Osteoarthritis and its management - Epidemiology, nutritional aspects and environmental factors

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Abstract

Osteoarthritis (OA) is the most prevalent chronic rheumatic diseases worldwide, with a strong impact on individual and population health. OA is a clinically heterogeneous disease presenting with different clinical phenotypes recognising systemic and local risk factors. The pathogenesis is multifactorial including constitutive features of the joint, non-modifiable and modifiable risk factors. Epidemiological studies highlight the link between metabolic syndrome and OA and the effect of interplay between immunological and metabolic processes is getting increasing emphasis because of to the discovery that metabolic syndrome is implicated in OA pathogenesis and progression. In addition, recent findings suggest a potential role of dietary factors in susceptibility and progression of OA. In this review, we summarise the most robust evidence on epidemiology and classical risk factors OA, also exploring the most recent evidence on metabolic changes and Mediterranean diet for OA as a possible target to impact on the natural history of the disease.

Abbreviations

OA, osteoarthritis

MRI, Magnetic Resonance Imaging

CI, Confidence Interval

GBD, Global Burden of Disease

DALY, Disability-adjusted life years

RR, Risk Ratio

HR, Hazard Ratio

IRR, Incidence Rate Ratio

ERs, Oestrogen Receptors

ROS, Reactive Oxygen Species

NF-kB, Nuclear Factor-kB

FAs, Fatty Acids

MetS, Metabolic Syndrome

GLUT-1, Glucose Transporter-1

SLC2A, Solute Carrier2A

MMP, Matrix Metalloproteinases

ECM, Extracellular Matrix

SOD-2, Superoxide Dismutases 2

BMI, Body Mass Index

OR, Odds Ratio

BF%, Percentage of Body Fat

SF, Synovial Fluid

DM, Diabetes Mellitus

IMT, Intima Media Thickness

NO, Nitric Oxide

IL, Interleukin

SFAs, Saturated Fatty Acids

MUFAS, Monounsaturated Fatty Acids

PUFAs, Polyunsaturated Fatty Acids

EVOO, Extra Virgin Olive Oil

WOMAC, Western Ontario and McMaster Universities Arthritis Index

aMED, Mediterranean Diet Score

SMD, Standardized Mean Difference

Highlights

1. OA is a highly prevalent chronic condition with major impact on individual and population health
2. Metabolic syndrome arises as immune-metabolic background in OA pathogenesis and progression
3. Obesity is the major modifiable risk factor to improve outcome
4. Diet might have a role beyond weight control
5. Mediterranean diet is a promising healthy life-style

Keywords (max 6)

Osteoarthritis, epidemiology, risk factors, environmental factors, obesity, Mediterranean diet.

1 Introduction

Osteoarthritis (OA) is the most prevalent chronic rheumatic disease worldwide, with a strong impact on individual and population health. OA is a heterogeneous disease presenting with different clinical phenotypes recognising different systemic and local risk factors. Among them, some factors are not modifiable, including gender and genetic background, while others are potentially modifiable, such as obesity and dietary habits. Recent findings suggest a potential role of dietary factors in susceptibility and progression of OA, as a possible target to impact on the natural history of the diseases.

In this review, we summarise the most robust evidence on epidemiology and classical risk factors OA, also exploring the most recent evidence on metabolic changes and Mediterranean diet for OA.

2 Epidemiology

2.1 Occurrence

OA is a clinically heterogeneous disease and different disease definitions, with a strong impact on epidemiological data. Radiologic definition is commonly based on typical elementary lesions on conventional radiology and includes both symptomatic and asymptomatic OA. More sensitive imaging modalities such as Magnetic Resonance Imaging (MRI) can detect the earliest phases of cartilage damage, with an undue increase of sensitivity, so that early detection of OA is still a clinical challenge.[1]

Considering symptomatic OA, the estimated lifetime risk of knee OA is about 14%, ranging from 9.6% for non-obese males to 23.8% in obese females, and even higher for symptomatic hand OA (39.8% (95% confidence interval [95%CI] 34.4, 45.3%)).[2,3]

Based on the most recent Global Burden of Disease (GBD) study, the global age-standardised prevalence of knee OA is 3.8% and hip OA is 0.85%, with no major changes from 1990 to 2010.[4] Symptomatic hand OA is even more common, with a prevalence of 8% in the US National Health and Nutrition Examination Survey and 7% in the Framingham cohort.[5]

The prevalence of OA widely varies across different geographic regions, because of demographic, genetic, environmental and lifestyle differences. Analysing geo-epidemiological data from an ecological point of view[6], geographical distribution of knee and hip OA fits only partially with obesity distribution, suggesting that other factors play a role.[4,7]

2.2 Impact

OA impacts on several aspects and dimension of individual and population health, and despite stable worldwide standardised prevalence, global population aging will necessarily increase impact of the disease.

Globally, of the 291 conditions studied in the GBD, hip and knee OA were ranked as the 11th highest contributor to global disability (measured by years lived with disability) and 38th highest in Disability-adjusted life years (DALY), in 2010. Hip and knee OA was placed below diabetes and falls, and just above drug use disorders and other hearing loss.[4]

Despite OA is regarded as a disease of elderly people, disability strongly impacts on workability. OA, particularly knee OA, shows the greater odds of sick leave or disability among so-called 'women-dominated' or 'men-dominated' occupational sectors.[8]

A recent analysis estimating productivity costs of work loss associated with OA in Canada, showed that 44.4% of non-employment due to illness was associated with OA, with a projected increasing impact over time.[9]

Beyond physical function, OA also negatively impact mental health. Increasing evidence indicate that: patients with knee or hip OA have greater risk of depression; OA is associated with greater Odds of suicidal ideation; and OA patients show memory loss that was partially mediated by sleep and mood impairments (reviewed in [10]). Several studies evaluated the impact of OA on hard outcomes, such as cardiovascular morbidity and mortality. A recent meta-analysis showed a pooled Risk Ratio (RR) of 1.31 (95%CI 1.01, 1.71) of incident myocardial infarction, analysing age- and sex-adjusted data. When adjusting also for traditional cardiovascular risk factors the pooled RR became not significant (RR 1.02 (95%CI 0.92, 1,12)), suggesting that the excess of morbidity is mainly related to the clustering of cardiovascular risk factors (e.g. metabolic syndrome) in OA patients.[11] Another meta-analysis assessing overall mortality in OA did not find significant differences both for symptomatic and radiographic OA compared to the general population (Hazard Ratio (HR) 0.91 (95%CI 0.68, 1.23) and 1.13 (95%CI 0.95, 1.35), respectively).[12]

3 Classical risk factors

OA was in the past consider an effect of aging. Today we know that pathogenesis is multifactorial including constitutive features of the joint, non-modifiable and modifiable risk factors. OA could also be a consequence of other diseases that could affect joints directly.

3.1 Genetic factors

Twins study have revealed that genetic, independently from environmental factors, produced a 39% to 65% effect for knee and hand OA and up to 60% for hip OA. Genetic alterations encompass single gene disorders (for example gene encoding collagen protein) determining a large effect as in the early onset OA to multiple genetic variants with modest effects, more typical of late-onset OA [13,14]. Several studies have discovered different susceptibility loci dependent on different ethnic groups (Asian vs European), gender and joint sites (Table1).[15–19]

3.2 Gender

OA is more common in female, especially in elderly subjects. In a meta-analysis by Srikanth et al. the prevalence of OA resulted significantly lower in male for knee (RR 0.63 (95%CI 0.53, 0.75)) and hand OA (RR 0.81 (95%CI 0.73, 0.90)) but not for hip (RR 1.18 (95%CI 0.91, 1.52)) and overall OA (RR 0.93 (95%CI 0.80, 1.08)). These results can be in part explained by the increased lifespan and by a greater tendency in the self-reporting of the symptoms of female gender.[20] Despite most of studies evaluating incidence were

small and heterogeneous, especially for knee and hand OA, the Incidence Rate Ratio (IRR) was lower in males for knee OA (IRR 0.55 (95%CI 0.32, 0.94)) and hip OA (IRR 0.64 (95%CI 0.48, 0.86)), while no significant difference was observed for hand OA (IRR 0.65 (95%CI 0.35, 1.20).[20]

Post-menopausal rise of OA in women and the detection of oestrogen receptors (ERs) in joints highlight the attention on a possible role of hormones in the pathogenesis of OA. Animal models of ovariectomized females showed an increased risk of OA compared to controls. In vitro and in vivo studies, both in animal and human models, demonstrated multiple oestrogen effects on cartilage, subchondral bone, muscle, synovial membrane and ligaments. In the cartilage, oestrogens promote the production of proteoglycans by chondrocytes, inhibit the production of dangerous mediators (cyclooxygenase 2, reactive oxygen species (ROS), inducible nitric oxide synthetase and nuclear factor-kB (NF-kB)), finally, in animal models, they reduce the cartilage damage. In the subchondral bone, oestrogens can regulate osteoblastic activity, bone growth, remodelling, mineralization and they can reduce the production of osteophytes.[21] Various studies have reported that polymorphisms of the gene coding for aromatase (enzyme essential for the production of oestrogen) and ERs can predispose to the development of OA. Further support on the role of oestrogens comes from studies with ER-analogue-like drugs or selective ERs modulators that seem to slow down the development of OA (knee and hip) as well as the development of osteoporosis, especially in the initial phase of menopause. Studies on prevalence of OA supported the influence hormones and menopause showing a presence of OA three times higher among females aged 45-64 years than males.[22]

3.3 Age

Prevalence of OA increases with age with a peak incidence between 55 and 64 years. Several mechanisms have been proposed to explain the role of aging in development of OA including the aging of chondrocytes with blocking of cell proliferation, mitochondrial senescence and mitochondrial dysfunction with a consequent oxidative stress associated to excessive production and reduced clearance of ROS. During aging, pro-inflammatory cytokines are increased, also due to an increase in fat mass, which can itself induce the production of adipokines and cytokines. Finally, enhancement in oxidative stress, associated with increased levels of free fatty acids (FAs) and hyperglycaemia, can promote the destruction of the tissue matrix inducing an alteration of mechanical charge and consequent damage of cartilage.[23]

4 Metabolic syndrome

Epidemiological studies highlight the link between metabolic syndrome (MetS, combination of obesity, hypertension, hyperglycaemia, insulin resistance and dyslipidaemia) and OA.

4.1 Immunometabolism

The effect of interplay between immunological and metabolic processes is getting increasing emphasis because of to the discovery that MetS and related conditions are implicated in a variety of chronic diseases including OA.[24,25] This led to extensive research in the field of metabolic profile mainly focused on

chondrocytes. Articular cartilage is an avascular and hypocellular structure based on a delicate balance between anabolic and catabolic activities and in which nutritional factors exert a pivotal influence. Glucose is a crucial energy substrate that drives chondrogenesis and the synthesis of glycosaminoglycans, being their precursor.[26] The extracellular glucose concentration affects some chondrocyte metabolism and genes expression. Rosa et al. demonstrated that normal human chondrocytes modulated the cellular expression of the Glucose Transporter (GLUT)-1, a member of the GLUT/solute carrier(SLC2A) facilitative glucose transporter family, subject to both anabolic and catabolic stimuli control.[27] Compared with normal chondrocytes, OA chondrocytes exposed to a high glucose level were unable to down-regulate GLUT-1, leading to the intracellular accumulation of glucose and increased oxidative stress with prolonged ROS production.[27] The same authors demonstrated that exposure to high glucose increased RNA levels of matrix metalloproteinases (MMP)-1 and 13, implicated in the breakdown of extracellular matrix (ECM), thus promoting a chondrocyte catabolic gene expression program linked to subsequent articular cartilage degradation.[28] This downregulation can constitute an important pathogenic mechanism by which conditions characterized by hyperglycaemia, such as Diabetes Mellitus (DM) and other situations involving impaired glucose metabolism, can promote degenerative changes in chondrocytes that facilitate the development and progression of OA.[28] Anaerobic glycolysis is the primary ATP-producing pathway of cartilage [29]. In presence of or glucose deprivation or nutrient stress, chondrocytes own the metabolic flexibility of promoting cell survival and ECM biosynthesis during a nutrient stress or glucose deprivation by upregulating mitochondrial respiration.[24] This shift, strictly coupled with a substantial reduction in the expression and activity of the mitochondrial antioxidant enzyme superoxide dismutases 2 (SOD-2), could make chondrocytes more susceptible to oxidative damage, as argued by Lane et al.[30] In fact, mitochondrial dysfunction and the associated redox imbalance between the production of ROS and the antioxidant capacity of the cell is hypothesized to be a key mechanism contributing to cartilage degeneration and the pathogenesis of OA.[23]

The hypoxic environment has a pathogenic role in OA as well. In low oxygen conditions, normal chondrocytes increased their ability to take up glucose by up-regulating GLUT-1 in response to hypoxia, by contrast, GLUT1 mRNA expression is significantly reduced in OA.[31] Oxidative stress in OA chondrocyte accumulate mitochondrial DNA damage and end-stage OA cartilage chondrocytes display a reduced mitochondrial DNA repair capacity and increased apoptosis. All these changes enhance the responsiveness of chondrocytes to cytokine-induced inflammation through NF-κB activation and modulate matrix loss increasing the production of MMPs.[24,32] In the end, when ROS production exceeds the antioxidant capacities, the oxidative stress lead to structural and functional cartilage damages like cell death and matrix degradation.[33]

4.2 Obesity

The association between body weight and OA is reported in the literature for knee OA and with contrasting evidence for hip and hand OA. In a case control study of Oliveira et al. the adjusted Odds Ratio (OR) of OA for patients with high Body Mass Index (BMI) was 8.3 (CI95% 1.2, 56.5), OR 1.4 (CI95% 0.1, 17.5) and OR 9.3 (CI95% 2.4, 35.6%) for hand, hip and knee OA, respectively.[34] A further analysis from the Rotterdam cohort, including patients aged> 55 years with a follow-up of 6.6 years, confirmed that BMI> 27.5 was associated with an increased risk of incident OA (defined as a baseline Kellgren and Lawrence index of grade 0 or 1, and grade> 2 at follow-up measurement) for knee but not for hip (OR 3.3 (CI95% 2.1, 5.3) vs 1.0 (CI95% 0.7, 1.5)). Also progressive OA defined as a Joint Space Narrowing reduction of> 1 mm and of> 1.5 mm at follow-up and as an increase of at least 1 grade of Kellgren and Lawrence was significant associated with BMI> 27.5 only for knee but not for hip (OR 1.4 (CI95% 0.8, 2.6), 3.2 (CI95% 1.1, 9.7) and 2.1 (CI95% 1.2, 3.7) for knee and OR 0.9 (CI95% 0.6, 1.3), 1.5 (CI95 % 0.6, 3.7) and 1.3 (CI95% 0.9, 1.8) for hip respectively.[35]

Given the association between hand OA and BMI reported in some studies, the effect of over-loading cannot be the only responsible mechanism. A meta-analysis conducted by Jiang et al. including 21 observational studies for a total of 3,303,723 subjects, found that for a five-unit increase in BMI, the risk of hand OA was increased by 6% for radiographic OA (RR 1.06 (95%CI 1.02, 1.10)) and 25% for symptomatic OA (RR1.25 (95%CI 1.06, 1.49)).[36] Being BMI only a relationship between weight and height, it could not be a measure of the real distribution of lean and fat mass, so studies that evaluate only BMI could fail to demonstrate a link between obesity and OA. For example, a prospective study involving 130 patients with hand OA at baseline and re-evaluated both clinically and radiologically after 7 years, did not show an association between basal BMI, or BMI change and the increase in joints affected by OA, or worsening of pre-existent OA.[37] Beyond BMI, obesity can be measured as weight, waist circumference, waist-hip ratio and percentage of Body Fat (BF%). Lohmander et al. evaluated in a cohort of 28,449 subjects, the effect of these different measures on the risk of knee or hip replacement due to OA. Waist circumference, weight and especially BMI (> 30 Kg/m2) were associated with the risk of knee arthroplasty while for hip this association was lower, although present. Many studies demonstrate that metabolic and pro-inflammatory effects of obesity correlate more with BF% and waist circumference rather than BMI, so authors concluded that especially for knee OA, it could be more important than the mechanical mechanism of overweight.[38]

Adipose tissue promotes the production of inflammatory mediators responsible for cartilage damage. The adipose tissue in fact, through the production of adipokines, molecules with similar activity to cytokines, could play a role in the pathogenesis of OA independent of the overload through induction of inflammation and increased oxidative stress.[25] The adipokines are divided into resistin, visfatin and leptin, which increase proportionally with BMI and fat mass, while adiponectin is reduced in obese patients. They could be expressed differently in the serum and at the joint, for example leptin in synovial fluid (SF) resulted

significantly higher than the serum in female subjects, being produced directly by articular structures (infrapatellar fat, synovial tissue, osteophytes, cartilage).[39] Studies in vitro and in vivo highlight the complexity of action and expression of different adipokines in a balance between catabolic, pro-inflammatory and oxidative stress on one side and anabolic effects on the other side (Table 2).[40,41]

4.3 Dyslipidaemia

Obese and overweight patients have higher risk of developing hypercholesterolemia and dyslipidaemia. A higher prevalence of dyslipidaemia is observed in patient with OA compared with patient without OA (30% vs 8%) as reported in a meta-analysis including 306,044 subjects.[42] The risk of dyslipidaemia was increased in patient with hand OA (OR 2.12 (95%CI 1.46, 3.07)) and knee OA (OR 2.27 (95%CI 1.33, 3.89)) but not with hip OA (OR 0.86 (CI95% 0.68, 1.08)).[42] Several animal models demonstrate an increase in risk of OA in case of high fat rich diet and of hypercholesterolemia and especially with high plasma levels of LDL. One of the hypothesized mechanisms is that hypercholesterolemia causes oxidation of lipids and their deposits in the cartilage - as happens in the vessels during atherosclerosis – contributing to OA by reducing blood flow to the sub-chondral bone. Elevated levels of cholesterol could enhance inflammatory response. For example, in mouse knockout for ABCD1 receptor (increasing cholesterol efflux from cells), the increase of intracellular levels of cholesterol activates inflammatory response of macrophages. The oxidation of lipoproteins, through the production of radicals, activates NF-kB. Finally, high levels of oxidized cholesterol particles can induce (like aging) mitochondrial dysfunction and increase ROS in chondrocytes.[43] The association between atherosclerosis (evaluated carotid plaques and Intima-Media Thickness (IMT)) and incidence and progression of OA (knee, hand and hip) was described in the Rotterdam study. After adjustment for BMI and age, a significant association between IMT and prevalence of knee OA (OR 1.7 (CI95% 1.1, 2.7)) and progression of metacarpophalangeal OA (OR 2.9 (CI95% 1.18, 6.93)) were observed. Carotid plaques were significantly associated with distal interphalangeal joint OA (OR 1.4 (CI95% 1.2, 1.7)) and metacarpophalangeal OA (OR 1.5 (CI95% 1.1, 2.2)). All these results were confirmed only for women.[44]

4.4 Hyperglycaemia and insulin resistance

Results from a meta-analysis including 1,192,518 patients, showed a prevalence of OA among patient with DM of 29.5% (OR *vs* non DM 1.46 (CI95% 1.08, 1.96)).[45]

4.5 Exercise

Physical exercise and weight loss are strongly recommended (also from both European League Against Rheumatism and American College of Rheumatology guidelines) as cardinal intervention for OA prevention and treatment.[46,47] The exercise must be personalized according to the patient's preferences and abilities, the training programs can be individual, in groups, at home or in the gym. Exercises in water or on the ground have the same value and should be preferred according the physical characteristics and

preferences of the patient. A mixed approach (aerobic and strengthening) is recommended with the aim of reducing pain, improving proprioception and joint function. Abnormal overload, both occupational or in case of extreme sport activity, could be an additional risk factor for OA. Abnormal load is not only due to overweight but also joint instability, immobilization, or trauma. Population studies highlight the role of heavy physical work as a risk factor for knee and hip OA especially for heaviest manual work (knee OR 18.3 (CI95% 4.2, 79.4), hip OR 6.7 (CI95% 2.3, 19.5)).[48,49]

Abnormal load could differently regulate the inflammatory response inducing or inhibiting different mediators like Nitric Oxide (NO), Prostaglandin E2, and Interleukin (IL)-1. A possible link between inflammatory and mechanical factors in OA pathogenesis could be supported by the presence of mechanoreceptor on the surface of joint cells able to convert mechanic stimuli in pro-inflammatory signals.[50]

5 Dietary factors

5.1 Fatty acids

FAs can be divided into saturated FA (SFAs) if double bonds are present in the carbon chain; Monounsaturated Fatty Acids (MUFAs) if only one double bond is present; Polyunsaturated Fatty Acids (PUFAs) if two or more double bonds are present. The number indicates the location of the carbon involved in the first double bond from the omega (ω-n) end of their carbon chains (figure 1). Based on the ability or not to synthesize them de novo, FAs can be classified as not essential and essential. Normal cartilage consists of increased amount of SAFs and linoleic acid in a matured cartilage, this composition can be modulated by dietary FAs intake mainly due to their conversion to eicosanoids.[51] PUFAs of both the n-3 and the n-6 series are essential for human health but may have opposite effects on inflammatory responses, omega-3 PUFAs have anti-inflammatory effects whereas omega-6 PUFAs and SFAs have, on balance, proinflammatory effects.[52]

The increased dietary fat intake that has characterized Western countries in the last 40 years seems to be involved in the development of OA. In 2015, Wu et al. clearly demonstrated the pathogenetic role of FAs in a mouse model of OA.[53] In mice fed with high-fat diets rich in various FAs including SFAs, ω-6 PUFAs, and ω-3 PUFAs OA was induced by destabilizing the medial meniscus. The joints of SFAs and ω-6 fed mice exhibited increasing osteophyte formation, synovitis, as well as increasing infiltration of macrophages into synovial tissue versus control and ω-3, fed mice.[54] In a multivariate model adjusted for body mass, OA was only associated with dietary content irrespectively of body mass. Sekar et al. demonstrated the SFAs, especially stearic and palmitic acids, produced typical OA-like lesions in the rat knee joint.[55] The changes in cartilage combined with expression of the degenerative marker (MMP13) and hypertrophic marker (collagen 10) and decreased expression of the proteoglycan marker in the cartilage.[55]

A first in vivo study evaluated the relation of n-6 and n-3 PUFA levels with MRI knee structures in OA founding an inverse relation between total n-3 PUFAs and patellofemoral cartilage loss, but not tibiofemoral

cartilage loss or synovitis. A positive association was observed between the n-6 PUFA, arachidonic acid, and synovitis.[52] More recently, a prospective cohort study enrolling 2,082 people aged 45 through 79 with moderate radiographic knee OA has reported a significant positive relationship between total fat and SFAs intakes with knee quantitative joint space width loss. With increasing quartiles of SFA intake, the adjusted HR were 1.32 (95%CI 0.95, 1.82), 1.59 (95%CI 1.11, 2.27) and 1.60 (95% CI 1.02, 2.51) compared to the bottom quartile; for patients in top quartile there was a significant association between higher MUFA intake and reduced risk of OA progression, (adjusted HR 0.75 (95%CI 0.57, 0.98)).[56]

5.2 Vitamin D

Vitamin D receptors are expressed in human articular chondrocytes of OA cartilage, particularly in the superficial zone, in contrast with normal cartilage where vitamin D receptors are rarely observed.[57] Preclinical studies have suggested a positive effect of vitamin D on articular cartilage. In rats, vitamin D-deficient diet aggravated cartilage erosions and promoted the expression of MMP-9 and MMP-13, while supplementation counteracted this effect by regulating collagen II turnover through transforming growth factor-β1.[58] It has been hypothesized that vitamin D supplementation might be a feasible and cost-effective strategy for controlling symptoms and inducing structural improvement in patients with knee OA. Recently, two systematic reviews and meta-analysis have provided evidence regarding the effect of vitamin D supplementation on symptomatic knee osteoarthritis.[59,60] In the meta-analysis, four RCTs involving 1,136 patients were included. Pooled estimates suggested that vitamin D supplementation was associated with a significant reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, and WOMAC function, but not in WOMAC stiffness.[59] However, no effects were observed for the change in tibial cartilage volume SMD (standardized mean difference) 0.12 (95%CI -0.05, 0.29) or joint space width SMD 0.07 (95%CI -0.08, 0.23).[60]

5.3 Fiber intake

Dietary fibre is the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fibre includes polysaccharides, oligosaccharides, lignin, and associated plant substances.[61] Dietary fibre intake provides many health benefits in some of the aforementioned risk factors such as reducing the risk for developing diabetes, metabolic syndrome and obesity, improving serum lipid concentrations, blood glucose control and lowering blood pressure.[62] In light of this relation, in 2017 a first study investigated the association between dietary fibre and OA outcomes analysing data from two longitudinal cohorts involving more than 6,000 participants (4,796 from the Osteoarthritis Initiative and 1,268 from Framingham Offspring Osteoarthritis Study).[63] Findings consistently demonstrated that total fibre was inversely associated with risk of symptomatic OA with significantly lower risk at the highest versus lowest quartile OR 0.70 (95%CI 0.52, 0.94) for OA Initiative and 0.39 (95%CI 0.17, 0.88) for Framingham cohort. Dietary total

and cereal fibres were significantly inversely associated with knee pain worsening in OA Initiate cohort, while no apparent association was found with incident radiographic OA.[63]

5.4 Mediterranean diet

Mediterranean diet relies on daily consumption of extra virgin olive oil (EVOO) - the principal source of dietary fat mainly composed of MUFAs - non-refined cereals, vegetables, fruits non-fat or low-fat dairy products, weekly consumption of potatoes, olives, pulses and nuts and rarer consumption of poultry, eggs, sweets and red meat and meat products, the latter more typical in Western diet. Notably, in the Mediterranean diet the ratio of monounsaturated- to-saturated fats is about or more than 2, which is much higher than in other places of the world.[64] Mediterranean type diet has been positively influenced various chronic disease and recently preclinical and clinical studies have focused the attention on the potential association between the Mediterranean diet and OA.

A preclinical study assessed the impact of a diet enriched by different olive tree products on muscle function and cartilage preservation/restoration, in mechanically induced OA rat model [65]. Forty-eight 3-month-old healthy male Wistar outbred rats with OA induced by anterior cruciate ligament transection were subjected to physical activity on treadmill 5 days a week for 10 min daily and fed with experimental diets (standard diet enriched with Sicilian EVOO, Tunisian EVOO and Tunisian EVOO with leaves extract) for 12 weeks. Compared with a control group composed of sedentary rat fed with standard chow, Sicilian olive oil diet group displayed very slight structural alterations with a little reduction of cells in the cartilage layers (superficial, intermediate and deep zone) compared with the control group composed of sedentary rat fed with standard chow. The experimental EVOO groups showed generally increased lubricin, a lubricating chondroprotective glycoprotein, and decreased IL-6 expression and significant muscle hypertrophy suggesting the beneficial effects of physical activity coupled with EVOO-enriched diets on rat articular cartilage [66]. A preliminary in vivo study provided additional data on the effect of Mediterranean type diet on inflammatory and cartilage degradation biomarkers in patients with OA. In this randomized controlled trial participants were randomly allocated to the dietary intervention (DIET, n = 50) or control (CON, n = 49). The DIET group were asked to follow a Mediterranean type diet for 16 weeks whereas the CON group were asked to follow their normal diet. The dietary intervention reduced the pro-inflammatory cytokine IL-1α in the DIET group compared to no change in CON and a significant pre-to post-intervention decrease of serum cartilage oligomeric matrix protein (a marker of cartilage degradation) was evident in the DIET group with no change in the CON group.[65] From a functional clinical point of view, there was a significant improvement in knee flexion and hip rotation range of motion in the DIET group (Table 3).[65] Three observational studies investigated the impact of Mediterranean diet on OA from data collected in the Osteoarthritis Initiative (OAI) database. Adherence to the Mediterranean diet was evaluated using the Mediterranean diet score as proposed by Panagiotakos et al.[64] This score is based on a food frequency

questionnaire encompassing several foods commonly consumed within the Mediterranean diet. Each food has a score from 0 (less adherent) to 5 (better adherence); the total score ranges from 0 to 55, with higher values indicating higher adherence to a Mediterranean diet and categorized into quintiles.[67–69] A first study suggested that adherence to a Mediterranean diet was associated with lower prevalence of knee OA. A significant lower presence of knee OA was observed in participants with higher Mediterranean Diet Score (aMED) (Q4) compared to those with lower aMED Q1 (Q4: 25.2% vs. Q1: 33.8%; $p<0.0001$) and participants with the highest adherence to Mediterranean diet had a significantly reduced probability of knee OA (Table 3).[67] Two subsequent studies demonstrated that higher Mediterranean diet consumption was associated with better quality of life and decreased pain, disability, and depressive symptoms and with a significant improvement in knee cartilage as assessed by MRI (Table 3).[68,69]

6 Conclusions

OA optimal management remains one of the biggest unmet medical need in rheumatology, with no major disease modifying OA drugs available at present. Interfering with nutritional and environmental modifiable risk factors is a viable and safe strategy that might help in preventing and limiting the consequences of the disease.

7 Disclosure of potential conflict of interest

The authors declared no conflicts of interest.

8 Ethical statement

This article contains no clinical data.

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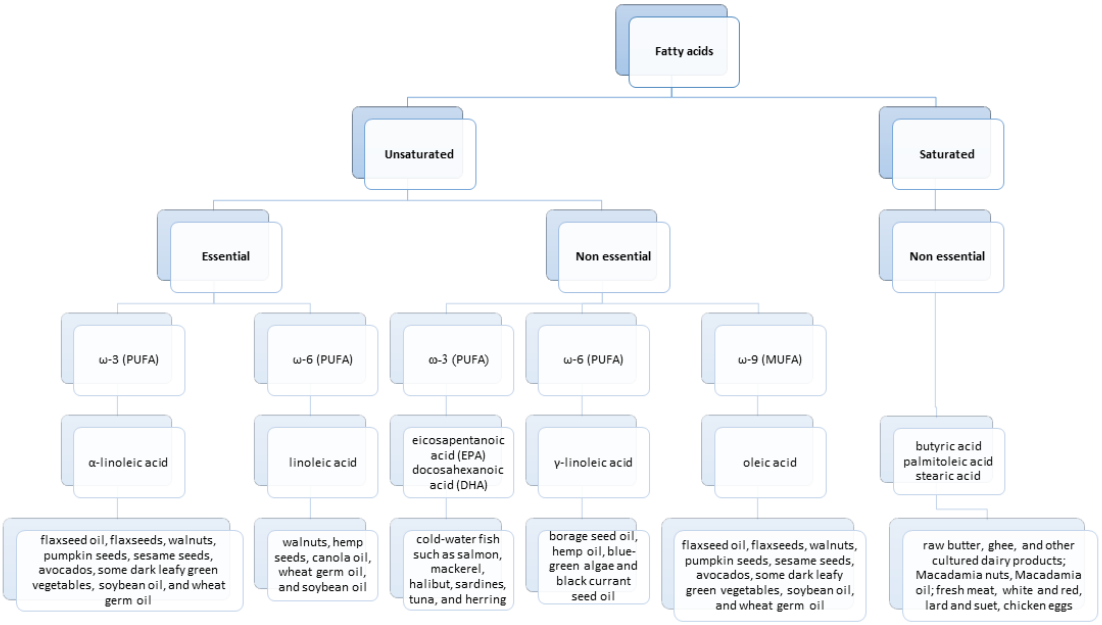
Figure.

Figure 1. Classification of fatty acids and source of different fatty acids in food.



List of abbreviations: PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids.

Table.

Table 1. Single nucleotide polymorphism significantly associated with increased risk of osteoarthritis [15–19].

SNP (locus)	Nearest gene	Gender	Ethnicity	Joint involved	Odds Ratio	Protein function
rs3815148 (7q22)	COG5	both	European	Knee and	1.1	Golgi morphology and function
	DUS4L	both	European	Hand Knee	1.1	Unknow
rs11718863 (3q21.3)	COL6A4P1	both	Asian	Knee	1.5	Collagen
rs7775228 (6p21.32)	HLA, QB1	both	Asian	Knee	1.5	Antigen presentation
rs19847262 (6p21.32)	BTNL2	both	Asian, European	Knee	1.5	Immunomodulatory function, T cell response
rs12107036 (3q28)	TP63	female	European	Knee	1.5	Transcription factor
rs8044769 (16q12.2)	FTO	female	European	Knee	1.1	Unknow
rs6976 (3p21.1)	GLT8D1	both	European	Knee	1.1	Glycosyltransferase
rs11842874 (13q34)	MCF2L	both	European	Hip and Knee	1.1	Cell movement
rs10948172 (6p21.1)	SUPT3H	male	European	Hip and Knee	1.1	Unknown
rs12901499 (15q22.33)	SMAD3	both	European	Hip and Knee	1.1	TGF-β signalling
variant in gene 19p13.11 (c1141G>C)	COMP	both	European (Icelanding)	Hip	10.0	Extracellular matrix
r532464664 (22q13.2)	CHADL	both	European (Icelanding)	Hip	5.0	Chondroadherin like protein
rs143383 (20q 11.22)	GDF5	both	Asian	Hip	1.5	Extracellular grow factor
rs12982744(19p13.3)	DOT1L	male	European	Hip	1.5	Histone and chromatin modifier
rs4836732 (9q33.1)	ASTN2	female	European	Hip	1.5	Neural migration
rs116855389 (20q13)	NCOA3	both	European	Hip	1.5	Nuclear receptor coactivator 3
rs835487 (12q23.3)	CHST11	both	European	Hip	1.1	Chondroitin sulphatation
rs10492367 (12p11.22)	KLHL42 PTHLH	both	European	Hip	1.1	Hormone
rs9350591	FILIP1	both	European	Hip	1.1	Interact with flaming
(6q13-q14.1)	SNP6	both	European	Hip		Ubiquitin like molecules
rs12915901 (15q21.3)	ALDH12	both	European	Hand	1.5	Retinoic acid regulatory gene

List of abbreviations: SNP, Single Nucleotide Polymorphism; TGF-β, Transforming growth factor beta.

Table 2. Summary of catabolic, pro-inflammatory and anabolic activity of principal adipokines.

Adipokine	SF vs Plasma levels	Catabolic effect	Inflammatory effect	Anabolic effect
Leptin	SF>Plasma	↑MMP ↑MMP with trombospondin motifs (ADAMTS-4 and ADAMTS-5) ↑NO	↑IL1ß, TNFα, IL6, IL8, MMP1, PGE2 and COX-2	↑ IGF1 and TGFβ ↑ chondrocytes proliferation ↑ differentiation and proliferation of osteoblast. ↑ collagen synthesis
Adiponectin	Plasma>SF	↑ NOS2, MMP-1,-3,-9	↑MCP1, IL6, IL8, PGE2	↑ osteoblast proliferation ↓ IL1b induced MMP-13 production and ↑ TIMP-1 and -2 ↑ IL10, IL1 receptor antagonist ↑ murine chondrocyte proliferation, aggrecan synthesis, matrix mineralization, ↑ expression of collagen type II and X
Resistin	Plasma>SF	↑ MMP1, MMP13 and ADAMTS-4 ↓ proteoglycan and collagen II production ↑ osteoclast differentiation	↑ IL6, TNFα, PGE2	↑ osteoblast proliferation
Visfatin	SF>plasma	↓ pro-anabolic effect of IGF1 ↓ production of collagen type II and proteoglycans ↑ MMP3-MMP13, ADAMTS-4 and ADAMTS-5 ↑ NO production	↑IL6, MCP1, IL1β, TNFα, PGE2	↓visfatin, ↓ the production of collagen type II and aggrecan ↑osteoblast differentiation and inhibit osteoclastogenesis (possible role in osteophyte formation)

List of abbreviations: SF, synovial fluid; MMP, Matrix Metalloproteinases; Interleukin, IL; TNFα, Tumor Necrosis Factor α; PGE2, Prostaglandin E2; COX, Cyclooxygenase; MCP1, Monocyte Chemo Attractant Protein 1; TGFβ, Transforming Grow Factor beta; IGF1, insulin grow factor 1; ADAMTS, A Disintegrin And Metalloproteinase with Thrombospondin Motifs 4; NO, Nitric oxide; NOS2, Nitric oxide synthase 2; TIMP, tissue inhibitors of metalloproteinases; IL, interleukin.

Table 3. Summary of studies on Mediterranean diet and osteoarthritis.

Authors, year	Type of study	N° of participants	Outcome	Results
Dyer et al. [65]	RCT	124 (99 completing the study)	Range of motion for most affected limb	Finger movement: baseline DIET 0.4 ± 0.5 CON 0.3 ± 0.6, after four months DIET 0.4 ± 0.4 CON 0.4 ± 0.6, p 0.26 Knee flexion (ROM) baseline DIET 112 ± 24 CON 121 ± 16, after four months DIET 122 ± 18 CON 116 ± 29, p 0.07 Hip rotation (ROM) baseline DIET 38 ± 16 CON 47 ± 15, after four months DIET 52 ± 19 CON 46 ± 24, p 0.01 Hip flexion (ROM) baseline DIET 12 ± 10 CON 13 ± 11, after four months DIET 17 ± 20 CON 14 ± 10, p 0.62
Veronese et al, 2017 [67]	Cohort prospective	4,358	Probability of knee OA	Association between adherence to Mediterranean diet and presence of knee osteoarthritis. Q1 aMED score 1 [reference] Q2 aMED score OR[1] 0.90 (0.75, 1.09) Q3 aMED score OR[1] 0.85 (0.70, 1.05) Q4 aMED score OR[1] 0.66 (0.55, 0.80)
Veronese et al, 2017 [68]	Cohort, prospective	4.470	SF-12 WOMAC CES-D	Association between low aMED and SF-12, WOMAC and CES-D: SF-12 MCs OR[2] 1.20 (1.05, 1.38) SF-12-PCs OR[2] 1.19 (1.01, 1.39) WOMAC OR[2] right knee total 1.17 (1.02, 1.33) WOMAC OR[2] left knee total 1.04 (0.91, 1.19) CES-D OR[2] 1.22 (0.96, 1.55)
Veronese et al, 2018 [69]	Cohort, prospective	783	Knee cartilage MRI parameters	Medial tibia mean cartilage thickness beta[1] 0.09 (0.06, 0.13) Medial tibia volume of cartilage beta[1] 0.07 (0.04, 0.10) Central medial femur mean cartilage thickness beta[1] 0.13 (0.01, 0.17) Central medial femur volume of cartilage beta[1] 0.12 (0.09, 0.15) Central medial tibial-femoral compartment mean cartilage thickness beta[1] 0.12 (0.09, 0.15) Medial tibial-femoral compartment cartilage volume beta[1] 0.09 (0.06, 0.12)

[1] adjusted for age, gender, ethnicity, body mass index, education, smoking habits, yearly income, Physical Activity Scale for Elderly score, Charlson comorbidity index, daily energy intake;
[2] adjusted for age, gender, ethnicity, BMI, education, smoking status, annual income, Charlson comorbidity index, use of analgesic drugs, and total energy intake.
List of abbreviations: aMED, Mediterranean Diet Score; SF-12, 12-Item Short-Form Health Outcome Survey; MCS, Mental health Composite Scale; PCS, Physical Composite Scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index, WOMAC; CES-D, Center for Epidemiologic Studies Depression Scale, CES-D; RCT, Randomized Controlled Trial; ROM, Range of Motion.