Journal of Pain & Relief

Loseli et al., J Pain Relief 2015, 4:3
DOI: 10.4172/21670846.1000180

Mini Review Open Access

A Review of Nutraceuticals in Joint Arthritis

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Rec date: Feb 16, 2015, **Acc date: Apr 20, 2015**, **Pub date: May 06, 2015**,

Abstract

The use of nutraceuticals and supplements is common in the management of joint pathology. Due to this popularity, it is important that clinicians are aware of these therapies and have a basic understanding of them. Scientific studies examining the effects of nutraceuticals in joint arthritis are increasing. This short update aims to provide a commentary on the recent developments of these therapies commonly used in rheumatoid and osteoarthritis aiming to summarise their characteristics and efficacy.

Keywords: Nutraceuticals; Osteoarthritis; Glucosamine; Chondroitin; Krill oil; Fish oil; Gamma linolenic acid; Avocado-soybean unsaponifiables

Introduction

Rheumatoid arthritis (RA) is a systemic chronic inflammatory joint disease that mainly affects synovial joints causing pain and disability. Patients with RA report achieving optimal pain relief as their highest priority [1]. Similarly, osteoarthritis (OA) is a chronic, disabling disease that is prevalent within our aging population. Treatment of OA has largely been centred on exercise, weight loss, analgesia and joint replacement surgery. RA management has seen recent success with the introduction of disease-modifying antirheumatic drugs [2].

Nevertheless, alternative therapies including nutraceuticals and supplements in the management of joint disease are on the rise. Nutraceuticals are foods or products that may provide health benefits and relief for some medical diseases. The European Nutraceutical Association defines nutraceuticals as "nutritional products which have effects that are relevant to health. In contrast to pharmaceuticals however, these are not synthetic substances or chemical compounds formulated for specific indications. These are products that contain nutrients (partly in concentrated form) and are assigned to the category of food". Some of the most commonly used nutraceuticals in joint pathology include glucosamine, chondroitin [3,4], krill oil, fish oil, gamma linolenic acid and avocado-soybean unsaponifiables [5]. There have been several clinical trials aiming to elucidate the efficacy of these products and the results have been variable [6].

Glucosamine

Glucosamine is an aminosaccharide that occurs naturally in the body. It is important in the biosynthesis of proteoglycan which is vital in maintaining cartilage integrity [7,8]. It is one of the most commonly used supplements in patients with OA at a recommended dose of 1.5 g daily. Glucosamine exists in many formulations, but it is the sulphated form that is more commonly used in clinical trials. Glucosamine and chondroitin, or a combination of the two has been extensively studied. Potential advantages of glucosamineuse are minimal adverse effects and possible clinical improvement of symptoms. Glucosamine is considered to be safe and serious or fatal adverse events have not been previously reported. Nevertheless, it should be used with caution in patients with shellfish allergies as it is extracted from chitin contained in shellfish [9]. Studies in the literature have raised questions regarding its efficacy in joint arthritis with various randomised control trials (RCTs) describing conflicting results. A recent meta-analysis of 3,803 patients (10 studies) compared glucosamine, chondroitin and placebo in patients with knee or hip OA [10]. These smaller studies concluded that compared with placebo; glucosamine, chondroitin, and their combination do not reduce joint pain or stem disease progression. In contrast, other studies suggested there is a synergistic effect when combining glucosamine with chondroitin in a subset of patients. The Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) was a multicentre, participant and investigator blinded trial of 1,583 patients. Participants were included if they were at least 40 years of age and showed clinical and radiographic evidence of OA. Patients were then randomly assigned to glucosamine, chondroitin, a combination of the two, a nonsteroidal anti-inflammatory drug (NSAID) or placebo [11]. Overall, it did not show significant improvement on pain relief. However, the subgroup with moderate to severe disease showed pain improvement when treated by a combination of glucosamine and chondroitin.

A Cochrane review of 4926 patients in 25 RCTs concluded that glucosamine did not improve pain compared to placebo [12]. The route and dosages used varied greatly, and the review showed improvement with glucosamine only in the commercially funded studies, however lack of adequate allocation concealment has to be noted. Recently, the American Academy of Orthopaedic Surgeons (AAOS) has released guidelines where they strongly recommended against the use of glucosamine, chondroitin or a combination in knee OA, and advised more conventional methods such as weight loss, exercise and NSAIDs. [13,14].

Chondroitin

Chondroitin is a major component of aggrecan, which is part of the cartilage ultrastructure [15]. Most preparations are from extracts of cartilaginous animal sources [16]. Like glucosamine, it is most

commonly marketed in the sulfated form, and the exact mechanism of action is not clearly understood. In-vitro animal studies have shown anti-inflammatory, anticatabolic, antiapoptotic, and antioxidant effects. However, this is yet to be directly extrapolated to human models [17-19]. Once again, the literature shows discrepancies regarding the clinical benefit of chondroitin [20]. A meta-analysis of 20 trials with 3846 patients received chondroitin sulphate for hip or knee OA [21]. A high degree of heterogeneity in addition to the small and low quality of the trials made definitive assessment difficult, but it was concluded that chondroitin had minimal or no symptomatic benefits and its use was discouraged by the authors. A recent meta-analysis from 3 RCTs demonstrated that chondroitin reduced the rate of decline in joint space width at a dose of 800 mg daily [22]. A Cochrane systematic review of 9,110 patients from 43 studies of randomised trials of mostly low quality studies, showed that chondroitin (alone or in combination with glucosamine) was better than placebo in improving pain in participants with OA in the short-term [23]. The majority of studies were in knee OA with follow-up periods ranging from 1 month to 3 years. 11 of the studies of less than 6 months duration found that chondroitin alone or in combination with glucosamine significantly more effective in improving pain scores than the comparator amongst these studies. However, when stratified by study size, those studies with smaller samples sizes of less than 100 participants had no statistical significance reduction in pain scores when comparing chondroitin against placebo. Of the 11 studies, only 3 had sample sizes more than 100 participants. When stratified further, studies that were commercially funded had significantly better pain scores than studies that were not. There was significantly less reduction in minimal joint space width with chondroitin compared to placebo groups, based on evidence of moderate to high quality. Adverse events were not reported suggesting that chondroitin seems to be well tolerated. Despite this, the latest AAOS guideline recommend against chondroitin use in the clinical setting [13,14].

Krill oil

Krill oil is extracted from Antarctic krill (Ephausia Superba), a type of zooplankton that is rich in phospholipids [24]. Like fish oil, it contains a high proportion of n-3 fatty acids. However, there are only a handful of studies assessing the benefits of krill oil. Arthritis induced mice with a krill oil supplemented diet showed significantly reduced arthritis scores, lower inflammatory cell infiltration into the joint and hind paw swelling compared to control mice [25]. A Randomised, double blinded control study of 90 patients suggests benefit from using krill oil [26]. Patients selected had confirmed cardiovascular disease, RA and OA with raised levels of C-reactive protein (CRP). Patients who received krill oil had significantly reduced CRP levels, pain and functional impairment scores. No adverse events were documented with patients using krill oil. Despite its growing popularity, more studies are needed to investigate the potential benefits in human studies.

Fish oil

Fish oil is obtained from the body of fatty fish, and contains fatty acids needed for biological processes. It is thought to influence metabolic pathways by reducing the overall inflammatory response [27]. A recent RCT analysing the effect of fish oil on clinical outcomes in RA showed that joint tenderness was significantly improved [28]. A subsequent meta-analysis of these studies found that over a 12 week period, fish oil provided improvements in both morning stiffness and tender-joint count [29]. Fish oil may also be used long-term as an adjunct or means of reducing other analgesic therapies. Caughley et al. showed a synergistic effect of fish oil and paracetamol likely via suppression of nociceptive prostaglandin E2 [30]. Reported adverse effects including intolerance, diarrhoea and gastroesophageal reflux [29]. It is common that patients are recommended to cease fish oil weeks prior to surgery. Evidence for this is tenuous and further studies are need. Fish oil may have a weak antiplatelet effect; however a recent meta-analysis did not show an increased risk of major bleeding post operatively [31].

Gamma linolenic acid (GLA)

GLA is an essential fatty acid derived from plant seed oils such as blackcurrant, primrose and borage seeds [32]. The authors of a recent Cochrane review looked at 7 studies at the effects of GLA in RA [33]. The studies were divided into small (525-540 mg) or large (1.4-2.8 g) dosage groups and time period. The greatest benefit seemed to be from doses 1.4 g/day for at least 6 months, which was statistically significant in improving self-reported Visual Analogue Scale (VAS) pain scores. Unlike the other agents discussed, there have been reports of patients having hypersensitivity reactions or seizures with primrose oil.

Avocado-soybean unsaponifiables (ASU)

ASUs are manufactured from unsaponifiable fractions of one-third avocado oil and two-thirds soybean oil [34]. They have displayed anabolic, anti-catabolic, and anti-inflammatory effects on chondrocytes and inhibit spontaneous and IL-1 induced collagenase activity which are thought to be of benefit in patients with OA [35]. 4 RCTs and 1 systematic review evaluated the effect of ASUs on knee and hip OA [36]. Of the herbal therapies analyzed, the evidence for ASUs was the most reassuring. ASUs decreased NSAID intake in 3 trials after 3 months of follow-up.

Another study compared ASUs and chondroitin sulfate in knee OA [37]. 361 patients were enrolled and it was found that there was no difference between the two groups after a 6-month followup period. A study by Maheu, et al. enrolled 399 patients with symptomatic hip OA [38]. There was no significant difference on mean joint space width in the ASU and placebo groups; however there was a rate of 20% less progression in the ASU group but this was not statistically significant. This suggests that there may be a potential for ASUs to slow the progression of OA.

Conclusion

The use of nutraceuticals in joint arthritis is a growing field. This is a short review on some of the most commonly used products. Overall, there is no strong evidence for the use of such products in influencing the natural progression of RA and OA.

However, some of these agents seem to reduce pain and improve function in some patients. Prescribing or counselling about the use of these products needs be to done with knowledge of their adverse effects and potential benefits. Further studies are needed to provide standardisation of outcomes, larger data sets with more regimented protocols. It is important that patients and clinicians are able to make informed decision about the use of these nutraceuticals based on scientific, medical and economic evidence.

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