

Preclinical Osteoarthritis

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Preclinical Osteoarthritis

Chapter 179

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Preclinical osteoarthritis (OA) is the early phase of the disease before abnormalities are apparent on a sensitive imaging modality such as ultrasound or magnetic resonance imaging.

The strongest evidence for the existence of preclinical OA is provided by the sequence of changes in biomarkers and pathologic stages observed after a major joint injury; this paradigm provides hope that these observations can be translated into diagnostic algorithms for the early detection of idiopathic OA.

Conventional OA risk factors function poorly for detection of preclinical OA.

Early diagnosis and intervention in OA would improve the likelihood of disease modification and thereby reduce medical costs, morbidity, and disability.

Reclassification of the disease as no longer a purely radiographic entity to a disease process that includes preclinical, preradiographic, and radiographic stages would provide a scenario amenable to the development of primary, secondary, and tertiary prevention strategies.

DEFINITION

Preclinical disease is defined as the very earliest phase of a disease process before it becomes clinically recognizable. Alternatively, it is the phase before the appearance of symptoms. For osteoarthritis (OA), clinically recognizable disease has generally been synonymous with the appearance of radiographic changes of OA, including joint space narrowing and osteophyte formation. With the advent of more sensitive imaging techniques, preradiographic stages of disease are recognizable; both magnetic resonance imaging (MRI)¹⁻³ and ultrasound^{4,5} have provided concrete evidence of structural joint abnormalities predating the quintessential radiographic changes associated with OA. These imaging techniques establish a new threshold for what constitutes definitive “clinically recognizable” disease.

It is currently difficult to define preclinical OA as the stage that predates symptoms for two reasons. For one, joint symptoms can be ascribed to multiple causes, and thus symptoms outside the context of the clinically recognizable structural changes of OA cannot currently be definitively diagnosed as being attributable to an OA disease process. Moreover, symptoms of OA wax and wane and might appear and disappear during the preclinical phase of OA, just as they do during the clinically recognizable phases of disease (see Chapter 173 for a discussion of the symptoms of OA). Until our understanding and diagnosis of the cause of early joint symptoms improve, this potentially waxing and waning symptom threshold abrogates our ability to currently define preclinical OA as a presymptomatic stage. Therefore, the focus of this chapter is on preclinical OA constituting the early phase of disease before OA-related abnormalities are detectable with MRI or ultrasound (or other sensitive imaging modality) ([Fig. 179.1](#)).

Of note, the “preclinical OA” described here should be distinguished from “preclinical models of OA,” which refer to animal models of disease⁶ and are discussed in Chapter 174.

EVIDENCE FOR PRECLINICAL OSTEOARTHRITIS

The World Health Organization defines chronic diseases as being of long duration and generally slow progression (www.who.int/topics/chronic_diseases/en/). Chronic diseases are characterized by complex causality, multiple risk factors, long latency periods, a prolonged course of illness, and functional impairment or disability (www.aihw.gov.au/chronic-diseases/). Many conditions can be considered chronic diseases, including coronary heart disease, chronic obstructive pulmonary disease, and osteoporosis. These chronic diseases are viewed as being amenable to preventive measures; such perception has led to the development of public health strategies to encourage healthy environments and lifestyles. For instance, it has led to efforts to control blood pressure and serum cholesterol levels to reduce the burden of heart disease and stroke. OA fits this chronic disease paradigm well. Such recognition that OA fits this chronic disease paradigm would be expected to broaden the scope of study beyond a focus on diagnosis, monitoring, and treatment of end-stage radiographic disease to include efforts to identify and characterize the preclinical and preradiographic stages to spearhead more effective endeavors to reduce the burden of disease.

The strongest evidence for the existence of preclinical OA is provided by the sequence of pathologic stages observed after a major joint injury. Unlike primary idiopathic OA, posttraumatic OA has a known time of onset, which makes it much more tractable as a method for detecting and monitoring preclinical OA. Based on longitudinal studies, intraarticular pathogenic processes initiated at the time of injury result in radiographic OA 10 to 20 years later.⁷ Longitudinal studies of the aftermath of severe joint injury have convincingly established the existence of a prolonged preclinical molecular phase of the disease characterized by protein and microRNA biomarker abnormalities.⁸⁻¹⁷ After knee injury, cartilage degradation is favored over repair, with increased collagen cleavage taking place.¹⁸⁻²⁰ Within the first month after joint injury in humans, elevations have been documented in the synovial fluid concentrations of cartilage proteoglycan fragments,^{8,20} metalloproteinases (MMP-3/stromelysin-1),^{10,13} tenascin-C,¹⁶ and collagen fragments.²⁰ Aggrecanase cleavage of aggrecan (at 392Glu-393Ala in the interglobular domain) is one of the early key events in arthritis and joint injuries.^{14,15} Elevations of cartilage components in serum can persist over decades after joint injury.⁹⁻¹³ The sustained increased release of cartilage macromolecular fragments after joint trauma is thought to be a harbinger for the development of posttraumatic radiographic OA in patients with injuries. Many of these fragments are not only biomarkers of early disease pathology but could themselves also

act to induce and prolong inflammation following joint injury^{16,21} and therefore represent biomarkers within the causal pathway of disease.

In the course of idiopathic (primary) OA devoid of a clear inciting severe acute injury, it is difficult to track the early events. Nevertheless, a few studies have identified premonitory alterations in biomarkers that herald the later appearance of idiopathic radiographic OA. In one study, patients in whom radiographic OA of the hand or knee developed 10 years later had significantly different serum concentrations of four proteins (increased MMP-7, increased interleukin-15, increased plasminogen activator inhibitor-1, and decreased soluble vascular adhesion protein-1) when compared with controls without radiographic OA in the ensuing decade.²² In another study, serum concentrations of the joint tissue components cartilage oligomeric matrix protein (COMP) and hyaluronan (HA) predicted the occurrence, 7 years later, of incident knee joint space narrowing (COMP and HA) and osteophyte formation (COMP).²³ Several studies have suggested that serum COMP predicts the development of radiographic hip OA between 6 and 8 years later.^{24,25} COMP is also increased in the absence of signs of radiographic hip OA in patients with symptoms of hip abnormality.²⁶ These biomarker abnormalities years before idiopathic radiographic OA support the existence of a preclinical phase of OA characterized by serologic abnormalities reflecting preclinical molecular alterations. The existence of preclinical OA is also suggested by the finding of macroscopically degenerated cartilage from cadaveric donors without a clinical history of OA.²⁷ Taken together, these studies demonstrate that metabolic alterations in articular cartilage occur long before radiologic changes are observed and support a chronic disease paradigm for OA that includes a preclinical phase as depicted in Figure 179.1.

DETECTION OF PRECLINICAL OSTEOARTHRITIS

About half the people with knee pain do not have radiographic OA.³ How might those with joint symptoms attributable to preclinical OA be discerned from those with joint symptoms resulting from some other cause? Attempts to identify preclinical OA and subsequent risk for clinically recognizable OA currently rely on a combination of conventional risk factors and the presence of cardinal signs and symptoms of OA. However, baseline conventional risk factors, signs, and symptoms have limited ability to predict subsequent incident radiographic OA 3 to 12 years later.^{28,29} For instance, the use of 10 diagnostic criteria in one study (age, sex, body mass index, previous injury, pain in the entire leg, difficulty descending stairs, palpable effusion, fixed flexion deformity, restricted knee flexion range of motion, and coarse crepitus) was poorly predictive of incident radiographic knee OA 3 years later, with an area under the receiver operating characteristic curve of just 0.59.²⁹ Another long-term (12-year) study that monitored

subjects with and without baseline clinical signs and symptoms of OA (crepitus, morning stiffness, knee bone enlargement, and age >38 years) but no baseline radiographic OA suggested an annual development of incident radiographic knee OA of 6.5% in the absence of clinical OA and 7.5% in the presence of clinical OA.²⁸ The limited prognostic ability of conventional risk factors is probably due in part to the fact that the progression from risk factor exposure to the development of radiographic OA depends on the variable likelihood that individuals exposed to the same risk factors will progress through the stages of preclinical OA to preradiographic OA to radiographic OA.

PROGRESSION OF OSTEOARTHRITIS

Since not all radiographic OA progresses to a severe grade of disease or results in joint replacement, by inference, probably not all preclinical or preradiographic OA progresses to more advanced stages of disease ([Fig. 179.2](#)).^{7,28,30} Several hypotheses are encompassed in the graphic in Figure 179.2 in which OA is depicted as a continuum (preclinical to preradiographic to radiographic). One, the rate of progression of OA accelerates with increasing severity of disease. Two, degradation and repair occur simultaneously at all stages of disease (small turning wheels reflecting turnover rates); the greater the degradation rate, the greater the synthetic repair required to meet the demands of the catabolic events (ever larger turnover cycles as the individual progresses further along the trajectory to OA). Third, an excess of catabolism over anabolism drives the trajectory to radiographic OA. Fourth, the mechanisms of progression will probably not be uniform in all OA phenotypes.³¹ Fifth, the proportion of at-risk individuals who proceed along the OA trajectory at any point in this continuum is uncertain.

Surprisingly little is known about the actual rates of progression through each stage. The rate of progression from preclinical OA to preradiographic OA is entirely unknown. In the specialized circumstance of severe acute joint injury, radiographic OA develops in 50% of individuals after an average of 10 to 20 years⁷; this equates to an estimated rate of progression during the preclinical stages of at least 2.5% to 5% annually. As described earlier, the rate of progression from the preradiographic phase to incident radiographic OA may be estimated from one study to be 6.5% to 7.5% annually in the absence or presence of symptoms.²⁸ The rate of progression from preradiographic to radiographic OA is estimated to be 2% to 19% annually based on calculations using data from the placebo arms of a number of studies summarized by Manno and colleagues³⁰ and shown in [Table 179.1](#); higher rates of progression were observed in subsets of subjects with a high symptom load. Further longitudinal studies are needed to provide more precise estimates of progression for each stage of disease and to understand how these rates may differ by patient subsets, joint type, and risk factors. The paradigm of joint injury in humans would seem to be the best place to start to gain such information.

TRIGGERING MECHANISMS

As proposed for other diseases,³² the action of additional potentiating "triggering" mechanisms in the presence of preclinical disease also influences progression to events or, in the case of OA, progression to preradiographic and radiographic OA. Given the waxing and waning nature of symptoms, there is every reason to believe that disease progression undergoes nonlinear or phasic progression; this has been supported by the observation that metabolic disturbances in cartilage turnover, as reflected by serum COMP concentrations, are phasic and elevated during periods of radiographic knee OA progression.³³ Molecular differences between the cartilages of different joint sites^{34,35}, and the generation of specific neoepitopes from joint tissues with metabolic disturbances suggest that biomarkers might be developed in future that reflect disease activity of specific joint types or even of OA specifically. Taken together, biomarkers indicative of joint tissue metabolism could constitute a means of detecting the preclinical molecular stages of OA in advance of preradiographic OA and assess the impact of specific triggering events.

With the recent recognition of a definite and central role for innate immunity in OA²¹ it is now possible to develop a holistic understanding of the pathogenesis of the disease process. From its inception, OA is an active disease process, not just a process of mechanical attrition, involving mechanical insults that activate mechanosensors to induce cellular responses to altered mechanical load, including the induction and activation of specific matrix degrading enzymes³⁶; this propagates inflammation through the generation of molecular fragments that act as disease associated molecular patterns to activate the innate immune response (Fig. 179.3) -- a major biologic transducer of disease progression. The cogwheel graphic in Figure 179.3, which symbolizes the ability of cogs to start and stop, portrays the penchant for OA to wax and wane. This representation shows the interaction of inciting mechanical insults and environmental factors, the potentiation by risk factors and genetics, and the resulting activation of an innate immune response and impaired wound healing³⁷ leading to the chronic disease process that we know as OA. Given this newly emerged understanding of the pathogenesis of OA, it is intriguing to speculate that a robust innate immune response would protect against infectious disease, particularly in the pre-antibiotic era, but be deleterious in potentiating age-related chronic diseases in our current postantibiotic era characterized by increasing longevity. There are in fact hints that the latter is true based on studies showing that low innate production of cytokines on *ex-vivo* stimulation of blood with lipopolysaccharide is associated with a lower risk for OA and the absence of OA in old age.^{38,39} Conversely, a robust repair response would be expected to protect from OA and prevent OA progression along the stages of disease (Fig. 179.2). The capacity for joint tissue repair differs by joint type^{35,40} and is likely a key determinant of OA prevalence and rates of progression. Data suggest a joint type specific gradient of repair

responses, with ankle>knee>hip repair capacity that would explain the rarity of severe ankle radiographic OA⁴¹ and the apparent greater rate of progression of hip versus knee OA (Manno³⁰). A better understanding of these differences could enhance our ability to identify at risk joints early in the disease development stage.

TREATMENT PARADIGMS

OA is a slow, insidious, and debilitating process that like other prominent chronic diseases, is probably more amenable to remission early in the disease process. Maintenance of cartilage homeostasis would be expected to halt progression of the disease. A tipping of the homeostatic balance in favor of anabolism over catabolism would be expected to reverse the disease. As noted by Luyten and coauthors,⁴² inactivation of inflammation and joint destruction would be sufficient in some patients at a very early stage of the disease; however, additional therapies targeting tissue restoration through cell proliferation and differentiation might be needed to achieve the ultimate goal of complete recovery of structural joint integrity. The pattern of biomarker alterations observed after joint injury matches the pattern of cartilage components released from cartilage stimulated *in vitro* with proinflammatory cytokines.^{20,43} Many treatments exist for *in-vitro* cartilage injury and suggest potential benefit. These biomarker observations provide great hope that disease-modifying therapies are within reach for early preclinical OA once it can be diagnosed reliably since there are already many known pharmacologic agents with chondroprotective effects in the cartilage explant model and acute injury animal models of OA.^{20,44}

POTENTIAL BENEFITS WITH EARLY DIAGNOSIS OF OSTEOARTHRITIS

Annual medical expenditures in the United States attributable to OA are estimated to be as high as \$185.5 billion, or 19% of the aggregate medical expenditures for the U.S. adult population.^{45,46} It is generally agreed that the prospect for early diagnosis and intervention in OA would improve the likelihood of disease modification and thereby reduce medical costs, morbidity, and disability. In this regard, OA fits the description provided by Machiavelli more than 500 years ago, "In the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."⁴⁷ A precedent for improved outcomes with early identification and treatment now exists for rheumatoid arthritis.^{48,49} This paradigm should help facilitate the approach to the diagnosis and treatment of OA.

SUMMARY

It is generally agreed that the early stages of OA would be more amenable to modification, including halting or slowing the disease process to prevent recalcitrant, disabling, and more costly late stages of the disease. Consensus, however, is needed for a new paradigm of OA that conceives of a pathologic continuum beginning with a preclinical stage; such a conception is the norm for other chronic diseases.⁵⁰ This would require reclassification of the disease from a purely radiographic entity to a disease process with a preclinical phase characterized by serologic abnormalities such as elevations of cartilage extracellular matrix components in body fluids, a preradiographic stage, and a radiographic stage. Just as not all radiographic OA progresses, it is likely that not all preclinical or preradiographic OA progress to later stages. To gain this information, more studies are needed to discern and monitor the disease process from its incipient to its end stages. The scenario of acute joint injury, with a known date of onset, provides a potential gateway to understand the preclinical stages of OA and offers the most promising context in which to elucidate the continuum of pathologic stages of this joint disorder. Ultimately, it will be important to establish the temporal relationship between changes in imaging markers and onset of symptoms and the molecular events that predate these manifestations of disease to achieve the goal of ultimately preventing and curing OA.

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Fig. 179.1

In this schema, osteoarthritis (OA) progresses through stages. Although tools for identifying preclinical OA are limited, events ensuing from acute joint injury attest to the existence of a relatively prolonged asymptomatic preclinical phase of OA before a preradiographic and, later, a radiographic stage. Each of these phases demands a different intervention strategy: the earliest preclinical phase with no apparent illness calls for primary preventive interventions to protect the health of the joint and prevent the appearance of clinically recognizable stages of disease; the

preradiographic phase of clinically recognizable but early disease requires secondary preventive measures to halt or slow progress of the disease, if possible, in its earliest stages; the radiographic phase of OA calls for tertiary preventive measures to prevent or reduce the illness of OA, namely the symptoms and disability in the face of a long-term health problem.

Fig. 179.2

At present, rates of evolution from preclinical to preradiographic to radiographic osteoarthritis (OA) are not precisely known. After a severe acute knee injury, the annual rate of progression in the preclinical phase of OA must be at least 2% to 5% annually to account for the overall average risk for development of radiographic OA of 50% by 10 to 20 years later⁷; under less extreme circumstances the rate is probably lower. Knowledge of rates of progression to radiographic OA from preradiographic OA are limited but may be estimated at 7% to 8% annually given the current information available.²⁸ The rate of progression of radiographic OA to more severe radiographic stages is estimated to be 2% to 19% annually based on calculations using data from the placebo arms of a number of studies (summarized by Manno and colleagues³⁰). These figures should be treated as rough estimates in need of refinement through future longitudinal studies with more comprehensive patient phenotyping of different joints and patient subtypes and sensitive imaging and biochemical markers.

Fig. 179.3

This model depicts osteoarthritis (OA) as a condition incited by the mechanical insults of microinjury, macroinjury, and environmental factors. The interaction of extrinsic inciting insults with potentiating intrinsic factors determines the relative susceptibility to progression of disease mediated by a biologic innate immune inflammatory response analogous to a chronic wound. The resulting pathology is manifested first as a preclinical (not clinically recognizable) entity, with progression in some individuals to preradiographic stages (detected by sensitive imaging modalities) and eventually to radiographic stages. The interacting cogwheels, able to turn intermittently, depict the penchant for OA activity to wax and wane. The exact timing of the onset of the illness of OA that includes symptoms in this continuum of OA pathogenesis is unclear at present.

TABLE 179.1
Summary of studies providing estimates of radiographic progression of osteoarthritis

Study (N in placebo arm)	Study duration (wk/yr)	Subjects with radiographic progression among those with baseline symptoms N progressors/N total (% progression; % per year)	All subjects with radiographic progression N progressors/N total (% progression; % per year)
Hip studies			
Echodiah (136)	156/3	30/52 (57.7%; 19.2%)	30/136 (22%; 7.3%)
Eradias (127)	156/3	24/46 (52.2%; 17.4%)	24/127 (19%; 6.3%)
Knee studies			
Pavelka (54)	156/3	3/14 (21.4%; 7.1%)	3/54 (6%; 2%)
Reginster (69)	156/3	12/26 (46.2%; 15.4%)	12/69 (17%; 5.7%)
Doxy (120)	120/2.31	16/37 (43.2%; 18.7%)	16/120 (13%; 5.6%)
Gait (50)	104/2	4/30 (13.3%; 6.7%)	4/50 (8%; 4%)
Kostar (625)	104/2	55/316 (17.4%; 8.7%)	55/625 (8.8%; 4.4%)
Stopp (163)	104/2	19/68 (27.9%; 14%)	19/163 (11.7%; 5.8%)

Progression is defined as change in joint space width greater than 0.5 mm by study end.

Data derived from Manno RL, Bingham CO 3rd, Paternotte S, et al. OARSI-OMERACT initiative: defining thresholds for symptomatic severity and structural changes in disease modifying osteoarthritis drug (DMOAD) clinical trials. *Osteoarthritis Cartilage* 2012;20:93-101.

Osteoarthritis Continuum and Treatment Paradigm





