



Significance and definition of early knee osteoarthritis

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Abstract: Osteoarthritis (OA) is a degenerative joint disease that causes joint dysfunction due to pain and restricted range of motion and it causes lowering of physical activity and the quality of life and results in a significant effect on the global burden of disease. Early diagnosis of OA in the knee joint is critical for effective treatment before facing severe irreversible pathology, and to develop new OA treatment techniques. Discussion on defining early OA has become more globally active. In this review, two proposals of the definition of early knee osteoarthritis, the Italian Rheumatology Association International and the First International Early OA Workshop proposed are introduced. These definitions of early OA have been proposed with a combination of “symptoms” of joint pain, “signs” such as joint stiffness, tenderness, or risk factors, and diagnostic imaging such as radiographs. Consensus on a more detailed classification and validation of the proposed definition of early OA are necessary to develop new treatment methods to suppress or prevent symptoms at an early stage before any progressive and irreversible change. Diagnostic imaging techniques such as MRI and ultrasound are superior compared to X-ray for visualization of soft tissues of joints and quantification of physical activity will become a key for the evaluation and development of new treatment strategies for early stages of osteoarthritis in the near future due to the fact that the structural and qualitative abnormalities of joints directly affect physical activity, and improvement of that will be the primary outcome of treatment for osteoarthritis in society.

Keywords: Early knee osteoarthritis; definition; intervention; medical device; exercise

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Significance of osteoarthritis (OA) in the global society

OA is a degenerative joint disease that causes joint dysfunction due to pain and restricted range of motion, that could result in lowering physical activity and the quality of life. Physical inactivity caused by OA is one of the global leading health risks of non-communicable diseases (NCDs) (1,2). Although many joints such as shoulder, elbow, wrist, spine, hip, knee, and ankle can be affected by OA, the knee joint is one of the most common and vulnerable joints among them.

The prevalence of knee OA increases with age and becomes prevalent within older adults. Roentgenographic knee OA of Kellgren-Lawrence II or higher in Japan is 35.2% for male and 57.1% for women at 60–69 years old, 48.2% for male and 71.9% for female at 70–79 years old, and 61.6% for male and 80.7% for female at the age of 80 or older (3). Although OA is considered one of the most common musculoskeletal disorders worldwide in recent years, the prevalence of OA was historically as low as 0.8% in male and 5.2% in female in the 1700–1800s, and it increased by 2.1 times in the mid-1900s (3). The reason for the increase in OA prevalence is not apparent since this

phenomenon was even observed in the adjusted age and BMI (4).

In addition to the decrease of physical activity, it is known that 42% of OA patients are depressed and has relations to mental disabilities (5). Approximately one out of ten OA workers were absent from work, and approximately seven had presenteeism with the depressive symptoms being more severe (6). OA is thus known to cause not only physical disabilities but also mental and social dysfunction and has a significant effect on the global burden of disease (7,8).

Significance of defining early knee osteoarthritis

The American College of Rheumatology (ACR) has developed criteria for the classification of OA of the knee and hip, mainly in order to promote uniformity in reporting OA in epidemiological and intervention studies. These criteria were developed

using combinations of clinical, laboratory, and radiographic criteria (9,10). These criteria were developed primarily for epidemiological purposes rather than for clinical use and are presumably mainly diagnostic for evident late-stage OA.

Since there have been no disease-modifying OA drugs (DMOADs) that can alter the development or pathology of OA, pharmaceutical therapy for symptomatic OA is being conducted not for joint disorders and consequent biomechanical changes, but the reduction of pain. Since long-lasting pain has been known to cause pain sensitization, which may make it difficult to treat pain effectively, early diagnosis and treatment are considered as a key. The effect of an exercise intervention on OA has been demonstrated (11,12), and patient education and weight control are also recommended for effective treatment (12). Since OA develops and deteriorates over time, it means that there is a wide window of opportunity to alter its developing course potentially. OA progression may be prevented (secondary prevention) or can be delayed through diagnosis at an early stage before the joint is irreversibly destroyed. When OA is treated appropriately at an early stage in which pathology of OA is still reversible, therapeutic or exercise treatment may be valid to stop progression or even heal OA. From the prevention and treatment aspects, a clear definition of early OA is paramount for diagnosis.

Thus, in order to discover and bring new OA treatment into practical use, further researches to demonstrate the usefulness of new drugs, medical devices, regenerative medicine, exercise intervention, and patient education for

secondary prevention before reaching severe OA are vital. It is important to diagnose early OA additionally for the development of new OA treatment technology as well.

Definition of early knee joint OA

As described above, the early diagnosis of OA in the knee joint is critical for effective treatment before facing severe irreversible pathology, and to develop new OA treatment techniques. Therefore, discussion on defining early OA has become more globally active (13-18), and this paper will introduce two recent ones of them.

Definition of early OA advocated by the Italian Rheumatology Association International Initiative (17)

A systematic review and three focus groups (6 expert clinicians of rheumatology, 5 female OA patients, 6 OA basic researchers), two discussion groups which consisted of 29 international experts in rheumatology, internal medicine, physical medicine, epidemiology from Albania, Belarus, Bulgaria, Croatia, France, Italy, Portugal, Romania, Russia, Serbia, Spain, Turkey, followed by a Delphi survey, ending in face-to-face workshop method were conducted in 2014 in Milan. Early symptomatic knee OA (ESKOA) was defined in the presence of (I) two mandatory symptoms (knee pain in the absence of any recent trauma or injury and very short joint stiffness, lasting for less than 10 min at the start of movement) even in the absence of risk factors, or (II) knee pain, and 1 or 2 risk factors or (III) three or more risk factors in the presence of at least one mandatory symptom, with symptoms lasting less than 6 months without active inflammatory arthritis, generalized pain, Kellgren-Lawrence grade >0, any recent knee trauma or injury, and less than 40 years of age.

Definition of early OA by the First International Early OA Workshop (18)

In November 2014, the first international early OA workshop was held in Tokyo. A research group with a total of 85 people that consisted of basic scientists, clinical scientists, rheumatologists, orthopedic surgeons and physiotherapists gathered, and early OA classification and draft standards were considered. In this workshop, after the introduction of related topics and discussion with the subcommittee, the following three classes of criteria were agreed upon: (I) pain, symptoms/signs, self-reported

function, and quality of life using tools such as KOOS: scoring $\leq 85\%$ in at least 2 out of these 4 categories; (II) clinical examination: at least 1 present out of joint line tenderness or crepitus; (III) knee radiographs: Kellgren & Lawrence (KL) grade of 0 or 1. Although there were discussions regarding MRI, it was not adopted as a criterion of early OA from the fact that there were no established consensus standards at that time. Biomarkers were also thought to be useful in the classification of this disease in the future, but the poor level of evidence made it so that it was decided not to be included in the criteria.

Future prospects for early OA

Several years have passed since the definition of early OA were started to be discussed globally, and several proposals have been put out. Definition of early OA with a combination of “symptoms” of joint pain, “signs” such as joint stiffness, tenderness, risk factors, and diagnostic imaging such as radiographs have been proposed. Knee osteoarthritis is a degenerative disorder of articular cartilage and includes the pathology of wide tissues such as the meniscus, synovial membrane, subchondral bone constituting the knee joint, ligament, joint capsule, tendon, and muscle. These integrated structural and qualitative abnormalities interfere with joint function, motor function, and physical activity. Furthermore, OA creates a burden both mentally and socially as well as physically and is recognized as a high global health risk causing NCD (19,20).

Consensus on a more detailed definition and classification of early OA is necessary to develop new treatment methods to suppress or prevent symptoms at an early stage before any progressive and irreversible change. Diagnostic imaging techniques such as MRI and ultrasound are superior compared to X-ray for visualization of soft tissues of joints, and quantitative evaluation of these two have been recently developed and become available. Japan has the highest number of MRI equipment adoption in the world, which makes an ideal clinical setting for evaluation of OA pathology. It also makes it possible to quantify physical activity directly as well. Recently developed wearable devices such as an accelerometer with a wireless reporting system can be used to measure physical activity quantitatively and will become a powerful tool to obtain joint biomechanics and physical activity in large scales to create big-data (21,22). Quantification of exercise and/or physical activity will be key for the evaluation and development of new treatment strategies for early stages of arthritis in the near future, due

to the fact that the structural and qualitative abnormalities of joints directly affect physical activity, and improvement of that will be the primary outcome of treatment for osteoarthritis in society.

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