



REVIEW

Dietary Interventions for Treatment of Chronic Pain: Oxidative Stress and Inflammation

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ABSTRACT

Chronic pain is highly prevalent in the United States, impacting 28.4% of the adult population, or 69.6 million people, as of 2016. Chronic pain is often associated with anxiety, depression, and restrictions in mobility and daily activities, substantially reducing quality of life. Analgesics, especially opioids, are one of the primary pharmaceutical treatment methods for chronic pain. However, prescription opioid misuse and abuse has become increasingly prevalent and concerning, prompting the need for research into alternative treatment methods which avoid the side effects of traditional treatments. Chronic pain is, in part, thought to be the result of oxidative stress and inflammation, and clinical research has indicated links between these conditions and diet. Thus, dietary interventions are a particularly promising therapeutic treatment for chronic pain, with numerous studies suggesting that diet has a noticeable effect on pain as far down as the cellular level. In this review article, data from a number of clinical trials assessing the effect of three diets—antioxidant-rich, low-carbohydrate, and Mediterranean—on oxidative stress and inflammation is compiled and discussed in

the context of chronic pain. Clinical data suggests that low-carbohydrate diets and Mediterranean diets both are especially promising dietary interventions.

Keywords: Chronic pain; Diet; Inflammation; Intervention; Low-carbohydrate; Mediterranean diet; Oxidative stress

Key Summary Points

Oxidative stress may play a role in chronic pain.

Diet influences oxidative stress and inflammation.

Low-carbohydrate diets may be beneficial for chronic pain via reductions in oxidative stress.

Mediterranean diets have shown promise for reducing pain and inflammation.

Diets may be beneficial alternatives or adjuncts for chronic pain management.

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DIGITAL FEATURES

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INTRODUCTION

Chronic pain is highly prevalent in the United States and affects 28.4% of the adult population, or 69.6 million people, as of 2016 [1]. This condition is often associated with anxiety, depression, and restrictions in mobility and daily activities, substantially reducing quality of life. Analgesics are the primary pharmaceutical treatment method for chronic pain, especially opioids [2]. However, prescription opioid misuse and abuse has become increasingly prevalent and concerning, and the side effects of these drugs can also contribute to substantial declines in health and quality of life [2, 3]. There is a growing need for research into alternative treatment methods that avoid the side effects of traditional treatments [2]. Dietary interventions are one such form of treatment, with numerous studies suggesting that diet has a noticeable effect on pain [4–20]. These effects may be due to the influences diet has on oxidative stress and inflammation, which are the widely hypothesized mechanisms for chronic pain. Inflammation is present in a number of painful conditions [21–28] and reduction of inflammation is often related to a decrease in pain [15, 29–31]. It is known that oxidative stress can contribute to inflammation [32, 33], so it is reasonable that both oxidative stress and inflammation may underlie chronic painful conditions.

In this review, a number of clinical trials of dietary interventions will be examined to assess whether clinical implementation of diet has a significant influence on oxidative stress, inflammation, or pain symptoms in order to assess the potential for diet as a therapeutic treatment for chronic pain. The intention of this narrative review is to summarize the clinical trials that have shown promise as a means to reduce oxidative stress and experienced pain in

patients with chronic pain conditions. This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

OXIDATIVE STRESS AND PAIN

Oxidative stress occurs when free radical compounds such as reactive oxygen species (ROS) or reactive nitrogen species (RNS) are imbalanced with antioxidant defense systems in the body [34–36]. When certain macronutrients are consumed in excess and are broken down, natural oxidative by-products of their metabolism triggers oxidative stress responses and production of more ROS when bound to their receptors – more so than the body is equipped to handle. Excessively high levels of free radicals cause damage to essential protein, lipid, and nucleic acid components of cells, eventually leading to damage and apoptosis [37]. Under normal conditions, ROS are produced as a byproduct of metabolism of molecular oxygen [38, 39], and serve important roles in signaling pathways and responses to changes of environmental conditions [38–41]. Furthermore, under normal conditions, the antioxidant defense system neutralizes excess free radicals to prevent damage [42–44]. While oxidative stress has been associated to painful conditions [26, 45–48], the direct link is not yet understood. It is hypothesized that oxidative stress contributes to pain by exacerbating pathological responses like inflammation and neuropathy, which both contribute to pain.

OXIDATIVE STRESS AND INFLAMMATION

Inflammation occurs when immune cells respond to a multitude of biochemical and physical influences, including infection, allergens, injury, radiation, and diet-induced oxidative stress [49, 50]. Inflammation as a whole involves the release of cytokines and chemokines from immune cells that can result in sensitivity as a function of the natural

healing processes. However, prolonged inflammation can result in chronic hypersensitivity and may be related to chronic pain. Chronic inflammation can produce a number of symptoms, particularly chronic pain [22, 23, 49]. During the immune response, increased oxygen consumption by immune cells such as mast cells and leukocytes causes the release and accumulation of ROS. This initiates a cycle in which pro-inflammatory mediators like cytokines and chemokines are produced, all of which activate and recruit additional inflammatory immune cells which, in turn, release additional ROS [51]. A number of influences on oxidative stress-induced inflammation have been identified, including transcription factors, chemokines, inflammatory cytokines, and microRNAs. In addition to promoting release of reactive species, these compounds can stimulate nociceptors and afferent pain neurons, thereby contributing to chronic pain [52].

DIETARY INFLUENCES ON OXIDATIVE STRESS AND INFLAMMATION

While oxidative stress can result from a number of physical and biochemical processes including UV radiation, smoking, and air pollution, studies have identified a number of dietary influences on oxidative stress. Nutritional stress has been shown to both increase free radicals and hinder the antioxidant defense system, thereby creating an imbalance in the local environment leading to oxidative stress [53]. Diets like the standard American diet (SAD), characterized by elevated intake of processed carbohydrates and saturated fats [54, 55], have been linked to increased postprandial oxidative stress in the short term and chronic elevation of oxidative stress markers in the long term [56–60].

Carbohydrates in particular have been identified as key source of oxidative stress, specifically through glucose oxidation [37]. In this process, glucose is oxidized into a superoxide anion radical species, which causes production of ROS and RNS if not properly degraded by the antioxidant defense system [61–66].

Furthermore, excess carbohydrates promote lipid peroxidation of low-density lipoprotein (LDL) cholesterol through superoxide-dependent pathways, causing additional production of free radicals [67, 68]. Excess carbohydrates allow for glycation reactions to occur between excess carbohydrates and other nutrients like lipids, proteins, and nucleic acids, producing advanced glycation end products (AGEs) [69–74].

DIETARY ANTIOXIDANTS

Oxidative stress may be the underlying mechanism for a variety of pain-related symptoms, and it occurs when there are too many free radical species to be managed by the body's innate antioxidant defense system. Thus, supplementation with dietary antioxidants intuitively arises as a potential treatment method. Dietary antioxidants can be found in a wide variety of over-the-counter vitamins and supplements, and they can also be obtained in whole foods such as berries, fruits, nuts, chocolate, vegetables, and green tea [75]. However, the research currently available is inconclusive as to whether antioxidants obtained through diet are metabolized in a way which supplements the body's innate antioxidant defense system and thereby minimizes oxidative stress. Likewise, clinical trials examining the effects of dietary antioxidants and inflammatory markers are also inconclusive.

A number of in vitro studies suggest that dietary antioxidants like vitamin C, vitamin E, beta-carotene, and flavonoids can reduce oxidative stress in biological systems [76–79]. For example, vitamin C has been shown to minimize oxidative stress damage to lipid and protein-based cellular components, and vitamin E has been shown to prevent lipid peroxidation [76, 78, 79]. In a randomized controlled trial, adherence to a polyphenol-rich diet significantly reduced levels of the oxidative stress biomarker urinary-8-isoprostane, indicating a link between dietary polyphenol supplementation and improvements in oxidative stress in humans [80]. However, a number of other clinical trials performed indicate that

consumption of these same antioxidants and others does not yield the same results demonstrated via *in vitro* testing [79]. Current clinical evidence suggests that oxidative biomarkers are lowered by antioxidant supplementation for individuals with above-baseline oxidative stress levels, but antioxidant supplementation does not have significant impact on individuals with normal levels of oxidative stress [79].

Clinical research on the impact of dietary antioxidants on inflammation are also inconclusive. In a controlled, randomized clinical trial, participants were given antioxidant pills containing carotenoids, mixed tocopherols, vitamin C, and selenium to double their antioxidant levels as verified by diet records and blood concentrations [81]. Three inflammatory markers (interleukin-6, IL-6; monocyte chemoattractant protein-1, MCP-1; soluble intercellular adhesion molecule-1, sICAM-1) were analyzed, and despite increased antioxidant levels, no significant changes were observed for any of the inflammatory markers over the 8-week period [81].

Even still, there still is evidence that dietary antioxidants may have an effect on pain, even if not through the inflammation pathway. A 2019 study performed on individuals with knee osteoarthritis showed that over a 4-month period, participants who consumed 40 g of freeze-dried blueberry powder daily exhibited less pain, stiffness, and had less difficulty performing daily activities when compared to participants consuming a placebo [7]. However, no significant changes were found in inflammatory biomarkers, indicating that, while an effect on pain may be observable, antioxidant supplementation may have a greater effect on minimizing oxidative stress than inflammation. However, oxidative stress markers were not examined in that study.

There are a number of limitations to investigation of dietary antioxidants in clinical trials which may influence their perceived efficacy. For one, dietary antioxidants are typically implemented in the clinical setting as secondary prevention methods, meaning they are implemented after oxidative stress has already caused progression of the disease state, at which point cellular damage has surpassed the

antioxidant defense system's capabilities. Furthermore, the exact mechanisms of many antioxidants and their relation to specific diseases (such as chronic pain) are unknown, thereby complicating whether failure of a particular dietary antioxidant for a condition can conclusively rule out all dietary antioxidants [79].

LOW-CARBOHYDRATE DIETS

Given the substantial impact carbohydrates have on producing oxidative stress, research has pointed to low-carbohydrate diets as means to reduce oxidative stress and potentially aid with chronic pain. While clinical data on implementation of these diets is limited given their recent attention, some clinical studies have been performed with positive results. In a randomized, controlled trial in groups administered either a hypocaloric high-protein diet (low calorie, high protein and low carbohydrate) or a hypocaloric high-carbohydrate diet (low calorie and high carbohydrate) over a 6-month period, participants in the high protein/lower carbohydrate group demonstrated a greater decrease in both oxidative stress and inflammatory markers [82]. While pain itself was not measured in this study, oxidative stress and inflammation are the theoretical underlying mechanisms for pain; however, more recent clinical studies have shown a more direct association between decreases in these biomarkers and decreased pain perception. In a randomized, controlled trial of 21 study participants diagnosed with knee osteoarthritis, study participants were assigned to either a low-carbohydrate diet (LCD), a low-fat diet (LFD), or their own diet over a period of 12 weeks. Participants in the LCD group showed reduced task-related pain, reduced self-reported pain, and lower oxidative stress blood serum biomarkers when compared to LFD and control group participants. However, the study noted a number of factors that may influence results that were not tested due to the low sample size, including race/ethnicity differences and sex differences [19]. Importantly though, these findings demonstrate the potential of a low-

carbohydrate diet as a therapeutic treatment for pain, as well as for other pain disorders associated with increased oxidative stress.

MEDITERRANEAN DIET

The Mediterranean diet has received attention due to positive experimental results with respect to cardiovascular disease and other conditions [83, 84]. While clinical studies vary in their implementation of the Mediterranean diet, the diet is generally defined by daily consumptions of fruits, vegetables, whole grains, and healthy fats, especially monounsaturated fatty acids (MUFAs) from virgin olive oil. Furthermore, the Mediterranean diet entails limited intake of red meat and dairy, with a focus on fish, poultry, beans, and eggs as the primary sources of protein [85]. While many of these characteristics contrast with the standard American diet, one key difference is in fat consumption. According to the 2015–2020 “Dietary Guidelines for Americans,” the recommendation for saturated fat consumption was 10% of total energy intake. However, saturated fats account for around 19% of the average American’s energy intake, while in the Mediterranean diet, saturated fats account for just 9%, with a greater emphasis on MUFA consumption [85, 86]. It is worth noting that the traditional version of the Mediterranean diet is naturally low in processed carbohydrates and may be considered a version of a low-carbohydrate diet.

In a 2014 study conducted among adults with elevated risk for cardiovascular disease, study participants were given a Mediterranean diet supplemented with either extra virgin olive oil or nuts for a 12-month period. When compared a low-fat diet group, the participants given the Mediterranean diet exhibited a significant reduction of inflammatory biomarkers C-reactive protein and IL-6. Interestingly, when comparing the two intervention groups, those given nuts showed more than double the reduction of inflammatory biomarkers [87]. Another study focusing on the effects of olive oil polyphenols in the Mediterranean diet assigned study participants a Mediterranean diet using virgin olive oil or washed olive oil,

which has a lower polyphenol count. When compared to the control group, both groups showed decreased plasma oxidative stress and inflammatory biomarkers [Konstantinidou, 2010 #5158]. Furthermore, gene expression was also examined in the context of atherosclerosis-related genes, which identified the key role of polyphenols in the down-regulation of proatherogenic genes, which normally contribute to arterial plaques [88]. These findings indicate that olive oil consumption in the Mediterranean diet may be an important factor in reduction of oxidative stress and inflammation. Furthermore, the identification of a link between olive oil polyphenols, a dietary antioxidant, and genetic changes may be an important precedent for studies examining oxidative stress and chronic pain-related genes.

DISCUSSION

The available data supports the notion that the most promising diets for addressing chronic pain through the oxidative stress and inflammation pathways are the low-carbohydrate diet and Mediterranean diet (Table 1). Dietary antioxidants appear to play a potential role in reduction of chronic pain; however, clinical data is less conclusive. Unfortunately, none of the diets studied are particularly well researched in the context of chronic pain with an emphasis on oxidative stress, and future studies will be required before clinicians should consider prescribing a diet as treatment for pain.

A number of limitations are present which influence the strength of the conclusions. First, results were limited due to the small number of clinical studies examining diet and oxidative stress/inflammation. This scarcity could be due to a number of factors, such as the novelty of the treatment method, but one key factor hindering the prevalence of clinical studies is that diet studies are particularly challenging due to the significant change in lifestyle required of patients. This key element makes diet interventions a less appealing treatment for most diseases over pharmaceutical treatments, even when medications have negative side effects. However, a strong case can be made that dietary

Table 1 Compilation of dietary clinical trials and outcomes

Diet	Study Population	Location	Duration	Primary Outcome	Reference
Low-carbohydrate	Adults with knee osteoarthritis	USA	12 weeks	Reduced evoked pain, reduced TBARS (oxidative stress)	[19]
Low-carbohydrate	Obese, premenopausal women	USA	6 months	Reduced markers of oxidative stress and inflammatory cytokines	[83]
Antioxidant (polyphenols)	Overweight/obese adults	Italy	8 weeks	Reduced urinary-8-isoprostane levels (oxidative stress)	[80]
Antioxidant (carotenoids, tocopherols, vitamin C, selenium)	Adults with elevated risk for cardiovascular disease	USA	8 weeks	No significant changes in inflammatory markers (IL-6, MCP-1, sICAM-1)	[81]
Antioxidant (Whole blueberries)	Adults with symptomatic knee osteoarthritis	USA	4 months	Reduced pain, stiffness, and movement difficulties, improved gait, no significant changes in inflammatory markers	[82]
High-fat (saturated)	Adults with metabolic syndrome	USA	8 hours	Increased postprandial TBARS (oxidative stress), increased IL-1 β (inflammation)	[59]
Mediterranean Diet: High unsaturated fat via Virgin Olive Oil (VOO) & Nuts vs low-fat	Adults with elevated risk for cardiovascular disease	Spain	12 months	Reduced IL-6 and sICAM (inflammatory markers) in MD groups	[88]
Mediterranean Diet (MD): High unsaturated fat via Virgin Olive Oil (VOO) polyphenols	Healthy adults	Spain	3 months	Reduced plasma oxidative stress and inflammatory markers in MD+VOO (retained polyphenols) group	[90]

Outcomes are color coded by overall effect, with green representing a positive effect, red representing a negative effect, and yellow representing no significant overall effect

interventions primarily have positive side effects. Thus, when deciding between treatments, both clinicians and patients should consider the costs and benefits of both pharmacotherapy and diet interventions. In fact, it may be the case that the two can be used in conjunction with the hope of tapering medication as the positive benefits of the diets are experienced.

Furthermore, within the few available studies examining the influence of diet on oxidative stress and inflammation, only two were specifically conducted in the context of chronic pain and measured pain of participants [7, 19]. While there is evidence to suggest the link between the oxidative stress/inflammation pathways and chronic pain, other potential factors beyond oxidative stress and inflammation may play important roles. Unless a study directly measures participants' perceived and evoked pain, there is a level of skepticism that must be maintained about the study's impact on chronic pain.

Inherent in clinical trials of diet interventions in this area are inconsistencies in diet characteristics make comparisons from study to study challenging. There are no standardized clinical research definitions for the exact specifications of a low-carbohydrate or Mediterranean diet; rather, exact implementation of a particular diet is subject to researchers' interpretations. Additionally, some interventions may focus on one macronutrient category (i.e., fats) and, in order to maintain an isocaloric diet, the other macronutrients have less rigor applied from day-to-day. Thus, a study may examine a low-fat diet, but some participants could increase their carbohydrate consumption while others increase proteins. Overall, the group as a whole reduced their fat intake, but the other aspects of the diet were dramatically different, possibly leading to variability in results.

A significant for the implementation of a dietary intervention is the substantial impact that one's socioeconomic status, environment, and culture have on diet and ability to access various foods. Chronic pain disproportionately affects minority groups [90] with typically lower socioeconomic status (SES) [91]. Similarly, epidemiological studies have shown that social

class and resulting SES predict the quality of a person's diet with higher SES being associated with healthier diets [92]. Over multiple studies comparing the Mediterranean diet to the Western diet, the Mediterranean diet is more expensive and the cost is positively related to adherence [93, 94]. It should be noted that one systematic review compared the cost of the Mediterranean diet to the average healthcare costs for a number of conditions between those adhering to the diet and those who did not. The researchers found that adoption of the Mediterranean diet increased quality of life and may extend lifespan to a moderate degree for those with various medical conditions [95]. Thus, the long-term gain in health and quality of life may supersede the short-term increase in cost.

Unfortunately, carbohydrates are typically the least expensive component of the standard American diet. Therefore, prescribing a low-carbohydrate diet is likely to increase daily food costs and is worth careful consideration, especially for those with lower SES. Furthermore, diet plays an especially important role in one's identity and culture. Thus, in prescribing a diet such as a low-carbohydrate diet, key cultural components of the standard diet should be identified and substitutes recommended to maintain the basics of the diet. For example, patients from cultures with high rice consumption could be advised to consider a lower-carbohydrate option such as "riced" cauliflower, which can be inexpensive satisfying cost-related issues.

CONCLUSIONS

Out of the diets identified to have clinical evidence supporting their potential to reduce oxidative stress, inflammation, and/or chronic pain, the most promising diets are the low-carbohydrate diet and the Mediterranean diet. Dietary antioxidant supplementation also appears to have an impact, but studies have had conflicting results. Added to that are the individual differences in absorption of vitamins and minerals between sexes [96] and across racial groups [97]. It is a possibility that diet

interventions will need to be tailored to patients based on conditions, sex, and race/culture. More research is needed to examine the ways that diets impact pain, inflammation and chronic pain, but the limited results are promising. With a sensitivity to SES and culture, diet interventions may be alternative or complimentary strategies for chronic pain that have the potential to promote health and extend lifespan.

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