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Nutraceutical Treatment in Knee Osteoarthritis

—Arthritis-Presentation of a Dietary Plan by Means of Additional Nutraceuticals in Lieu of the Detrimental Side Effects of Current Conventional Medicine

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Abstract

Arthritis (AR) is a disease that affects the joints and of which there are, remarkably, over 100 different types. Osteoarthritis (OA) is the most common type and knee osteoarthritis (KOA) is the most common subgroup of OA. KOA is a pathological degeneration of joints, connective tissue and the subchondral bone of the knee. The origin of the disease is not fully understood but the etiology includes risk factors such as age, gender, physiological trauma and BMI. It is a complex pathological state of cause, effect, and manifestation where the exact mechanisms responsible are not visible. Inflammatory mediators are involved in the progression of KOA and this cascade of reactions to the inflicted area is unfortunately chronic. Pain is a key feature, and it ranges from mild to severe. Patients are likely to use analgesics that are more potent than "over the counter" (OCT) drugs at some stage. As the condition develops over time the need increases and prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and steroids are used. NSAIDs can help reduce the pain as well as enhance the joints range of movements again. However not in an optimal way, nor do they have the ability to alter any of the mechanisms behind the disease. Inevitably, the side effects from the medicine will have a negative impact on the patient; even more so the longer they are used. Currently, alternative medicine and nutraceuticals can be controversial. Several countries and organizations consistently deny any beneficial outcome from these in the context of KOA-treatment. Official statements are made about the lack of evidence and consequently official non-recommendations are commonplace. This review will show viable complementary alternative medicine (CAM) that has been studied over decades with unequivocal positive results on KOA. These options exhibit minimal side effects and a high safety-margin. Included are up-to date clinical studies with current evidence of beneficial effects. This review presents key strategies for the arthritis pa-

tients. A dietary plan not to deviate from and the use of specific nutrients and herbs. The analysis of nutrachemicals include glucosamine, chondroitin sulfate, collagen type 1, undenatured collagen type II and hyaluronic acid. Therapeutic dosages of nutraceuticals as well as a specified diet designed to curb and to some extent reverse KOA. Traditional Chinese medicine consisting of *T. wilfordii*, *A. bidentate*, bromelain, Boswellia and *Curcuma longa*. To a certain extent these nutraceuticals have an ability that is absent in current pharmacological treatments. The ability to reverse and sometimes rebuild tissues and cells affected by KOA. All nutraceuticals in the review is evaluated with the standard methods WOMAC and VAS in order to measure degrees of pain, stiffness and functionalities of the knee.

Keywords

Arthritis, Osteoarthritis, Nutrition, Nutraceuticals, Herbs, Alternative Medicine

1. Introduction

OA is widespread in the world. It is the most common joint disease affecting 500 million people of the global population. Indeed, over the last 3 decades the number of diagnosed patients has doubled. Until recently it was viewed as a disease for elderly people. It is now evident that it is affecting ever-younger patients and the perception of KOA needs to be modified.

There are more underlying causes than age. Previously considered a result of wear-and-tear of the knee joint it is now recognized as a disease induced by a wide range of factors [1]. It is crucial to look at all causative factors in order to find functional medicine or interventions able to constrain the disease. Not only will KOA decrease quality of life for the patient as mobility are hindered and pain seeps into many facets of everyday life. It is also one of the biggest financial restraints in the healthcare system as these patients require extended physiotherapy, doctors' visits, medicinal treatments, surgeries and care-home assistance [2].

KOA is a progressive disease and typically spreads to other parts of the body. The inflammatory processes tend to get worse which leads to more pain and impediments for the patient.

One of the consequences from increased pain and deformation of the joints is total knee arthroplasty. There has been an unproportioned rise of this surgery and in United States alone it has doubled over the last decade. Unfortunately, this replacement is not a guarantee for a complete elimination of symptoms [3].

Acknowledged risk factors are age, genetics, repetitive physical trauma and lesions of the knee, obesity, gender, smoking, stress, alcohol, pollution, radiation. In addition, it can be argued that nutritional deficiencies may play a big part as a trigger to initiate KOA as well as amplifying the disease once it is established [4] [5].

1.1. Osteoarthritis (OA)

The joint consists of articular (hyaline) cartilage, articular bones and synovial fluid. The cartilage is 95% composed of extra cellular matrix (ECM). A dense matter of collagen, water, proteoglycans and highly specialized chondrocyte cells to facilitate a lubricated and smooth shield of support toward the (harsh) mechanical friction of articulation. The ECM is void of blood vessels and nerves and has a limited capacity to repair and heal. The bone endings—subchondral bone—are surrounded by the cartilage and a synovial membrane. The membrane supplies a synovial fluid to cushion the biomechanical pressure.

The consensus on KOA was until recently that it affected only an isolated part of the joint from a result of wear-and-tear. However, it involves 3 compartments of the knee equally and the root cause can be both endogenous as exogenous factors [4] [6] [7]. Age, gender, genetics, ethnicity, post-menopausal changes as internal causes. Stressors from the outside environment represents repetitive microtrauma, lifestyle factors, overweight, joint surgery and macrotrauma.

Signaling molecules from joint damage, injury to the knee's compartments, degradative lifestyle factors, senescence or mechanical stress load will eventually activate the innate immunity and in extension trigger an incipient KOA [1] [8].

Inflammatory responses are produced in order to repair and heal the affected tissues. However, the introduction of innate immunity set off a complex set of actions. Pro-inflammatory compounds will trigger cytokines, enzymes and chemokines with a dominating catabolic effect. There is a simultaneous downregulation of anabolic factors. The net result is that the ability of the joint to repair itself will decrease [6] [9] [10] [11].

The normal interplay between anabolic and catabolic metabolism in the articulate cartilage is usually a fine-tuned balance of continuous breakdown products from the dense pressure of the joint versus an anabolic response that builds new chondrocyte cells and surrounding tissue. From the onset of KOA this balance will shift into a more catabolic influence. Resorption of chondrocytes will leave the articular cartilage thinner over time. As the cartilage decreases—the less cushioned area between bones. Eventually joint-space-width between the bone endings narrows down. More friction will occur with accompanying pain as this gap becomes smaller.

The membrane of synovial fluid, synovium, is possibly the first part of the joint to be affected by KOA. Inflammation is triggered into a constant synovitis. The inflamed membrane swells up from the increased blood flow which results in effusion. The extra pressure from the effusion on the surrounding tissue is yet another nociception stimuli.

The metabolic shift in the compartments also includes subchondral bone. Contrary to articular cartilage there is an upgrade of anabolic factors. Osteocytes increase and bone mass can grow in width and length. Bone spurs can arise which are projections from bone, a foreign and morphed mass. This cause friction, pain and swelling [6] [12] [13].

There are many messengers involved in these processes that are enhanced in KOA. Certain key players take place front stage with a constant presence of detrimental influences. These include cytokine Interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α).

IL-1β and TNF-α are responsible for the release and activation of pro-inflammatory cytokines. Interleukin 6 (IL-6) and nuclear factor kappa B (NF-κB) are featured as 2 compounds that strongly participate in KOA. Both exert catabolic effects on the cartilage as well as increased inflammation [1] [4] [8] [9].

IL-1β generates catabolic effects on chondrocytes in several ways. It decreases type 2 collagen (CU-II). It escalates reactive oxygen species (ROS) as well as matrix metalloproteinases (MMPs) [6] [9] [14] TNF-α also increases the expression of MMPs.

CU-II is a crucial component of the ECM and provides a structure and gelatinous resistance to the repetitive pressure on articular bones.

MMPs are a family of enzymes part of the innate and adaptive immunity. They are involved in many processes that help maintain adequate repair and remodeling of tissue and bone. In the context of KOA the levels of MMPs are heightened to an abnormal and pathogenic extent. This gives rise to degradative effects on ECM and the release of certain cytokines and chemokines that cause further destruction [1] [6] [9] [15].

Cartilage damage and breakdown of CU-II are consequent results. MMP 1, 3, 13 and 17 are prominent in this particular context.

Reactive oxygen species (ROS) are molecules with signaling functions and various cell regulations such as growth and differentiation. They are also important intermediates in the process of inflammation. They improve blood flow to injured areas thus allowing white blood cells and nutrients to gather at the damaged site. However, they are very unstable and need to be regulated immediately to avoid excess oxidative stress and destruction of cells. These regulating factors are various detoxifying enzymes. They reinstall a balanced oxidative state. Superoxide dismutase (SOD) is one of the internal antioxidant (AO) enzymes that break down the reactive oxygen into ordinary levels and molecules again. SOD's ability to catalyze this reaction diminishes in KOA which means that one of the principal defense mechanisms against excess ROS is lost [6] [7].

The impaired AO defense coincides with increased levels of ROS. In the pathology of KOA more ROS are formed to combat the excess of inflammatory cytokines that flood the local tissue, cartilage and bone. This is a result from the oxidative stress created in the immunity reactions of KOA [6] [7].

When the body's AO systems fail to quell the rampage of ROS molecules, there is an urgency of additional antioxidants from dietary sources. There is a wide range of AOs in foods that effectively can provide the same results a SOD [6] [11] [16].

OA is not an autoimmune disease like other forms of rheumatism such as arthritic rheumatism or lupus. However, they share several characteristics. Both innate and complementary parts of immunity are involved in the progression of

the disease [16]. This reaction is local and not as severe, widespread or complex as the autoimmune forms of arthritis. But it is an overactivity where the defense mechanisms and mediators are produced in quantities and speed that complicate the real purpose of immunity which is to heal and repair [1] [6]. OA typically spreads to other places over time; usually, the hips and shoulders.

The chronic state of KOA means that the cycle of pathological processes will keep going and it is imperative to decrease and curb these reactions. It is at times a "quieter" disease with deceptive calm. But the fight is constant, and the aim will always be to suppress any possibility for arthritis to spread, increase in pain and create more havoc.

1.2. Glucosamine Sulfate and Chondroitin Sulfate

Glucosamine and chondroitin are 2 molecules of the joint. Both are part of the cartilage, ECM and synovium and critical for these compartments of the joint to function optimally. Glucosamine is an amino sugar that is a key component of glycosaminoglycans (GAGs). GAGs are polysaccharides that in turn make up a big part of the structure to the cartilage. They are responsible for the synovial fluid to be maintained at a sufficient amount and consistency thick enough to withstand the mechanical pressure. Chondroitin is a proteoglycan that work closely with GAGs in the knee joint. It is part of the regulation of osmotic pressure of ECM which is necessary for cartilage tissue resistance [12]. They also have antioxidant capacities where they exert chondrocyte protection from inflammatory cytokines like IL-1β [17].

These molecules decline with age and especially in a state of KOA. During KOA the metabolic change and damage signals shift the body's ability to repair and rebuild glucosamine and chondroitin again.

This in turn will affect the function of the knee as the lubrication decreases and inflammation is upgraded. This results in more stiffness and pain as the joint's gap-width becomes narrower and the articular bones meet in friction [18].

These are very common in supplemental form as glucosamine sulfate (GS) and chondroitin sulfate (CS), either alone or in combination. They are natural products made from shellfish and animal cartilage, widely used in clinics and popular in the health market for patients with KOA. They are well known products throughout the world and have been for decades.

GS and CS can help replenish the levels back to quantities that resemble a pre-arthritic state. Mostly they are symptomatic drugs and may possibly reverse some characteristics of the disease.

They are symptomatic slow acting drugs for osteoarthritis (SYSADOAS) and disease modifying osteoarthritic drugs (DMOADS) to a degree. Although there are controversies surrounding these labels of efficacy regarding GS and CS.

Currently there are 70 countries that officially approve GS and CS as medicines. They can be prescribed by physicians. Patients will receive knowledge about these SYSADOAS and can make their own decision whether to try them.

They are approved in Europe and by some of the leading osteoarthritic research organizations of the world. European alliance of associations for rheumatology (EULAR) officially recommends them. Osteoarthritic research society international (OARSI) have had changing consensus on the matter. Today they recognize GS and CS as SYSADOAs but not as DMOADs.

A shift in recommendations took place 2007, specifically after a report from AHRQ was published. This was based on one medium sized RCT, the GAIT trial [19]. The results showed that GS and CS have minimal effects without significant benefits. Several countries and organizations stopped endorsing the drugs. The aftermath from the GAIT trial is still relevant. Countries like the United States and Sweden changed their official recommendations and are now advising the public against these supplements [19]. Combined with these statements they acknowledge that there may be benefits to gain from their use and that they are safe. No adverse events (AEs) noteworthy [20] [21]. Official approval merely falls short of the inconsistent results from clinical studies.

There have been many more clinical studies published since 2007. Up to date studies that confirms the positive effects from these supplements [12] [17] [21]. Additionally—the authors of the GAIT-trial made a post hoc analysis in 2008 stating that their conclusion in the trial was incomplete. A big majority of the patients included in the trial suffered mild to modest symptoms. Only a small minority was on the modest-severe scale. Patients of the latter had a successful outcome where their symptoms improved significantly. This is noteworthy and the authors consequently wrote about this in the post-hoc analysis, recommending more and larger studies with patients suffering on a modest-severe scale. They recanted their consensus over non-recommendation to one that now acknowledges potential effects [22].

The author of this article review would argue that the complete disregard many physicians place toward these supplements is less than optimal. Patients with KOA would benefit from information that includes all potent supplements and drugs. Studies over the last decade show positive results in which the authors recommend the supplements. Most often with the caveat that more studies are warranted. The disease is complex and so is any treatment. There is no general treatment with GS and CS that suits all patients. It may require experimenting and adjusting for the patient. GS can improve stiffness and CS the elasticity and motion [12] [17]. A subsequent result is less pain. It is likely that a combination may be superior to the separate parts.

There is a lot to gain with GS and CS. Not least because of the fact that they are considered safe with only minimal AEs.

It has to be stated that there are no pharmaceuticals, NSAIDs and steroidal drugs that are without side effects either [6] [22].

In fact, these AEs intensify over time. Leading to injurious consequences for the heart, kidneys and gastrointestinal tract [1] [3] [8] [12].

This is something that physicians can agree on.

Typical dose is around 1500 mg/day for GS and CS respectively.

1.3. Collagen Types 1 and 2

There are 2 types of collagens that are relevant in the context of KOA. Type 1 and type 2. They are used extensively as arthritic supplements in the forms of hydrolyzed collagen type 1 (HC) and undenatured collagen type 2 (CU-II). They are to some extent novelties in relation to clinical studies and confirmed results mainly concerning CU-II.

However-there are many studies and meta-analyses that reveal impressive effects on KOA. It may be a question of correct usage of the supplements in order to attain these beneficial results. An understanding on how they work, in what order to use them and at what dosage.

Collagen is an all-pervading protein in the body. Type 1 collagen is found in skin and tendons. Type 2 is found mainly in cartilage and make an equally significant part of joint structure and elasticity with results parallel to GS and CS.

It is recommended to start with CU-II. The supplement form is minimally processed to make it as similar to innate structure as possible. It seems likely that CU-II has the ability to not only restore some of the decreased levels of collagens in the knee, but in fact altering the inflamed immune reactions to CU-II. This is made possible by a process of "oral tolerance" [23] [24].

In the process of OA there is an overreaction of immune cells toward important structural compounds such as chondrocytes, glucosamine, hyaluronic acid and collagens in the joint. When oral UC-II is applied it is presented as an antigen by the innate immunity and is identified it as harmless. It seems that small doses can introduce a reaction of T-cells in the Peyer's Patches to generate Treg's. These are a form of T-cells that can regulate immune responses and, in this context, specifically alter the catabolic effects from T-, B-cells, macrophages, cytokines, chemokines and MMPs. The body can acknowledge UC-II as an endogenous substance again and cease the breakdown of this protein [9] [10] [25].

There are remaining questions regarding the efficacy of CU-II. However, evidence show that there is a decrease of the urinary degradation marker CTX-2 [10] [25] which suggests that CU-II does arrest the catabolic effects.

Type 1 collagen in supplemental from is hydrolyzed and dissolved into smaller peptides. It is altered into a denatured form of collagen for better absorption. This has been proven to have several beneficial effects in the joint [25] [26]. It affects fibroblasts in the ECM to rebuild collagen. The direct influence from the peptides of HC triggers fibroblasts to gather at the site and repair it.

This is a way of reversing some of the damaging factors of KOA where fibroblasts cannot function normally. There is an offset in the balance of fibroblastic cells. There is both an excess production where inflammatory fibrosis ultimately can be formed as well as degradative effects where the synthesis of collagen is disrupted [25].

A regeneration of collagen and chondrocytes in the joint tissues will lead to less inflammation and pain.

However, the pathological processes in KOA need to be constrained in order for HC to be optimized. Therefore, treatments should begin with CU-II that can exert an immune-modulatory effect first [26]. Possibly for a period of up to 6 months.

HC supplement is traditionally taken orally but is now available as intra-articular injections. CU-II is made from animal bones and tendons and CH from cow chicken sternum. They are considered very safe. A typical dosage of CU-II is 10 mg and with hydrolyzed collagen it is 40 mg.

1.4. Intra-Articular Hyaluronic Acid

Hyaluronan is a part of the polysaccharides in GAGs and is a crucial part of the ECM and synovial fluid.

It affects both structure and viscous properties of the joint. It accumulates in the ECM during inflammation and can regulate the expression of inflammatory mediators. This in turn can attenuate the reaction.

There is a symptomatic relief with less pain and a better range of motion of the knee. One strong factor behind this is the decrease of inflammatory mediators IL-1B, IL-6 and MMPs that are likely to cause the ease of symptoms [27] [28]. Considering its restorative effects on injured tissue it is an integral part of the knee joint.

Levels of hyaluronan drop during a state of KOA and a method used to restore these is with intra-articular hyaluronic acid (IA-HA) injections. It is a well-known alternative to NSAIDs and corticosteroid injections and it comes with a high safety margin [28]. Particularly when compared to conventional medicine. Efficacy is high however more research is needed regarding long-term evaluation and uniform doses.

A common practice is 1 - 5 injections with beneficial results. There is some uncertainty whether the treatment should be continuous, for what period of time and at what dosages. New research show that it does have a successful long-term effect on internal hyaluronan levels [28].

There is a general consensus on the efficacy and safety of IA-HA injections. Studies show that they can be as effective as NSAIDs and corticosteroids [27]. However, it is a treatment with a heterogeneous effect. Consequently, it can be recommended for the patient to try one injection and then decide upon follow-up treatments.

The method is approved and recommended in many countries as a viable treatment for KOA.

It can certainly be a justified part of KOA therapy.

1.5. Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is a common treatment in Asia for various ailments. It is a broad term that includes herbal medicine (CHM) as well as

physical therapy like acupuncture and massage. These branches of TCM have beneficial effects on KOA. There are certain herbs that are recurrent in these nutraceutical therapies and about 17 specific ones in the context of KOA.

One formulation called "FJHQT"/"Boogie" is popular in Japan and China and is reported to decrease the levels of IL-1β and knee effusion [3]. Another CHM blend called "DHJST" show impressive results on VAS and WOMAC scores of KOA-patients.

There is an increase in the use of CHM in Asian countries and the number of clinical studies are expanding. Beneficial results support the validity of these herbs in several ways.

CHM have anti-inflammatory and chondroprotective effects. They have the ability to reduce joint effusion and exert analgesic relief [29].

Ever more KOA patients have to undergo surgery to replace the knee. However, the process of total knee arthroplasty (TKA) is not a guarantee for less pain and the arthritic condition will remain. Studies show a decreased risk of TKA in the treatment with TCM [3]. Herbal formulations and acupuncture are involved. Acupuncture treatments can both decrease the sensitivity of nociceptors, as trigger a release of endorphins that blocks some of the pain [3]. Consistent acupuncture therapy is recommended in KOA.

The use of TCM is already reducing hospitalization costs significantly is the result.

1.6. *Achyranthes bidentate* Blume

A. bidentate Blume (AB) is one of the key herbs of TCM in general but also with a biologic specificity of actions toward degenerative changes in KOA. AB herb originates from a flowering plant of the Amaranth family. It is also found under the name "Niuxi" in Asian countries.

It has been used for medicinal purposes for thousands of years and recent research can now illuminate the mechanisms behind it. The content of saponins is important as primary metabolites and mode of actions in AB.

AB has clearly defined effects on OA and in particular—KOA. The main pathway to achieve this is through the inhibition of IL-1β and thus, by extension, also NF-κB [3] [14].

The detrimental effects that IL-1β and NF-κB has on cartilage, ECM and chondrocytes are a crucial factor of KOA. The decrease of these will in turn arrest part of the breakdown of these tissues.

Irrelevant of potency and heterogeneous effects of AB, it is considered a DMOA certified herb.

This is not possible as of yet with any conventional treatment like NSAIDs and steroids.

AB can decrease deterioration of bone and cartilage and release swelling through better circulation [14].

Dosage between 3 - 30 mcg/day.

1.7. *Tripterygium wilfordii* Hook F

Tripterygium wilfordii Hook F (TwHF) is another herb with a long tradition in ECM treatment. It is also known as "Lei Gong Teng" or "Thunder God Vine". Its leaves and roots are used for medicinal relief in conditions of inflammation and overactivity of the innate immunity.

It does not have a robust body of scientific evidence pertaining to KOA specifically but certain research shows very promising effects. What is generally acknowledged is the beneficial effects of TwHF on inflammation and autoimmune disorders. The herb is used for several of the big health issues today, neurodegenerative and atherosclerosis conditions [30].

Active compounds in TwHF, mainly triptolide, are used as anti-inflammatory mediators as well as regulators of an imbalanced cytokine production. The catabolic effects of cytokines IL-1β, COX-2, TNF-α, MMP 3 and 13 are diminished which is a necessity to halt the pathologies of KOA and improve the condition [6] [30] [31].

Dosage suggestion: 20 - 30 mg/day. AEs are low in general, but precaution is needed for correct preparation.

1.8. *Boswellia serrata*

Boswellia is a herbal extract from the boswellia tree. It is a traditional medicine of Indian folk remedies as well as Asian CHM treatments. Its most active compound is the boswellic acid, "AKBA".

AKBA is particularly beneficial in joint diseases and osteoarthritis, but the traditional usage is much wider. Expanding to diseases of neurodegenerative nature, chronic pain syndrome, analgesics and blood circulation. AKBA has anti-inflammatory properties where the main mechanism behind it is the inhibition of 5-lipoxygenase (5-LOX). A major influence of proinflammatory leukotrienes.

Aflapin is a derivate from *Boswellia serrata* gum resin which contain AKBA enriched oil. It has an enhanced bioavailability compared to boswellia and seems to be more efficacious in the inhibition of 5-LOX, MMP-3 and other inflammatory mediators [16] [32].

Boswellia and aflapin have distinctive effects on KOA with clear improvements of pain scores and joint mobility [16] [32] [33].

More research is warranted to further expand the beneficial effects.

Dosage suggestion:

Aflapin 100 mg/day

Boswellia extract 100 - 300 mg. Boswellia extract can be taken orally and by injections.

It is considered safe.

2. Bromelain

Bromelain is an active enzyme deriving from the pineapple stem. It is a highly

absorbable compound with a multitude of anti-inflammatory, circulatory and anticancerous effects [34]. It is a very safe nutraceutical therapy to commit to [35] [36].

The mode of action is through the chemical compounds of thiols which are highly potent antioxidants. They synchronize with other compounds like phosphatase and perioxidase leading to less oxidative stress and catabolic effects by cytokines.

It can decrease the level of inflammatory PGE2 mediators as well as bradykinin levels [34] [35] [36]. Both are associated with pain thus can improve KOA patient's quality of life.

The pineapple stem is a by-product and subsequently waste in the manufacturing of the popular fruit. As such it is a cost-effective compound to utilize for medicinal use.

Dosage: very varied due to its low toxicity but general suggestion 100 - 400 mg/day.

2.1. Turmeric (*Curcuma longa*)

Turmeric is a perennial herb with a rhizome that is used for nutritional spice and medicinal purposes. It is a member of the Ginger family (Zingiberazeae) and is a highly potent polyphenol with AO properties.

The rhizome is boiled, dried and grounded into a powder that constitutes the spice. It contains essential oils, campesterol, minerals and curcuminoids. The polyphenolic pigments of curcuminoids constitute around 3% of the turmeric stem and hold a high concentration of medicinal compounds.

Curcumin is the primary curcuminoid and it has been studied extensively for its anti-inflammatory, antioxidant and immune-modulatory properties. It is confirmed to be a beneficial nutraceutical in the treatment of KOA [6] [8] [37].

Curcumin has the ability to inhibit both COX-2 and NF-κB signaling pathways [6] [8] [37]. These are responsible for the production of inflammatory cytokines like IL-6, IL-8, TNF-α and β cells. Induced levels of these cytokines are some of the worst culprits in the processes of KOA. Without the inhibition of NSAIDs or nutraceuticals these cytokines can cause oxidative stress that result in free radical toxicity.

The imbalance between impaired antioxidant defense and increased ROS is established in KOA [11]. This overpowering of ROS will cause cell damage and ultimately various pathological expressions.

Curcumins inhibitory effect on NF-κB, COX-2 and its derivative mediator E2 will lead to a reduced amount of cell loss when chondrocyte apoptosis decrease [37]. Inflammation markers are reduced, and the AO enzymes will be activated into a stronger defense that leads to a better oxidative balance.

Curcumin is easily overlooked due to its poor bioavailability and a lack of knowledge regarding turmeric powder versus curcumin extract.

As a therapeutic agent it should be taken as curcumin extract supplements and for better uptake it must be coupled with fat as it is lipophilic. It works well

with oleuropein in olive oil [11]. Moreover, curcumin needs a mediator to facilitate the transition through the intestinal membrane into the bloodstream as well as decrease the breakdown in the liver. The alkaloid piperine in black pepper has a documented efficacy [37].

With all these considerations in place curcumin can be as potent as NSAIDs are on pain, stiffness and mobility [37].

Recommended dose: 1 - 2 g/day. It is likely that 2 g/day is needed in OA.

Regarded as very safe with minimal AEs. Cost effective in comparison to conventional care.

2.2. Diet and Nutrition in KOA

A balanced diet of nutrient dense foods is a crucial complement to any treatment in KOA. It is an essential part of keeping pathology at bay and should be implemented ideally even before the induction of the disease. However, most people are naturally unaware of the fact that this pathology is taking hold.

When it is introduced, it is a chronic condition and must be treated as such. This means that a continuous input of antioxidants and regenerative nutrients should be part of a daily diet in order to combat the destructive mechanisms of KOA. Any person suffering with arthritis should focus on healthy eating habits and accumulate knowledge regarding the nutrients they need—and in what food sources to find them.

Moreover, they will benefit from trying therapeutic dosages of certain phytochemicals. In relation to OA and in this regard—KOA—there are several phytonutrients that have been extensively researched. The patient can apply these 1 - 2 at a time without concern. Many of them come with extreme low toxicity and very few AEs.

There are specific micronutrients that need to be maintained at sufficient levels. This is to a large extent achieved by a healthy and varied diet. Micronutrients of vitamins and minerals, phytochemicals, polyphenols, fish oils and a correct ratio of fatty acids.

It is not uncommon for arthritis patients to be in a state of imbalance as KOA breaks out. Whether it is due to nutritional deficiencies, oxidative stress, alkaline-acid imbalance, sensitivities toward foods or environment, sedentary lifestyle or a dysfunctional microbiome. In fact, there is a steadily increasing trend of nutritional deficiencies that exacerbate arthritis as well as make these individuals more prone to developing it in the first place. In US alone, just one in 10 adults eats the recommended intake vegetables and fruits. Furthermore, as this extends to arthritis patients the situation will inevitably impact their condition in a negative way.

It is likely a preferable alternative to apply an elimination diet in situations with uncertain food-intolerances. The patient can explore possible food sensitivities in order to exclude them in the future. As the immune system is overactive in KOA it is not beneficial to enhance this problem with further reactions from food.

KOA is highly prevalent among postmenopausal women. These patients constitute a significant portion of KOA patients in general. Hormonal imbalances from ageing factors can affect the microbiome in several ways out of which food sensitivities may be one. The nightshade family is a group of vegetables that are mentioned as aggravating foods in KOA. The cause is unknown but theorized to be connected to alkaloids, solanine or oxalates [15] [18] [38].

A brief overview of key nutrients in KOA:

Vitamin: A, B, C, D, E and K.

Minerals: Magnesium (Mg), Selenium (Se), Zinc (Zn), Copper (Cu), Calcium (Ca), Manganese (Mn), Sulfur (S), Boron (B).

Omega-3 fatty acids

Omega-6 fatty acids

Polyphenols and phytonutrients.

The diet should be plant based with a wide array of vegetables and fruits of all colors, follow general guidelines of the Mediterranean diet, incorporate fat fish 2 - 4 times/week alternatively by supplements, include organic berries, green tea and phytonutrients such as herbs and spices.

Iron is not necessarily included in scientific reviews on KOA and nutrition. However, iron can be considered indispensable when it comes to optimal immunity. Special precautions are warranted for sufficient uptake. The recommended diet in KOA is in large parts exclusive of red meat and liver. Without these iron-packed organs there is a need for non-heme iron of plants and vegetables to be optimized. The utilization is best achieved with additional C-vitamin.

2.3. Oxidative Stress and Antioxidants in KOA

Both external and internal influences will trigger an influx of ROS that will shift the body from homeostasis to redox imbalance. Several events happen simultaneously that overwhelm the body's capacity of reducing oxidants. When the fine-tuned dance of antioxidants-oxidants are altered in favor of an oxidative state the result is damaged tissues.

The internal environment is trigged by the onset of KOA. Chronic signals of injury activate immune reactions with a flow of pro-inflammatory cytokines and mediators. This leads to a production of ROS which in turn create more inflammation in a viscous circle.

The metabolic changes of the knee where catabolic processes override the rebuilding of tissue also affect ROS to be produced. Decreasing levels of cartilage tissue makes it difficult to withstand the mechanical pressure which causes additional levels of ROS.

Enzymatic antioxidants like SOD and GPx are impaired in KOA which leads to a weakened defense. This exacerbates the situation of ROS further as the reactive oxygen cannot be broken down properly.

People with arthritis oftentimes lean on NSAIDs and steroids in order to regain some mobility of the knee and combat the pain from inflammation. The pharmacological effects can diminish over time and accumulating side effects are

unavoidable.

Dietary AOs in all its forms have the ability to arrest inflammation and keep it at bay. Some have antiapoptropic and chondroprotective effects by arresting the destructive mechanisms of KOA-induced senescence as well as impede on the catabolic metabolism [7].

These AOs are found in almost all plants, certain vitamins, minerals, and fatty acids.

2.4. Polyphenols

Polyphenols are plant compounds with various health promoting effects. There are thousands of subtypes that can be divided into flavonoids and non-flavonoid groups. Alternatively, 4 divisions of flavonoids, phenolic acids, stilbenes and lignans. All these include very potent AOs to counteract the effects of ROS and inflammatory mediators.

One leading principle is that nutrients and phytochemicals primarily should be ingested from foods before supplements. There are examples where it may be beneficial with supplemental polyphenols in KOA but it must be within a margin of safety.

Some of the most important flavonoids are *catechins*, *quercetin*, *kaemperol*, *myricetin*, *luteolin*, *isoflavones* and *proanthocyanidins*. They all possess anti-inflammatory, antioxidant and immune regulating properties [18].

Catechins. Found in green tea and is one of the more potent flavonoids. The AOs of catechins can inhibit the pace of damage on cartilage [15]. Optimal intake: 4 - 6 cups/day or 500 mg/day.

Proanthocyanidins. Very strong AO easily absorbed in both water and lipids. Example of sources from foods or extracts: blueberry, black currant, strawberry, grape peel, pine bark, red wine.

Quercetin. Anti-nociceptive and cartilage protective effects [11] [13]. Primary sources: fruits and vegetables, onions, apple, red grapes, green leafy vegetables and citrus fruits. Supplement dosage suggestion: 500 - 2000 mg/day.

Kaempferol. Similar properties to Quercetin. Decreases apoptosis and modulate angiogenesis thus encourages a chondroprotective role in KOA. Food sources: green leafy vegetables, herbs, onion, berries, fruits and more. Extract dosages may vary between 100 - 200 mg/day.

Myricetin. A nutraceutical with anti-nociceptive, antimicrobial and neuroprotective activities [4] [39]. Common sources: vegetables, fruit, nuts, berries and tea.

Luteolin. A common flavonoid with a long history in TCM treatments. Found in many plants. It is a strong antioxidant with potential anticancerous properties. Found in many plants such as: peppers, parsley, artichoke, celery, cabbage, onions and herbs.

Isoflavons. Polyphenols with inhibitory effects on 1L-1β, IL-6, MMP3 and TNF [4] [6]. They also play a role in estrogen regulation which in turn exert beneficial effects on bone building and differentiation. Food sources: mostly le-

gumes.

Resveratrol. A stilbenoid that is the focus of many clinical studies. It has the ability to decrease IL-6, MMP-3, 1L-6, COX-2 and TNF [4] [6] [11] [40]. Food sources: tea, grapes, peanut, wine and berries of vaccinium species. Suggested dosage in OA: 1 g/day.

Lignans. Polyphenols with apoptotic effects. Sources: nuts, seeds, grains, vegetables.

Saponins. A very diverse group of plant compounds. Soap-like properties with aqueous extracts. Used as pharmaceuticals in conventional and traditional medicine. Antioxidant, anti-inflammatory, immune- and hypocholesterolemic effects among others [6] [13]. Sources: legumes and a variety of plants.

Carotenoids. Category of phytonutrients with potent health promoting plant pigments—yellow, orange, red and green. Antioxidant, anti-inflammatory and immune modulatory [6] [11]. Provitamin A carotenoids can be converted to vitamin A in the liver. Beta-carotene may decrease elevated cholesterol levels. Lycopene, a red pigment, stands out as another strong antioxidant. It may be beneficial in bone health. Carotenoids to be taken with fat for absorption. Sources: plants, algae and bacteria.

Coenzyme Q10 (*ubiquinone*). Antioxidant with inhibitory effects on inflammatory mediators of KOA [11]. Cartilage protective and pain modulator. Sources: organ meats such as reindeer, pork heart, chicken liver. Fatty fish, vegetables, legumes are other sources. Suggested dosage: not established. Broad reference between 50 - 1000 mg/day. Considered as a safe supplement however people with comorbidities are advised to consult with a doctor.

2.5. Fiber

Immune- and anti-inflammatory effects. A sufficient daily amount of dietary fiber is a fundament for optimal microbiome and overall health. Approximately 30 gram/day including 25% soluble fiber is recommended. Sources: wholegrains, beans, nuts, non-starchy vegetables and more.

There are additional nutrients that can be recommended in KOA. Well-researched foods and supplements like: *green-lipped mussels*, *rose hip-extract*, *devil's claw*, *ginger*/*gingerols*, *black kohosh*, *capsaicin cream*, *butea* and *Bu Gu Zhi* [13] [18] [32] [39] [41].

2.6. Vitamins

Certain vitamins are powerful antioxidants and very important in the context of KOA. Namely vitamin *A*, *C*, *D*, *E* and *K*.

Vitamin A (*retinoids*). Fat-soluble antioxidant and immune modulator. Deficiencies can arise in vegans where supplemental form is a solution. Vitamin A should not exceed upper-level recommendation.

B-complex. 8 types of B-vitamins. They work synergistically in foods and supplemental form is optimally taken as a complex. If taken as isolated parts do not extend supplementation longer than needed as it may tilt the synergic effects.

Their beneficial effects take various expressions. B2 (riboflavin) recycles glutathione, a crucial antioxidant of the body. B3 (Niacin) may decrease inflammatory symptoms in OA. B6 (Pyridoxin) levels decrease in inflammation and low levels of the vitamin in turn induce increased inflammation in a cycle effect [42]. B-vitamin sources: lentils, wholegrains, green vegetable, banana, chili and more.

Vitamin C (*Ascorbic acid*). Not only an important antioxidant but equally crucial for the maintenance of cartilage, collagen and connective tissue [13] [42] [43]. Sources: broccoli, bell peppers, citrus fruits, strawberry, onion.

Vitamin D (*Calciferol*). Heavy influence on immunity with anti-inflammatory effects as well as bone differentiation and nerve—muscle functions [44] [45] [46]. Supplemental intake is common due to a subpar level in diets and the lack of sun exposure.

A combination with vitamin K is required in supplemental form. This helps calcium absorption to be directed to bones and teeth and not soft tissue like blood vessels [45].

Sources: dairy, eggs, meat, dark green leafy vegetables and more.

Vitamin E (*tocopherols*/*tocotrienols*). Fat-soluble vitamin. Powerful antioxidant [11] [13] [43]. Consists of 8 isomers where α- and γ-tocopherol stand out with additional potent effects on inflammation and oxidative stress. However, as a supplement it can be recommended to take all isomers in combination as they exert a synchronized effect. Deficiency is linked to diseases such as cancer, heart disease and other inflammatory conditions. Sources: vegetable oils, sunflower seeds, nuts, olives, spinach, soybeans, broccoli, collard greens and more.

Vitamin K (*Phylloquinone*/*Menaquinone*). Fat-soluble vitamin. Main regulator of calcification of joint tissues. Mineralized plaque-building of soft tissue is a feature of OA [44] [47]. It obstructs optimal function by hardening of cartilage, synovium and tendons. These calcium deposits can be triggered by inflammatory cytokines and chondrocyte apoptosis, as well as cause inflammation and pain as a follow-up effect [44] [45]. By way of vitamin K-dependent carboxylation process the mineralization of calcium can be directed to hard tissue of bone and teeth. Vitamin K and D work in tandem to direct calcium deposition. Sources: egg yolk, meat, liver, fermented foods, leafy greens, vegetables, legumes, fish and more.

2.7. Minerals

Magnesium (*Mg*). Widely involved in biological functions and inflammatory processes. It is imperative for bone and muscle metabolism and as such a key mineral in the regulation of pathological increase of osteocytes in KOA. Mg deficiency has a clear association to OA with injurious effects on cartilage, chondrocytes, calcification and elevated pain sensitivity [42] [48].

An onset of hyperalgesia can be triggered if there is a simultaneous deficiency of fiber as they are modifiers to Mg [48].

Zink (*Zn*). Essential antioxidant with preventive effects on KOA. It promotes chondrocyte proliferation and plays an inhibitory role in cartilage degradation

via reduction of IL-1β, IL-6, MMP 13 and oxidative stress [6]. Zink status is closely linked to inflammation and homeostasis of the immune system [4]. Sources: shellfish, meat, legumes, seeds, nuts, dairy and more.

Calcium (*Ca*). Improves bone health by differentiation of osteoblasts. Metabolic roles in both ECM and chondrocyte production where a calcium deficiency may impede chondrocyte function. A sufficient intake of calcium has preventive effect of fractures caused by regular use of corticoids.

Selenium (*Se*). Significant antioxidant imperative to metabolic homeostasis in the joint. Deficiency linked to the outbreak and severity of OA. Required levels of Se enhances the immunity defense and promote cartilage regeneration [4] [42]. Sources: Brazil nuts, fish, oysters, pork, beef, chicken, whole grains and more.

Copper (*Cu*). Important for bone health and an optimal defense system. Involved in the regeneration of articular cartilage and subchondral bone. Cu-deficiency can reduce the integrity of the cartilage and enhance OA pathology [6] [42]. Sources: nuts, seeds, oyster and other shellfish, whole grains, beans, organ meats, potatoes and more.

Manganese (*Mn*). Necessary for normal metabolism of articular cartilage as well as for reparation of this tissue. Mn deficiency can exacerbate KOA with consequent deformity to the cartilage. Strong AO properties. Sources: mussels, tofu, sweet potato, pine nuts, brown rice, leafy vegetables, black pepper and more.

Boron (*B*). A key mineral in bone health. It decreases inflammatory biomarkers and enhances absorption of Mg and vitamin D. Low intake is associated with higher incidence and progression of OA [18] [49]. Sources: prunes, avocados, almond, peanut, dates, wine, beans and more.

Sulfur (*S*). A mineral necessary as building block to amino acids cysteine and methionine which constitute key parts of glutathione—a major cellular antioxidant [13]. Sources: turkey, allium vegetables, nuts, legumes, cruciferous vegetables and more.

MSM is a natural compound consisting partly of sulfur. MSM supplementation improves inflammation, oxidative stress and muscle-joint pain [13] [18] [39]. A micronutrient with a high safety profile and advantageous for bone and joint health; inflammation and physical function. Well tolerated supplement. Recommended together with ascorbic acid.

Dosages between 1, 5 - 5 g/day for MSM and Ascorbic acid respectively have been suggested for OA-patients.

2.8. Fish Oil

Contains essential polyunsaturated omega-3 fatty acids, EPA and DHA. Notable for its anti-inflammatory properties and modulation of cholesterol levels, as well as other effects. A large body of research suggests that EPA and DHA reduce pain and stiffness in OA-patients as well as increase mobility [5] [40] [46].

The level of cholesterol in arthritis patients tend to be elevated [5] [50] LDL is

increased and HDL decreased. Sufficient amount of omega 3-lipids and a beneficial ratio between omega-3 versus omega 6-fatty acids may improve this [51]. Suggested ratio of omega-6 to omega-3 approximately 4:1. A common profile of fat ratio in western diets are 10:1 or above.

Recommended dosage: intake of fat fish 2 - 4 times/week alternatively supplement 450 mg EPA + DHA/day. If the intake of fat fish exceeds a twice-weekly consumption the food source should be controlled for toxin concentration.

Marine origin over vegan as the latter is not as potent.

The intake of saturated fats could optimally be kept at a minimum for the benefit of monounsaturated fats like olive and rapeseed oil [40].

2.9. Conclusions

Major risk factors for developing KOA are overweight, nutritional deficiencies, excessive and repetitive mechanical stress to the knee and a sedentary lifestyle. These influences can trigger this disease on their own but also activate dormant pathologies into an inception of KOA. Once KOA is introduced in the body it is imperative to maintain BMI within a normal range and not subject the knee to added stress and pressure. The need for exercise and motion becomes an obligatory part of everyday life. Whether that is swimming, yoga and/or physical therapy.

Diet and phytonutrients will be crucial for well-being. The medicinal properties can decrease inflammatory markers, oxidative stress and modulate immunity reactions.

This will hinder the pathology in its wake and in further progression. In fact, reverting its mechanisms to a degree.

A diet based on whole grains, vegetables, fruits, legumes, fish, lean meat, fermented dairy, polyphenols, phytonutrients and correct ratio lipids is most advantageous. There is a need to avoid excessive amounts of sugar as this can increase inflammation. Many of these compounds have positive effects on the microbiome where beneficial bacteria are produced, and an increased gut health is promoted. This in turn have a plethora of favourable effects throughout the body.

Nutritional deficiencies have a clear association to arthritis patients [46]. This is suggestive of a subpar dietary profile both before and during the disease. Ultimately this leaves them prone to be in a more susceptible and weak state.

Last but not least. Any person suffering with arthritis of any form need to gain knowledge. Information regarding the conventional drugs that seem unavoidable in this pathology and its side effects that will intensify over time.

Equally so-stay informed about the ways in which the symptoms can improve and even prevent parts of KOA.

Be conscious of the fact that lifestyle, exercise, diet and supplements can make a huge shift in pain, range of motion and progression of the condition. Ultimately reduce the need for pharmacological drugs.

As the alternative treatments of traditional herbs, roots and physical therapies

become more ingrained in the western sphere with continuous research to validate its efficacy—one can hope for a future with a more holistic approach to medicine.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Abbreviations

AO	Antioxidants
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality's
CAM	Complementary medicinal options
CHM	Chinese Herbal Medicine
CS	Chondroitin sulfate
COX-2	Cyclooxygenase-2
DHA	Docosahexaenoic acid
DMOAD	Disease-modifying treatments for osteoarthritis
ECM	Extra Cellular Matrix
EPA	Eicosapentaenoic acid
EULAR	European Alliance of Associations for Rheumatology
FDA	US Food and Drug Administration
GAG	Glycosaminoglycans
GPx	Glutathione Peroxidase
GS	Glucosamine sulfate
HA	Hyaluronic acid
HC	Hydrolyzed Collagen
HDL	High-density lipoprotein
IA-HA	Intra-articular Hyaluronic Acid
IL	Interleukin
KOA	Knee osteoarthritis
LDL	Low-density lipoprotein
MMP	Matrix metalloproteinase
MSM	Methylsulfonylmethane
NSAID	Non-steroidal Anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
RCT	Randomized Clinical Trial
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
SYSADOA	Symptomatic slow acting drugs for osteoarthritis
TCM	Traditional Chinese medicine
TNF-α	Tumor Necrosis Factor Alpha
UC-II	Collagen type 2
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index