatory due to their role in prostaglandin synthesis.<sup>16,17</sup> Eicosanoids such as prostaglandins and thromboxanes are synthesised through the cyclooxygenase pathway from arachidonic acid, an Omega-6 PUFA.<sup>17</sup>

As mentioned above, LPS enter the circulation when the gut microbiome barrier is damaged. LPS are thought to enter systemic circulation through the opening of intestinal tight-junctions between two epithelial cells.<sup>10</sup> High fat diets, such as the Western diet, have been shown to not only increase the amount of LPS producing bacteria in the GM, but also cause intestinal barrier dysfunction as well as increased intestinal permeability, hence allowing LPS to pass into the bloodstream more easily.<sup>10</sup>

### 3.4 Dietary interventions to aid chronic pain

Whilst a high Omega-6 to Omega-3 ratio has been shown to increase inflammation, a lower ratio with

therefore higher levels of Omega-3 has been shown to reduce the risk of many chronic diseases as well as inflammation.<sup>10,15</sup> Indeed, Omega-3 PUFAs have been found to enhance the epithelial barrier function of the gut by modifying the lipid composition of those cells, with a study on rats showing that Omega-3 PUFA supplementation leads to decreased intestinal barrier dysfunction.<sup>10,18</sup> It would be of interest to see if these findings could be replicated in human studies, due to the limited ability to correlate findings in rats to those in humans. Furthermore, Omega-3 PUFAs also inhibit the arachidonic pathway by acting as competitive inhibitors for the conversion of arachidonic acid.<sup>11</sup> This leads to decreased production of prostaglandins, whilst also giving rise to the synthesis of low-inflammatory leukotrienes which have been found to act as antagonists to arachidonic acid derived mediators.<sup>17</sup>

A cross-sectional study evaluating pain in adults with knee osteoarthritis found that in those with a higher Omega-6 to Omega-3 ratio there were higher scores for clinical pain and functional limitations, whilst a lower ratio was associated with lower levels of pain and psychological distress as well as improved physical functioning.<sup>16</sup> These findings are of course limited due to the fact it is a cross-sectional study. It should also be noted that those in the higher ratio group had a greater body mass index compared to those in the lower ratio group.

A systematic review showed that Omega-3 PUFA supplementation was associated with a reduction in the risk of chronic pain, with a pooled random effects standardised weighted mean difference (SMD) of -0.40, which shows improvement as a value of 0 indicated absence of effect.<sup>17</sup> Furthermore, those supplemented with low-dose (SMD -0.55) and short duration (-0.56) Omega-3 PUFAs were shown to be the most effective.<sup>17</sup> Those affected by dysmenorrhoea, migraines, osteoarthritis and rheumatoid arthritis were shown to have benefitted the most from the supplementation.

Similarly, a randomised placebo control trial (RCT) showed that fish oil supplementation for 16 weeks on 32 participants significantly reduced their pain score, with a 42% reduction in overall pain compared to the placebo group.<sup>19</sup> Indeed, 31 participants were given placebo and reported a pain score of 0.2 +/- 1.5, whilst those taking fish oil supplementation reported a pain score of -5.4 +/- 1.6 ( $P < 0.012$ ). This study is limited by the fact it was performed in those suffering with osteoarthritis only, with 70% of those participating describing their pain as "mild". Another RCT on

the role of Omega-3 PUFAs in the prevention of migraines, showed that in those receiving the Omega-3 supplements there was a reduction of over 80% per month in the number of days of headache, compared to 33% improvement in the placebo controlled group.<sup>20</sup> This was limited by the small sample size of 51 and once again by it specifically targeting migraines as opposed to chronic pain as a whole.

A systematic review evaluating different diets and chronic MSK pain showed that pain-reducing diets included Mediterranean, vegan and vegetarian diets but that the pain-relieving effects may be due to their anti-inflammatory characteristics.<sup>12</sup> It has been shown that these type of diets protect the diversity and stability of the gut microbiome, with high levels of dietary fibres, high Omega-3 PUFAs and low Omega-6 to Omega-3 ratio.<sup>12,21</sup>

A systematic review and meta-analysis on nutritional interventions for chronic pain showed that nutritional interventions had a significant effect on pain reduction with an overall change of -0.905 ( $P = 0.000$ ), with the most positive effect occurring when altering a dietary pattern (-1.415,  $P = 0.030$ ) or intake of one specific nutrient (-1.415,  $P = 0.000$ ) compared to those who had specific supplements (-1.213,  $P = 0.001$ ) or fasting (-0.056,  $P = 0.863$ ) prescribed.<sup>4</sup> These altered diets included vegan, vegetarian and Mediterranean diets, which as previously stated, have high levels of Omega-3 and low Omega-6 to Omega-3 ratio.<sup>12</sup> It was noted that many of the studies included were of limited quality and explored a wide range of nutritional interventions.

## Conclusion

Research has shown that the gut microbiome plays an important role in pain regulation, primarily through inflammation, with studies illustrating that Omega-6 and a high Omega-6 to Omega-3 ratio are important contributors. However, despite some RCTs showing improvement in pain with Omega-3 supplementation, systematic reviews have shown that a healthy well-balanced diet which contains high levels of Omega-3 seems to provide the most pain relief as opposed to the use of individual supplements. More research is needed in the field of nutrition and chronic pain, with more high quality interventional studies as well as those looking at nutrition advice in those with chronic pain. It would seem appropriate for nutritional advice to be included in the management of chronic pain, be that through patient information leaflets that could be distributed in general practice or pain management groups or the inclusion of a dietician in pain management programmes such as the body reprogramming one in Plymouth.



### Data availability statement

The publication is supported by multiple datasets, which are openly available at locations cited in the reference section. No new data were created in this study.

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