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Review

The Relevance of Diet in Musculoskeletal Clinical Practice—A Narrative Review

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Abstract

Musculoskeletal (MSK) pain is a multifaceted problem, with many contributors. The assessment of these contributions by clinicians has evolved to include not only the musculoskeletal and nervous systems, but also psychosocial contributions. Nutrition, however, has not been considered as a potential contributor in the same way, despite a significant body of evidence showing that amending one's diet may significantly reduce pain and inflammation. Historically, when the biomedical model was considered the gold standard for patient management, MSK medicine failed to adequately manage a significant cohort of patients, owing to potential psychosocial contributors to pain and disability being largely ignored. This review argues that clinicians may be making the same mistake with diet, failing to grasp the relevance of nutrition in MSK pain states. Clinicians should consider utilising a 'nutritionally-informed' approach for their patients, encouraging a reduction in

ultra-processed foods and refined carbohydrates, whilst encouraging a focus on nutrient dense whole-foods.

Keywords
Diet; carbohydrate; osteoarthritis; antioxidants; physiology; inflammation; ultra-processed foods; metabolism

1. Introduction

Diet determines the fuel provided for cellular energetics and metabolic processes. It can either facilitate health and vitality or drive metabolic dysregulation and disease. The prevalence of chronic metabolic (or lifestyle) diseases, such as obesity and diabetes, is growing rapidly. Of the 19,000 patients accessing tertiary adult pain services in Australia and New Zealand in 2022, 45% had three or more comorbidities [1]. As such, nutrition and metabolic health are a relevant consideration for most patients under the care of MSK clinicians, with evidence showing that dietary change may significantly reduce MSK pain [2, 3]. Despite this, MSK clinicians are unlikely to evaluate the role of diet as part of a physical assessment and are poorly equipped to guide patients toward dietary changes to improve pain outcomes. Owing to the vagaries of scope of practice, clinicians with an interest in diet/nutrition are often uncertain as to what advice they may offer. Diet can have both a positive and negative impact on pain [4, 5], with therapeutic nutrition a plausible pain-management strategy [6, 7]. By considering how simple dietary advice might impact the MSK system positively, clinicians may offer useful, non-controversial advice to compliment treatment.

Our modern diet has altered radically since the industrial revolution. Notable changes include altered fatty acid composition through the introduction of industrially processed oils and trans-fats, glycaemic load (high intake of refined carbohydrate and added sugar), micronutrient balance (such as lower intakes of vitamins D and K) and altered dietary fibre intake. The standard Western diet is now high in ultra-processed, hyperpalatable, nutrient-poor foods (UPFs). These changes in diet quality and composition are a source of oxidative stress, which drives low-grade systemic inflammation (metaflammation), resulting in not only chronic disease [8, 9], but MSK pain too [10]. Common MSK pain presentations related to poor nutrition include joint pain (e.g., spinal, knee, hip), tendinopathy (e.g., rotator cuff, Achilles, gluteal), nerve dysfunction (e.g., sciatica, diabetic neuropathy) and headache [11].

Given these potential links between nutrition and MSK pain presentations, the consideration of habitual diet and how it might be contributing to overall inflammatory loading and soft tissue health is an underutilised pain management tool. A recent systematic review and meta-analysis of whole-food diets used to treat chronic pain subjects, showed that diet had an overall positive effect on pain outcomes, regardless of diet type. It concluded that diet quality, nutrient density, and weight-loss all likely played a role in pain reduction. The recommendation for future research was to consider how nutrition might modulate pain physiology (such as inflammation, oxidative stress and nervous system excitability) [3]. General nutrition recommendations for people with chronic pain include a whole-food diet that includes vegetables, fruit, quality meat, dairy, healthy

fats, adequate water, and the reduction of both UPF and added sugars [11]. This review aims to outline several biological mechanisms that may contribute to pain, as well as suggest specific dietary advice that can both easily and safely be given within the context of MSK clinical practice.

2. Biological Mechanisms Linking Pain

2.1 Obesity and Pain

Adipose tissue is a dynamic and highly metabolically active endocrine organ, producing a range of signalling molecules (hormones such as adiponectin, leptin and resistin) that regulate hunger and metabolism. When the body is under chronic stress (physical or emotional), adipose tissue releases adipocytokines that trigger inflammatory cascades, with resultant chronic metaflammation [12]. There are various proposed mechanisms that trigger such a response, including: a) increased gut permeability, allowing entry of antigens and/or dietary components (such as lipopolysaccharides from gram positive bacteria or free-fatty acids), which trigger pattern recognition receptors on adipocytes; b) reduced oxygen supply and increased mechanical load on the adipocyte, owing to fat accumulation; and c) adipocyte death, with hypertrophic adipocytes more susceptible to injury and death [12, 13]. Given the potential inflammatory properties of adipose tissue, its relationship to pain presentations becomes relevant, and could be presented to patients in a way that is physiologically informed to minimise the stigma of obesity [14].

Chronic pain is frequently co-morbid with obesity, with potential pain contributors including increased inflammation, increased joint loading and changes in the microbiome [13]. High BMI is linked to a range of MSK complaints including greater pain severity in hands, feet, knees, and hips [15]. Obesity is also associated with the presence and severity of low back pain, irrespective of age and sex [16]. A lifetime BMI over 25 increases the risk of degenerative disc disease, with a stronger effect observed if BMI is high in early adulthood compared to middle-age [17]. Historical data demonstrates that a poor-quality diet contributes to obesity, and lifestyle interventions that reduce adiposity to improve metabolic outcomes [18, 19], could also plausibly contribute to pain reduction. Research into UPF demonstrates its unique ability to both increase weight and ad libitum caloric intake [20], hence addressing the quality of the habitual diet is critical to weight management and subsequently important for pain outcomes.

Whilst patient obesity has long been considered disadvantageous in pain states, the inference has been that excess bodyweight places increased mechanical load on the body, trunk, and lower limbs in particular, resulting in increased pain. Such a hypothesis fails to explain the increased prevalence of MSK dysfunction in the (relative) non-weightbearing upper limb in this population [21]. For example, hyaline cartilage thickness increases in response to progressive loading [22], with logic suggesting that lower limb chondral health should thus be better in the obese. However, such is not the case, suggesting that increased bodyweight may not be the main contributor to pain in symptomatic lower limb osteoarthritis (OA). The significant driver instead appears to be inflammation, with inflammatory cytokines produced by adipocytes (adipokines) driving immune-mediated inflammation of the synovium. This metabolic OA (a newly defined phenotype of OA) associated with metabolic syndrome and obesity, results in pain as well as the progression of joint degradation [23, 24]. Biomechanical load is also relevant but extends beyond the simple ‘wear and tear’ analogy. Mechanoreceptors located in chondral cartilage detect obesity load and trigger inflammatory signalling within the chondrocytes [25]. Increased levels of leptin in obese

individuals have been shown to be pro-inflammatory [26] and have a direct association with cartilage inflammation and degeneration [25, 27].

The relationship between changes in the microbiome, obesity and pain is emerging. It is unclear whether the changes are directly related to obesity or are due to the inflammation that it generates. A reduction in the diversity of the microbiome has been demonstrated in people with chronic widespread pain (such as fibromyalgia) [28] as well as a change in overall microbiome composition in those with chronic low back pain [29]. As noted earlier, non-weight bearing joints are also common pain sites in obese subjects. Microbiome changes are a plausible contributing factor, with diet-related gut dysbiosis and increased gut permeability facilitating inflammatory processes in hand OA [30].

2.2 Inflammation and Pain

Prolonged inflammation can facilitate chronic pain. Many inflammatory and neuropathic pain conditions are associated with the NLRP3 (nucleotide-binding oligomerization domain and leucine-rich repeat protein 3) inflammasome, an upstream inflammatory precursor to a wide range of inflammatory pathways [31]. Pro-inflammatory cytokines are linked to the amplification of nervous system excitability seen in central sensitisation [32], with an increase in systemic inflammation demonstrated in chronic low back pain [33], chronic neck pain intensity, disability, and hyperalgesia [34], and general chronic pain presentations [35].

Tendon healing requires an initial inflammatory response however it is adversely affected by prolonged low‑grade inflammation [36], with inflammatory mechanisms linking obesity and chronic tendinopathy [37]. Hyaline cartilage is also adversely affected by inflammation as noted previously in the context of obesity, with the NLRP3 inflammasome promoting several pro-inflammatory pathways, facilitating enzymes that cause matrix degeneration [38].

2.3 Glycaemic Control and Pain

Glycaemic control refers to the body's ability to maintain blood glucose concentrations within a narrow 'healthy' band. Chronic elevation of blood glucose (hyperglycaemia) results in increased production of insulin to lower glucose to acceptable levels. When insulin remains high (hyperinsulinaemia), the ability of insulin to produce its normal response in various tissues is blunted (insulin resistance), requiring even greater insulin production. Blood glucose measures (such as fasting blood glucose and HbA1c) are not necessarily good indicators of hyperinsulinaemia, as the higher insulin production may still be able to lower blood glucose to acceptable levels. As such, hyperinsulinaemia may go undiagnosed for many years. Both hyperglycaemia and hyperinsulinaemia are linked with MSK pain conditions.

Type 2 diabetes (T2DM) is characterised by chronic hyperglycaemia and hyperinsulinaemia with an increased risk of developing MSK pain [39]. MSK conditions with greater prevalence in T2DM include carpal tunnel syndrome, frozen shoulder contracture syndrome, palmar flexor tenosynovitis (trigger finger) and Dupuytren's disease [40], along with emerging evidence implicating diabetes mellitus as a contributing factor in lumbar degenerative disc disease [41]. This is reflected in a higher number of doctor visits for MSK conditions in diabetics versus non-diabetics [42]. In a large study, mean fasting glucose concentrations were higher in subjects with OA vs

subjects without OA, yet diagnosed T2DM was only present in 5.5% subjects [43], suggesting that elevated blood glucose even at pre-diabetic levels is associated with OA progression.

Given the fact that insulin levels increase for many years prior to a T2DM diagnosis, and the high rates of pre-diabetes and metabolic syndrome in the general population, glycaemic control and increased insulin levels should be screened for in MSK pain. Hyperinsulinaemia plays a role in exacerbating inflammation and cartilage degeneration [44] as well as potentially in the development of central pain with fibromyalgia [45].

2.4 Oxidative Stress and Pain

The formation of free radicals such as reactive oxygen species (ROS) are an inevitable byproduct of aerobic glucose oxidation. ROS form a part of normal metabolism, acting as signalling molecules to provide a dynamic response to changing metabolic conditions. However, high ROS concentrations cause both cell damage and apoptosis. Antioxidative systems within the cell are needed to scavenge ROS or transform them into less reactive compounds. Oxidative stress results when endogenous antioxidant defences are overwhelmed and cannot maintain balance [46]. Oxidative stress is implicated in many painful MSK conditions [47] by facilitating inflammation (implicated in intervertebral disc degeneration [48] for example), neuropathy [46] and central sensitisation [47, 49].

2.5 Chemical Additives and Pain

UPF typically has lower nutritional quality (such as reduced vitamins and minerals), non-food additives (such as emulsifiers and preservatives), changes to the food matrix (such as removal of fibre), plus the presence of other contaminants from processing or packaging [50]. The impact of these on the gut biome and cells in the body appears to trigger low-grade inflammation that in turn drives metabolic dysregulation [50] and underpins many MSK pain disorders. UPF has been demonstrated to increase both post-prandial and chronic levels of oxidative stress [46], and may also be responsible for astrocyte activation, producing neuroinflammation and maladaptive neuroplasticity [51] associated with the progression from acute-to-chronic pain.

3. Therapeutic Nutrition Advice for MSK Pain

3.1 Recommendation 1: Minimise Ultra-Processed Food Intake

Reduction in dietary intake of UPF has been shown to benefit MSK health. In a cross-sectional analysis, researchers found a positive association between an energy dense dietary pattern (characterised by high consumption of UPF) and chronic low back pain, but found a negative correlation with high protein dietary pattern (characterised by consumption of meat, eggs, legumes, and nuts) [52].

The NOVA classification system [53] (Table 1) can be used as a simple guide for patients to understand ultra-processed foods. An additional recommendation is to read the ingredient list on food label packaging and ensure that the listed ingredients are whole foods and not additives. Encouraging home cooking from source ingredients will encourage a minimally processed diet.

Table 1 NOVA Classification.

Nova 1	Nova 2	Nova 3	Nova 4
Unprocessed or minimally processed foods	**Processed ingredients**	**Processed foods**	**Ultra-processed food and drinks**
Unprocessed foods include the natural edible food parts of plants and animals. Minimally processed foods have been slightly altered for the main purpose of preservation, but which does not substantially change the nutritional content of the food. Examples include cleaning and removing inedible or unwanted parts, grinding, refrigeration, pasteurization, fermentation, freezing, and vacuum-packaging.	Food ingredients derived from a minimally processed food by pressing, refining, grinding, or milling. They are typically not eaten on their own but used to prepare minimally processed foods.	Foods from either of the two previous groups that have added salt, sugar, or fats. These foods usually are made from at least 2-3 ingredients and can be readily eaten without further preparation.	These are foods from the prior group that go beyond the incorporation of salt, sweeteners, or fat to include artificial colours and flavours and preservatives that promote shelf stability, preserve texture, and increase palatability. Several processing steps using multiple ingredients comprise the ultra-processed food. They are typically ready-to-eat with minimal additional preparation. These foods tend to be low in fibre and nutrients.
Fresh fruits, vegetables, whole grains, rice, nuts, meats, seafood, herbs, eggs, and milk.	oils from plants, seeds, and nuts, or flour and pastas formed from whole grains.	canned fruits and vegetables, some cheeses, freshly made bread, and canned fish.	sugary drinks, flavoured milks, energy drinks, packaged breads and buns, cookies, crackers, chips & fries, takeaway food, ice-cream, flavoured yoghurts, breakfast cereals, frozen dinners, hotdogs, chicken nuggets, pizza, burgers, sauces, and luncheon meats.

3.2 Recommendation 2: Optimise Omega-3 Intake

There is good evidence that increasing dietary omega-3 polyunsaturated fatty acid intake improves MSK health. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) represent 2-different, but equally important groups of essential fatty acids. Omega-3 PUFAs are precursors for molecules (such as resolvins) that regulate and resolve inflammation [54], thus higher levels of omega-3 PUFAs (such as linolenic acid and eicosapentaenoic acid) are associated with lower levels of inflammatory mediators and anti-nociception [55, 56]. Omega-6 PUFAs (such as linoleic acid and arachidonic acid) are equally important [57] and contribute to several necessary pro-inflammatory functions, including the generation of prostaglandins (derived from arachidonic acid), vital to the inflammatory process.

High levels of omega-6 PUFAs are associated with inflammation and nociceptive processing [56, 58]. A diet containing a high ratio of omega-6:omega-3 PUFAs is associated with many pain conditions [58, 59], with a high ratio positively associated with inflammatory biomarkers such as

C-reactive protein (CRP) in people with chronic pain [60]. The standard Western Diet provides an omega-6:omega-3 PUFA ratio as high as 20:1, markedly greater than the 4:1 ratio or less, proposed for optimal health [61]). An increase in omega-3 PUFAs has been shown to reduce inflammation, pain, and tissue degeneration [62, 63].

The removal of UPF from the diet improves the omega-6:omega-3 ratio by default, as many of these foods are cooked in, or use vegetable oils that are predominately highly processed omega-6 fats. The focus of this recommendation would be the inclusion of whole foods such as oily fish, grass-fed beef, dark leafy greens, free-range eggs, chia, walnuts, and flax seeds to increase omega-3 consumption. Omega-3 supplementation could be considered for those who cannot eat foods with adequate omega-3.

3.3 Recommendation 3: Optimise Antioxidant Intake

Oxidative stress can occur from many environmental sources (such as pollution or smoking), however habitual diet also influences oxidative stress levels, either negatively (by increasing free radicals through UPF) or positively (through whole foods containing antioxidants). As such, antioxidants consumed through the diet are vital for optimal cellular health. Many compounds found in whole foods have been demonstrated to have anti-inflammatory, antioxidant and antinociceptive properties. These include phytochemicals such as polyphenols and flavonoids found in foods such as vegetables, berries, fruits, nuts, tea, herbs, and spices [46, 64], and are characteristics of whole-food dietary patterns such as the Mediterranean diet. Consumption of vegetables, which contain many antioxidants, is inversely associated with inflammation and oxidative stress in adults: the higher the consumption of vegetables, the lower the occurrence of inflammation and oxidative stress [65]. This benefit can be seen in specific conditions, with the antioxidant effect from phytochemical-containing foods playing a protective role by regulating pathways involved in the destruction of the extracellular matrix in intervertebral discs [48]. The removal of discretionary UPF, in conjunction with a focus on varied whole foods, will promote a diet higher in antioxidants.

3.4 Recommendation 4: Minimise Refined Carbohydrate (CHO) and Added Sugars

Metabolism of CHO results in ROS production, leading to inflammation if there is inadequate antioxidant defence [46]. In addition, excess dietary CHO will promote hyperglycaemia, facilitating glycation with other molecules (such as proteins and lipids) and resulting in advanced glycation end products (AGEs) [46]. The accumulation of AGEs is associated with the duration of hyperglycaemia [66], however AGEs are also acquired exogenously through diet, with the highest contribution from foods that are ultra-processed and contain refined CHO [67]. Owing to their slow metabolism, AGEs tend to accumulate and cause abnormal cross-linking of proteins, such as collagen, which alters their structure and function leading to tissue fibrosis [68]. Furthermore, AGE receptors on numerous cell types are activated, resulting in inflammation [67]. AGEs also produce ROS, further adding to oxidative stress load. AGEs accumulate in various neuromusculoskeletal tissues, such as bone, cartilage, muscle, tendon, ligament, and nerve, where they adversely affect their biomechanical properties, triggering damage [66]. They are linked to many varied aging and diabetes-related pathological conditions, including OA, osteoporosis, sarcopenia, tendinopathy and neuropathy [66].

An ever-increasing body of evidence suggests that reducing dietary CHO may reduce systemic inflammation [69, 70], thereby benefiting MSK health. A low CHO diet is defined as any diet below 130 g/day CHO or 26% total energy intake (TEI). A very low-CHO is less than 50 g/day or 10% TEI. The Australian dietary guidelines recommend limiting added sugars, but still recommend between 45-65% TEI coming from CHO [71]. These dietary guidelines are designed for a healthy population to reduce the risk of chronic disease, however, they do not provide recommendations for those already burdened with chronic disease. The U.S National Institutes of Health reports that one in three adults has metabolic syndrome, and with the noted links between metabolic health and pain, a more nuanced discussion around CHO intake is required. Because a low CHO diet does not adhere to current government dietary guidelines, in some circles, it continues to be rejected as an option, despite growing evidence to the contrary [72].

A diet high in added sugar and processed CHO leads to insulin resistance, and a pro-inflammatory state [72]. High blood glucose levels have been shown to affect pain and inflammation, both separately and in combination [69], with high blood glucose levels driving systemic low-grade inflammation, resulting in sensitisation of sensory neurons (via receptors/channels on neurons and microglia) [73]. The reduction of dietary CHO is a potential treatment to reduce neuronal excitability, thereby benefiting pain states [74]. Further evidence that reducing glucose will improve pain outcomes is the advocating of metformin (antihyperglycemic drug) for the treatment of chronic pain [75].

Whilst the implementation of a very-low CHO diet for chronic pain treatment may be controversial (but with a growing body of supporting evidence [76-78]), and in the purview of a dietitian to administer, the simple recommendation to reduce refined UPF, CHO and added sugars is universally endorsed. A recent clinical trial, involving chronic MSK pain sufferers, compared a very-low CHO diet to one that removed UPF. Both groups realised a significant improvement in pain, with greater reduction in both pain and inflammation in the very-low CHO group. Authors observed that the simple removal of UPF reduced CHO intake by 57 g/day, down to 156 g/day (34% TEI), a CHO intake below the recommended national dietary guidelines [76]. The overarching recommendation, regardless of the various mechanisms related to pain physiology, is to focus on a variety of whole real foods and remove UPF from the habitual diet.

4. Clinical Example - Knee Osteoarthritis

Osteoarthritis (OA) is the most common and disabling rheumatic disease worldwide, affecting 15% of the population [79]. It is an active disease process, with hyaline cartilage destruction driven by both biomechanical and, more importantly, pro-inflammatory factors. The main pathophysiological mechanism underlying obesity-associated OA is chronic inflammation [80].

Regular exercise is accepted as the cornerstone of non-surgical active management of knee OA, with physical therapies playing an important role. Whilst a significant percentage of knee OA patients realise improvement, there is also a significant subgroup who do not [81]. Considering the adverse effects of drug therapy, limited efficacy of surgical intervention in mild-to-moderate cases and long-term public health benefits of effective treatment for OA, chronic metaflammation should be considered a potential significant driver of a patient's recalcitrant knee pain. By removing UPFs, increasing omega-3 intake, focusing on nutrient-dense whole foods, plus reducing

refined CHO and sugar intake, we may modulate physiological processes in a way that improves pain outcomes.

A recent RCT tested the efficacy of 2-dietary interventions vs a control diet in knee OA [77]. 21-adults with knee OA (age 65-75) followed a low-CHO (ad libitum) vs low-fat (calorie-restricted) vs 'continue to eat as usual' diet for 12-weeks. A variety of outcome measures including functional pain (repeated chair stand, timed walk, temporal summation), self-reported pain, quality of life (QoL) and depression score were used. Bloods were analysed pre- and post-diet intervention for oxidative stress. The low CHO diet group improved self-reported pain, functional pain and QoL compared to both the low-fat and control diets. Despite both the low-fat and low-CHO diet groups losing significant weight (greater than 7.5% body-weight on average), the low-CHO diet significantly reduced oxidative stress (CRP, leptin) vs both the low-fat and control diets, with a reduction in oxidative stress correlating to reduced functional pain [77].

In a secondary analysis of a study involving a CHO-restricted diet in type-2 diabetics, knee outcome measures (KOOS) were used to assess the effect of diet on knee function and to identify if changes in weight, central abdominal fat, glycaemic status, or CRP levels were associated with knee pain improvement. The low-CHO group demonstrated significant improvement in KOOS at both 1- and 2-years vs controls who showed no significant change at any time point. A reduction in central abdominal fat and reduction in CRP levels were associated with an improvement in KOOS [82].

Whilst physical therapies play an important role in the non-surgical management of knee OA, clinicians may be able to affect greater improvements if they consider discussing diet with their patient as part of an active management approach. Particularly important would be the notion that focusing on weight-loss may not be the key, but rather aiming to reduce the pro-inflammatory nature of one's diet.

5. Conclusion

Pain may be underpinned by a variety of different drivers. The multiple biological mechanisms impacted by diet that have been described are linked by the commonality of increased inflammatory loading. As such, the pro-inflammatory nature of a patient's diet should be one consideration. Modifying food intake may improve chronic pain and/or inflammation in MSK pain patients. Why have we not seen the evolution of 'nutritionally-informed' patient management? Whilst MSK clinicians neither wish, nor claim, to be dietitians, they have an opportunity based on recent evidence to guide people in the direction of better nutritional wellbeing, confidently discussing the relevance of diet in chronic systemic inflammation. If the patient's nutritional health appears to be complex, a dietetic referral would be the considered next step. Clinicians involved in treating MSK pain states are encouraged to consider diet as a potential contributor to a patient's pain and dysfunction, in much the same way they do when considering the relevance of mental health.

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Competing Interests

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