

# Arthritis - Natural Alternatives for Joint Integrity, Function and Comfort

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*Evidence-Based Use of Supplements*

## ABSTRACT

The pain associated with arthritis is difficult to overcome and reduces quality of life. Conventional treatment methods focus largely on symptomatic intervention and are limited in their efficacy and sometimes in their safety. Accumulating evidence suggest that carefully formulated supplements offer a safe and cost-effective way to better address joint health and to both prevent and treat joint disease. Here, we describe pharmacological and non-pharmacological interventions for arthritis and discuss the data on the effects of individual ingredients on joint health and joint pain.

### Joint Health

Arthritic pain, which is the leading cause of disability in the United States, is both common and chronic. Unfortunately, quality of life and functional outcomes are worse for those with arthritic pain than they are for those with many other chronic conditions.<sup>1</sup> Conventional treatments for arthritis are associated with significant drawbacks, and different mechanisms underlying arthritis – which range from degeneration to inflammation – complicates the development of effective interventional strategies for overlapping symptoms, such as pain and immobility. A new approach to prevent and treat arthritis and to boost joint health is needed.

### Osteoarthritis

The most common type of arthritis is osteoarthritis, which is degenerative. More than 25% of adults suffer from osteoarthritis.<sup>2</sup> The condition is caused by the breakdown of cartilage that cushions the bones. The symptoms of osteoarthritis occur when bones rub against one another.<sup>3,4</sup> The degeneration of cartilage that is observed in osteoarthritis likely occurs as a result of pro-inflammatory cytokines and oxidative stress.<sup>5</sup> These physiological changes can result from several factors, including aging, sport-related injury, obesity, or genetic predisposition.<sup>2</sup>

In high income countries, up to 80% of people over the age of 65 have osteoarthritis. It was estimated that in 2015, nearly 31 million adults in the United States suffered from this disease.<sup>6</sup> The lifetime risk for developing osteoarthritis specifically in the knee is 45%. Knee osteoarthritis is indeed the most common form of osteoarthritis.<sup>7</sup>

### Rheumatoid Arthritis

Another common form of arthritis is rheumatoid arthritis, which is an inflammatory form of the disease.<sup>3,8</sup> It was estimated that 1.5 million adults in the United States had rheumatoid arthritis in 2007.<sup>6</sup> Rheumatoid arthritis is characterized by immune system attack of the joints. The resulting inflammation thickens the tissue that lines the joints, which can damage or destroy

cartilage. Eventually, joints can suffer irreversible deformity.<sup>6</sup> Rheumatoid arthritis is associated with a high burden of cardiovascular disease, and those with rheumatoid arthritis are also more likely to endure infections, to develop lung disease and lymphoproliferative cancers, and to suffer from depression.<sup>9–11</sup>

### CONVENTIONAL TREATMENTS

Management strategies for arthritis range from lifestyle changes to invasive surgeries and also include topical treatments, physical therapy, non-steroidal anti-inflammatory drugs, and injections.<sup>12</sup> However, no conventionally used intervention slows disease progression or restores degraded cartilage.<sup>2</sup>

### Pharmacological Interventions for Arthritis

Currently available pharmacological options for arthritis are limited in their ability to modify or reverse the disease.<sup>13</sup> Nonetheless, there are several drug approaches that are currently used to manage symptoms of the disease. These strategies include:

#### *Analgesics*

Analgesics combat pain but do not affect inflammation. Patients with arthritis may be given over-the-counter analgesics like acetaminophen or may be prescribed narcotics with oxycodone or hydrocodone. However, certain pain medications have proven ineffective in reducing pain, and toxicity issues are of concern.<sup>14,15</sup> Analgesics therefore offer relief to only some patients with arthritis and must be used sparingly.

#### *Nonsteroidal anti-inflammatory drugs (NSAIDs)*

NSAIDs can lower both pain and inflammation. Over-the-counter options include ibuprofen and naproxen sodium. Unfortunately, NSAIDs taken orally can have deleterious effects, including serious, potentially fatal ones. For instance, these drugs can significantly increase heart attack risk.<sup>16,17</sup> They can also jeopardize renal health.<sup>18</sup>

When it comes to joint health, NSAIDs may be helpful in the short-term because they combat inflammation. However, they may damage cartilage in the long-term. Data have shown, for instance, that NSAIDs lead to higher levels of

cartilage volume loss than do COX-2 inhibitors.<sup>18,19</sup>

Oral NSAIDs are not recommended for certain patients with comorbid conditions because NSAIDs have the potential to exacerbate those conditions.<sup>20–22</sup> To try to circumvent the risks associated with oral NSAIDs, scientists have formulated cream and gel NSAIDs, which are discussed below.

#### *Corticosteroids*

Corticosteroids suppress the immune system and lower inflammation. These drugs, which include cortisone and prednisone, are often taken orally. However, they can also be injected directly into joints. Unfortunately, even intra-articular injections of corticosteroids only provide moderate pain relief and minimal benefits regarding physical functioning.<sup>23</sup>

For those with rheumatoid arthritis, the glucocorticoid class of corticosteroids has also been shown to increase the risk of infection and cardiovascular disease more so than other treatments and are associated with serious long-term side effects.<sup>24,25</sup>

#### *Disease-modifying antirheumatic drugs (DMARDs)*

DMARDs are often used in the treatment of rheumatoid arthritis, where the aim is to reduce the swelling and inflammation that results from immune system activation.<sup>8</sup> These drugs work by preventing the immune system from attacking the joints. Examples of these drugs are methotrexate and hydroxychloroquine. A comprehensive meta-analysis found that DMARDs reduce radiographic erosions in rheumatoid arthritis.<sup>26</sup>

Though DMARDs may be effective in combatting symptoms of arthritis, their toxicity profile has led experts to claim that it is undesirable to use DMARDs in a long-term capacity.<sup>27</sup> Consistent with this notion, research into patient experience with DMARDs has shown that patients are surprised by their side effects and perceive the drugs as strong.<sup>28</sup>

### **Non-Pharmacological Interventions for Arthritis**

#### *Surgery*

As with any surgery, joint surgeries pose risks and require recovery time. Joint surgeries can also fail, requiring further surgery. These revision surgeries too can fail.<sup>29</sup> Though there have been significant research efforts to address why joint surgeries fail, the insights from this research has not eliminated these failures.<sup>30–33</sup> Also complicating the joint surgery landscape are claims that the data supporting the value of these techniques are weak.<sup>34</sup>

#### • **Preventative Surgery**

Surgery is sometimes recommended as a preventative strategy for people at risk for<sup>1</sup> arthritis. For instance, it is well-established that joint misalignment enhances the risk for osteoarthritis. To prevent osteoarthritis onset, osteotomy can be performed to realign the joints. However, this procedure is associated with failure rates that are generally higher than those for joint replacements, which are undergone after arthritis onset.<sup>34</sup> A review of the literature revealed that about a quarter of all tibial osteotomies, for example, fail within 10 years and require further surgery.<sup>35</sup>

#### • **Joint Replacement**

Arthroplasty, or total joint replacement, involves replacing the damaged joint with an artificial joint. Like osteotomies, these surgeries can fail, requiring revision surgery. In the case of wrist arthroplasty, the high incidence of implant failure has led surgeons to often recommend restricted activity following surgery, meaning that more active patients may not be ideally suited for this procedure.<sup>36</sup> However, replacements are most common when arthritis occurs in the

knee are most common when arthritis occurs in the knee or hip, where failure rates may be lower.<sup>4</sup> The overall risk of failure for hip replacement, for instance, has been estimated to be about 1% per year.<sup>34,37</sup>

Certain factors increase one's risk of joint replacement failure. Perhaps counterintuitively, failure rates are higher amongst younger and more active recipients. They have also been shown to be higher when performed by surgeons with a low surgery volume.<sup>38,39</sup> Research on the causes of failure in total knee arthroplasty has shown that in patients aged 55 or younger, replacements tend to fail due to polyethylene wear, loosening, and infection.<sup>32,40</sup>

#### • **Joint Fusion**

Joint fusion is often performed on small joints like those found in the ankle, wrist, or fingers. In joint fusion, the ends of the problematic joints are removed, and the joints are fused together into one unit.<sup>41</sup> Like with osteotomies and arthroplasties, joint fusion has its limitations. For instance, though fusion is the most common procedure performed on those with advanced ankle arthritis, the consequent immobilization often prevents those who want to retain ankle motion from undergoing this procedure.<sup>34</sup>

#### *Weight loss*

Theoretically one would think that weight loss would help arthritic patients by reducing the pressure on joints. However, the role of weight in arthritis presents an interesting paradox. While obesity is associated with faster disability progression in those with rheumatoid arthritis, so too is weight loss.<sup>42</sup> Weight loss is in fact a strong predictor of death in those with rheumatoid arthritis.<sup>43</sup> BMI also predicts mortality in this population.<sup>44</sup> This paradox may help to explain why the potential benefits of exercise on those with arthritis are also debated.<sup>45</sup>

#### *Exercise & physical therapy*

It has been suggested that joint movement can improve arthritis by strengthening muscles that surround the joints, but experts disagree on the impact of physical therapy as well as exercise on arthritis patients.<sup>45–47</sup> Data on how these activities affect arthritis likely differ due to focus on distinct types of activities and distinct types of arthritis.

Consistent with this view, while exercise in general is thought to be beneficial for those with rheumatoid arthritis, the specific type of exercise appears to matter for osteoarthritis patients.<sup>48,49</sup> For instance, in this latter group, strength and flexibility exercises when combined with aerobic exercise appears to reduce pain and disability more so than does walking alone.<sup>50,51</sup> Recent reviews also conclude that aquatic exercise may provide small and short-term benefits for those with knee and hip osteoarthritis.<sup>52</sup>

#### *Assistive devices*

Assistive devices have been developed to help protect joints and minimize pain. However, research into how well these devices actually serve patients has shown that the utility of these devices is often limited by lack of information and education on how to beneficially use the devices.<sup>53</sup> Nonetheless, there has been relatively little research into the impact of assistive devices on those with arthritis, so experts recommend more research to help elucidate the role that these devices could play.<sup>54</sup> One relevant detail that has been revealed, however, is that osteoarthritis patients appear to use these devices more frequently than do those with rheumatoid arthritis.<sup>55</sup>

#### *Acupuncture*

Acupuncture has been proposed as a way to reduce pain in those with arthritis.<sup>56</sup> Claims about the effectiveness of acupuncture have been criticized for potentially containing bias and reflecting deficiencies in reporting, but recent

castudies demonstrating benefits of acupuncture in arthritis have aimed to overcome these weaknesses.<sup>57–59</sup>

A recent review concluded that acupuncture may benefit patients with rheumatoid arthritis without any adverse side effects. Another comprehensive review covering 10 trials and nearly 1500 patients found that acupuncture is also effective for reducing pain and physical dysfunction in those with knee osteoarthritis.<sup>61</sup> Though the specific ways that acupuncture may achieve its effects in arthritis are not clear, the authors of this review suggested a few potential mechanisms, including immune function regulation, antioxidant effects, and the combatting of inflammation.<sup>60</sup>

#### *Massage & aromatherapy*

It has been proposed that massages may increase blood flow and relieve pain in patients with arthritis. A study on the effect of moderate pressure massage therapy on those with knee arthritis showed that this intervention improved range of motion and reduced pain.<sup>62</sup> Some data point to the value of combining massages with other activities, such as aromatherapy, reflexology, acupuncture, and sauna to achieve pain reduction in patients with rheumatoid arthritis.<sup>63,64</sup>

A systematic review published in 2017 concluded that the evidence pointing to the value of massage therapy to help those with arthritis is of low to moderate quality and that more data are needed to determine if massage therapy may be more effective in reducing pain or improving function than nonactive therapies for arthritis.<sup>65</sup> Indeed, some research suggests that active therapies involving movement provide more benefits for arthritis patients than do passive therapies like massage.<sup>66</sup> Since then, new studies have been undertaken that have pointed to the value of weekly massage for the short-term treatment of knee osteoarthritis and to the ability of a massage-essential oil combination therapy to improve pain in those with hand arthritis.<sup>67,68</sup>

#### *Topicals*

There are several topical options to treat arthritis, which have been developed with the aim of interfering with pain signal transmission to the joints. Though evidence on the efficacy of these topical counterirritants is mixed, topical NSAIDs have been deemed effective and safe for osteoarthritis and are often recommended as a first-line therapy, especially in older patients.<sup>69–73</sup>

As mentioned above, topical NSAIDs offer an alternative to oral NSAIDs and allow patients to circumvent the gastrointestinal risks associated with the oral form of these drugs. NSAID topicals may help with pain management not only in older patients but also in those with certain comorbidities who do not have other good long-term options to address their pain.<sup>74,75</sup>

Data show that the NSAID, diclofenac sodium, applied as a gel at a dose of 1% can provide analgesia for osteoarthritis patients without significant risk of adverse side effects.<sup>76</sup> Consistent with these results, researchers have suggested diclofenac patches may represent the most effective topical treatment for pain associated with osteoarthritis.<sup>69</sup>

It is possible that other topical formulations could benefit arthritis patients as well, as a meta-analysis comparing specific types of topicals found that topical NSAIDs and topical capsaicin improve pain to a similar extent in those with osteoarthritis.<sup>77</sup> Research has long shown that capsaicin treatment leads to better pain outcomes than placebo in both osteoarthritis and rheumatoid arthritis.<sup>78</sup> Preclinical research has also shown that the topical application of an essential oil ointment reduces the severity of an animal model of rheumatoid arthritis by inhibiting inflammatory processes.<sup>79</sup>

## **Supplements for Arthritis – Which Ones Have the Best Clinical Support?**

Given the plethora of options for treating arthritic pain, determining which intervention or combination of interventions is most appropriate can be overwhelming for both patients and healthcare providers. There is wide variability in how patients respond to treatment, so there is often trial and error and a significant amount of time that goes into determining if and how arthritic pain can be managed.<sup>80</sup>

Also of concern is that the use of pharmacological treatments is often prolonged, which adds the complications of safety and tolerability to the challenge of efficacy.<sup>12</sup> Experts agree that non-pharmacological treatments for arthritis should be tried before pharmacological ones and that due to the invasiveness and associated complications, surgery should be reserved as a last resort when all else fails.<sup>81–83</sup>

Healthy supplementation of non-pharmacological ingredients may therefore provide an opportunity to confer similar benefits as more aggressive options while bypassing safety concerns. Indeed, recent analyses have shown that natural products have produced more clinically meaningful results in patients with osteoarthritis than those achieved with traditional osteoarthritis treatments.<sup>84,85</sup> Given these results, there is growing interest in identifying natural products that can enhance joint health.<sup>84–86</sup>

The challenge then becomes determining what should be included in a supplemental formulation. While dozens of ingredients have been touted as helpful for joint health, it is impractical to include so many ingredients in one formulation or to include those for which incredibly high doses are required for achieving effects. Optimizing joint health supplements requires balancing the scientific evidence of efficacy and safety along with dosage information to create a formulation that is most likely to promote health.

There are data that suggest that some of the best-known ingredients for joint health supplements, such as glucosamine sulfate and chondroitin sulfate, are ineffective, and in those studies that do find some efficacy, large doses are required to achieve desired results.<sup>87</sup> If doses of these values are used in joint health supplements, they unfortunately often require that other beneficial ingredients, which may be effective at lower doses, are excluded from the formulation.

Below are ingredients that appear to demonstrate real-life clinical efficacy related to joint health and some brief descriptions of the relevant evidence. In addition, we provide personal anecdotal evidence and subjective ratings on how effective or synergistic we have observed the specific ingredients to be. This anecdotal information is based on the author's experience with his severely compromised medial menisci in both knees and arthritis degeneration following decades of significant participation in basketball and tennis. Given his education and training and access to relevant supplements, the author was able to systematically assess the real-world benefits of these ingredients – alone and in combination.

#### **Feverfew Extract**

According to the National Institutes of Health, people currently use feverfew as a dietary supplement for rheumatoid arthritis.<sup>88</sup> Basic science research aimed at understanding how feverfew may benefit arthritis patients has revealed that the extract inhibits the release of enzymes from cells of the immune system that are found in inflamed joints.<sup>89</sup> Parthenolide, which is

responsible for some of feverfew's bioactivity, has also been shown to improve the severity of joint destruction in animal models of rheumatoid arthritis.<sup>90</sup>

At the molecular level, feverfew appears to act through several distinct pathways and pathway points, which may help to explain its therapeutic potential. It can, for instance, suppress the activation of NFkappaB.<sup>91</sup> It can reduce thromboxane B2 (TXB2) and leukotriene 4 (LTB4) generation in a dose-dependent manner.<sup>90</sup> It can also inhibit THP-1 cells' release of lipopolysaccharides (LPS)-mediated TNF-alpha and CCL2 (MCP-1).<sup>92</sup>

## Ginger

Preclinical and clinical research consistently show that ginger alleviates symptoms related to both osteoarthritis and rheumatoid arthritis. The substance, which is rich in phenolics like shogaols and gingerols, has been shown in vitro to be as effective in combatting inflammation as the steroid betamethasone.<sup>93,94</sup> Consuming ginger is also associated with reduced inflammation.<sup>95</sup> One study showed that people with both osteoarthritis and rheumatoid arthritis who took powdered ginger as a dietary supplement experienced pain relief within 3 months.<sup>96</sup>

A meta-analysis of placebo-controlled trials investigating the effect and safety of ginger in patients with osteoarthritis found that ginger was an efficacious and reasonably safe treatment for osteoarthritis.<sup>97</sup> In fact, ginger has been demonstrated to be as effective in treating osteoarthritis as the NSAID diclofenac, but also safer, with less impact on the stomach mucosa.<sup>98</sup>

Ginger therapy has been shown to continuously improve symptoms in patients with osteoarthritis when implemented over a 24-week period.<sup>99</sup> A study that investigated the use of ginger extract in 60 patients aged 50 to 75 found that the extract can relieve joint pain related to osteoarthritis.<sup>93</sup> Researchers who have studied the influence ginger can have on symptoms observed in specific joints, such as the knee, and shown the power of ginger to reduce symptoms.<sup>100</sup>

From the perspective of rheumatoid arthritis, data show that ginger is protective.<sup>101</sup> Preclinical research has shown that higher doses of ginger intake reduce arthritis severity and complications more so than do lower doses.<sup>93</sup> Research suggests that ginger improves symptoms of rheumatoid arthritis through modulation of genetic expression of specific proteins involved in immunity and inflammation.<sup>102</sup>

Ginger therapy research has revealed no negative effects associated with the therapy, suggesting that ginger is a safe therapeutic option.<sup>99,103</sup> Mechanistic data demonstrate that ginger's anti-inflammatory properties contribute to its therapeutic potential. Specifically, ginger inhibits chemokine expression, thereby reducing symptoms related to immune response.<sup>95,104</sup>

## Boswellia Extract

Boswellia extract has known anti-arthritic and analgesic properties, and it has been shown to be effective in joint diseases including rheumatoid arthritis. <sup>105,106</sup> Experts claim it may be a promising alternative to non-steroidal anti-inflammatory drugs.<sup>107</sup>

Researchers have also suggested that Boswellia could be an effective therapeutic option because the compound is capable of relieving arthritic symptoms with fewer risks than other therapeutic options.<sup>108</sup> Indeed, this extract has been shown to be more effective than both placebo and valdecoxib in relieving pain and in improving function in

those with knee osteoarthritis.<sup>108,109</sup>

A study conducted on 30 patients with knee osteoarthritis showed that an 8-week regimen of Boswellia extract reduced knee pain and swelling. It also increased both walking distance and knee flexion.<sup>105</sup>

The positive effects of Boswellia on arthritis may occur through its impact on the immune system.<sup>105,110</sup> Resins from Boswellia have been shown to influence the immune system through anti-inflammatory activities that are distinct from those induced by non-steroidal anti-inflammatory drugs. Specifically, Boswellia appears to inhibit 5-lipoxygenase and also influence various cytokines.<sup>106</sup>

## Hyaluronic Acid

Hyaluronic acid, also known as hyaluronan, has been shown to confer therapeutic benefits in patients with osteoarthritis as well as those with synovitis.<sup>111,112</sup> Research has shown that it is more effective than corticosteroids in treating joint symptoms.<sup>113</sup> It has also been shown to be safe in patient populations.<sup>114</sup>

A Japanese study that involved giving patients with chronic knee pain a mixture containing 60 mg of hyaluronic acid each day for two weeks led to significant reductions in knee pain.<sup>115</sup> A similar study in the US where those with knee osteoarthritis were treated daily with a mixture containing 80 mg of hyaluronic acid over 2 months also improved knee pain. In addition, those taking the mixture displayed greater improvements in physical function than those taking placebo.<sup>116</sup>

Preclinical data have demonstrated positive effects of hyaluronic acid in preserving joint cartilage in models of arthritis and osteoarthritis.<sup>117</sup> Inflammation and oxidative stress enhance the degradation of hyaluronic acid. Because hyaluronic acid is necessary for the synovial fluid found in the cavities of synovial joints to function properly and adequately lubricate the joints,<sup>118</sup> supplementing this substance may help to improve pain and functioning in those with joint problems.

## Vitamin C

Studies in patients with rheumatoid arthritis have shown that they tend to be ascorbic-acid deficient and that vitamin C supplementation resolves their lesions.<sup>119</sup> Vitamin C consumption is indeed associated with lower levels of cartilage loss in osteoarthritis.<sup>120</sup> Data demonstrating that vitamin C may prevent incident knee osteoarthritis has led researchers to conclude that this simple, inexpensive, and widely available ingredient should be further explored as a way to combat the burden of osteoarthritis.<sup>121</sup>

Preclinical research has shown that vitamin C can prevent progression of osteoarthritis through its antioxidant effects and by reducing inflammation and apoptosis. Interestingly, this research has also demonstrated that the benefits of vitamin C are not dose-dependent, suggesting that once a certain threshold of vitamin C intake is achieved, additional vitamin C consumption does not provide added benefits.<sup>120</sup>

## Boron

People with arthritis have lower concentrations of boron in synovial fluid, femur heads, and bones.<sup>122</sup> It has been reestimated that in parts of the world where boron intake is less than or equivalent to 1 milligram (mg) per day, arthritis incidence is between 20% and 70%, whereas in areas where boron intake is greater, between 3 mg to 10 mg, arthritis incidence is less than 10%.<sup>122</sup>

A study testing the effects of 6 mg of boron supplementation daily found that 50% of those taking the supplement experienced improvements in their osteoarthritis. By contrast, only 10% of those taking placebo saw such improvements.<sup>122</sup> Research into how boron may help those with arthritis has revealed that boron's antioxidant properties likely account for at least some of its benefits. Indeed, these antioxidant properties appear to make boron an advantageous supplement for the repair of osteochondral defects.<sup>123</sup>

Calcium fructoborate is the most heavily studied boron-based supplement.<sup>124</sup> Research has shown that it safely provides pain relief and boost flexibility in those with arthritis. Studies into the molecular mechanisms by which calcium fructoborate achieves its effects have shown that it modulates inflammation in advantageous ways.<sup>125</sup>

## Magnesium

Magnesium deficiency has been identified as a major risk factor for osteoarthritis, with low levels of magnesium increasing one's risk for developing osteoarthritis and for suffering more significantly from its progression.<sup>126–128</sup> There also appears to be a dose-response relationship between serum magnesium and the prevalence of knee chondrocalcinosis, even when magnesium levels are in the normal range.<sup>129</sup> A recent study on the relationship between dietary magnesium and knee osteoarthritis showed that higher magnesium intake is associated with better knee cartilage architecture.<sup>130</sup> The authors therefore suggest that magnesium may provide an effective prevention or treatment option with respect to knee osteoarthritis.

Preclinical research has provided support for the idea that magnesium supplements are capable of providing an effective therapy for osteoarthritis and that magnesium could work through multiple mechanisms to help osteoarthritis patients.<sup>126</sup> For instance, magnesium can help with inflammation, defective biosynthesis of chondrocytes, and cartilage damage. Magnesium deficiency is indeed increasingly recognized as a contributor to inflammatory diseases like rheumatoid arthritis.<sup>131</sup>

Magnesium also appears to be related to bone mineral density of certain joints, such as the hip.<sup>132</sup> Consistent with the notion that magnesium is related to bone integrity, it has also been observed that lower levels of magnesium are observed in patients with fractures.<sup>133</sup> A new meta-analysis supports this notion that higher daily intakes of magnesium may be associated with lower risk for fracture in knee osteoarthritis patients.<sup>134</sup>

## Glucosamine Sulfate and Chondroitin Sulfate

Glucosamine and chondroitin sulfate have in certain studies been associated with symptom improvements in those with osteoarthritis.<sup>135–139</sup> Some data point to the potential for glucosamine sulfate and chondroitin sulfate to help with pain relief and to inhibit inflammation and improve range of motion.<sup>140</sup> Glucosamine as well as chondroitin sulfate supplements have also been shown to be well-tolerated by patients, with no significant adverse side effects.<sup>140–142</sup>

Researchers have suggested that glucosamine sulfate and chondroitin sulfate can help those with osteoarthritis by modifying joint structure and interfering with the progression of the disease.<sup>143</sup> For instance, multiple studies suggest that glucosamine sulfate prevents the narrowing of the space in joints that is observed in mild-to-moderate osteoarthritis of the knee.<sup>137</sup> However, recent systematic meta-analyses have found that neither oral glucosamine sulfate nor oral chondroitin sulfate lead to significant changes in joint narrowing.<sup>144,145</sup> In addition, a recent

magnetic resonance imaging (MRI) study evaluating the impact of oral glucosamine supplementation on structural lesions in knee joints found no evidence of structural benefits to the knee for those taking glucosamine.<sup>146</sup>

The composition of chondroitin sulfate found in the fluid of healthy versus diseased joints has differs, suggesting that more deranged joints may have lower levels of chondroitin sulfate.<sup>147</sup> Though one interpretation of this observation is that supplementation may reverse damage to the joints, it is unclear if chondroitin sulfate supplementation can have such an effect.

An article published in *Orthopedics* in 2018 discusses a National-Institutes of Health-sponsored Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) and highlights the lack of clarity this trial provided on the efficacy of glucosamine and chondroitin in arthritis.<sup>148</sup> The article also points to the mixed results regarding these substances and the high level of placebo effects and confounding data that occurs due to the use of rescue analgesics.

A recent meta-analysis evaluated the ability of oral chondroitin and glucosamine to reduce pain and improve function in those with knee and/or hip osteoarthritis. Results showed that glucosamine could impact these patients, but only by helping with joint stiffness, whereas chondroitin could alleviate pain and enhance function. Combining the substances, though, did not result in outcomes that were any better than what was achieved with placebo.<sup>149</sup>

Though certain data have pointed to the treatment potential of chondroitin and glucosamine for osteoarthritis, it is heavily debated within the scientific community whether these substances provide any value over placebo.<sup>150–153</sup> Critics of data supporting glucosamine sulfate as a treatment for osteoarthritis, for instance, point to the small numbers of patients studied in the experiments used to claim that this substance has therapeutic value.<sup>154</sup> Critics also highlight study design flaws and conclude that there is insufficient evidence to determine that glucosamine sulfate causes beneficial changes in patients with osteoarthritis.

According to a recent comprehensive review of the literature, the effect sizes associated with studies that suggest a therapeutic effect of both glucosamine and chondroitin are small and likely not clinically relevant. The studies also suffer from a high risk of bias. Thus, though there do not seem to be safety concerns associated with chondroitin and glucosamine, researchers have concluded that there is no convincing evidence for their use in treating osteoarthritis.

## CONCLUSION

The disability and pain associated with arthritis is being addressed with several potential solutions, but each solution is plagued by weaknesses. Additionally, given that the idea of pre-arthritis has newly evolved,<sup>155</sup> there will be more and more people looking for ways to prevent arthritis and promote joint health before their joints deteriorate to the point where they are diagnosed with arthritis. This population of patients with pre-arthritis is likely to prefer simple, noninvasive, cost effective approaches like supplementation to address their pre-arthritis. Experts also agree that patient-driven treatments should be the initial focus of joint health, before people rely on passive therapies that are delivered by healthcare professionals.<sup>156</sup>

Supplementing the diet with ingredients that are proving effective in protecting joints is a simple, safe, and cost-effective way to deal with arthritis before resorting to other measures. A major open, multicenter clinical trial has shown that a supplement containing some of the ingredients we

have discussed here – including chondroitin sulfate, glucosamine sulfate, and devil’s claw – reduced pain and enhanced locomotor function in patients with knee osteoarthritis and patients with hip osteoarthritis.<sup>157</sup> These findings were published in 2019 and highlight the shift toward supplementation to address chronic inflammatory diseases like arthritis as well as the accumulating data to support this type of approach.

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