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Identifying and Treating Pre-Clinical and Early Osteoarthritis

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Synopsis

Osteoarthritis is the most common form of arthritis and nonsurgical treatments of disease have limited efficacy. Studies suggest, at least for disease in the knee, that most persons with painful OA already have extensive structural disease including malalignment, which may preclude successful stabilization or reversal of disease. This provides a strong rationale for developing strategies to prevent disease or to identify and treat it early. A variety of approaches, reviewed here, are likely to capture those at high risk of or with early disease; imaging techniques offer great promise of characterizing structural changes before they are irreversible. However, given the absence of effective treatments, it is unclear whether structural disease could be successfully slowed or prevented in those with early symptoms or those at high risk of disease.

Keywords

osteoarthritis; knee pain; magnetic resonance imaging; biomarkers

Introduction

Osteoarthritis (OA) is the most common form of arthritis. While prevalence estimates differ depending on the country and how disease was assessed, OA clearly affects millions of persons in the United States and a similar number in Europe. In developing countries it is also the most common form of arthritis. Osteoarthritis prevalence increases with age and with obesity, and the rapidly increasing demand for knee and hip replacements is due in part to the burgeoning population of those with OA because of the aging of the population and increasing rates of obesity. OA is the most common cause of mobility disability in the world and its overall impact as a cause of years lived with disability and limited quality of life is rising (1).

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One of the central reasons for the increase in demand for knee and hip replacements is that medical and rehabilitative treatments for OA are not terribly effective. There are no treatments, which have been shown consistently to delay the structural progression of disease, and none are approved by regulatory agencies for this purpose. Meta-analyses suggest that nonsurgical treatments such as exercise, anti-inflammatory medications and others all have modest efficacy at best. New more effective treatments for established disease are badly needed.

One major reason why treatments are not delaying joint replacement surgery may be that treatment begins too late in the course of OA to have an effect. Many of the structural findings uncovered in recent comprehensive cohort studies of persons with knee OA have suggested that most persons with disease have advanced structural findings in the knee by the time they are clinically diagnosed and have frequent knee pain. Varus or valgus malalignment, meniscal damage such as tears and prevalent cartilage loss are all common features of middle-aged and older persons with new onset chronic knee pain (2). X-ray evidence of OA is a relatively late phenomenon in the structural evolution of this disease. For example, alterations in the shape of the periarticular bones often precedes the development of radiographic disease by 5-10 years (3). MRI abnormalities are present several years before disease development in most cases. Many of these structural changes are not known to be reversible and, to the extent they drive disease progression, a patient presenting with knee pain is often on the downslope of that trajectory.

A recent focus on changes in the peripheral and central nervous system that develop as part of osteoarthritic pain suggests that nervous system related changes have also occurred in many persons by the time they develop the chronic pain of OA. These nervous system changes make treatment more challenging and pain more severe than might have occurred had the disease been identified and treated earlier (4).

Therefore, the rationale for focusing on early OA is that irreversible structural changes may not yet be established and that chronic nervous system sensitization to pain has not yet evolved. To target early OA, the choice might include those with early disease vs. those at high risk of disease who do not yet have symptoms or early disease.

The evolution of OA from the earliest evidence of joint injury to end-stage disease is shown in Figure 1. Early osteochondral lesions are usually unaccompanied by symptoms in middle-aged and elderly persons. Even meniscal tears which are common and occur incidentally are often not associated with knee pain or other symptoms (5). The initial defect in cartilage or initial meniscal tear or extrusion is followed by a constellation of features including more damage in the initial location leading to asymmetry of the joint and malalignment, bony remodeling and damage to adjacent tissues (6). For example, an incidental meniscal tear puts a knee at high risk of adjacent cartilage damage and of meniscal extrusion. There is tissue loss between the two bones and narrowing of the joint on that side, initially to a subtle degree that is not visible on the x-ray. First symptoms occur only after this process is far advanced and are mild and intermittent. The patient usually does not seek care until symptoms including pain are more troublesome or frequent. By the time symptoms are present, roughly 80% of knees have clinically important frontal plane malalignment (varus

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or valgus) and even knees without frontal plane malalignment often have patellofemoral malalignment. This malalignment increases stress or focal loading across the affected region of the joint. Cartilage loss and/or meniscal damage is the rule (7).

Other features of disease that can coexist at the time include ligamentous laxity, proprioceptive deficiencies, muscle weakness and synovitis. While some of these such as muscle weakness and synovitis may be amenable to therapy, for others there is no known therapy. Thus, for early treatment approaches to be successful at least for knee OA, patients need to be identified at a point prior to the development of meniscal damage, substantial cartilage loss or malalignment. Waiting for x-ray evidence of disease for diagnosis is almost certainly too late since many of the irreversible structural findings accompany x-ray changes. Ideally, an approach that either targets those at high risk who are willing to consider preventive therapy or those with very early disease constitute the most likely route for success.

Risk Factors: Identifying those at high risk of early OA

Age—The major risk factor for OA is older age (8;9). In all joints and among both genders, OA prevalence increases steeply with age starting at around age 50 or 55. A multitude of factors contributes to this increase including the senescence of cartilage leading to its fragility (10), the failure of periarticular structures which provide protection against joint damage during weight bearing, including increasing muscle weakness with age, neurosensory failure with age, and ligamentous laxity. Because of these changes many of which are age-related and the challenge in reversing them, targeting early OA may need to focus on persons in middle age who may be at high risk of developing OA earlier than expected. Since knee and hip replacements are often reserved for older persons, early onset of OA when a person is in their 30's or 40's poses special therapeutic challenges, and payoff for any prevention strategy may be great.

Obesity—Obesity plays a major role in increasing the risk of OA of the knee and, to a lesser extent, the hip. Jiang et al (11) have suggested that eliminating the problem of obesity might prevent up to 50% of knee OA in the United States and a lesser proportion in countries where obesity is not as prevalent. Effects of obesity in causing OA may be complex. Obesity not only increases the risk of knee and hip OA but increases the risk of hand OA too, suggesting that its effects on disease are not completely mediated by effects on mechanical load. Indeed, adipokines have been linked with OA occurrence, although there are no clear-cut data yet suggesting that the effects of leptin or other adipokines are independent of the loading effect of weight. Convincing evidence demonstrating the role of adipokines might point to an opportunity for slowing the rate of progression of disease in those who are obese.

Gender—Women are at substantially higher risk of OA than men in all joints except the hips. Women are more likely than men to get structural disease in their joints and for a given level of structural disease, women are also more likely to have joint pain (12). While women have higher rates of OA than men, this gender difference does not develop until the sixth decade, when women have just gone through or are going through menopause. This has

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obviously raised questions about whether estrogen or hormonal loss triggers OA, a matter yet unresolved despite many studies.

Traumatic joint injury—Among the most potent risk factors for OA is major injury such as from sports leading to an anterior cruciate ligament or meniscal tear. In the knee, such major injuries account for approximately 10% of all OA, but in joints that are rarely affected by OA such as the ankles, injuries account for more than 70% of OA cases (13). Meniscal damage, including tears and extrusion, has been consistently shown to be among the most potent risk factors for later development of OA. Even incidental tears with no recollected injury pose a very high risk of later disease and a partial meniscectomy does not necessarily reduce this risk. Similarly ACL tears even without concomitant meniscal tears increase the risk of OA later, and surgical treatment does not appear to lessen that risk.

Injuries like ACL and meniscal tears may represent a special opportunity to prevent OA. They happen in young persons whose joints are otherwise normal without the coexisting pathomechanics and bone shape alterations that typify clinical OA. Animal studies (14) have identified a superhealer strain of mice that, faced with traumatic joint injury, heal without arthritis. Characteristics of these mice include a blunted inflammatory response suggesting that prolific inflammation may be a major cause of permanent joint damage after an injury and that ablating this inflammatory response may lessen the ultimate joint damage. There are ongoing trials testing whether disease can be prevented by administering potent anti-inflammatory treatments early after either ACL or meniscal tears.

In the knee, frontal plane malalignment (see Figure 2) either in the varus or valgus direction is a major cause of disease progression. Usually malalignment develops as a consequence of disease when cartilage loss or meniscal extrusion narrows one side of the joint. However, even among normal pre-diseased knees, there is a modest variation in alignment status and some normal people have varus or valgus knees without any pre-existing knee damage. Recent studies (15;16) have shown definitively that pre-damaged knees with malalignment are at modestly increased risk of developing OA. This is probably because such knees experience increased focal loads at the site of malalignment and these loads ultimately lead to tissue breakdown, especially as a person becomes older and their intra-articular soft tissue becomes more fragile.

The hip and congenital abnormalities—The hip is a special case in which joints at high risk of OA may be readily identified. A large percentage of hip OA cases occur on the background of preexisting anatomic abnormalities. These abnormalities include hip dysplasia, which, when severe is detected and corrected at birth but when present on a mild basis often persists into adulthood. Other developmental abnormalities include slipped capital femoral epiphysis (SCFE) and Legg-Perthes disease which occur more commonly in boys than girls. Lastly, recent years have seen the identification and characterization of the major hip anatomic abnormality, femoroacetabular impingement (FAI) which (17) clearly predilects to later hip OA. FAI has two often coexisting subtypes, CAM deformity and pincer deformity, the latter more common in girls. Cam deformities may arise before the closure of the epiphysis and be brought on by athletic or other activities. FAI symptoms may occur in teenage years or early adulthood and may be correctable with osteotomy surgery,

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although the efficacy of this surgery is yet to be proven. Such surgery, if effective, might prevent OA from developing later.

Genetic risk—After combining data from multiple large scale studies of OA in which genetic material was obtained from subjects, Loughlin and colleagues (18) uncovered a set of genetic abnormalities associated with an increased risk of OA, most prominently among them an abnormality in the gene GDF5. Neither GDF5 nor other genes currently identified as predisposing to OA is associated with a high risk of disease; One compelling hypothesis is that these genes increases the risk of disease by altering joint shape (19) and if so, they may inform us of joint shapes that predispose to later OA and help to identify persons at high risk of OA. The genes so far identified are more commonly associated with joint-specific than generalized OA.

The role of inflammation in OA—Inflammation is a clearly a component of OA whether defined as the presence of inflammatory cytokines in joint tissues such as cartilage matrix, synovial fluid or as histologic evidence of synovitis which is present variably in OA knees and hands (20;21). While present in most joints with OA to some extent, the impact of inflammation on OA joints is not clear, as any effects in clinical OA may be overwhelmed by disease mechanopathology. Synovitis clearly increases the risk of joint pain and its severity (21) and it is likely that inflammation within the joint contributes to pain sensitization which occurs in many persons with chronic OA (4). There is however, no consistent evidence that synovitis leads to cartilage loss independent of other structural findings that drive this loss (e.g. meniscal tears). And studies consistently show that persons with radiographic OA do not have elevated systemic levels of acute phase reactants (22-24). Trials testing different anti-inflammatory approaches for OA, many used in rheumatoid arthritis, are ongoing.

The Feasibility of Identifying Early OA

A number of strategies have been tested to determine whether they can successfully identify persons with early OA. The best tested is to examine persons with a few months of knee pain at a point when their x-rays are either normal or show only very mild disease and follow them to determine if they are likely to develop OA and whether there are any predictors that might identify those who do develop disease. Of two such studies, one with only a 3-year follow-up found that 42% had incident radiographic OA at follow-up and reported that there were no factors that identified persons at highest risk (25). On the other hand Thorstensson and colleagues (26) followed 143 subjects with limited history of chronic knee pain and found that 86% developed radiographic OA over 12 years. In work from the Framingham Study (27), those with unilateral knee OA had a >90% likelihood of developing OA in the contralateral knee over a 10-year follow-up and most of those contralateral knees that developed OA were also frequently painful. These data collectively suggest that chronic knee pain accurately identifies middle-aged persons at high risk of later OA, although that disease may not develop right away and that those with unilateral disease are at extremely high risk of developing bilateral disease. In these studies, developing OA is defined as developing an x-ray positive for OA and, as noted earlier, radiographic positivity is a relatively late feature of disease.

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MRI findings suggestive of OA are present in the majority of middle-aged persons with chronic knee pain including even the majority of those whose x-rays do not show OA (28). In a study of 255 persons drawn from the community with knee pain, 124 or 49% had negative x-rays but clear-cut evidence of OA by MRI. Thirty-eight percent had radiographic OA and only 13% or 33 subjects had no OA by either imaging modality. Thus, either chronic knee pain alone or knee pain coupled with MRI findings suggesting OA (e.g. cartilage loss) might accurately identify early disease. The salient concern is whether even these pre-radiographic MRI-based findings are early enough that treatment can prevent further damage.

Special High-Risk Groups

There are unique groups at especially high risk of OA who might be excellent targets for disease prevention. Among these are young people who have sustained major knee injuries including those with meniscal or anterior cruciate ligament tears. Such persons are at extremely high risk of developing OA within 10-20 years and their disease evolves often by the fourth decade or even earlier. Because inflammatory response to the injury may drive some of the later destructive joint changes, exciting opportunities to prevent disease may include suppressing the inflammatory response to the injury as suggested by animal models of disease (see earlier).

As noted earlier, hip OA is often preceded by a variety of pre-arthritic anatomic abnormalities.. Surgery to correct these developmental abnormalities including FAI could prevent later hip OA, although there is currently no evidence that correction of the abnormalities actually does. Identification of factors that prevent the development of these abnormalities could ultimately prevent the later development of disease too. Thus hip anatomic abnormalities offer a special case where early changes that predispose to OA might be prevented.

Other at-risk persons include those who come from families where there is a high risk of OA. Commonly, these are families with an inheritance of joint specific disease----hip OA or thumb base OA, etc. Unusually, there are families with generalized disease where a young person not yet affected is at high risk of developing disease, especially if they carry the gene that predisposes to disease. Most genetic factors identified so far do not increase the risk of disease sufficiently to characterize persons with these genes as at high risk (18;29). However, like in rheumatoid arthritis, persons carrying a combination of genes each conferring a modest increased risk of disease are at high risk of disease.

Another opportunity for disease prevention is available in persons who present with one joint affected with OA. Their risk of developing disease in other joints, especially the contralateral as yet unaffected joint, is high. To the extent that prevention strategies can be developed, these persons are certainly at risk and would benefit from such opportunities.

Imaging Approaches to Identify Persons with Early Disease

Imaging techniques have become available to detect the earliest changes in cartilage that might represent compositional alterations of early disease. The use of these techniques assumes that disease begins in cartilage. We now recognize (10) that the process of disease

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even early on clearly involves an interplay between cartilage and other structures within the joint and that all of these are acted upon by loading, with levels of excessive focal loading often driving the process. Even so, to the extent that cartilage plays a role in its own destruction or that abnormalities within cartilage provide evidence that abnormal loading is causing damage, imaging that detects subtle cartilage abnormalities may provide strong evidence that early OA exists regardless of cause. Imaging of intra-articular structures such as cartilage, synovium and bone can show early evidence of disease before the irreversible pathomechanics of disease are established.

An appreciation for the information provided by imaging necessitates a brief exposition of cartilage biology. The two major molecular components of cartilage are type II collagen which provides the skeleton of cartilage and aggrecan, a macromolecular aggregate consisting of a core hyaluronic acid molecule surrounded by glycosaminoglycan (GAG) side chains that are highly negatively charged. The GAG molecules are covalently bound through link proteins to the hyaluronic acid; when cartilage is compressed, the electrostatic repulsion that ensues derives from these negative charges being forced into close proximity. When this pressure is released, the electric charges can dissipate. The negative charges from GAGs in aggrecan provide cartilage with its compressive stiffness.

The process of aggrecan degradation is mediated by two enzymes, ADAMTS4 and ADAMTS5, with the latter probably the more important. In contrast, collagen degradation is mediated by a series of matrix metalloproteinases, especially 1, 8 and 13 with the last of these being critical. In terms of early disruption of cartilage matrix, the loss of aggrecan is almost certainly reversible whereas the loss of collagen matrix is not (30). With the loss of aggrecan comes a loss of compressive stiffness, a physical softening of cartilage and a tendency for that local area to swell as it imbibes proton ions from water. Imaging or other physical diagnostic tests that depend on measuring softness or local swelling might successfully identify early compositional changes in cartilage that are reversible, as might attempts to detect a depletion of negative charges that especially occur in cartilage after aggrecan depletion.

While conventional magnetic resonance imaging is clearly superior to radiographs in revealing evidence of damage to intra-articular structures such as cartilage and menisci, conventional MRI does not generally reveal compositional changes in these tissues. It only shows evidence of damage to the tissues when cartilage has been worn away or menisci torn. Techniques have been developed, especially using magnetic resonance imaging, that identify regional abnormalities within cartilage based either on the disruption to their collagen network or to loss of aggrecan.

When aggrecan is depleted, the high concentration and negative charges becomes less homogeneous and diminishes in some regions. MRI techniques which take advantage of this heterogeneity and the depletion of GAGs and their negative charges within regions of cartilage can successfully identify regions of compositional damage (31).

The best validated of these is delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC). dGEMRIC involves measuring the T1 relaxation time of cartilage

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some time (typically 90 minutes) after the intravenous injection of Gd-DTPA contrast agent. Since both the Gd-DTPA and the proteoglycans are negatively charged, the concentration of gadolinium in cartilage depends on proteoglycan content. As gadolinium reduces the T1 relaxation time, a T1 map acquired after administration of Gd-DTPA should be related to the proteoglycan content.

In-vivo dGEMRIC of autologous chondrocyte implantation cartilage has been validated against GAG concentration of biopsies [1]. In OA, in-vivo dGEMRIC has been shown to correlate well with GAG content measured after joint replacement [2][4]. dGEMRIC of ex-vivo cartilage specimens from patients with OA correlates with GAG content [4, 5] better than morphologic measures [6], although the applicability of ex-vivo results is limited. Results comparing dGEMRIC with arthroscopic findings have been mixed [3, 7, 8]. The reproducibility of dGEMRIC measurements has been high in healthy volunteers, patients with early OA, and patients with a history of ACL injury [9-12].

dGEMRIC differentiates between normal and osteoarthritic cartilage and correlates with severity of disease [13, 14]. It may also predict the development of OA changes [15, 16]. Changes have been demonstrated in association with meniscal pathology [17, 18], acetabular dysplasia [19], FAI [20, 21], anterior cruciate ligament injury [18, 22, 23] and patellar dislocation [24]. Improvement in dGEMRIC values has been seen in patients after weight loss [26], collagen hydrolysate [27] and exercise [28, 29]

In sum, dGEMRIC is a reproducible technique, which can be implemented on standard clinical MRI scanners. It depends on the proteoglycan concentration and is therefore potentially useful in early OA. Unfortunately, it is practically challenging; it typically requires a double dose of gadolinium based contrast agent, which is already implicated as a cause of serious although rare adverse events. Further, one cannot image a joint immediately after gadolinium injection but rather, for knees at least, the patient needs to walk around for 90 minutes to allow the gadolinium to diffuse into cartilage. The type and duration of activity may affect the results of the scan since dGEMRIC is probably influenced by other factors in addition to proteoglycan concentration, such as transport mechanisms and cartilage thickness, although in early OA these may act synergistically to increase its sensitivity [30, 31].

Given the inconvenience and possible risk of gadolinium as a contrast agent, other approaches have been developed that offer promise in the evaluation of early cartilage injury but that have not been as well validated or studied as dGEMRIC.

T2 measurements of articular cartilage have been widely used in clinical studies of osteoarthritis, including the large Osteoarthritis Initiative study. Measurements are straightforward and relatively fast to acquire using multiple echo spin-echo sequences.

T2 has been linked to collagen, proteoglycan and water content [32-36]. Its reproducibility has been high in OA patients and normal controls [37, 38]. T2 is increased in osteoarthritis, including early OA and is related to OA severity [39, 40]. It has been shown to predict radiographic OA [41], however the relationships between T2 increases and subsequent cartilage loss, although statistically significant in at least one study, are inconsistent and

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weak. T2 is increased in a variety of conditions including FAI [42], anterior cruciate ligament injury [43] and after partial meniscectomy [44].

Although straightforward to measure and used in many clinical studies, the disadvantages of T2 are its complex and incompletely understood dependence on underlying structure and composition, and the change in measurements with orientation due to the magic angle effect. Furthermore, if T2 mapping predominantly reflects disruption or destruction of collagen, then T2 mapping may not be ideal for assessing reversible cartilage disease, since once collagen is destroyed, the matrix is thought to be irreversibly damaged.

T1-rho has been advocated as a measurement, which is more sensitive to GAG concentration than T2 (and hence better for assessing early OA) but which does not require intravenous contrast. T1-rho is the relaxation time under the influence of a spin-lock pulse and is calculated from multiple images acquired with different spin-lock pulse durations.

Several studies have demonstrated a correlation between T1-rho measured in vivo and GAG measurements after joint replacement in OA, although the strength of the correlation has differed [34, 35, 45]. Correlations have also been shown with macroscopic grade of cartilage damage [45, 46]. Reproducibility of T1-rho measurements has been variable [38, 47].

T1-rho has been shown to be increased in OA, including early OA [39, 48] and to increase with disease severity [40, 49]. It also predicts the progression of morphological changes [50]. T1-rho is increased in the presence of FAI [42], patellar maltracking [51], anterior cruciate ligament injury [43] and meniscal injury [52]. Progression has been demonstrated after anterior cruciate ligament reconstruction [43] and partial meniscectomy [44].

A number of studies have looked at both T1-rho and T2 measurements. Although outcomes from both have often been broadly similar, T1-rho may be more sensitive with larger changes [35, 39, 46, 48, 53], however this may be partly offset by poorer reproducibility [38].

T1-rho therefore has the advantage it may be more sensitive than T2 for assessing early cartilage change and, unlike dGEMRIC, it does not require intravenous contrast agent. Its disadvantages include sensitivity to field inhomogeneities which make it technically challenging and time consuming.

Sodium MRI is an attractive means of assessing early cartilage change in osteoarthritis because the positively charged sodium ions map to negatively charged GAGs. Because the sodium nuclei resonate at a lower frequency than the hydrogen nuclei at a particular magnetic field strength, different hardware, including a different radiofrequency coil, is required. Signal from sodium is inherently very low so images are of low resolution and time consuming to acquire.

In vitro sodium imaging of cartilage has shown good correlation with GAG measurements [54, 55]. Reproducibility has been demonstrated in healthy volunteers and OA patients [56, 57]. Sodium MRI of cartilage has shown differences from controls in OA including early

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OA [58]. It has been used to study cartilage repair tissue [59] and correlates strongly with T1-rho [60] and dGEMRIC [61].

Sodium imaging has the advantage of being a more direct measure of GAG content. However it is technically challenging, requires high field strengths and specialist hardware and has the major limitation of low signal-to-noise and hence resolution.

Glycosaminoglycan chemical exchange saturation transfer (gagCEST) imaging makes use of the hydrogen nuclei of amide and hydroxyl groups in GAGs which resonate at a slightly different frequency to those of water. Although these cannot be imaged directly, they can be saturated by a radiofrequency pulse at the appropriate frequency; this saturation is then transferred to nearby water protons, reducing the signal from the bulk water which forms the image. Static and radiofrequency field inhomogeneities make the technique technically challenging, particularly at lower field strengths, and gagCEST is often performed at 7 Tesla. gagCEST has been shown to correlate well with sodium imaging in patients who had undergone cartilage repair surgery [62]. Although not yet widely used, gagCEST may be useful in early osteoarthritis as it offers the potential to map GAG content at higher resolution than sodium imaging. However it is technically demanding and will probably require high magnetic field strengths.

Future Considerations/Summary

Identifying those at high risk of or with early osteoarthritis may offer an opportunity to successfully intervene to lessen the burden of disease on patients and society. Those with chronic joint pain but with no x-ray features of osteoarthritis and those drawn from high risk groups with imaging studies suggesting early structural changes of disease may be good candidates for treatment. Future studies need to test strategies to treat these persons and to identify who, among them, would most benefit from any treatment.

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Key Points Box

- The limited efficacy of current nonsurgical treatments for osteoarthritis may be due partly to their use at a late point in the evolution of disease when structural deterioration is often advanced. This provides a rationale for identifying persons with early disease or those at high risk.
- Persons at especially high risk of later disease who would be good targets for treatment are those with sports-related major knee injuries, those with anatomic abnormalities of their hips associated with a high rate of later OA and those from families with an unusually high risk of early disease.
- Chronic knee pain is a harbinger of knee osteoarthritis.
- Evolving imaging approaches using magnetic resonance imaging hold promise in identifying joints with reversible structural findings that represent early lesions of OA.

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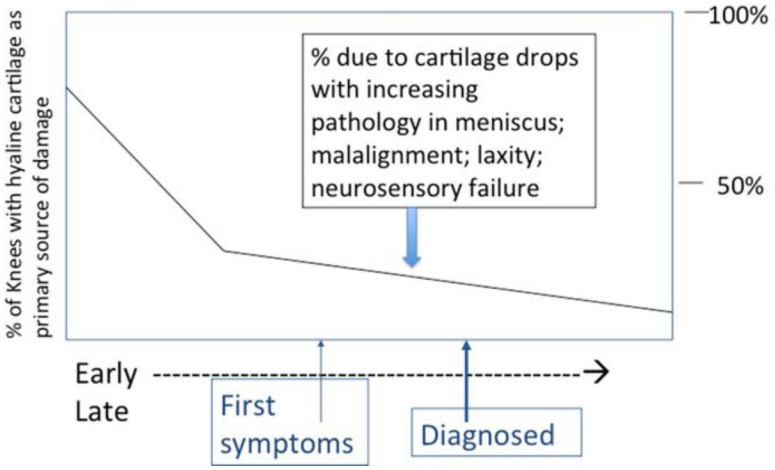

Figure 1. Source of Joint Damage by Stage of Osteoarthritis Development

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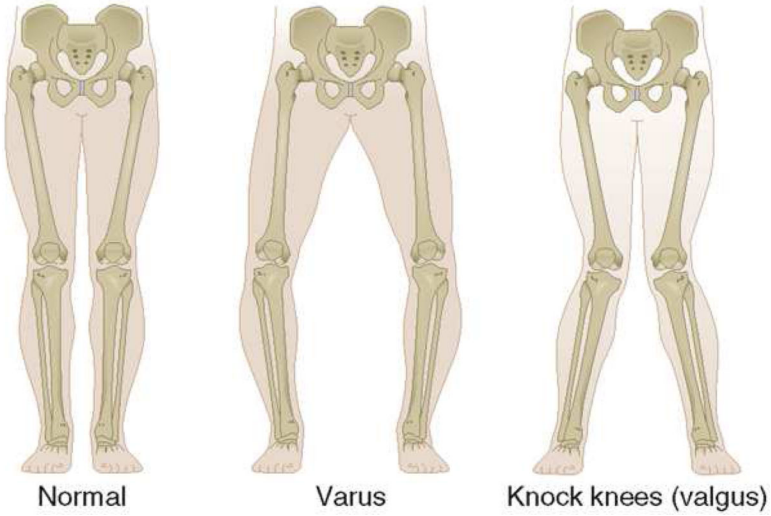

Figure 2.

Different frontal plane alignments. Varus and Valgus alignments increase stress across medial and lateral knee compartments respectively.