



## Conference on ‘Nutrition and healthy ageing’ Symposium 3: Nutritional modulation of the ageing trajectory

### The potential for dietary factors to prevent or treat osteoarthritis

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Osteoarthritis (OA) is a degenerative joint disease for which there are no disease-modifying drugs. It is a leading cause of disability in the UK. Increasing age and obesity are both major risk factors for OA and the health and economic burden of this disease will increase in the future. Focusing on compounds from the habitual diet that may prevent the onset or slow the progression of OA is a strategy that has been under-investigated to date. An approach that relies on dietary modification is clearly attractive in terms of risk/benefit and more likely to be implementable at the population level. However, before undertaking a full clinical trial to examine potential efficacy, detailed molecular studies are required in order to optimise the design. This review focuses on potential dietary factors that may reduce the risk or progression of OA, including micronutrients, fatty acids, flavonoids and other phytochemicals. It therefore ignores data coming from classical inflammatory arthritides and nutraceuticals such as glucosamine and chondroitin. In conclusion, diet offers a route by which the health of the joint can be protected and OA incidence or progression decreased. In a chronic disease, with risk factors increasing in the population and with no pharmaceutical cure, an understanding of this will be crucial.

**Osteoarthritis: Diet: Cartilage: Bioactive: Polyphenol: Phytochemical: Flavonoid**

Osteoarthritis (OA) is a degenerative joint disease characterised by degradation of articular cartilage, thickening of subchondral bone and osteophyte formation. Incidence and prevalence of OA has been difficult to assess, in part because of heterogeneity in definitions of the disease. A recent meta-analysis suggested that overall prevalence of OA at different anatomical sites was 23.9% (knee), 10.9% (hip) and 43.3% (hand), although only the prevalence of knee OA showed a gender difference between women and men (27.3 and 21%, respectively)<sup>(1)</sup>.

Osteoarthritis is a leading cause of disability in the UK. A recent survey<sup>(2)</sup> found 8.5 million people in the UK with OA, with 71% of these in constant pain. There are no effective disease-modifying drugs to treat

OA and drugs that relieve pain are often insufficient. Joint replacement is offered to patients at end-stage disease with 66 436 hip and 77 578 knee replacements due to OA performed in the UK in 2011<sup>(3)</sup>.

Two major risk factors for OA are increasing age (most affected patients are aged >45 years and the greatest morbidity is seen in patients aged >60 years)<sup>(4)</sup> and increasing obesity<sup>(5)</sup>. With changing demographics, OA is an increasing public health and economic burden. The economic costs of OA in the UK are largely unknown, but direct costs have been estimated at approximately £1 billion/year. With inclusion of indirect costs, estimates from the USA range up to £8 billion/year<sup>(6)</sup>.

**Abbreviations:** ADAMTS, a disintegrin and metalloproteinase domain with thrombospondin motifs; ASU, avocado-soyabean unsaponifiables; COX cyclooxygenase; Gla, γ-carboxyglutamic acid; MMP, matrix metalloproteinase; OA, osteoarthritis.

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## Micronutrients

### Vitamin C

Although the ability to slow or stop the progression of OA would have individual and population-level benefits, few pharmaceutical companies maintain OA as a disease area. This is in part because there is no precedent. Furthermore, OA generally progresses slowly, and there are no current validated biomarkers for cartilage destruction (joint space narrowing, assessed on X-ray, is the only Food and Drug Administration approved end point in a clinical trial)<sup>(7)</sup>. Issues of toxicity, in a disease that is not life-threatening, can also make drug development problematic. It is possible to overcome at least some of these issues by selection of the patient group (where particular sub-groups are known to progress more rapidly), and by establishing the dose of drug that gives efficacy within the target tissue (i.e. cartilage)<sup>(8)</sup>.

Focusing on compounds from the habitual diet that may prevent the onset or slow the progression of OA is an alternative strategy. Since in essence, all of the population can be viewed as at risk for the development of OA in old age, an approach that relies on dietary modification is clearly more attractive in terms of risk/benefit and more likely to be implementable. However, detailed molecular studies ahead of a full clinical trial are required in order to design trials optimally that will examine potential efficacy.

There are currently limited data on the inter-relationship between diet and OA. Data come from a variety of studies: *in vitro* cell and tissue explant models, animal models, epidemiological associations and intervention trials. There is a large variability between studies, e.g. in animal models, a dietary intake approach would be optimal in order to relate to human exposure, but some studies use intra-articular injection and/or concentrations not achievable through the diet. The intervention trials conducted to date have many different designs, number of patients, time length and outcome measures, often with too few patients and of short duration. There is a need for better quality data before dietary advice can be given. However, clinical trials in OA are expensive and it is not clear who will or should fund them.

This brief review focuses predominantly on potential dietary factors than may reduce the risk or progression of the disease. It focuses only on OA, mainly ignoring data coming from more overtly inflammatory arthritides.

Two pertinent 'nutraceuticals' will not be discussed, but should be mentioned: glucosamine and chondroitin. Glucosamine is a sugar and precursor for glycosaminoglycan and therefore proteoglycan biosynthesis. Chondroitin is a glycosaminoglycan, a form of which is found in aggrecan, the major proteoglycan in cartilage. Hydrochloride and sulphate salts of both glucosamine and chondroitin have been extensively examined in laboratory models and clinical trials. The efficacy of these compounds remains controversial, but most recent analyses appear to indicate that high-grade preparations of chondroitin sulphate and glucosamine sulphate, may have efficacy in OA<sup>(9-13)</sup>.

In prospective studies examining micronutrient intakes, the Framingham study identified a protective association between higher intake of vitamin C and the progression of radiographic knee OA<sup>(14)</sup> and a higher vitamin C intake was also associated with lower risk of knee pain<sup>(14,15)</sup>. However, a longitudinal study showed no protective effect of vitamin C supplements on the progression of knee OA, although in multivariate analyses vitamin C supplements were beneficial in preventing the development of knee OA<sup>(16)</sup>. In healthy subjects, vitamin C intake has been associated with reduced risk of bone marrow lesions on MRI<sup>(17)</sup>. In these publications, vitamin C has been viewed simply as an antioxidant, but it should not be forgotten that vitamin C is a co-factor enabling the proline and lysine hydroxylation essential for correct collagen biosynthesis. It also has effects on regulating the expression and translation of collagen, a major component of many connective tissues including cartilage and bone<sup>(18)</sup>. Animal model data (all from the guinea pig) are conflicting. Early studies showed that dietary ascorbate decreased pathology in surgically induced OA<sup>(19)</sup>. In a further study, additional ascorbate in the drinking water showed a protective effect on spontaneous cartilage lesions, but no effect on pathology post-surgery<sup>(20)</sup>. Most recently, ascorbate supplementation increased disease severity in spontaneous OA<sup>(21)</sup>.

### Vitamin E

The Framingham study identified a weak protective association between higher intake of vitamin E and the progression of radiographic knee OA<sup>(14)</sup>. A study examining tocopherol isoforms and radiographic knee OA suggested complex associations<sup>(22)</sup> and intervention trials of vitamin E have to date been contradictory<sup>(23)</sup>. *In vitro* data in chondrocytes are sparse, but a recent study suggests that vitamin E protects against hydrogen peroxide-induced changes in extracellular matrix gene expression<sup>(24)</sup>.

### Vitamin D

Vitamin D has multiple functions in the musculoskeletal system, particularly in bone health and pathologies<sup>(25)</sup>. Many studies have explored the association between vitamin D levels and OA. Recent systematic review suggests that low serum concentrations of 25-hydroxyvitamin D are associated with increased radiographic progression of OA, but associations are weaker with symptoms of disease<sup>(26)</sup>. A recent longitudinal study demonstrated the converse, that moderate vitamin D deficiency predicts both knee and hip pain, independent of structural change<sup>(27)</sup>. However, a recent 2-year intervention trial showed no decrease in knee pain or structural change in patients with knee OA, with knee function significantly worse following vitamin D intervention<sup>(28)</sup>. Further intervention trials are ongoing<sup>(29)</sup>. Vitamin D supplementation in a rat post-surgical model of OA showed a protective effect during the early phase of the

disease, but not during the later phase<sup>(30)</sup>. However, this was scored using condyle width, an unusual method. Interestingly vitamin D receptor-deficient mice showed aggravated inflammation and cartilage damage when crossed into a TNF transgenic model<sup>(31)</sup>.

#### Other micronutrients

In a Japanese population (Research on Osteoarthritis Against Disability), low habitual vitamin K intake was the only dietary factor associated with the increased prevalence of radiographic knee OA in a cross-sectional study<sup>(32)</sup>. This supports data from US cohorts where low vitamin K was associated with OA in the hand and knee<sup>(33,34)</sup>. However, a further study, using minimum joint space width and osteophytosis as variables showed an association of vitamins K, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub> and C with the former and vitamins E, K, B<sub>1</sub>, B<sub>2</sub>, niacin (B<sub>3</sub>) and B<sub>6</sub> with the latter, both in women only<sup>(35)</sup>. Vitamin K is an essential co-factor for the formation of  $\gamma$ -carboxyglutamic acid (Gla) residues, and Gla-containing proteins include osteocalcin and matrix Gla protein, both expressed in the skeleton. Vitamin K regulates mineralisation in both bone and cartilage<sup>(36)</sup>. Polymorphisms in the matrix Gla protein gene have been associated with hand OA<sup>(37)</sup>, and serum levels of under-carboxylated osteocalcin may be associated with synovitis in knee OA<sup>(38)</sup>. Niacinamide, a form of vitamin B<sub>3</sub>, has been examined in a pilot scale clinical study of OA and reported to show improvements at 12 weeks<sup>(39)</sup>.

An association between dietary magnesium intake and knee OA was demonstrated in the Johnston County Osteoarthritis Project, but this varied with ethnicity<sup>(40)</sup>. This is supported by data from the Twins UK registry where discordant twin pair analysis showed a decrease in magnesium in co-twins with OA<sup>(41)</sup>. Selenium has been implicated the osteoarthropathy of Kashin–Beck disease; meta-analysis of supplementation studies supports the benefit of supplementation in children, but highlights the low quality of methodology<sup>(42)</sup>.

#### Lipid metabolism

Recent studies have suggested that OA may be part of metabolic syndrome<sup>(43)</sup>. Alterations in lipid metabolism may be key to this, with population-based studies suggesting that serum cholesterol is a risk factor for OA (reviewed in<sup>(44)</sup>). Population studies also suggest that statin use is associated with a reduction in OA incidence and/or progression<sup>(45,46)</sup>, but studies of pain and function in patients with OA have shown no association<sup>(47)</sup>. This area therefore remains controversial. It has been reported that high levels of fat and fatty acids are found in osteoarthritic joint tissues and that this is associated with pathology<sup>(48,49)</sup>. *n*-3 PUFA, but not *n*-6 PUFA were found to be associated with the specific loss of cartilage in the Multicenter Osteoarthritis Study population of people at risk of OA<sup>(50)</sup>. In healthy individuals, consumption of SFA or *n*-6 PUFA (but not *n*-3 PUFA) was associated with an increased risk of bone marrow lesions<sup>(51,52)</sup>. In animal models, a high-fat diet accelerated progression of OA<sup>(53)</sup>, while *n*-3 PUFA

reduced disease<sup>(54)</sup>. Studies in isolated chondrocytes showed that *n*-3 PUFA inhibited IL-1-induced *MMP3*, *MMP13*, *ADAMTS4*, *ADAMTS5* and *COX2* (matrix metalloproteinase (MMP); a disintegrin and metalloproteinase domain with thrombospondin motifs (ADAMTS); cyclooxygenase (COX)) expression, while *n*-6 PUFA had no effect<sup>(55,56)</sup>. A small improvement in OA in dogs was seen with fish oil supplementation<sup>(57,58)</sup>. Interestingly, a supplement rich in fish oil, Phytalgic, was shown to improve function and pain in OA patients<sup>(59)</sup>, although the design of this trial has been criticised<sup>(60)</sup>.

#### Diet-derived bioactives

Typically, foods contain multiple bioactive compounds and these can impact upon many biological pathways<sup>(61)</sup>. Diet-derived bioactives can be classified into several groups, e.g. flavonoids (and related compounds), carotenoids, plant sterols, glucosinolates and others<sup>(62)</sup>.

#### Flavonoids

Flavonoids are polyphenols and include flavan-3-ols, flavonols, flavones, isoflavones, flavanones and anthocyanins. More than 6000 different flavonoids have been found and they are widely distributed in plants, with several hundred found in edible plants<sup>(63,64)</sup>.

#### Flavonols

Flavonols are found in many foods and are exemplified by quercetin, myricetin and kaempferol<sup>(64)</sup>. Quercetin and kaempferol showed no activity against IL-1-induced *MMP13* levels in SW1353 chondrosarcoma cells<sup>(65)</sup>. However, Lay *et al.* report that quercetin is able to block aggrecan loss from articular cartilage potentially via inhibition of *ADAMTS4* and *ADAMTS5*<sup>(66)</sup> and Lee *et al.* show that myricetin can inhibit IL-1 induction of *MMP1* from a synovial cell line<sup>(67)</sup>.

#### Flavones

In fruit and vegetables, flavones are found in celery and parsley, mainly luteolin and apigenin. In the skin of citrus fruit, polymethoxylated flavones are also found, e.g. tangeretin, nobletin and sinensetin<sup>(64)</sup>. Luteolin and nobletin have been shown to inhibit aggrecanases *ADAMTS4* and *ADAMTS5*, both *in vitro*<sup>(68,69)</sup> and *in vivo*<sup>(68)</sup>. Luteolin appears to be selective as a better *ADAMTS* than *MMP* inhibitor<sup>(69)</sup>, it also has anti-inflammatory activity, which could play a role in chondroprotection<sup>(70)</sup>. Nobletin, tangeretin and sinensetin all repress the IL-1 induction of *MMP9* in synovial cells, with nobletin also active in chondrocytes<sup>(71)</sup>. Apigenin was shown to be a potent inhibitor of IL-1-induced *MMP13* expression in SW1353 chondrosarcoma cells, potentially via activator protein 1 and the JAK/STAT (Janus kinase (JAK) and signal transducer and activator of transcription (STAT)) pathway, with no activity against NF- $\kappa$ B<sup>(65)</sup>. It has also been shown to block IL-1-induced glycosaminoglycan release<sup>(65)</sup> and hyaluronan release<sup>(72)</sup> from cartilage explants *in vitro*.

### Flavan-3-ols

These exist as both monomer (catechins) and polymer (proanthocyanidins) forms<sup>(64)</sup>. Green tea polyphenols were shown to be effective in a model of inflammatory arthritis<sup>(73)</sup>. Catechins from green tea (and also present in other foods including dark chocolate) can inhibit cartilage degradation *in vitro*, particularly those containing a gallate ester<sup>(74)</sup>. Epigallocatechin gallate and epicatechin gallate have been shown to be effective (submicromolar) inhibitors of ADAMTS4 and ADAMTS5 aggrecanase activity, indeed significantly more than their ability to inhibit MMP1 and MMP13 collagenase activity<sup>(75)</sup>. Other anti-inflammatory activities have been described (e.g.<sup>(76)</sup>) that suggests promise in OA (reviewed in<sup>(77)</sup>), but no human clinical trials have been performed to date.

While not a diet-derived bioactive, Flavocoxid, a mixture of baicalin (a flavone) from *Scutellaria baicalensis* and catechins from *Acacia catechu*, is marketed as Limbrel, a 'medical food' which inhibits COX2 and 5-lipoxygenase<sup>(78)</sup>. An assessment of the major catechins from *A. catechu* suggests that they are predominantly those described earlier found in green tea<sup>(79)</sup>. Small clinical trials have suggested that Limbrel shows efficacy in OA (e.g.<sup>(80)</sup>), but recently severe liver toxicity has been described in some patients<sup>(81)</sup>.

A grape seed proanthocyanidin extract is protective in the monosodium iodoacetate model of OA in the rat, showing chondroprotection and decreased pain<sup>(82)</sup>. Specifically, procyanidin B3 abrogates cartilage destruction and heterotopic cartilage formation in a surgical model of OA in the mouse<sup>(83)</sup>. It was shown to block IL-1 repression of matrix gene expression *in vitro* and also decrease inducible nitric oxide synthase *in vitro* and *in vivo*<sup>(83)</sup>.

Another mixture not derived from the diet, Pycnogenol is a pine bark extract rich in procyanidins<sup>(84)</sup>. It has been reported to inhibit NF- $\kappa$ B activation and the activity of some MMP<sup>(85,86)</sup>. Three small clinical trials have been performed in OA with positive outcomes reported (e.g.<sup>(87,88)</sup>). However, a Cochrane review of Pycnogenol in chronic diseases (including OA) stated that it was not possible to reach definite conclusions on either efficacy or safety of Pycnogenol<sup>(89)</sup>.

### Anthocyanins

Anthocyanins are responsible for the red/blue pigmentation in fruits and vegetables<sup>(64)</sup>. To date most studies have been performed using fruit juices or extracts that are rich in anthocyanins. A recent clinical trial examined tart cherry juice in patients with knee OA<sup>(90)</sup>. No difference in disease scores compared with placebo was uncovered, but high-sensitivity C-reactive protein was significantly lowered and this was associated with decreased score<sup>(90)</sup>. Pomegranate juice or extracts, which have been reported to contain anthocyanins and many other flavonoids including flavanols, have been shown to inhibit IL-1-induced MMP expression in chondrocytes via inhibition of MAP kinases and NF- $\kappa$ B<sup>(91-93)</sup>. Such extracts also show efficacy in the

monosodium iodoacetate model of OA in mice<sup>(94)</sup>. Raspberry extract<sup>(95)</sup> and red orange extract<sup>(96)</sup> have also been reported to have some efficacy *in vitro* and *in vivo*.

### Isoflavones

Isoflavones are diphenolic compounds with structural similarity to oestrogens, and are consequently referred to as phytoestrogens. They are found mainly in legumes and soya is a major source of isoflavones in the diet<sup>(64)</sup>. Data in chondrocytes show that one isoflavone, genistein, reduces the production of inflammatory molecules such as COX2 and nitric oxide<sup>(97)</sup>. Extracellular matrix synthesis in cartilage may increase or decrease, potentially with increasing dose<sup>(98,99)</sup>. In the rat inflammatory collagen-induced arthritis model, soya protein appears to be protective<sup>(100)</sup>, however, no significant effect of soya intake was measurable on OA severity in Cynomolgus monkeys<sup>(101)</sup>. One human study suggested beneficial effects of soya protein supplementation on function, symptoms and biochemical markers of OA, particularly in men<sup>(102)</sup>.

### Flavanones

Flavanones are present in the diet at high concentrations only in citrus fruits including naringenin from grapefruit, hesperetin from oranges and eriodictyol from lemons<sup>(64)</sup>. No effect was seen for naringenin on IL-1-induced MMP13 production in SW1353 chondrosarcoma cells<sup>(65)</sup>. However, hesperetin, its glycoside hesperidin or its derivatives, show efficacy in inflammatory models of arthritis<sup>(103-105)</sup>. Red orange juice extract showed repression of inflammatory molecules in chondrocytes as mentioned earlier<sup>(96)</sup>.

### Carotenoids

$\beta$ -Carotene is the most widely known carotenoid and is a precursor to vitamin A<sup>(106)</sup>. Vitamin A and its derivatives, retinoids, are known to have profound effects on cartilage and the skeleton and may contribute to OA<sup>(107)</sup>. The Framingham study identified a weak protective association between intake of  $\beta$ -carotene and the progression of radiographic knee OA<sup>(14)</sup>. A case-control study in the Johnston County Osteoarthritis Project examined the association between serum levels of several carotenoids (lutein, zeaxanthin,  $\beta$ -cryptoxanthin, lycopene,  $\alpha$ -carotene and  $\beta$ -carotene) and OA<sup>(108)</sup>. People with high levels of lutein or  $\beta$ -cryptoxanthin were less likely to have knee OA, while those with high levels of trans- $\beta$ -carotene or zeaxanthin were more likely to have knee OA. Similarly, a cross-sectional study in a Japanese population with radiographic knee OA examined the association between serum levels of several carotenoids (lutein, zeaxanthin, cantaxanthin, cryptoxanthin, lycopene,  $\alpha$ -carotene and  $\beta$ -carotene) and OA, but found nothing significant<sup>(109)</sup>. It is worth noting that there is evidence that  $\beta$ -cryptoxanthin is associated with a decreased risk of inflammatory arthritis (e.g.<sup>(110)</sup>). In healthy, middle-aged people, lutein and



zeaxanthin intake were associated with decreased risk of cartilage defects on MRI and  $\beta$ -cryptoxanthin intake was inversely associated with tibial plateau bone area<sup>(17)</sup>.

#### Plant sterols

As discussed earlier, there is a positive association between serum cholesterol and OA, with statin use appearing to show efficacy in disease incidence and/or progression. Intake of plant phytosterols/stanols significantly reduce LDL cholesterol and total cholesterol in intervention trials<sup>(111,112)</sup> and of the three phytosterols tested, (stigmasterol, sitosterol and campesterol), stigmasterol bound best to chondrocyte membranes<sup>(113)</sup>. It inhibited IL-1-induced MMP and ADAMTS4 expression, although had no effect on ADAMTS5, potentially via its ability to inhibit NF- $\kappa$ B activation<sup>(113)</sup>. Intra-articular injection of stigmasterol was shown to suppress MMP expression and reduce cartilage degradation in a rabbit anterior cruciate ligament transection model of OA<sup>(114)</sup>.

#### Glucosinolates

Glucosinolates are found in cruciferous vegetables and are the precursors of isothiocyanates. Broccoli is rich in glucoraphanin, and when the vegetable is chopped or chewed, it is exposed to the action of an enzyme myrosinase to yield sulforaphane, the isothiocyanate. In chondrocytes, sulforaphane was initially shown to decrease shear stress-induced apoptosis<sup>(115)</sup>. More recently, it has been shown to exhibit pro-survival and anti-apoptotic activities when cell death is induced by a variety of stimuli<sup>(116)</sup>. Sulforaphane has been shown to block IL-1 and TNF $\alpha$  induction of MMP1 and MMP13 expression, as well as PGE2 and nitric oxide in chondrocytes<sup>(117)</sup> and inhibit cartilage degradation *in vitro*<sup>(118)</sup>. Later work showed that it was effective in inhibiting expression of ADAMTS4 and ADAMTS5, and abrogating cartilage destruction in the 'destabilisation of the medial meniscus' model of OA in the mouse, acting as a direct inhibitor of NF- $\kappa$ B<sup>(119)</sup>.

#### Resveratrol

Resveratrol is a plant-derived phenol of the stilbenoid class, found at high concentrations in the skin of red grapes and in red wine. It has come to the fore as an activator of the histone deacetylase Sirt1, which has important roles in cell survival and as a mimic of caloric restriction that extends lifespan in many models<sup>(120)</sup>. Sirt1 is intimately involved in OA with deletion of Sirt1 in mice causing more rapid development of OA in a post-surgical model<sup>(121)</sup>. Resveratrol decreases OA score when directly injected intraarticularly in the rabbit anterior cruciate ligament transection model of OA<sup>(122,123)</sup>. It is an NF- $\kappa$ B inhibitor in chondrocytes and blocks inflammation and apoptosis<sup>(124–126)</sup>. It has also been shown to decrease proteolysis (e.g. MMP and ADAMTS) and enhance extracellular matrix synthesis<sup>(127)</sup>.

Interestingly, resveratrol has been shown to display synergistic effects on chondrocyte phenotype and apoptosis with curcumin (see later)<sup>(128,129)</sup>. These compounds

both inhibit NF- $\kappa$ B, but are known to act via different mechanisms.

#### Curcumin

Curcumin is the major curcuminoid found in the spice, turmeric. It has been shown to be an NF- $\kappa$ B inhibitor<sup>(130)</sup>, and used in chondrocytes as an inhibitor of oncostatin M-, IL-1- and TNF $\alpha$ -induced signalling<sup>(131–133)</sup>. Here it was shown to inhibit c-Jun N-terminal kinase, activator protein 1, STAT and mitogen-activated protein kinase signalling, to inhibit expression of key MMP in cartilage and proposed to have potential clinical utility. Innes *et al.* used a turmeric extract in a clinical trial of OA in the dog, with clinical assessments showing significant improvement<sup>(134)</sup>. The anti-catabolic effects of curcumin in human articular chondrocytes were confirmed<sup>(135)</sup> and its impact extended to include anti-apoptotic activity<sup>(136)</sup>, pro-anabolic effects on matrix expression<sup>(66,136)</sup>, inhibition of COX2 expression and other inflammatory mediators<sup>(137,138)</sup>. Efficacy was also shown in cartilage explants<sup>(66,139)</sup> and murine models of inflammatory arthritis<sup>(140)</sup>, although not yet OA. Curcumin itself has poor solubility and bioavailability<sup>(141)</sup>, but a curcumin-phosphatidylcholine complex (Meriva), designed to overcome this, has shown some efficacy in small-scale clinical trials<sup>(142,143)</sup>. As discussed earlier, a thorough understanding of mechanism of action has led to experiments showing synergy between curcumin and resveratrol<sup>(128,129)</sup>.

#### Avocado-soyabean unsaponifiables

While not truly dietary-derived, avocado-soyabean unsaponifiables (ASU), Piascledine, has been developed by Laboratoire Expanscience and is the unsaponifiable fraction of one-third avocado oil and two-thirds soyabean oil. It is a mixture of tocopherols, plant sterols and other molecules<sup>(144)</sup>. A recent moderate-sized trial of Piascledine in hip OA (the ERADIAS study) over 3 years showed that while there was no significant difference in mean joint space width loss between treatment and placebo, there were significantly less progressors in the treatment group. There was no difference in clinical outcomes including pain or analgesic/non-steroidal anti-inflammatory drug use<sup>(145)</sup>. This was somewhat similar to an earlier smaller study examining structural modification<sup>(146)</sup>, but very different from other earlier trials, where ASU demonstrated reductions in pain, functional disability or non-steroidal anti-inflammatory drug use in patients with hip or knee OA over 3–6 months<sup>(147–149)</sup>. In a dog anterior cruciate ligament transection model of OA, ASU reduced disease severity and decreased MMP13 production<sup>(150)</sup>, although in an ovine model of post-meniscectomy OA, ASU was described to have a 'subtle, but statistically significant' effect on cartilage<sup>(151)</sup>. *In vitro* data showed that ASU exhibit anti-catabolic (MMP expression), anti-inflammatory (PGE2, nitric oxide, COX2) and pro-anabolic (type II collagen and aggrecan synthesis) in chondrocytes. It has also been shown to inhibit NF- $\kappa$ B activity<sup>(152–154)</sup>. It should also be pointed out that other formulations of ASU exist

and one from Nutramax has been shown to have similar *in vitro* activity in chondrocytes<sup>(155)</sup>. Data from equine chondrocytes suggest that this ASU can act synergistically with epigallocatechin gallate<sup>(156)</sup>. The relative merits of each preparation have been the subject of debate<sup>(144,157,158)</sup>.

### Ginger

There have been several small clinical trials exploring the efficacy of ginger extract in the treatment of OA. Trials using *Zingiber officinale* extract showed variable outcome and a review found that evidence for its efficacy in OA was weak<sup>(159)</sup>. A mixture of extracts from *Z. officinale* and *Alpinia galangal* used in a short (6-week) study showed a significant effect in reducing clinical symptoms<sup>(160)</sup>. *In vitro* research suggests that ginger extract can decrease production of inflammatory mediators from chondrocytes<sup>(161)</sup> and synoviocytes<sup>(162)</sup>.

### Sulphur-containing compounds

A cross-sectional study in twins demonstrated that consumption of both allium vegetables and also non-citrus fruits showed a protective association with hip OA<sup>(163)</sup>. Furthermore, diallyl disulphide, a compound from garlic, was shown to inhibit IL-1-induced *MMP1*, *MMP3* and *MMP13* expression<sup>(163)</sup>. Diallyl sulphide has also been shown to block expression of these enzymes and ameliorate cartilage destruction when administered intraarticularly in the rabbit anterior cruciate ligament transection model of OA<sup>(164)</sup>.

### Others

Interestingly, data on the progression of knee OA, coming from the Osteoarthritis Initiative showed that frequent soft drink consumption is associated with increased disease progression in men, independent of obesity<sup>(165)</sup>. This obviously requires replication. An extract of edible bird's nest (which is made from swiftlet saliva), has been shown to have anti-catabolic, anti-inflammatory and pro-anabolic activity on human osteoarthritic chondrocytes<sup>(166)</sup>. Sesamin, a lignan from sesame seeds has been reported to be chondroprotective in an explant assay, decreasing MMP expression and activation<sup>(167)</sup>. An extract of a variety of mint which overexpressed rosmarinic acid inhibits lipopolysaccharide-induced glycosaminoglycan release and inflammatory mediators from porcine cartilage explants<sup>(168)</sup>.

### Conclusions

There are many compounds present in the habitual diet, which have been shown to have activity in both laboratory models of OA and/or human disease. Where examined, many of these compounds appear to be inhibitors of the NF- $\kappa$ B pathway. This signalling pathway has been shown to play a role in the development and progression of OA<sup>(169)</sup>. Two studies suggest that using a combination of compounds, which inhibit the NF- $\kappa$ B pathway via different mechanisms gives a synergistic response<sup>(128,129)</sup>. It would thus be important to understand

the mode of NF- $\kappa$ B inhibition for all compounds with this activity. In order to achieve synergy, it will also be important to discover compounds which do not act via this mechanism. Since habitual dietary intakes vary widely, an understanding of food combinations, which protect the joint, may be key and this may also be a means to develop specific food products or offer targeted advice to reduce risk.

Basic science provides information on the mechanisms of cartilage protection in healthy tissue and the prevention of cartilage destruction in disease. The design of randomised clinical trials in the longer term needs to include 'at risk' populations (in which incidence of OA can be used as an outcome measure), as well as patients with existing OA. This is in line with the current European Food Standards Agency recommendations that the design of human trials must demonstrate a preventative effect on the healthy joint, separately from an impact on established OA *per se* to establish claims in both areas.

In summary, diet offers a route by which the health of the joint can be protected and OA incidence or progression decreased. In a chronic disease, with risk factors increasing in the population and with no pharmaceutical cure, an understanding of this will be crucial.

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### Conflicts of Interest

None.

### Authorship

All authors have contributed to writing and/or critically reviewing and editing the manuscript.

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