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19.9 Osteoarthritis 4473 Epidemiology and risk factors The epidemiology of osteoarthritis is complex, which reflects the variation in the applied definition, the specific joint involved, and the heterogeneity of the osteoarthritis phenotype. Epidemiological studies, particularly analyses of large prospective cohorts, provide important information about risk factors that provide insight into the aetiology of osteoarthritis. This is supported by several well- recognized associations with the prevalence and incidence of osteo- arthritis in peripheral joints. These include both nonmodifiable (e.g. age, gender, trauma, alignment and genetic predisposition) and modifiable (e.g. obesity, occupational injury) risk factors, the latter being prospective interventional targets for treatment and prevention. Prevalence The knee, hip, and hand are the most frequently affected joints, and the prevalence of osteoarthritis increases with age, which is the most important risk factor. This may represent a senescent impairment of tissue regeneration in addition to a cumulative effect of other risk fac- tors associated with ageing. Approximately 14% of adults older than 25 years and 34% of adults older than 64 years have clinical osteo- arthritis of one joint or more. Symptomatic clinical osteoarthritis of the knee, hip, and hand are more prevalent in females. The popula- tion prevalence of osteoarthritis of the hip and knee in the United Kingdom is also greater with than without obesity (Fig. 19.9.3). However, in a meta-analysis of osteoarthritis prevalence studies in adults older than 55 years, women have higher knee and hand osteo- arthritis prevalence but there is no significant gender difference for hip osteoarthritis. In the same meta-analysis no significant gender differences were observed in the prevalence of knee, hip, or hand osteoarthritis among adults below 55 years of age. Women tended to have greater prevalence of osteoarthritis when nonradiographic (e.g. clinical) methods were used for defining the condition. In adults aged 45

years and older in the American Johnston County project and Framingham cohorts, the prevalence of knee radiographic osteoarthritis was 28% and 19% respectively, whereas the symptomatic knee osteoarthritis prevalence was 17% and 7% re- spectively. In adults aged 60 years and older, 37% and 12% had knee radiographic osteoarthritis and symptomatic knee osteoarthritis, re- spectively. In the United Kingdom, 18% of adults above the age of 45 have self-reported knee osteoarthritis. In a meta-analysis, a history of prior knee injury increased the risk of prevalent knee osteoarth- ritis fourfold. In adults of 45 years or more in the USA Johnston County pro- ject, the prevalence of hip radiographic osteoarthritis was 28% while symptomatic osteoarthritis was 9%. In adults in the United Kingdom over 45 years, 11% have self-reported hip osteoarthritis. In adults over the age of 60 years the clinical American College of Rheumatology (ACR) criteria for hand osteoarthritis (Table 19.9.2) were met by 8%, while typical hand osteoarthritis symptoms were reported by 22% of adults over 70 years of age. Among adults above the age of 50, the prevalence of symptomatic and foot radiographic osteoarthritis was 17%. Incidence Generic risk factors for the incidence of the knee, hip, and hand osteoarthritis include age and female gender. Occupational ex- posure to increased biomechanical stresses increases the risk of hip and knee (after adjusting for age, gender, body mass index, and pre- vious trauma). Participation in sporting activities and the presence of osteoarthritis in other joints increases the risk of incident hip and knee osteoarthritis. Age and gender The age and sex-standardized incidence rates of symptomatic osteo- arthritis in adults of 20 years and older are 240, 88, and 100 (per 100 000 person-years) for the knee, hip, and hand, respectively. The incidence of symptomatic osteoarthritis of the knee, hip, and hand increases with age, with women having higher rates than men, particularly after 50 years of age. Among women the incidence of clinical osteoarthritis of the hip and knee increases rapidly between 50 and 75 years and then decreases thereafter. However, incident clinical hand osteoarthritis peaks in women in peri- and post- menopausal years between 55 and 60 years and decreases thereafter. Among men the incidence of clinical osteoarthritis of the knee, hip, and hand increases from 50 to 75 years and then decreases. A meta- analysis and large primary care database reported a greater risk of osteoarthritis incidence among women for the knee, hip, and hand, respectively (Fig. 19.9.4). Obesity Obesity increases the biomechanical load upon weight-bearing joints, which may explain its association with knee osteoarth- ritis. Obesity is the strongest potentially modifiable risk factor in Population prevalence of hip osteoarthritis (total) and knee osteoarthritis (total) of selected risk factors in England Population prevalence 2 9 16 23 30 Hip osteoarthritis (total), Obese Hip osteoarthritis (total), Healthy weight Knee osteoarthritis (total), Obese Knee osteoarthritis (total), Healthy weight Fig. 19.9.3 Population prevalence of hip and knee osteoarthritis, with and without obesity. From the Musculoskeletal Calculator, © Arthritis Research UK, developed by Imperial College London.

 meta-analyses and confers more than a threefold greater risk of inci- dent knee osteoarthritis and a greater risk of disease-associated knee pain incidence and structural progression. Obesity is associated with incident hand osteoarthritis and self-reported knee osteoarth- ritis, but not hip osteoarthritis. There is conflicting evidence as to whether obesity is associated with structural progression of hip or knee arthritis, but there is no association between body mass index and hand osteoarthritis pain or structural progression. Obesity dir- ectly increases the biomechanical load in weight-bearing joints, which may also promote the production of pro-inflammatory cyto- kines (including adipokines) that mediate the catabolic processes of osteoarthritis. Joint injury Joint injury can cause damage to articular cartilage, bone, me- niscus, and rupture of the anterior cruciate ligament, all of which can cause a

biomechanically adverse environment within the joint that predisposes to further deterioration of the joint tissues. Joint injury has been associated with subsequent incident knee pain in a systematic review and meta-analysis of cohort studies, and also a ninefold greater odds of progression to end-stage knee radiographic osteoarthritis in 48 months among knees without baseline knee osteoarthritis. Bone shape and malalignment There is increasing evidence that clinical osteoarthritis is a conse- quence of the failure to effectively dissipate adverse biomechanical forces within a susceptible joint. Bone shape within joints has long been recognized as a predisposing factor for adverse biomechanics. The presence of an aspherical femoral head (a cam-deformity) is associated with femoro-acetabular impingement and is associated with delamination of the acetabular cartilage and confers up to a tenfold greater risk of end-stage hip osteoarthritis within five years. Similarly, the expansion of the three-dimensional shape of tibial and femoral bones is associated with incident knee radiographic osteoarthritis. Malalignment of the knees unequally distributes load across the medial and lateral femoro-tibial joint compartment which results in a varus (bow-legged) or valgus (knock knees) de- formity. The compartment with the greater load as a consequence of the malalignment is more likely to develop radiographic osteoarth- ritis and structural progression of cartilage damage. Genetics and epigenetics Genetic studies within family-based studies and extreme osteoarth- ritis phenotypes have confirmed the strength of genetic predispos- ition to osteoarthritis. The identification of genes associated with osteoarthritis through association studies confer only small effect sizes, but single-nucleotide polymorphisms (SNP) have been associ- ated with established risk factors such as obesity (FTO) and hip bone shape (FRZB). One SNP near the NCOA3 gene reached genome- wide significance level. The NCOA3 gene is clinically important because it is expressed in articular cartilage and its expression was significantly reduced in damaged cartilage compared to normal car- tilage in femoral heads removed at the time of hip replacement. As osteoarthritis is likely a complex polygenetic problem, genomics alone will be unlikely to stratify individuals into those who will or will not develop osteoarthritis, but may lead to the development of new therapeutic targets. Epigenetic studies have indicated the disruption of cartilage homeostasis may reflect environmental factors promoting abnormal expression of genes that disrupt the anabolic and catabolic processes that regulate cartilage integrity. The alteration in gene expression of KNEE OA 20.00 18.00 16.00 14.00 12.00 10.00 8.00 6.00 4.00 2.00 0.00 40–<45 45–<50 50–<55 55–<60 60–<65 65–<70 70–<75 75–<80 80–<85 85 and older HIP OA HAND OA Fig. 19.9.4 The incidence of osteoarthritis. Age and gender-specific incidence rates (/1000 person-years) of knee osteoarthritis (black), hip osteoarthritis (red), and hand osteoarthritis (green). Solid, All population; short dash line, women; long dash line, men. Reproduced from Prieto-Alhambra D et al. (2014). Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Annals of the Rheumatic Diseases, 73(9), 1659–1664, copyright 2014 with permission from BMJ Publishing Group Ltd.

19.9 Osteoarthritis 4475 anti-inflammatory or pro-inflammatory cytokines, articular car- tilage proteins, matrix proteases, and transcription factors may be involved in the pathogenesis of osteoarthritis and represent im- portant novel therapeutic targets. Structural progression Structural progression is usually defined as imaging evidence of structural deterioration in a joint, though soluble biomarkers may also reflect this process. Conventionally these have been sur- rogate measures of cartilage damage from conventional radiog- raphy. Radiographic structural progression can be assessed by measuring joint space narrowing using semi-quantitative tools like the Osteoarthristis Research Society International (OARSI) atlas or quantitative tools. The Kellgren

Lawrence grade is a composite measure of joint space narrowing, osteophytes, subchondral sclerosis that is described on an ordinal scale (Table 19.9.1, Fig. 19.9.1). Joint space width is used as a surrogate for assessing cartilage thick- ness, but in the knee it reflects a construct of reduction in hyaline articular cartilage thickness along with meniscal extrusion and de- generation. The Kellgren Lawrence scoring does not represent an interval variable where individual categories are equidistant from each other. It is therefore important to recognize that the proportion of knees that progress from one grade to the next are not comparable for all starting points in the scale. With its three dimensional visualization of joint tissues, MRI has broadened concepts of structural progression. The quantification of MRI cartilage volume affords advantages over conventional radiog- raphy because structural loss of cartilage can be detected in the pre- radiographic osteoarthritis phase and in end-stage osteoarthritis, after the total loss of joint space width ('bone on bone' or Kellgren Lawrence grade 4). MRI also demonstrates structures other than cartilage (Fig. 19.9.2, Table 19.9.3) that might be used to measure structural progression such as bone marrow lesions or bone shape. The structural progression measured by radiographic osteoarth- ritis of knee, hip, and hand osteoarthritis is typically slow and takes place over several years, but matters can also remain stable over years. Structural progression varies by joint affected. In knees the mean annual risk of progression of Kellgren Lawrence grade is 5.6% ± 4.9% and mean rate of joint space narrowing is 0.13 ± 0.15 mm/ year, with change occurring in only a small group of 'progressors'. Radiographic improvement is atypical. MRI-determined cartilage volume loss in knee osteoarthritis progresses at a mean rate of 4% per annum and more than half of all knees are 'progressors'. Loss of cartilage volume occurs more rapidly with increasing age, body mass index, and lower limb muscle weakness, but also with coexisting structural changes such as bone marrow lesions and meniscal damage (Fig. 19.9.2). Muscle weakness has not been considered to be a risk factor for structural progression based upon a systematic review of studies using conventional radiography (not MRI). Symptom progression Studies that refer to osteoarthritis 'progression' generally refer to structural progression, though sometimes progression to joint re- placement is used as a surrogate for presumed worsening of pain and structure. Clinical osteoarthritis symptom progression is not well defined and could refer to progression of pain severity or the new incidence of pain within individuals usually in cohort studies. Pain can be serially measured using numeric rating or visual analogue scales or using standardized questionnaires that ask patients to quantify pain severity. Among knees with radiographic osteoarth- ritis, little change is observed in knee pain over six years except when large increases in radiographic structural severity are observed. bone marrow lesions and bone shape are independently associated with future increases in knee pain severity and incident knee pain respectively. The probability of joint replacement is increased by increasing severity of joint pain, increasing radiographic osteoarth- ritis severity, MRI-demonstrated bone marrow lesions, cartilage and meniscal damage, and synovitis that indicate joint failure. Secondary osteoarthritis The term 'primary' or idiopathic osteoarthritis is less frequently used now, perhaps because we understand the frequency of pre- osteoarthritis lesions (like meniscal damage) that would often not be detected in routine clinical practice and for which patients often have no knowledge (probably arising from minor or forgotten trauma). However osteoarthritis does occur secondary to other diseases. Congenital or developmental causes include bone dysplasias such as epiphyseal dysplasia, localized diseases such as Perthe's disease of the hip, congenital hip dislocation, and slipped femoral epiphysis. Endocrinological predisposing diseases include acromegaly, diabetes mellitus, hyperparathyroidism, and hypothyroidism. Metabolic predisposing diseases include haemochromatosis, ochronosis (alkaptonuria), Gaucher's disease, and Wilson's disease. Finally neuropathic (Charcot joints), calcium deposition diseases (primary pseudogout),

haemoglobinopathies, and other bone and joint diseases may also cause secondary osteoarthritis. Impact of osteoarthritis Individuals with osteoarthritis suffer pain which is associated with disability and reduced quality of life. The impact of osteoarthritis on an individual's function, mood, relationships, occupation, and leisure activities may be extensive. Workers with osteoarthritis reported more frequent pain, greater use of healthcare resources and costs, reduced productivity, and poorer quality of life as self-rated osteoarthritis severity increased. One in eight individuals with clinical osteoarthritis suffer self- reported unbearable pain and one in five give up holidays, hobbies, and leisure activities. One-third of people with the condition retire early, give up work, or reduce the number of hours they work be- cause of their condition. Those who retire early do so an average of eight years early. Furthermore, two-thirds of sufferers report an increase in their own costs including travel and treatment which in total equates to a mean of £480 per person each year. Clinical osteoarthritis is the most common worldwide cause of mobility disability and it is increasingly accountable as a cause for years lived with disability and limitation of quality of life. The lived experiences of people with osteoarthritis can be influ- enced for better or for worse by one or a combination of the fol- lowing: functional impairment, attitudes towards osteoarthritis symptoms, personal perceptions of osteoarthritis, and perceived per- ceptions of other people towards osteoarthritis. Favourable changes in any of these may improve the lives of those living with osteoarth- ritis (Fig. 19.9.5). A systematic review of generalized osteoarthritis indicates this is associated with poorer quality of life, function, and increased disability. Increasing osteoarthritis joint burden is also as- sociated with increasing risk of depression.

section 19 Rheumatological disorders 4476 Health economic impact Clinical osteoarthritis is associated with pain, disability, absen- teeism, and early retirement. The socioeconomic burden ranges from one to two-and-a-half per cent of gross domestic productivity in developed countries. The economic burden of osteoarthritis on society and health services is tremendous. This is generated through a combination of direct and indirect costs. Individuals with osteo- arthritis have double the rate of absenteeism compared with con- trols in North American and Swedish population-based cohorts. The mean total direct and indirect costs are two to three fold higher and there was a 40–50% increased risk of disability pension in com- parison with the general population. Osteoarthritis has a tremen- dous economic impact that will only continue to grow with its rising prevalence. In the United Kingdom between 1991 and 2006, 25 845 hips and 23 260 knees underwent total joint replacement. The estimated mortality-adjusted lifetime risk of total hip replacement (THR) at age 50 was 11.6% for women and 7.1% for men. For total knee replacement (TKR) the risks were 10.8% for women and 8.1% for men. Clinical osteoarthritis represents more than 93% of all joint replace- ment indications and the total annual cost of joint replacements is estimated at £852 million in the United Kingdom in 2010. Mortality Case series of individuals with osteoarthritis have reported both and an increased mortality and normal mortality rates compared with national statistics of the general population. Symptomatic osteoarthritis of the hip and knee was reported to confer approxi- mately a two-fold greater risk of cardiovascular (CV) and dementia- associated deaths. While this association did not adequately adjust for the confounding effects of disability and comorbidity in the general population, walking disability was found to be a major risk factor for mortality among individuals with osteoarthritis. A sub- sequent population cohort reported that osteoarthritis did not confer a greater risk of CV events but disability was independently associated with this outcome after adjusting for the presence of symptomatic and asymptomatic radiographic osteoarthritis. An analysis of the Framingham population cohort reported that hand osteoarthritis did not confer a greater risk of mortality but

symp- tomatic hand radiographic osteoarthritis conferred a greater risk of CV events than asymptomatic hand radiographic osteoarthritis. A cohort in North America, designed to describe osteoporotic frac- tures and recruited from secondary care, described a greater risk of all cause and cardiovascular (CVD) mortality conferred by the pres- ence of hip radiographic osteoarthritis compared to the absence of radiographic osteoarthritis of the hip. This effect was independent of poor physical function but the causal effect was significantly ex- plained by poor physical function. Therefore a greater burden of osteoarthritis and subsequent disability may be important risk fac- tors for mortality. Pathogenesis and pathological features Osteoarthritis is a syndrome of deterioration of synovial joints that is characterized by focal and progressive loss of the hyaline articular cartilage of joints, bone changes beneath the cartilage, synovial in- flammation, and debilitating pain. There is no single pathway of pathogenesis but in order for a structurally normal joint to become osteoarthritic, this requires a sufficient burden of joint tissue structural damage, biomechan- ical adversity along with a varying combination of risk factors (see epidemiology). These inflammatory, metabolic and genetic con- tributory factors may drive a subsequent heterogenous cascade of biomechanical and biochemical pathologies that overwhelm normal repair processes and establish the joint ‘failure’ that presents as clin- ical osteoarthritis. This pathogenesis is likely to progress through a sequence of stages that can be described macroscopically using MRI studies and microscopically using histological studies. Functional impairment Factors affecting lived experiences of osteoarthritis Attitudes towards osteoarthritis symptoms Personal perceptions of osteoarthritis Perceived perceptions of other people towards osteoarthritis Fig. 19.9.5 The factors affecting lived experiences of osteoarthritis. From Smith T et al. (2014). Living with osteoarthritis: a systematic review and meta-ethnography. Scand J Rheumatol, 43(6), 441–52, copyright © Scandinavian Rheumatology Research Foundation, reprinted by permission of Taylor & Francis Ltd (http://www.tandfonline. com) on behalf of Scandinavian Rheumatology Research Foundation.

19.9 Osteoarthritis 4477 Macroscopic In early asymptomatic stages only individual tissues are likely to be in- volved and cartilage defects, meniscal degeneration, and bone marrow lesions are all known to be present among individuals without knee osteoarthritis symptoms. These lesions (Fig. 19.9.2, Table 19.9.3) are associated with incident knee radiographic osteoarthritis and struc- tural progression of cartilage volume or thickness loss. It is likely that a ‘domino effect’ occurs where an inciting event such as a meniscal tear predisposes to cartilage loss, adjacent bone marrow lesions, meniscal extrusion, and malalignment which establishes a progressive bio- mechanically adverse environment within the joint. Microscopic Osteoarthritis represents whole- joint ‘failure’. Normal joint struc- ture and function depend upon the ability of constituent tissues to perceive and respond to stress, strain, and load. This is particularly true of the articular cartilage and subchondral bone. The cells within these tissues ensure the joint’s ability to receive and dissipate stress is maintained by homeostatic reparative processes. This includes the chondrocytes that maintain a substantial extracellular matrix. Chondrocytes synthesize molecules to restore the cartilage matrix, but also produce pro-inflammatory cytokines (e.g. interleukin-1) and tissue destructive enzymes (e.g. metalloproteinases) which de- crease anabolic matrix synthesis (Fig. 19.9.6). Cartilage and joint structural integrity and function are lost as a net catabolic process is established during the clinical osteoarthritis process. An extension of the calcified cartilage zone increases biomechanical forces across the cartilage and adjacent bone. Biomechanical derangements within the joint can stimulate the production of further catabolic enzymes. In parallel with these cartilage derangements the cellular activity in subchondral bone changes, probably to

attempt to ad- just to biomechanical forces. This results in resorption and the pro- duction of an increased volume of immature unmineralized bone. This may compromise the biomechanical support for the overlying cartilage which may augment the biomechanical forces transmitted through cartilage resulting in further damage. Furthermore an in- creased permeability at the junction between the articular cartilage and bone (osteochondral junction), driven by microcracks in the cartilage and subchondral angiogenesis, exposes the cartilage to an abnormal biochemical environment (Fig. 19.9.7). Synovial inflam- mation is precipitated by cartilage debris and catabolic mediators entering the synovial cavity. Synovial macrophages produce some of the chemokines and metalloproteinases that degrade cartilage (Fig. 19.9.6). This in turn amplifies synovial inflammation, cre- ating a potentially vicious cycle between these tissues. Pain Pain is a characteristic feature of osteoarthritis and is typically activity-related or mechanically-exacerbated and is relieved by rest. Pain may be intermittent initially but can be more chronic over time. As osteoarthritis becomes more advanced, patients report pain with different qualities (such as ‘a burning sensation’) which may reflect neuropathic pain, and central pain mechanisms including sensitiza- tion may reduce pain thresholds. Osteoarthritis pain is generated from damaged joint tissues where irritative chemical, mechanical or thermal stimuli precipitate af- ferent nociceptive neurons to depolarize and send nociceptive sig- nals to the sensory cortex via the dorsal horn of the spinal cord. The signals passed to and through the central nervous system may be enhanced by central sensitization. Nociceptive fibres richly in- nervate the synovium and subchondral bone, and while the cartilage is aneural in normal joints, it may be innervated by new nociceptive fibres as osteoarthritis progresses. The concordance between conventional radiography structural pathology and knee pain is poor. Little change in pain is observed in knee pain in knees with radiographic osteoarthritis over six years except when large increases in radiographic osteoarthritis structural severity are observed. Cartilage Cytokines Cartilage destruction Proteinases Chondrocytes Osteoclasts Osteoblasts Bone Cytokines Subchondral bone Synovial fibroblasts Synovial macrophages Synovium Cytokines (1L–1β, 1L–6, 1L–17, TNF) Inflammatory cells Intrinsic/external stimuli MMPs ADAMTS–4 Aggrecan Type II collagen Fig. 19.9.6 Pathogenesis of osteoarthritis. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Rheumatology. Kapoor M et al. (2011). Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Volume 7(1), 33–42, copyright 2011.

 Conventional radiography is not as sensitive or specific in detecting structural pathology and progression as MRI. The osteo- arthritic joint tissue lesions detected by MRI (e.g. cartilage defects, meniscal tears, bone marrow lesions—see Fig. 19.9.2) are preva- lent in knees without radiographic osteoarthritis and these are associated with incident symptoms which highlights the import- ance of peripheral joint structural lesions in the pathogenesis of nociception. Biochemical biomarkers Biochemical biomarkers in osteoarthritis are measures of the pathogenic process of joint deterioration that can be measured in the blood or urine. A recent review has identified that the best described biochemical biomarkers are in the context of hip and knee osteoarthritis and are considered to be a measure of collagen degradation (urinary CTX-II, serum COMP), osteophyte burden or synovitis (serum hyaluronic acid) and bone turnover (urine/ serum NTX-1). Considerable research efforts have been made to determine if they can be used for as surrogate measures for diag- nostic purposes or to reflect how a patient feels, functions, or sur- vives. Currently none of these biochemical markers, are sufficiently discriminating to be used as surrogate outcome measures. Management Clinical features The National Institute for Health and Care Excellence (NICE) and the European League Against Rheumatism (EULAR)

guidelines advise that appropriate symptoms, clinical findings, and age at onset can be used to clinically diagnose osteoarthritis. Activity-related joint pain reported in patients over the age of 45 with less than 30 minutes of morning joint stiffness can be considered to have osteoarthritis without further investigation. The likelihood is in- creased further by risk factors (see Epidemiology and risk factors) and joint-specific examination findings of pathology including knee crepitus or Heberden's nodes in the hands. Investigation X-rays and laboratory analysis of blood and synovial fluid are not necessary for the clinical diagnosis of osteoarthritis. However in the presence of atypical features that suggest the presence of diagnoses other than osteoarthritis, these tests may be used for distinguishing inflammatory arthritis, septic arthritis, or malignant bone pain. These features include rapid progression of symptoms, a hot swollen joint, or prolonged morning stiffness of more than one hour. Treatment Recent years have seen the emergence of a large number of evidence-based guidelines from important musculoskeletal or- ganizations. These are based on the published literature, expert opinion and, to a lesser extent, patient opinion (all three sources are valid for comprehensive guidelines). There is generally broad agreement across these guidelines in which therapies they recom- mend, though some discrepancies are obvious in Table 19.9.4. Treatments may vary in efficacy according to the anatomical loca- tion of osteoarthritis; most of the published evidence derives from knee osteoarthritis trials. VEGF ↑ MMP3 OPG/RANK/ RANKL Key Osteoblast Osteoclast Macrophage Chondrocyte PDGF NGF Tidemark Chondrocyte cluster NCC CC SOX9 TGX–α WISP–1 Perivascular nerve fibre BV SCB Sclerostin VEGF Sclerostin Aggrecan HGF Fig. 19.9.7 Pathogenesis of osteoarthritis: osteochondral disruption. Reprinted from Suri S and Walsh DA (2012). Osteochondral alterations in osteoarthritis. Bone, 51(2), 204–211. Copyright 2012, with permission from Elsevier.

19.9 Osteoarthritis 4479 Holistic assessment The management of osteoarthritis should be personally-tailored for each individual. This should initially include a comprehensive assessment to ensure a robust and realistic management strategy is achieved. The package of interventions required will differ depending on patient needs and osteoarthritis severity but should include learning self-management strategies which are associated with better functional and pain outcomes. The assessment of phys- ical status should identify reversible risk factors like muscle weak- ness, obesity, and the severity and distribution of joint involvement. The assessment of functional ability should describe the arthritis- related limitations in the context of daily living activities and em- ployment. Personalized management strategies should be based upon the patient's health education needs, health beliefs, and mo- tivation for self-management. These inform the personally-tailored strategy required to encourage and teach the importance of lifestyle modification and exercise. Both nonpharmacological and pharmacological interventions are used, separately but more commonly in combination, in the treat- ment of osteoarthritis (Table 19.9.4). Nonpharmacological interventions Guidelines for the management of osteoarthritis unanimously recommend the provision of health education and to encourage self-management. All individuals with osteoarthritis should comprehend their arthritis reflects a failed repair process usually arising due to several joint insults, their personal risk factors (e.g. obesity) and their prognosis. This information should be reinforced at subsequent consultations and with both electronic and written resources. All patients with osteoarthritis should be offered advice on exer- cise that initially focusses on local muscle strengthening and then general aerobic fitness thereafter. A Cochrane review finds that land-based knee and hip exercise programmes can reduce pain and improve physical function. Exercise programmes must be tolerable and realistic to promote adherence and should therefore be tailored to the severity of the osteoarthritis at presentation. It is unlikely that a

patient with painful knee osteoarthritis, that cannot perform a straight leg raise, will significantly benefit from walking without quadriceps strengthening first. Exercise programmes for individuals with significant muscle weakness should begin with low-impact ex- ercises such as cycling on exercise bikes and walking laps in a swim- ming pool. Depending upon each individuals capability, the ‘dose’ of exercise should be titrated up. Overweight or obese individuals should be offered a dietician’s re- view or dietary advice because weight loss is associated with reduc- tion in pain and better function (though there is little evidence for benefits on structural progression). Aids and devices (e.g. splints for base of thumb osteoarthritis and devices for opening jars) help with everyday activities. Recommended footwear for individuals with Table 19.9.4 Summary of evidenced-based guidelines for osteoarthritis treatments Guideline NICE 2014 OARSI 2014 OARSI 2014 EULAR 2013 ACR 2012 ACR 2012 ACR 2012 Site of osteoarthritis all sites knee multijoint knee and hip hand knee hip Exercise/physiotherapy (water- and land-based) + + + + NE + + Education, self-management + + + + (+) (+) (+) Weight loss in obesity + + + + NE + + Thermotherapy (eg hot packs/spa) + NR (+) NE (+) (+) (+) Acupuncture – NR NR NE NE (+) NE Transcutaneous electrical nerve stimulation + NR – NE NE (+) NE Aids, adaptations, braces, footwear (site specific) + (+) (+) + (+) (+) (+) Paracetamol + (+) + NE NE (+) (+) Topical NSAIDs + + NR NE (+) (+) NR Oral NSAIDs (lowest possible dose) + (+) (+) NE (+) (+) (+) Topical capsaicin +a (+) NR NE (+) – NE Opioids (for refractory pain) (+) NR NR NE – (+) NR Glucosamine and chondroitin sulphate – NR NR NE NE – – Duloxetine NE NR + NE NE (+) NR Risedronate NE – – NE NE NE NE Strontium – NE NE NE NE NE NE Intra-articular corticosteroids + (+) + NE – (+) (+) Intra-articular hyaluronans – NR – NE – (+) NR Surgery—lavage/debridement –b NE NE NE NE NE NE Surgery—TJR/arthroplasty (site specific) (+) + NE NE NE NE NE This is not a head-to-head comparison of the guidelines but a summary of the recommendations; each guideline addresses different anatomical sites

- treatment is unconditionally recommended; (+) treatment is conditionally recommended; - treatment is not recommended; a excluding hip osteoarthritis; b unless there is a clear history of mechanical knee locking; NR = no recommendation for treatment despite reviewing the evidence; NE = treatment not evaluated; TJR = total joint replacement Reprinted with permission from Barr A and Conaghan P (2014). Osteoarthritis: recent advances in diagnosis and management. Prescriber, 51(21), 26–33.

section 19 Rheumatological disorders 4480 osteoarthritis includes shoes with no heel elevation, thick shock- absorbing soles, and adequate plantar arch support. In summary, the multidisciplinary patient-centred combination of exercise self-management and education should set realistic goals with regular reassessment and encouragement to maintain the re- quired lifestyle changes. Pharmacological interventions Before prescribing pharmacological treatments for osteoarthritis, practitioners should holistically consider, the individual’s existing pharmacotherapy, age, risk of cardiovascular and gastrointestinal comorbidity, and probability of treatment adherence. When pre- scribing analgesia, the practitioner should also consider the drug half-life, dose-regimen, and the route of administration. The first-line pharmacological treatments are topical NSAIDs and oral paracetamol due to their favourable risk:benefit ratio. However recent evidence suggests that paracetamol, may have greater tox- icity than is generally appreciated, and be a less effective analgesic in osteoarthritis than previously thought (Table 19.9.5). In one study, after 13 weeks of regularly taking either ibuprofen or paracetamol three times a day for knee osteoarthritis, one in five participants lost more than 1 g per decilitre of haemoglobin. A systematic review identified a dose-response effect on cardiovascular, gastrointestinal, and renal adverse events. Topical

capsaicin is a chilli pepper extract that depletes neurotransmitters in sensory terminals and attenuates the central transmission of peripheral pain impulses from the joint. It is generally recommended as supplementary analgesic for hand and knee osteoarthritis and is again safe. Should further analgesia be required, practitioners should con- sider oral nonsteroidal anti-inflammatory drugs (NSAIDS), selective COX-2 inhibitors, and then opiates, acknowledging the greater risk of toxicity, particularly with increasing age and comorbidities. Nutraceuticals, including glucosamine sulphate and chondroitin sulphate products, are natural compounds consisting of glycosa- minoglycan unit components and glycosaminoglycans respectively. Despite the substantial volume of published evidence, they are often not recommended due to the lack of certainty of clinically important analgesic or structural benefits. However nutraceuticals have been re- ported to afford small benefits in pain relief in low quality trials. The intra-articular injection of corticosteroids is a useful short- term adjunct in the treatment of moderate to severe osteoarth-ritis pain, which may facilitate muscle strengthening and exercise. Hyaluronan (HA, or hyaluronic acid) is a high molecular-weight gly- cosaminoglycan, a naturally occurring synovial fluid and cartilage component. It provides the visco-elastic properties of synovial fluid that may provide lubricating and shock-absorbing properties. Intra- articular HA is not recommended for osteoarthritis by the NICE guideline; in contrast the ACR guideline conditionally recommends its use in individuals older than 74 years with knee osteoarthritis pain that is refractory to conventional pharmacological therapies. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor and has demonstrated efficacy in reducing musculoskel- etal pain with a favourable adverse event profile. The analgesic ef- fects of duloxetine in osteoarthritis are thought to be mediated by enhancement of serotonergic and noradrenergic activity which at- tenuates nociceptive impulse transmission in the central nervous system. The evidence-base for the use of duloxetine is limited to knee osteoarthritis. It is a licensed treatment for chronic musculo- skeletal osteoarthritic pain in the United States and the OARSI and ACR guidelines recommend its use in multijoint osteoarthritis and knee osteoarthritis, respectively. Joint surgery Surgical intervention in osteoarthritis may include arthroscopic sur- gery or partial or complete joint replacement. Arthroscopic debride- ment and lavage are not recommended as treatment for osteoarthritis, except when there is a clear history of true mechanical locking of an osteoarthritic knee. True locking may represent displaced meniscal material but in the absence of true locking arthroscopic procedures do not confer better clinical outcomes than sham surgery, even with symptoms of ‘giving way’ (frequently a symptom of muscle weakness) or radiographic evidence of loose bodies. However joint surgery should be considered if a patient with osteoarthritis suffers persistent symptoms, despite adequate use of the nonpharmacological and pharmacological interventions described here. In this circumstance clinicians should consider an orthopaedic referral to primarily con- sider joint replacement. The patient should be provided with infor- mation to understand the risks and benefits of pursuing nonsurgical and surgical treatments, including the postsurgical rehabilitation implications. This ensures the patient can make informed autono- mous decisions and their preferences and opinions are respected. Referrals to an orthopaedic surgeon should not be precluded by age, comorbidity, obesity, smoking, or gender. The referring practitioner should make a timely referral before severe pain and an established functional limitation occur. In younger patients with advanced osteoarthritis, the discussion on advantages of primary arthroplasty must be tempered by awareness of the increased likelihood of revi- sion arthroplasty with less favourable outcomes. Conclusions Clinical osteoarthritis represents a process of joint failure with a great variety of risk factors and complex pathogenic pathways. It Table 19.9.5 Relationship between effect size for pain relief and quality of randomized controlled trial All trials ES (95% CI)

High-quality trials (Jaded = 5), ES (95% CI) Acupuncture 0.35 (0.15, 0.55) 0.22 (0.01, 0.44) Acetaminophen 0.14 (0.05, 0.23) 0.10 (−0.03, 0.23) NSAIDs 0.29 (0.22, 0.35) 0.39 (0.24, 0.55) Topical NSAIDs 0.44 (0.27, 0.62) 0.42 (0.19, 0.65) IAHA 0.60 (0.37, 0.83) 0.22 (−0.11, 0.54) GS 0.58 (0.30, 0.87) 0.29 (0.003, 0.57) CS 0.75 (0.50, 1.01) 0.005 (−0.11, 0.12) ASU 0.38 (0.01, 0.76) 0.22 (−0.06, 0.51) Lavage/debridement 0.21 (−0.12, 0.54) −0.11 (−0.30, 0.08) ES, effect size; NSAIDs, non-steroidal anti-inflammatory drugs; IAHA, intra-articular hyaluronic acid; GS, glucosamine; CS, chondroitin sulphate; ASU, avocado soybean unsponifiables Reprinted from Zhang W et al. (2010). OARSI recommendations for the management of hip and knee osteoarthritis Part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis and Cartilage, 18(4), 476–499. Copyright 2010, with permission from Elsevier.

19.9 Osteoarthritis 4481 confers a huge burden on individuals and health economies alike which is expected to increase in ageing and increasingly obese populations. Current treatments consist of moderately effective nonpharmacological and pharmacological pain-relieving therapies. There are currently no licensed structure-modifying therapies. Joint replacement reduces pain but joint prostheses have a finite life ex- pectancy and revision surgery offers less favourable outcomes. FURTHER READING arcOGEN Consortium, et al. (2012) Identification of new suscepti- bility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet, 380, 815–23. Arthritis Care (2012). OANation Survey 2012. http://www.arthritiscare. org.uk/LivingwithArthritis/oanation-2012 Culliford DJ, et al. (2012). The lifetime risk of total hip and knee arthroplasty: results from the UK general practice research database. Osteoarthritis Cartilage, 20, 519–24. Evangelou E, et al. (2014). A meta-analysis of genome-wide associ- ation studies identifies novel variants associated with osteoarthritis of the hip. Ann Rheum Dis, 73, 2130–6. Fernandes L, et al. (2013). EULAR recommendations for the
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