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Osteoarthritis (C Lozada, Section Editor)

Nutraceutical/Alternative Remedies in the Management of OA

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Opinion statement

Treating patients with osteoarthritis requires careful individualization in order to achieve patient-specific goals, which may vary from obtaining short-term pain relief to achieving long-term maintenance of function or even preservation of cartilage. In response to specific patient goals, the provider makes use of a toolbox of physical, adjunctive, alternative, pharmacologic, and operative interventions. Among the alternative category are the nutraceuticals, which will be reviewed here with particular attention given to those agents with randomized control trial (RCT) data showing statistically significant benefits. Some of these can be used to minimize patient symptoms with very low risks. The safety of these agents is particularly important in treating patients with osteoarthritis as many of the patients are older with significant comorbidities. Further, it is very likely that it will be necessary for the patients to continue treatment for many years.

Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide [1, 2]. Not only is it the most common arthropathy overall, it is becoming increasingly common as the average age of world populations increases. It is a major cause of disability and of work productivity loss [3] as well as a significant cause of pain. OA is a disease found in the most ancient of skeletal remains of our species and is also present in much older vertebrate species [4, 5]. The frequent association with antecedent trauma, advancing age, obesity, and chronicity led first to the understanding that it was the result of a purely mechanical process as is reflected in the osteoarthritis synonym degenerative joint disease (DJD). Although the complete process of pathogenesis remains unknown, a growing appreciation exists for the role of inflammatory, catabolic, and repair mechanisms in this process in addition to those related to traditional wear and tear [5]. As our choice of available therapies arises directly from our understanding of the pathogenesis, this broadened

understanding of pathogenesis has resulted in some novel therapeutic options [6].

Several factors continue to limit the development of therapeutics for OA. These include the need to address the broadly dissimilar goals of therapy and especially the long timeline of disease development and progression. While most clinical trials assess the control of OA pain of the hip and/or knee over 3–6 months, the disease progresses over a period of years in most cases. However, symptomatic involvement is also common in the spine, hands and other joints as well. These additional sites generally do not benefit as substantially from surgical approaches as do the hip and knee. Thus, in some respects, these are more challenging forms of OA to manage, especially as the safety of nociceptive therapies often declines significantly over time (increased potential for addiction).

Historically, treatments have been focused on modifying the associated mechanical factors and resultant pain leading to the standard treatment emphases on weight loss, use of appliances, joint replacement surgery, and the use of nociceptive medications especially the non-steroidal anti-inflammatory drugs (NSAIDs) [7]. The hope that nutraceuticals could augment normal repair processes and thereby improve structural outcomes was met with tremendous enthusiasm. Unfortunately, the results of RCT over the last decade are viewed with important differences of opinion worldwide; some countries continue to recommend the use of nutraceuticals in their guidelines, while others list them as treatments to be avoided [8••, 9, 10]. Nevertheless, broad agreement exists on the paucity of adverse events with use of these agents. The focus of this paper is on nutraceutical and alternative remedies that have achieved statistical evidence for efficacy by meta-analysis for pain and/or structural benefit in OA. A table of agents with only preliminary data is also included (Table 1).

Treatment

- Nutraceutical use is most often viewed as food-like supplement.
- The benefits of nutraceutical use for OA have been difficult to document and are small.
- Most nutraceuticals are generally considered safe.
- Recommendations in Europe and North America necessarily differ as products are not strictly comparable and professional orgainizations may interpret study results differently.

Many studies have examined the role of trauma, alignment abnormalities, and of nutritional deficiencies such as vitamin C, D, or E as possible etiologic factors for the development of new onset OA, but fewer studies have addressed their role in progression. More recently, studies have examined the replacement of nutritional substrates thought to benefit cartilage and bone growth and repair as treatments for already extant disease. However, the unusually long timeline of disease development and progression in OA has likely limited the ability of clinical trials to actually demonstrate benefit. Finding suitable agents for delay of new onset disease and for limitation of disease progression remain major unmet goals. Guidelines and recommendations to help providers developed by European and North American professional societies have been published and are reviewed at regular intervals [7, 11, 12••, 13, 14, 15••]. Interestingly, their results are often in conflict.

Nutraceutical/alternative remedies

Nutraceutical and alternative remedies are products taken orally that are derived from natural products and/or foods. In the USA, they often are known as

Table 1. Additional nutraceuticals/alternative remedies with preliminary data

Supplement	OA indication	Origin of material	Mechanism	Selected reference	Efficacy	Safety
Cat's claw	Pain	Uncaria tomentosa	Antioxidant	[20]	Suggestive	Animal ok
Devil's claw	Pain	*Harpagophytum procumbens*	Increase SOD, antioxidant, decrease NFkB	[59, 60]	Back, hip and knees	Dyspepsia, diminished taste
Eggshell membrane	Pain/stiffness	Chicken egg	Anti-inflammatory	[61]	Yes @10 days	No SAE
Fish oil	Pain	Fish	Decrease NFkB	[62, 63]	No dose effect, small benefit	Halitosis
Garlic	Incident hip OA	*Allium sativum*	S inhibition	[64]	? Efficacy	Halitosis, dyspepsia
Ginger	Pain/stiffness	Genus sp. root	Inhibit iNOS	[65–69]	No	GRAS per FDA
MSM	Pain	–	–	[70–73]	No	Maybe
Perna canaliculus lips	Pain	Green-lipped mussels	Alter microbiome, antioxidant	[74–77]	? Efficacy	Gastrointestinal, possibly shellfish allergy
Pineapple	Pain	Bromelain	Decrease PGE2	[78]	No	Nausea
Rose hips	Pain	Roses	Antioxidant	[79]	Suggestive	Gastrointestinal
SAMe	Pain/function	Synthetic	General metabolism	[60]	? Efficacy	Increased sympathetic like symptoms
Sesame seeds	Chondroprotection	Sesamum	Stimulates matrix	[80]	Yes	Yes
Turmeric	Pain/inflammation	*Curcuma longa*	Inhibit NFkB	[81, 82]	No	GRAS per FDA
Willow bark	Pain	Salix sp	Inhibit COX2	[83, 84]	Yes	Gastric

GRAS generally recognized as safe, *iNOS* inducible nitric oxide synthetase, *SOD* super oxide dismutase, *NFkB* nuclear factor kappa B, *MSM* methylsulfonyl methane
? efficacy when not enough evidence to judge

"dietary supplements" and as such they are not regulated by the Food and Drug Administration (FDA), while in Europe, many of the same products are regulated by European Regulatory Authorities as medications. The extent of product information available for most nutraceutical treatment approaches is much less than that available for traditional pharmacologic therapies. "Proprietary" and regulatory differences throughout the world seem to limit the amount of detailed information available for our analysis. Informative factors such as product quantity, purity, and even animal source of the material are often unavailable information. Hence, comments about nutraceuticals including glucosamine, chondroitin, and avocado/soy unsaponifiables probably do not apply equally to all preparations available in your formulary.

The use of these agents is very popular among individuals afflicted with osteoarthritis. For example, in a recent review from Catalonian Spain, 21.2% of self-identified osteoarthritis patients were using chondroitin sulfate. Additionally, 15.8% of these individuals were using glucosamine either alone or in combination [16]. In addition, use of nutraceuticals overall is twice as popular among female patients and more common among older but not the oldest individuals [17–19]. Numerous agents continue to undergo assessment and may then be added to this list as their RCT data become available. In most cases, the agents are administered orally, though some data for their topical, intramuscular, and intra-articular use also exist. Because of limited quality and generalizability of these data, they will not be reviewed here. Several excellent overall reviews of nutraceuticals are available that address some of the less well studied agents, which have not yet shown promise as documented by meta-analysis showing significant effect size [20, 21•, 22] (Table 1). Thus far, most of these have only short-term data available. I have indicated a judgment as to efficacy, but the level of confidence for these agents is very low.

Indications for nutraceutical use

Joint pain is a cardinal symptom shared by many patients with symptomatic OA and one that is part of the definition of OA as outlined by the American College of Rheumatology (ACR) [23]. It is the symptom that most clinical trials in OA treatments have been designed to address. Consequently, we will review the evidence related to its treatment first. Typically, response to pain and functional outcomes have been assessed using validated measures such as the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Besides joint pain, preservation of function and maintenance of structure are the most studied treatment indications. Both of these are usually assessed as secondary trial outcomes and therefore clinical trials are not specifically powered to provide definitive findings addressing these outcomes. Common functional outcomes include the use of the Health Assessment Questionnaire (HAQ), the Lequesne functional index, and tests such as the 6-min walk time [24].

To assess structural outcomes, many studies have measured cartilage thickness in knees or hips using standardized radiographs carefully assessing joint space width as a surrogate for cartilage thickness [25]. Because MRI is more sensitive and able to focus on specific anatomic distributions, MRI studies have increasingly become the preferred method. An additional advantage is that MRIs allow much shorter study durations and can assess the entire cartilage

surface [26–30]. Many fewer effect sizes for structural outcomes are available since much fewer data have been published related to structural outcomes.

Nutraceutical agents

Avocado soybean unsaponifiables

Avocado soybean unsaponifiables (ASU) are a mixture of oils derived from these two plant foods that do not make soap when reacted under alkaline hydrolysis conditions. This product is sold as a medication in France (Piascledine) and as a supplement in many other countries [31]. The studies have usually used ASU in a dose of 300 mg a day by mouth taken as a single capsule. Some gastrointestinal, cutaneous, and general adverse events are observed at rates equivalent to placebo in short-term trials [32, 33]. No contraindications have been detailed and no information is available about "drug–drug" interaction. The capsules are moderately expensive at about $1/day (Table 2). The mechanism of action thought to be important for ASO is inhibition of Il-1 β, and metalloproteinases –3 and –13 and possibly other antioxidant actions [34]. Evidence for increased synthesis of collagen in articular chondrocyte cultures suggests an anabolic action is active as well (Table 3) [35].

Short duration trials with primary pain outcomes and a meta-analysis have demonstrated efficacy for the treatment of OA pain (Table 3) [34, 36]. Interestingly, the benefits seem to persist even after discontinuation of the ASU [32]. The ES for pain is reported at 0.38 (0.001; 0.76) with a number needed to treat (NNT) of 6. The ES was slightly smaller at 0.22 (–0.06; 0.51) when only high-quality trials were considered [37]. A trial of ASU directly compared to chondroitin sulfate has been reported and no statistically significant difference was found [38]. Overall, 50% of subjects responded to either therapy.

No effect size has been reported for structural outcomes with ASU, but there has been at least one trial designed for a primary structural outcome with little or no benefit for those with OA of the hip [39]. Taken together, the data support a therapeutic trial of 1–3 months for control of pain in an individual patient until further information can guide decisions regarding

Table 2. Estimated cost/benefit data

Treatment	Relative costs $[a] per day	E/T ratio[b]
Avocado soy unsaponifiables	1	2.3
Chondroitin sulfate (CS)	0.3	3.5
Glucosamine salt (G)	0.1	2.8
Rosehips	0.2–0.6	1.8
G and CS	0.3	NA

CS chondroitin sulfate, *G* glucosamine, *NA* not available
[a]US dollars
[b]The efficacy to safety ratio (E/T) as calculated here using the median efficacy score divided by the estimated toxicity score [12••] used here just for relative comparison

Table 3. Nutraceutical/alternative remedies for treatment of pain and maintenance of structure in OA

Agent	Dose	Effect size pain	structure	Mechanism
ASU	300 mg/d	0.38 (0.001, 0.76)	NA	Anti-IL 1β, Anti-metalloproteinase –3, –13 Anabolic
Chondroitin sulfate	1200 mg/d	0.75 (0.5, 1.01)	0.26 (0.16, 0.36)	Anabolic
Glucosamine salt	1500 mg/d	0.46 (0.23, 0.69)	0.24 (0.04, 0.43)	Building block, inhibit inflammation through NF κ B, inhibit catabolism, anabolic
Rosehips	2–3 g/day	0.37 (0.13, 0.60)	NA	Antioxidant Inhibit metalloproteinase

ASU avocado soy unsaponifiables, *NA* not available

structural outcomes. If it is not effective for pain at 3 months, then ASU should be discontinued.

Chondroitin sulfate

Chondroitin sulfate (CS) is a molecule key to the building of new articular cartilage. For therapeutic use, it is typically isolated from animal cartilage through a multi-step chemical extraction process. There is a large variation in the quality of the resulting extracts commercially available [40]. The mechanisms thought to be involved in treating OA are related to a dose-dependent increase in collagen and aggrecan synthesis [35]. It is not costly as a day's therapy runs about 35 cents US (Table 2).

It is given as 400 mg orally three times daily and although it has a high molecular weight, intact absorption has been shown [41]. It has very few, if any, adverse drug reactions (ADR), and when all are considered together in comparison to placebo, the relative risk (RR) was indistinguishable from 1.0 [37]. In the glucosamine/chondroitin arthritis intervention trial (GAIT), no serious ADRs related to CS use were observed and the overall rate of events was like that of placebo (Table 3) [42]. The theoretical interaction of CS with the coagulation cascade means that caution should be used when it is used with anticoagulants.

Trials with pain outcomes have revealed a very broad variation in benefit since an overall ES has been reported as 0.75 (0.5; 1.01) with a NNT of 5, while when restricted to high-quality trials, the ES was markedly smaller at 0.005 (–0.11; 0.12) (Table 3) [37]. This large difference in results remains unexplained although sponsorship bias, CS quality differences and other explanations have all been proposed. A meta-analysis of 43 separate trials revealed that CS resulted in clinically meaningfully better pain scores in studies of less than 6 months duration [43]. CS is often taken in combination with another nutraceutical and some results related to combination use are described below.

Several trials have contributed to the evidence that CS is beneficial for structural outcomes. They include both traditional radiographic and MRI-

based outcomes [25, 44]. A meta-analysis reported in 2010 suggests efficacy for structural outcomes with an effect size of 0.23 (0.11; 0.35) [45]. When reviewed by OARSI and published in 2010, the ES was similarly estimated at 0.26 (0.16; 0.36).

Glucosamine salts

Glucosamine (G) is a substrate used in the building of new glycosaminoglycan, aggrecan, and other glycosylated proteins. For commercial use, glucosamine is typically purified from shellfish. It has most often been supplied as one of two salts; one a sulfate (GS) and the other a hydrochloride (GH). Far more data exits for the sulfate salt. After ingestion, both glucosamine salts dissolve to yield the same molecule [46]. G is absorbed rapidly and has a half-life of about 14 h with once daily administration. The usual dose is 1500 mg daily although some split the dose and others argue for a once daily dose. Recent reports suggest that N-acetylated glucosamine might be more biologically active than either above salt because of improved bioavailability suggesting that it might also be a therapeutic agent [47]. Patients who are known to have shellfish allergy should not take glucosamine salts and some concern about potential worsening of glucose tolerance and/or of hypertension exist, based mostly on theoretical concerns [48, 49]. At least one study has undertaken to look specifically at diabetes and G use and found that clinically important changes were not observed [48]. Significant reports of worsening of diabetes in large clinical trials have not been reported. It has very few ADRs such that when all are considered together, the RR as compared to placebo was indistinguishable from 1.0 [37]. The use of G has no described drug–drug interactions and is not expensive as a day's therapy is near 35 cents. In GAIT, two serious ADRs were observed in the G arm; a myocardial infarction and a cerebrovascular accident, both of which were not felt to be related to treatment (Table 2) [42].

The mechanism(s) of action most important to treatment of OA is not known, as many effects are described including inhibition of inflammatory and catabolic pathways [50]. Many of the supporting data are based on in vitro assay systems using markedly higher concentrations than even pharmacologic doses would achieve in vivo. These mechanisms include inhibition of nuclear factor kappa B (NF k B), COX-2, and phospholipase A-2 (Table 3) [50].

Glucosamine is the most studied supplement for the treatment of OA, with well over 25 separate clinical trials performed throughout the world. For GS relief of pain, an estimated ES = 0.58 (0.3; 0.87) with a NNT of 5. The estimate is somewhat smaller in high-quality trials at ES = 0.29 (0.003; 0.57) [37]. While for GH, the ES = −0.02 (−0.15; 0.11). Reasons to account for the large difference in results by salt are at this point subject to debate although some differences in vitro have been shown at similar molar concentrations [50]. G is often taken in combination with another nutraceutical and some results for combination use are described below.

Minimal evidence supporting a structural benefit when using G has been provided. For example post-menopausal women with OA of the knee

appear to have benefited by nearly 20% compared to placebo in a study by Bruyere et al. [51]. However, the ES for structure in meta-analysis and systematic reviews is only 0.24 (0.04; 0.43) for knee OA [37]. However, for a disease that progresses over a period of years, a small chronic benefit may be all that is needed. The GAIT ancillary arm treated with GH did not show statistical slowing of joint space width loss in OA of the knee [52]. Similarly, using GH, the "Joints on Glucosamine" (JOG) study found no evidence of altered biomarkers or MRI measures of cartilage loss [53]. The data at this point support a therapeutic trial for pain symptoms in individual patients, while use for structural indications requires additional evidence.

Rosehips

Long used as a natural source of vitamin supplement through its use as a tea, rosehips contain a number of potentially active compounds including vitamin C and flavonoids. The typical dose is 2–6 g taken in divided doses 2–3 times daily. No contraindications have been described nor have drug–drug interactions. No side effects are associated with its use although gastrointestinal symptoms are reported. The cost of rosehips is somewhat high at 20–60 cents (US) daily (Table 2). Mechanisms attributed to rosehips usually relate to the antioxidant properties of the vitamins, although other mechanisms could be involved as well. In vitro evidence for inhibition of metalloproteinases has also been shown (Table 3) [54].

Studies of rosehips in OA are limited to short duration trials using pain outcomes. The data show a ES for pain of 0.37 (0.13; 0.6) with an associated NNT of 6. Unfortunately, we do not know if these benefits are maintained for longer than 3 months and no evidence supporting efficacy for a structural outcome has been published.

Combination product use

Glucosamine+chondroitin sulfate

Nutraceuticals are often sold in combinations making comparison very challenging as different compounds, doses and sources all contribute to the observed variability. In addition, few RCTs have examined the combinations directly and none has performed head to head trials. The combination of GH and CS was found to benefit pain in patients with moderate to severe pain severity in GAIT [49]. This result was then used to design a non-inferiority trial to directly examine the results in more detail. The resultant Multicentre Osteoarthritis interVEntion trial with SYSADOA (MOVES) trial found the combination to be non-inferior to celecoxib for the treatment of pain in OA of the knee [49, 55].

The GAIT ancillary study did not support a benefit for a structural outcome and MOVES did not examine it. However, two studies, one an RCT using a traditional radiologic JSW outcome in comparison to placebo treatment and the other an examination of the Osteoarthritis Initiative (OAI) using MRI over 2 years, each support a structural benefit [55, 56]. Some

manufacturers have offered a number of other combination products with other agents including minerals, ASU, and methylsulfonylmethane (MSM) added to G + CS. Published trial data using these products are not available for either pain or structural outcomes.

Conclusions

Despite the striking incidence, prevalence, and the disabling nature of OA, we have very little of proven value to offer patients in the way of therapy leading one author to query "if all placebos are created equal" [57•, 58]. This is in part secondary to some unusual features of OA such as its very slow rate of progression, but also to limitations in our abilities to objectively measure appropriate outcomes such as pain and cartilage health. Despite this, providers daily recognize the gross unmet need that is represented in our patient's disability from OA. Approaches to therapy vary throughout the world, but stress efforts that involve modification of host factors such as weight loss in the overweight patient, adjunctive measures including shoe wedges, canes, and walkers, the judicious use of pharmacologic agents like NSAIDs and analgesic medications, and surgical approaches including total joint arthroplasty.

Nutraceutical/alternative treatments with evidence of significant effect size for control of pain associated with OA and agents thought able to slow joint damage have been reviewed above. Because control of pain can be assessed by each patient, a therapeutic trial of these very safe agents is appropriate. If no relief is present in 1–3 months, no continuation is advised. As shown in Table 3, an E/T ratio suggests CS followed or combined with G as the best therapeutic options. It is likely that no outward benefit would be appreciated for structural outcomes in an individual patient. Hence, a therapeutic trial of one is not recommended for these outcomes. Instead, continued well-controlled clinical trials that may validate the benefits, best dosing and preferred agents remains our best option at this time. We watch with interest for new data from such RCTs.

Compliance with Ethical Standards

Conflict of Interest

Dr. Allen Sawitzke reports grants from National Institutes of Health, grants from Bioiberica S.A., and personal fees from Bioiberica S.A. during the conduct of the study.

Dr. Daniel Clegg reports grants from National Institutes of Health, personal fees from Bioiberica S.A. during the conduct of the study.

Human and Animal Rights and Informed Consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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