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FACTORES DE RIESGO OSTEOARTROSIS

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Risk factors for and possible causes of osteoarthritis

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INTRODUCTION — Osteoarthritis was previously thought to be a normal consequence of aging, thereby leading to the term degenerative joint disease. However, it is now realized that osteoarthritis results from a complex interplay of multiple factors, including joint integrity, genetics, local inflammation, mechanical forces, and cellular and biochemical processes [1]. A discussion of how these factors interact to cause cartilage loss and related bony changes is presented separately. (See "Pathogenesis of osteoarthritis".)

Rarely, inherited conditions may predispose individuals to develop osteoarthritis. For the majority of patients, osteoarthritis is linked to one or more factors, such as aging, occupation, trauma, and repetitive, small insults over time. These associations are strongest for osteoarthritis of the knee and hand and are less strong for the hip. How these factors interact with genetics and other factors in the development of osteoarthritis remains unclear.

The risk factors for and possible causes of osteoarthritis will be reviewed here. Clinical manifestations, classification, and diagnosis are presented separately. (See "Clinical manifestations of osteoarthritis" and "Diagnosis and classification of osteoarthritis".)

The management of osteoarthritis, including nonpharmacologic approaches, pharmacologic treatment, and surgical therapies, is discussed separately. (See "Nonpharmacologic therapy of osteoarthritis" and "Pharmacologic therapy of osteoarthritis" and "Surgical therapy of osteoarthritis".)

RISK FACTORS AND POSSIBLE CAUSES — Multiple risk factors have been linked to osteoarthritis in epidemiology studies including:

- Age
- Female versus male sex
- Obesity
- Lack of osteoporosis
- Occupation
- Sports activities
- Previous injury
- Muscle weakness
- Proprioceptive deficits
- Genetic elements
- Acromegaly
- Calcium crystal deposition disease

AGE — Advanced age is one of the strongest risk factors associated with osteoarthritis [2-5]. The National Health and Nutrition Examination Survey found the prevalence of this disease to be less than 0.1 percent in those aged 25 to 34 years old versus a rate of over 80 percent in people over age 55 [2,6]. These findings are consistent with those of early studies:

- In 1958, a study found osteoarthritis in 83 and 87 percent of males and females aged 55 to 64 years old, respectively.
- In 1973, age related increases in osteoarthritis were reported in both men (incident osteoarthritis of 9.4 percent in those aged 15 to 24 versus 97 percent in those over age 65) and women (incident osteoarthritis of 7.6 percent in those aged 15 to 24 versus 97 percent in patients at age 65 and over) [7].

FEMALE SEX — Innumerable studies have found that female sex is associated with an increased risk of osteoarthritis [3,8]. The relative risk of developing osteoarthritis for women has been estimated to be 2.6 after adjustment for age, weight, and smoking [8]. Women with OA are also more likely than men to experience rapid structural damage and to undergo total hip arthroplasty [9]. The reason for these increased risks in women remains unclear, but it may be related to hormones, genetics, or other undetermined factors. (See "Pathogenesis of osteoarthritis".)

OBESITY — Obesity is perhaps the strongest modifiable risk factor for the development of osteoarthritis. Although multiple studies have demonstrated a relationship between obesity and osteoarthritis, newer studies better define this association and its implications on the prevention of disease [3-6,8,10-18].

Since the association of obesity as a risk factor for osteoarthritis varies by joint, the following review will be conducted according to the principle affected anatomic areas in osteoarthritis: the knees, hands, and hips.

Knee — Utilizing data from the Chingford study, two studies have quantified a strong association between obesity and osteoarthritis of the knee [13,19]. In these studies, height, weight, waist, and the circumference of the hips and mid-thigh were measured, and subjects were divided into tertiles based on body mass index. Women of age 45 to 64 were considered to have osteoarthritis if their Kellgren and Lawrence score was two or greater [13,19].

When compared with the lowest obesity tertile, patients in the highest tertile in one of the studies had an odds ratio of 6.17 for radiographic osteoarthritis and 8.57 for radiographic and

symptomatic osteoarthritis [13]. For every two unit increase in body mass index (equivalent to approximately 5 kg), the odds ratio for radiographic knee osteoarthritis increased by 1.36. The distribution of fat, however, was not found to be significant. Limitations of the study include its cross sectional nature and the predominance of Caucasians.

A follow-up, longitudinal study of this patient population evaluated the risk for the development of contralateral knee osteoarthritis in middle aged women with established unilateral disease [14]. This Chingford population again consisted of predominantly Caucasian, middle class females, and, as in the previous study, patients with unilateral knee osteoarthritis of grade 2 or above by the Kellgren and Lawrence scale were included. Of the 67 women with unilateral disease, 20 (34 percent) developed contralateral disease by radiographic criteria at 24 months. Among those with incident osteoarthritis, only 10 percent of patients with low body mass index (BMI) tertile developed osteoarthritis versus 25 and 47 percent in the middle and highest tertile, respectively. The relative risk was 4.69 from the lowest to highest obesity tertile. Furthermore, the risk of contralateral osteoarthritis increased by 6.5 percent for each additional 5 kilogram of weight. Female patients with unilateral osteoarthritis are, therefore, at high risk of developing contralateral disease, and an enhanced risk is associated with increasing weight.

Among older adults, the combination of obesity and heavy physical activity is associated with an enhanced risk of osteoarthritis of the knee, defined radiologically. Using data from the Framingham heart study (the Framingham Osteoarthritis Study), older individuals (average age of 70 years) in the upper tertile of BMI who performed at least three hours per day of significant physical activity had an odds ratio of 13 of developing knee osteoarthritis [20]. Lesser degrees of activity were not associated with an enhanced risk. In another, younger cohort of Framingham residents (mean age 53 years) followed for nine years, the incidence of symptomatic or radiographic OA of the knee was not significantly different in those with lower versus higher levels of self-reported physical activity regardless of initial weight or BMI [21].

The prevalence of symptomatic osteoarthritis of the knee among patients with radiographic osteoarthritis in the Framingham Osteoarthritis Study cohort increased over the 20 years between 1983 to 1985 and 2002 to 2005, after adjustment for both age and body mass index (from 26 to 49 percent in women and from 19 to 49 percent in men) [22]. Knee pain and obesity also increased in the same interval in this cohort and in national survey data in the US. However, increased obesity only explained a portion of the change (about 10 to 25 percent), and, notably, radiographic knee osteoarthritis did not increase during this interval. The precise factors responsible for these increases in symptom prevalence and an increased rate of knee joint replacement surgery during this period are uncertain.

Hand — Utilizing data from the Tecumseh Community Health Study, one study prospectively evaluated the risks for developing osteoarthritis of the hand. Patients with pre-existing osteoarthritis or rheumatoid arthritis were excluded. A weight index was calculated utilizing sex-specific desired weight to height ratios from Metropolitan Life actuarial tables; obesity was defined as an index of greater than 120 percent. Over the 23 year period, there was a 41 percent incidence of hand osteoarthritis as defined by radiographic criteria in the Atlas of Standard Radiographs of Arthritis. Obesity was associated with a relative risk of 3.12 for the development of hand osteoarthritis. This enhanced rate occurred in obese patients without pre-existing disease, thereby supporting the hypothesis that obesity is causal in osteoarthritis. The findings of this study support the postulate that decreased exercise resulting from joint pain is not the only reason why obesity is associated with osteoarthritis.

Hip — Although obesity may cause osteoarthritis of the knees and hands, less consistent data support a relationship between hip osteoarthritis and obesity [4,7,15-17]. One study of Finnish patients age 30 and over selected from a population registry found hip osteoarthritis (as defined

by clinical and radiographic criteria) in 6 and 4 percent of women and men, respectively [4]. The incidence of arthritis increased with increased body mass index, with an enhanced odds ratio of 2.8 for bilateral hip disease from the lowest and highest weight groups. However, this report was flawed in part because of a cross-sectional design. Nevertheless, in an all-women study, a significant correlation with obesity was seen [23]. A significant association between BMI and total hip arthroplasty for OA was also noted in a cohort of over one million Norwegian men and women [24].

By comparison, another study of over 1000 male medical students found that increased body mass index measured at ages 20 to 39 years enhanced the risk of developing knee, but not hip, osteoarthritis at follow-up at 36 years [25].

Risk reduction — The risk of osteoarthritis associated with obesity may be modifiable. As an example, one report of 64 patients with osteoarthritis of recent onset from the Framingham knee osteoarthritis study found a correlation between weight change and osteoarthritis [5]. Most cases of osteoarthritis occurred in women who had gained at least four units of body mass index or in those with gains of between two and four BMI units. The lowest rate of incident disease occurred in women who lost two to four BMI units. By examining the rate over time, any increase in BMI was correlated with a nonsignificant trend toward higher risk for symptomatic osteoarthritis, and a loss in BMI was significantly correlated with a decreased risk. Unfortunately, the findings of the study are weakened by its reliance upon the recall of the date of symptom onset.

Since obesity is the most modifiable risk factor associated with the development of osteoarthritis, clinicians should counsel their patients that weight loss will decrease their risk. It is likely that even modest weight loss will provide some benefit.

Associated disability — Osteoarthritis due to obesity is also associated with significant morbidity. One study, for example, examined the relationships between obesity, osteoarthritis, and disability [3]. Using a patient population in a rural southeastern section of the United States which included a significant proportion of African-Americans, the study sought independent risk factors for disability from osteoarthritis. Variables included age, race, sex, level of education, marital status, knee pain on most days, severity of knee pain, the Health Assessment Questionnaire (HAQ), body mass index, and knee radiographs. Only age (particularly age greater than 75), female sex, obesity, and knee pain severity had independent impacts on mean HAQ scores. Specifically, obesity was significantly associated with a worse HAQ score and more severe knee pain. This study is important in both its examination of the functional status of its cohort and its inclusion of a significant number of African-American patients.

LACK OF OSTEOPOROSIS — Higher bone mass is associated with an increased risk of hip osteoarthritis in older women [26-28]. As an example, the radiographs of 4855 women aged 65 and older were examined for radiographic evidence of osteoarthritis and compared with measurements of bone mineral density [28]. Women with moderate to severe evidence of osteoarthritis had higher bone mineral density measurements than those without osteoarthritis. This inverse association between osteoporosis and osteoarthritis was supported by a large cross-sectional study which controlled for the effects of estrogen replacement therapy [29].

A similar relation exists between bone mineral density and the prevalence of osteoarthritis of the knee. In the Framingham study population, the prevalence of radiographic osteoarthritis was 17 percent in 115 women in the lowest quartile of bone mineral density and increased steadily to 34 percent for those in the highest quartile of bone density [30]. Despite the positive association between bone density and radiographic prevalence of osteoarthritis, the same study found that women who were more osteopenic were more likely to have progressive worsening

of their osteoarthritis, at least radiographically, than those with higher bone density.

Estrogen replacement therapy — The prevention of bone loss via estrogen replacement therapy (ERT) should, therefore, enhance the development of osteoarthritis. Support for this hypothesis is provided by the results of some animal models of osteoarthritis in which the administration of estrogen promoted cartilage damage [31,32]. This result, however, was not found in other studies [33,34].

Some clinical studies suggest that postmenopausal ERT protects women from developing large joint osteoarthritis (thereby resulting in a lower than expected risk of knee and hip osteoarthritis), while others show only a neutral effect [35-37]. Of these studies, four evaluated the effect of ERT on prevalent disease, and one studied the effect on incident and progressive radiographic disease. A meta-analysis of the four prevalence studies suggested an inverse relationship. This association was supported by another study which reported a strong inverse relationship between ERT and osteoarthritis among women receiving long term ERT for both prevalent radiographic osteoarthritis and incident osteoarthritis [38].

However, one case-control study failed to confirm the finding that ERT protects women from developing osteoarthritis [39]. Although there was a modest but nonsignificant inverse association between past use and the development of osteoarthritis, ongoing use was not associated with osteoarthritis risk. Likewise, in a four year prospective study of ERT in women (HERS trial) that randomly assigned subjects to estrogen/progestin or placebo, there was no significant difference in the prevalence of knee pain or in the degree of disability between those on ERT or placebo [40].

As the evidence from studies is conflicting, there may be many potential co-variables that may not have been adequately controlled. Although a randomized, prospective clinical trial might help to clarify the effect of ERT on the development of osteoarthritis, such a trial seems unlikely to be performed given current concern about the risks of such therapy in postmenopausal women.

OCCUPATION — The role of occupation and osteoarthritis has been examined in multiple studies [1-11], and reports have linked knee osteoarthritis with specific occupations, including cotton workers, dock workers [12], shipyard workers [9], and carpenters [13]. Hand and hip osteoarthritis have also all been evaluated and linked to occupations associated with physical labor. Despite these associations, it is unclear whether a change in occupation lessens the risk of osteoarthritis.

Mechanisms for the association between occupation and osteoarthritis remain unclear but may involve joint loading and repetitive damage over time. Since these processes likely differ from joint area to joint area, occupational osteoarthritis will be examined separately by affected joint area.

Knee — Certain occupational activities, especially those related to repetitive knee bending, appear to be risk factors for the development of knee osteoarthritis. As an example, a case-control study of patients with symptomatic knee osteoarthritis attempted to define specific occupational activities which favor the development of the disorder [41]. Analysis found increased odds ratios with greater than 30 minutes of squatting (OR = 6.9), greater than 30 minutes of kneeling (OR = 3.4), and climbing more than 10 flights of stairs per day (OR = 2.7). These results suggest that prolonged knee bending was a risk factor for osteoarthritis via mechanical loading. Similar associations with knee bending have been found in population-based studies [10,20,42,43]. The combination of obesity and occupational bent knee activities

leads to an even higher risk of knee osteoarthritis (OR = 14.7) [44].

Hip — Mechanical stresses associated with certain occupations also appear to be associated with an increased risk of hip osteoarthritis. One retrospective study examining occupational hip osteoarthritis evaluated all outpatient urograms over a five year period in which both hips were visualized in males 60 to 75 years old [45]. Osteoarthritis was defined as joint spaces less than 2.5 mm or as the presence of a prosthetic hip replacement. The control group consisted of patients with at least 3.5 mm of joint space in the hip and no other evidence of osteoarthritis such as cysts, sclerosis, or osteophytes. Patients were interviewed for occupational activity, sports, and hobbies. The following results were reported:

- Although no occupational association with osteoarthritis was found overall, analysis of severe hip osteoarthritis (defined as a joint space of less than 1.5 mm) revealed an increased odds ratio for working at least one year as a farmer (OR = 1.6) or as a construction worker/laborer (OR = 1.5). Farmers with at least 10 years of work experience had higher odds ratios (OR = 2.0).
- A correlation existed between standing more than two hours and cases of osteoarthritis (OR = 1.7), a finding which remained valid after subgroup analysis for severe osteoarthritis (OR = 2.7).
- Associations with arthritis were found with more than 20 years of jobs entailing heavy lifting (OR = 2.5) or walking more than two miles per day (OR = 1.6).
- No length of exposure relationship with osteoarthritis was observed with construction workers, and no associations were found with sports activity.

Problems with this study include recall bias and non-standardized definitions of osteoarthritis. A similar association was found in a second study examining Japanese patients with severe OA [46].

SPORTS ACTIVITIES — Several uncontrolled, cross-sectional studies have compared the prevalence of osteoarthritis in groups engaged in regular exercise, utilizing radiographs as the main outcome measurement. In one review, the following sports were associated with an increased risk of osteoarthritis in the indicated joints [47]:

- Wrestling (cervical spine, knees, and elbows)
- Boxing (carpometacarpal joints)
- Pitching in baseball (shoulders and elbows)
- Cycling (patellofemoral joints)
- Recreational parachuting (spine, knees, and ankles)
- Cricket (fingers)
- Gymnastics (shoulders, wrists, and elbows)
- Ballet dancing (talar joints)
- Soccer (hips, knees, ankles, cervical spine, and talar joints)
- Football (knees, feet, and ankles)

The same sport may not yield an increased risk for the recreational participant but may increase the risk for the competitive athlete.

The lack of suitable control groups has been a major limitation in the interpretation of these studies and casts doubt on the conclusions [48]. In addition, the cross sectional study design employed by these studies introduces significant selection bias as subjects who continue to exercise and, therefore, serve as the study group may continue to exercise by virtue of the fact that they have not developed arthritis. By comparison, those that develop arthritis stop

exercising and are included in the control group.

Evidence from a number of studies has failed to demonstrate that running increases the risk of osteoarthritis of the knee. The evidence is presented separately. (See "Overview of running injuries of the lower extremity".)

PREVIOUS INJURY — Previous injury and/or joint abnormalities appear to favor the development of osteoarthritis of the knee. Hip dislocation or congenital dysplasia also enhances the risk of hip osteoarthritis [49-51]. (See "Clinical features and diagnosis of developmental dysplasia of the hip".)

Knee injury — One study of the role of knee injury, for example, found that all 6 of 20 long-distance runners with knee pain who showed clinical and radiographic evidence of knee osteoarthritis had pre-existing biomechanical abnormalities of the knee (such as abnormalities of alignment, namely genu varus, and/or previous knee injury) [52]. Subsequent studies have corroborated the association between ligamentous or meniscal injury to the knee or surgical meniscectomy and subsequent increased risk for osteoarthritis [53-55]. Among patients with documented cruciate ligament tears and painful arthritis, less than one-half recollect a knee injury [56]. Older age at the time of trauma or surgery appears to predict a more rapid deterioration to osteoarthritis of the involved knee [54,55]. Having OA of the hands is an independent risk factor for developing OA of the operated knee, a point that suggests an interplay of heritable and environmental factors [57,58].

Abnormalities of the meniscus are common among patients with OA of the knee [59]. In most cases, there is no recollected knee trauma. As an example, when 32 patients with symptomatic OA of the knee had MR imaging, some meniscal abnormality was present in 75 percent [60]. The rate of knee articular cartilage loss over two years of observation was significantly greater in those with meniscal damage at baseline. Whether meniscal damage occurred before or after the onset of symptoms could not be determined.

Amputation — Amputation of one lower extremity usually increases the amount of weight borne on the unaffected limb, even when a prosthesis is used. This may account for the increased prevalence of osteoarthritis of the contralateral knee, which has been observed in unilateral amputees [61,62].

MUSCLE WEAKNESS — There are conflicting data on the relationship between muscle strength and osteoarthritis. Evidence supporting a role for muscle weakness as a risk factor for osteoarthritis is the finding that weakness of the quadriceps muscle group, which is common in patients with osteoarthritis [63], antedated the development of knee pain and muscle atrophy in seniors and predicted the severity of radiographic and symptomatic osteoarthritis of the knee, even when adjusted for potential confounding variables [64]. The authors of this study concluded that weakness of the quadriceps group may be etiologically related to the initiation and/or progression of osteoarthritis in some patients.

Among patients with knee pain but without radiographic changes indicative of osteoarthritis, less than average quadriceps strength and endurance may be predictive of subsequent development of arthritic changes. This was illustrated in a study of 94 such individuals whose quadriceps function was assessed by the maximum number of times they could rise from a seated position using only one leg (each leg was tested with a five minute rest between sides) [65]. The number of repetitions (total of right and left sides) was significantly less for those who developed radiographic evidence of arthritis than for those who did not (median of 17 versus 25 repetitions, respectively). Also studied was a group of 54 subjects with knee pain **and** radiographic arthritis at baseline; in this group with prevalent OA, there was no significant

difference in quadriceps endurance between those who progressed radiographically and those who did not.

However, in a group of patients with symptomatic osteoarthritis of their knees, quadriceps muscle strength that was less than the median for 237 patients was not associated with more rapid progression of radiographic osteoarthritis grade during 18 months of follow-up [66]. After adjustment for contributing factors, the rates of worsening were 0.098 and 0.153 for lower and higher muscle strength, respectively, a difference that was not statistically significant. In a hypothesis-generating analysis of subgroups, knee malalignment, either varus or valgus, was associated with significantly more radiographic progression in those with higher than in those with lower quadriceps strength at baseline. This study did not report on symptomatic or functional changes during the follow-up period, nor was muscle strength measured at other times than baseline. These provocative findings have yet to be tested as a primary hypothesis.

MUSCLE STRENGTH — Enhanced hand strength may favor the development of osteoarthritis of the proximal joints of the hand, particularly among men. An analysis of nearly 750 subjects from the Framingham osteoarthritis study found that men with high maximal grip strength had a nearly threefold increased risk (compared with those with low maximal strength) for disease involving the proximal interphalangeal, metacarpophalangeal, and thumb base joints [67]. By comparison, women with high maximal grip strength had a higher incidence of disease only in the metacarpophalangeal joints. No association for either men or women was observed between strength and osteoarthritis in the distal interphalangeal joints.

In the study cited earlier, a post-hoc analysis suggested that among those with malalignment, increased quadriceps strength at baseline might predispose to more rapid progression than that seen among subjects with lower quadriceps muscle strength [66].

SUMMARY OF RISK ASSOCIATED WITH PHYSICAL EXERCISE — The following conclusions are supported by the available data regarding the risk for developing osteoarthritis of weight-bearing joints due to physical activity [21,48,68]:

- Neuroanatomically normal joints are at increased risk of developing osteoarthritis in the absence of adequate exercise.
- Neuroanatomically normal joints are **not** at increased risk upon exposure to repetitive, low-impact, recreational exercise.
- Neuroanatomically abnormal joints are at increased risk upon exposure to repetitive, low impact, recreational exercise.
- Neuroanatomically normal joints are at increased risk upon exposure to repetitive, high-impact exercise.

PROPRIOCEPTIVE DEFICITS — A proprioceptive deficit has been noted in humans with knee osteoarthritis and may underlie some cases of osteoarthritis. This deficit is thought to reflect damage to mechanoreceptors in or around the involved joint rather than an underlying, generalized neurologic defect [69]. The Charcot joint is a classic example of joint damage caused by the inability to appropriately sense and respond neurologically. (See "Diabetic neuropathic arthropathy".)

GENETIC FACTORS — Genetic factors are implicated in the development of osteoarthritis via the results of conventional twin and non-twin sibling, population, and modern molecular studies [70-73]. Genetic factors may have more influence on the expression of some subsets of osteoarthritis than others [71]. Microsatellite DNA markers may be helpful in identifying the role of genetics in these different subsets by evaluating whether test candidate genes are

responsible for or are linked to the illness in familial disorders.

Twin and non-twin sibling studies — A genetic influence for osteoarthritis of the hands and knees was noted in a study using screening radiographs of 500 unselected female twins aged 45 to 70 years [74]. Correlations of osteoarthritis were consistently twofold higher in 130 pairs of identical compared with non-identical twins. The influence of genetic factors was estimated to be between 39 to 65 percent, independent of known environmental or demographic variables [74]. Both the tibiofemoral and patellofemoral compartments of the knee appeared to be influenced by genetic factors, but the proximal interphalangeal joints failed to demonstrate a genetic component. Other twin studies have found that the degree of influence of genetic factors for the development of osteoarthritis of the hip is approximately 60 percent, while that for cervical and lumbar disc degeneration is 70 percent [75,76].

A genetic component for the development of hand and lumbar spine, but not knee or hip, osteoarthritis was found in a study of non-twin siblings. In one report of 118 subjects with osteoarthritis and 257 non-twin siblings, the influence of genetic factors for hand and back osteoarthritis was approximately 55 and 75 percent [72]. In another study of nearly 3000 people with OA affecting the carpal metacarpal joint of the thumb or the interphalangeal joints of the fingers, there was a twofold increase in risk for sisters of women with hand OA and a five- to sevenfold increase in the relative risk of having arthritis if the sibling had "severe" OA [77].

Genome-wide scanning

Hand OA — Genome-wide scanning in 296 pedigrees was performed in order to identify loci associated with radiographic osteoarthritis of the hands [78]. Eight sites of potential linkage were found on chromosomes 1, 7, 9, 13, and 19. The most tightly linked was a region on the short end of chromosome 1. Subsequent analysis in 267 pedigrees suggested that OA of specific joints of the hands, particularly the first carpometacarpal joint and the distal interphalangeal (DIP) joints, was linked to different sites [79].

Other investigators identified a locus on chromosome 11 that was associated with the risk of osteoarthritis of the hip in the female members of 481 families that had at least one severely affected index case (requiring total hip arthroplasty) [80]. Two sites within the 11q region were suggested by more detailed mapping of this region [81]. Other sites of interest include ones on chromosome 4, two on chromosome 16 [82], and ones on chromosomes 2 and 19 [83].

Idiopathic OA of the hands, specifically of the distal interphalangeal and first carpal-metacarpal joints in patients and families in Iceland, was linked to regions on chromosomes 4, 3, and 2 [84]. A mutation in the gene for a noncollagenous matrix protein, matrilin-3 (MATN3), segregated with hand OA in several families. In the Icelandic population, approximately 2 percent of those with hand OA carry the mutated gene; carriage confers a twofold increase in the relative risk for hand OA.

Knee OA — Genome-wide screening of unrelated women with OA of the knee and controls in British and Canadians of European ancestry noted a reproducible association with a marker within the gene for LRCH1 [85]. This study initially identified a potential association between 335 women with OA who were awaiting or had undergone total knee replacement and a control group of equal size. Replication of the association was observed in two additional groups of 246 and 211 cases of OA of the knee in the UK and Canada, respectively, and unaffected controls. A polymorphism in LRCH1 on chromosome 13 was 1 of 31 single nucleotide polymorphisms that was significantly more frequent in cases than controls. The marker (rs91242a C/T) allele frequency was significantly higher in cases than controls, 23 and 17 percent, respectively, (OR = 1.44) in the initial study, and exhibited the strongest and most consistent effect of the initially

identified loci when all three samples were considered. The function of the LRCH1 gene product is unknown, but it has regions that are homologous to those of actin-binding proteins that regulate cells shape and participate in intracellular signaling.

Haplotype associations — Primary generalized "nodal" osteoarthritis, characterized by Heberden's nodes, Bouchard's nodes, and involvement of the hips and knees, appears to have a genetic component [86]. This form of osteoarthritis has been associated with HLA-A1,B8 [87] and HLA-B8 [88] haplotypes and with alpha-1 antitrypsin isoforms; however, several studies have not found this association [89,90].

Mutations in proteins involved in bone or articular cartilage structure or metabolism — Potential genetic abnormalities which predispose to osteoarthritis include structural defects in collagen and alterations in cartilage or bone metabolism [71]. These defects may influence the effect of additional risk factors, such as obesity, on the development of osteoarthritis [71].

COL2A1 gene — Proposed candidate osteoarthritic genes include the collagen genes that encode for type II collagen. A number of studies have shown linkage in different families and in a population-based study between generalized osteoarthritis (usually with mild chondrodysplasia) and mutations in the COL2A1 gene on chromosome 12 [91-95]. In one family, for example, a single base mutation in COL2A1 was noted in all affected members of a family but in none of the unaffected members or unrelated individuals [93]. Mutations in the COL2A1 gene have also been linked to the Stickler syndrome. (See 'Stickler syndrome' below.)

Evidence of pathogenicity comes from an animal study in which insertion of the mutant human COL2A1 gene into mice lacking the normal complement of the murine equivalent gene produced early degeneration of vertebral discs and osteoarthritic changes in peripheral joints [96].

A different mutation in the COL2A1 gene in a single extended family has been associated with several clinical syndromes affecting the hip, including premature osteoarthritis, osteonecrosis, and Legg-Calvé-Perthes disease [97]. (See "Osteonecrosis (avascular necrosis of bone)", section on 'Other causes'.)

Other extracellular matrix proteins — The genetic nature of primary generalized osteoarthritis may be heterogeneous, and mutations in genes other than COL2A1 may be responsible. The role of mutations in genes encoding minor collagen types and extracellular matrix proteins, such as aggrecan, decorin, and the link protein, therefore, needs to be further investigated.

The gene for one such matrix protein, asporin, appears to be a promising candidate. This was illustrated in a multifaceted study of polymorphisms of the asporin gene in a Japanese population [98]. An exploratory investigation suggested that an allele that increases the number of aspartic acid residues in one portion of the molecule from 13 (D13-allele) to 14 residues (D14-allele) was associated with osteoarthritis of the knee. A subsequent study in 393 patients with symptomatic OA of the knee and 374 controls indicated that having one or more of the asporin D14-alleles conferred a twofold increased risk of symptomatic and radiographic osteoarthritis compared with the more common D13-allele (OR 2.00, 95% CI 1.4-2.8) [98]. A somewhat smaller, but also statistically significant, increase in risk was also seen for the asporin D14-allele and OA of the hip (OR 1.71, 95% CI 1.1-2.6).

In vitro, asporin produced from the D14-allele suppresses transforming growth factor-beta (TGF-beta) stimulated synthesis of the major articular cartilage structural proteins, type-II collagen and aggrecan, by cultured chondrocytes. This and a demonstrated ability of asporin to physically bind to TGF-beta lend biologic plausibility to the observed association between the

asporin genetic polymorphism and OA of the hip and knee [98].

The D14-allele of asporin may not be a major contributor to risk in other populations. This was illustrated in a study in the United Kingdom of 1247 patients who had joint replacement surgery for OA and 748 controls [99]. In this predominantly Caucasian population, the D14-allele frequency was greater and the D13-allele frequency was less than those in the Japanese population. Overall, there was no significant association found in this population between asporin aspartate repeat genotype and osteoarthritis. Among various subsets defined by sex and affected joint, a possible association with the D14-allele in men with OA of the hip (odds ratio 1.48, 95% CI 1.05-2.01) was noted. Exploration of the contribution of asporin gene polymorphism to OA in other populations will be of interest.

Endocrine/metabolic genetic effects — Conflicting evidence exists concerning the association of specific polymorphisms of the genes for the vitamin D receptor and the estrogen receptor and a predisposition for OA [100-105]. In a well-designed case control study, however, no association was observed between OA and these polymorphisms [100].

One report noted an increased frequency of heterozygous carriage of the hemochromatosis HFE gene allele (C282Y) in older people with osteoarthritis of the hands compared with healthy young controls (16 versus 4 percent) [106]. No significant difference in frequency of another hemochromatosis-associated allele (HFE H63D) was found in the OA affected and control groups. (See "Genetics of hereditary hemochromatosis", section on 'The HFE gene'.)

Genetic linkage to a region on chromosome 2 (2q13-32) has been noted in severe osteoarthritis (eg, resulting in joint replacement) [106]. A cluster of interleukin 1 (IL-1) related genes, those for IL-1 α , IL-1 β , and the IL-1 receptor antagonist (IL1RN), lies in this region of the chromosome. Limited data suggest that polymorphisms of the IL-1B (-511T allele) and IL1RN (variable number of terminal repeats [VNTR] 2 allele) genes are associated with radiographic osteoarthritis of the hip [107]. An association with the IL-1 gene cluster has biologic plausibility because of the catabolic effects that IL-1 has on chondrocytes and articular cartilage, particularly the enhanced production of matrix degrading metalloproteinases. (See "Pathogenesis of osteoarthritis", section on 'Catabolic cytokines'.) Further study of this putative association in other populations is anticipated.

Other — The AACT, ADAM12, BMP2, ESR1, CILP, COX2, OPG, TNFAIP6, and FRZB genes may be associated with an increased susceptibility to OA to a variable degree in women and/or men, and the ADAM12, CILP, OPG, and TNA genes may be related to the risk of progression of radiographic OA [108-110].

Stickler syndrome — Hereditary arthro-ophthalmopathy (Stickler syndrome) is a familial form of premature osteoarthritis characterized by vitreous degeneration, retinal detachment, and premature degenerative joint disease [111,112]; it is a relatively rare autosomal dominant disease [71]. Using linkage analysis, Stickler syndrome is linked to type II procollagen gene (COL2A1) in 25 to 50 percent of involved families [113-115]; in some of the remaining families, the defect is in type XI collagen (COL11A2) [116]. (See "Syndromes with craniofacial abnormalities", section on 'Stickler and Marshall syndromes'.)

Familial chondrocalcinosis — Familial chondrocalcinosis is an inherited form of premature osteoarthritis [117]. In this disorder, calcium-containing crystals are deposited in joint tissue which progresses to severe degenerative osteoarthritis at an early age [118,119]. An autosomal dominant mode of inheritance is observed, with age of onset between the second and fifth decades of life [118,119]. (See "Pathogenesis and etiology of calcium pyrophosphate crystal

deposition disease".)

Linkage analysis has isolated suspect genetic areas in familial chondrocalcinosis and early osteoarthritis. As examples:

- A genetic linkage has been found with chromosome 8q in a large New England family [71,120].
- A second family with chondrocalcinosis and recurrent childhood seizures has been described with linkage to markers on chromosome 5p [121].
- Early developments of osteoarthritis, spondyloepiphyseal dysplasia, and CPPD have been linked to a point mutation in a type II procollagen gene [122].

Other — Several forms of familial osteoarthritis associated with chondrodysplasia have also been noted. They also have an autosomal dominant pattern of inheritance [123]. Osteoarthritis is also a feature of familial hydroxyapatite deposition disease, spondyloepiphyseal dysplasia, Kniest dysplasia, multiple epiphyseal dysplasia, and metaphyseal chondrodysplasia [124].

ACROMEGALY — Acromegaly has been associated with the development of secondary osteoarthritis, presumably due to the effects of elevated growth hormone levels on bone and cartilage. (See "Causes and clinical manifestations of acromegaly".) However, whether a true causal relationship exists between these disorders remains unclear. Most studies purporting this association lack a comparison between older acromegalic patients and an older control population [125]. In addition, the incidence of osteoarthritis in patients with growth hormone deficiency has not been studied.

In an attempt to overcome these design deficiencies, one review evaluated the prevalence of osteoarthritis in 26 patients with acromegaly (mean age of 73 years), 22 with growth hormone deficiency (mean age of 69 years), and 260 healthy controls (age range of 70 to 75 years) [126]. The prevalence of osteoarthritis as assessed by hand and knee radiographs was **no** greater in the acromegalic patients than in the controls except in the proximal interphalangeal joints. In addition, patients with growth hormone deficiency had a significantly decreased prevalence of osteoarthritis compared with controls. These data may have been biased by the age of study and by treatment for acromegaly, which may have affected the development of osteoarthritis.

CALCIUM CRYSTALS — Intraarticular calcium-containing crystals including calcium pyrophosphate dihydrate (CPPD) deposition and basic calcium phosphate (BCP) (hydroxyapatite, octacalcium phosphate, tricalcium phosphate) appear to coexist with cartilage damage in patients with osteoarthritis [127]. However, it has not yet been established if this relationship is pathogenetically important or if it is an epiphenomenon [128,129]. (See "Pathogenesis of osteoarthritis".)

Both CPPD and BCP crystals are commonly found in osteoarthritic cartilage and have been observed within chondrocytes [130-133]. The prevalence of BCP crystals in the synovial fluid of patients with knee osteoarthritis has been noted to be between 30 and 60 percent [134,135]. In addition, CPPD crystals were noted in 70 percent of patients with knee osteoarthritis and pain refractory to nonsteroidal antiinflammatory drugs and/or intraarticular corticosteroids [136]. Calcium-containing crystals have also been frequently described in osteoarthritis involving the shoulders, wrists, and elbows [118]. (See "Clinical manifestations and diagnosis of calcium pyrophosphate crystal deposition disease".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain

language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: Osteoarthritis symptoms and diagnosis (Beyond the Basics)" and "Patient information: Osteoarthritis treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Osteoarthritis results from a complex interplay of multiple factors, many of which have been linked to osteoarthritis (OA) in epidemiologic studies, such as aging, occupation, trauma, and repetitive, small insults over time. These associations are strongest for OA of the knee and hand and are less strong for that of the hip. Rarely, inherited conditions may predispose individuals to develop osteoarthritis. (See 'Introduction' above and 'Risk factors and possible causes' above.)
- Age and gender are important risk factors for OA. Advanced age is one of the strongest risk factors, and numerous studies have found that female sex is associated with an increased relative risk of OA (estimated 2.6) after adjustment for age, weight, and smoking. Studies in women have also found that higher bone mass is associated with an increased risk of hip osteoarthritis and have shown an inverse relationship between receipt of long term postmenopausal hormone therapy and osteoarthritis. (See 'Age' above and 'Female sex' above and 'Lack of osteoporosis' above and 'Estrogen replacement therapy' above.)
- Obesity may be the strongest modifiable risk factor for OA, but the risk varies by joint. The association is strongest for the knees and hands but is less consistent for the hip. It is likely that even modest weight loss will provide some benefit in modifying risk. (See 'Obesity' above and 'Knee' above and 'Hand' above and 'Hip' above and 'Risk reduction' above.)
- Physical activities related to both occupation and sports affect the risk of OA, as do previous injuries and muscle strength. Mechanisms for the association between specific occupations and OA of the knees, hands, or hips may involve joint loading and repetitive damage over time. (See 'Occupation' above and 'Sports activities' above and 'Previous injury' above and 'Muscle weakness' above and 'Muscle strength' above and 'Summary of risk associated with physical exercise' above.)

Taken together, the studies on physical activity indicate that:

- Neuroanatomically normal joints are at increased risk of developing osteoarthritis in the absence of adequate exercise.
- Neuroanatomically normal joints are **not** at increased risk upon exposure to repetitive, low-impact, recreational exercise.
- Neuroanatomically abnormal joints are at increased risk upon exposure to repetitive, low impact, recreational exercise.
- Neuroanatomically normal joints are at increased risk upon exposure to repetitive, high-

impact exercise.

- Genetic factors have been implicated in the development of OA, based upon conventional twin and non-twin sibling, population, and modern molecular studies. Such factors may have more influence on the expression of some subsets of OA than others. As examples, primary generalized "nodal" OA, characterized by Heberden's nodes, Bouchard's nodes, and involvement of the hips and knees, appears to have a genetic component; and genetic abnormalities in collagen or alterations in cartilage or bone metabolism may also predispose to OA. (See 'Genetic factors' above and 'Genome-wide scanning' above and 'Mutations in proteins involved in bone or articular cartilage structure or metabolism' above and 'Stickler syndrome' above.)
- Inherited and acquired metabolic conditions, particularly those associated with calcium deposition, can also influence the development of OA, including calcium crystal diseases, familial chondrocalcinosis, acromegaly, and other disorders. (See 'Calcium crystals' above and 'Familial chondrocalcinosis' above and 'Acromegaly' above and 'Other' above.)

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- 136

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