INTRODUCTION

Osteoarthritis (OA) is a progressive and irreversible loss of the cartilaginous joint due to biological, chemical, and viscoelastic changes to the cartilage, synovium, subchondral bone, and synovial fluid. Articular cartilage deterioration and ongoing discomfort are features of osteoarthritis, resulting in disability, loss of function, lower quality of life (QoL), and financial burden. Approximately 20% of people worldwide are thought to have OA. Recent analyses have found regional and country-specific variations, nevertheless. According to estimates, the prevalence of OA is 10–17% in Europe, 12–21% in North America, 2–4% in South America, and 16–29% in nations in Asia, Africa, and the Middle East. In OA pathophysiology, synovial fluid (SF) plays a major role, and the severity of OA can be determined from the SF status. Most SF comprises water, proteins, proteoglycans, glycosaminoglycans (GAGs), lipids, tiny inorganic ions, and metabolites such as amino acids or sugars. Additionally, SF components’ parts frequently have several uses. For instance, hyaluronic acid (HA) controls the biological activity of advanced glycation end products, cytokines, and enzymes linked to OA while preserving the intricate viscoelastic properties of SF. Given the strong interactions between the various SF components, normal joint function depends on the composition of the SF. Therefore, a reliable method for clinically diagnosing OA may involve tests that reflect the complete SF chemical, biological, or viscoelastic profile. Analysis of SF is an appealing target for the early diagnosis of OA damage because it allows for collecting various layers of information from the clinic and the laboratory.

On the other hand, OA can be diagnosed through anamnesis, physical examination, and diagnostic imaging. Because of the disease’s complexity, identifying osteoarthritis damage, whether through clinical observation or laboratory tests, remains difficult. Numerous clinical
imaging, histology, biochemical assay, and analytical chemistry methods have been suggested to diagnose osteoarthritis. These include computed tomography, magnetic resonance imaging, and ultrasound, in addition to traditional radiographs. Each imaging modality offers the orthopaedist crucial and frequently complements diagnostic and disease progression information. However, none of these platforms succeed in offering crucial details on the molecular structure of extracellular matrix (ECM) components, including SE. One of the promising diagnostic modalities that can depict ECM components, especially in cartilage and synovial fluid of the joint, is vibrational spectroscopy.

Vibrational spectroscopy has been utilized to investigate joint tissues, and the spectra found in animal and human arthritic cartilage or subchondral bone revealed early chemical changes. The “molecular fingerprint” that vibrational spectroscopy produces is a snapshot of the sample’s biomolecular makeup, and differences therein can be used to distinguish between various pathologies, including as early diagnostic modality for OA. Here, we review the recent advances of vibrational spectroscopy as a promising modality for diagnosing early OA.

METHODS
The literature review uses studies published online on three electronic data sources, namely PubMed, Cochrane Library, Wiley Online Library, and Google Scholar, using the keywords “osteoarthritis”, “imaging”, “diagnostic”, “spectroscopy”, “vibrational spectroscopy”, “cartilage”, “synovial fluid”. The results of the studies that match the search criteria are then analyzed using a narrative synthesis to produce a literature review.

DISCUSSION
Joint composition and pathophysiology of osteoarthritis (OA)
A joint is a complex biological system comprising bone, synovial fluid, mineralized and non-mineralized cartilage, and a synovium membrane. The joint’s anatomy is shown in Figure 1. Cartilage is linked to the patella, femur, and tibia’s joint surfaces in the synovium, while synovial fluid fills the space between and around the joint. The synovium covers the joint; outside of the synovium, additional fibrous and ligamentous layers support the joint during motion and further confine the entire joint. Since the synovium is avascular, diffusion regulates the transport of nutrients to the joint. In diarthrodial joints, synovial fluid, a plasma dialysate, covers the joint cavity space and is crucial for preserving joint health and function. Water, proteins, glycosaminoglycans, lipids, tiny inorganic salts, and metabolites like amino acids or sugars make up the majority of the ingredients in synovial fluid. Functions of the synovial fluid include lubrication of the cartilage surfaces, nutrition diffusion, compression resistance, and molecular signaling.

Osteoarthritis (OA) has an incredibly complicated pathophysiology, encompassing local biomechanical elements and environmental and genetic influences. In the past, the pathological definition of osteoarthritis was a localized, gradual loss of hyaline cartilage accompanied by changes in the underlying bone. According to more recent studies, Osteoarthritis may be seen as a disease affecting the entire joint. In addition to the surrounding muscles and ligaments, biological, chemical, and viscoelastic changes impact the cartilage, synovium, subchondral bone, and synovial fluid.

A complicated chain of biological, mechanical, and chemical events that result in the loss of articular cartilage function is thought to be caused by the degradation of extracellular matrix components, such as the cleavage of glycosaminoglycans or a loss of collagen cross-linking. A changed matrix composition, a pathological reaction to mechanical stress, and programmed cell death all play a role in the pathologic syndrome at the level of the articular chondrocyte, with changes to the cartilage extracellular matrix proteins probably occurring first.

Since the thickening of the subchondral bone plate, increased bone mineral density, and increased bone stiffness are prominent symptoms of osteoarthritis, the involvement of subchondral bone has been investigated in current disease models. Additionally, there is a link between mineral deposits in synovial fluid and osteoarthritis in its mature stages. In addition to plate thickening, radiography and other imaging tests have revealed changes in the chemistry and architecture of the bone. Subchondral bone’s material
Types of vibrational spectroscopy techniques

Imaging and laboratory tests are generally used to diagnose OA. Conventional imaging procedures include X-rays, optical coherence tomography (OCT), magnetic resonance imaging (MRI), and ultrasonic diagnostics. Although the techniques above are frequently employed in clinical practice, they are often time-consuming, expensive, and even harmful. It is critical to create quick, non-destructive methods. Researchers from all across the world are becoming more interested in the promising technique known as vibrational spectroscopy.7,9

Types of vibrational spectroscopy include near-infrared (NIR), infrared (IR), and Raman spectroscopy, which creates a vibrational spectrum from the vibrating of molecules or atomic groups brought on by electromagnetic radiation. To examine the spectrum variations between healthy and OA-affected joints, NIR/IR/Raman spectra of SF, articular cartilage, and/or subchondral bone were gathered, as shown in Figure 2.11,13 The SF spectrum shows that in OA-affected joints, protein concentration increased while carotenoid content declined. Furthermore, variations in GAG and PG concentrations and the positioning of collagen fibers in joints were identified by the spectra of articular cartilage. Figure 2 shows that (a) is the healthy joint and (b) is the osteoarthritis joint. The SF composition, the composition of the articular cartilage, and the mineralization element in the subchondral bone all vary in an OA-affected joint. In (c) and (d), descriptions of the primary OA biomarkers in SF and articular cartilage are provided.13

The first type of vibrational spectroscopy is near-infrared spectroscopy (NIR). NIR spectroscopy displays the overtones and/or combination bands of stretching and bending vibrations of C-H, N-H, and O-H bonds ranging from 12,500 to 4000 cm\(^{-1}\). According to the NIR principle, a sample is exposed to a beam of NIR light with a continuous wavelength. Suppose some groups' vibrational or rotational frequencies match the NIR lights. In that case, the molecule will absorb energy for an energy-level transition, and the light at that wavelength is absorbed.10

In Figure 3, we can see the application of NIR as vibrational spectroscopy to detect early OA. The SF collected from the joint capsule is dried and then either membrane-formed or directly analyzed. The splitter separates the light source into two beams, which are then reflected onto two mirrors, one of which is a fixed mirror and the other of which is a moving mirror. The light is recombined and transmitted to the sample after being reflected, and the change in the light beam following the sample's reflection and absorption is then noted. Chemometrics is used to analyze the spectrum data at the end.13,14

The second type of vibrational spectroscopy is infrared spectroscopy (IR). The basic principles of IR and NIR spectroscopy are similar, although the two techniques use different acquisition bands. In the 4000-400 cm\(^{-1}\) range, IR spectroscopy technology is utilized to study molecule interactions. Each molecule has a distinct IR absorption spectrum dictated by its content and structure, which can be used for structural study and identification. Fourier transform infrared (FTIR) spectroscopy is one of the IR kinds, and it is a straightforward technique used to examine the composition of macromolecules in biological materials. Because it can be examined in situ by a probe, it has benefits for the study of organisms and the early diagnosis of OA.5,10,15

The last type of vibrational spectroscopy is Raman spectroscopy, which is based on the Raman scattering principle. Different wavelengths of Rayleigh and Raman scattering are produced when a laser beam strikes a sample. In contrast to Raman scattering, which differs from the frequency of the incident light and can reflect particular intermolecular vibrations like CC, C=C, CO, and CH, Rayleigh scattering is consistent with the wavelength of the incident light.8,16

Figure 3. Near infra-red (NIR) spectroscopy principal method.13

Figure 4. Detection of articular cartilage using Raman spectroscopy. Wavelength spectrum (a) depicted normal articular cartilage, while (b) depicted articular cartilage in osteoarthritis.18

Figure 2. Wavelength spectrum (a) depicted normal articular cartilage, while (b) depicted articular cartilage in osteoarthritis.
Figure 5. Detection of articular cartilage using Raman spectroscopy.13

Application of vibrational spectroscopy on detecting early osteoarthritis (OA) through Synovial Fluid (SF) analysis

Articular cartilage degradation, disintegration, and fragmentation accompany the early development of OA. Moreover, changes in the content and concentration of SF metabolites in OA have been seen in several investigations. As a result, SF analysis is helpful for OA research based on chemical composition and physical characteristics. The two basic approaches for gathering SF from spectroscopy are as follows: the SF must first be dried onto a film before the reflection spectrum can be collected and analyzed. This classification rate is more than 95% and can detect arthritis. The second way involves using the transmitting module to retrieve the SF spectrum. NIR spectroscopy is a valuable technique for diagnosing OA based on SF analysis. Research has shown that it can identify the kind of arthritis and the viability of severity ratings using SF analysis. Further investigation is necessary before this technology can be used for SF analysis, which could eventually lead to the development of novel theories that could provide light on the mechanism behind OA.9,10,13

The application of Raman spectroscopy to detect changes of SF in joints for the early diagnosis of OA was shown in the study by Esmonde-White et al., who conducted a study on the relationship between synovial fluid from NIR-Raman spectroscopy and radiographic knee joint damage ratings in OA patients. NIR-Raman spectroscopy was used to investigate changes in the SF composition of patients, and K-cluster analysis was used to evaluate the results. The outcomes demonstrated that patients with various degrees of OA displayed varied spectrum indications of SF.9,15,16 One of the key components of SF, hyaluronic acid, is a crucial biomarker in diagnosing OA. Amide III (1250 cm⁻¹) and C-C, C-O bonds (1155 cm⁻¹) levels in HA rose as OA progressed, demonstrating the possibility of Raman spectroscopy concerning the diagnosis of OA by SF analysis. Researchers have been looking for biomarkers in SF that can be used to detect OA earlier and more reliably. However, signal augmentation techniques must be developed due to the complexity of SF’s composition and the difficulty in studying it successfully in isolation.13,17,18

Raman spectroscopy detected and distinguished normal and osteoarthritis articular cartilage based on the pattern of the wavelength spectrum. As we can see in Figure 4, cartilage detected in the range of 1220-1360 cm⁻¹ and displays Raman spectral patterns in the amide III band areas of human knee cartilage in normal and severe osteoarthritis conditions.18

Application of vibrational spectroscopy on detecting early osteoarthritis (OA) through cartilage and bone subchondral analysis

Normal hyaline cartilage has a water content of 70%–80%, most of which is bound to GAG (glycosaminoglycans). Deformities in the cartilage matrix, which include GAG, moisture, and collagen, frequently appear in the early stages of OA. Proteoglycans and GAG are essential for cartilage, which is the primary symptom of OA. Hence, their accurate identification is necessary for an early diagnosis of the disease. Afara et al. studied the NIR spectra of articular cartilage in mice with OA at four different stages (1, 2, 4, and 6 weeks), and the spectral data revealed that the spectral intensity increased over time, primarily due to changes in the cartilage moisture content. This demonstrated that the method could detect early manifestations of cartilage degeneration.16

The other study by Palukuru et al. determined that cartilage tissue with a thickness of 20 to 60 m was most suited for examination based on collagen and PG at 1336 and 856 cm⁻¹ for changes in the linear absorption band intensity. They employed NIR spectroscopy to predict the relative quantity of collagen and PG as well as the fraction of collagen using partial least squares (PLS) modeling in the spectral region of 4000-6000 cm⁻¹.11

For IR spectroscopy, it is possible to obtain the full diseased joint image and the matching spectral image of each pixel using IR spectroscopy, allowing for both macro and micro perspectives to be used in the diagnostic analysis. To compare the differences in depth between healthy and OA cartilage, Yin et al. used one type of IR spectroscopy called FTIR to analyze the amounts of collagen and PG present. Their findings demonstrated that healthy and OA-affected participants differed in the degree to which PG levels were dependent. Therefore, early detection of OA could be achieved by using the FTIR approach to identify changes in cartilage composition.12

Changes in articular cartilage can also be detected by Raman spectroscopy. According to Figure 5, a laser illuminates the articular cartilage during Raman spectroscopy, and the sample itself scatters to produce the scattering light. The filter makes Raman scattering light, which is then processed by a detector to reveal the Raman spectrum. Chemometrics is utilized in the analysis of spectral data.13

Another major indication of OA is the growth of subchondral bone; OA can be diagnosed by studying alterations in it. Researchers evaluated OA patients’ and healthy individuals’ knee subchondral bone using internal and external Raman spectroscopies. They discovered through multivariate analysis that OA patients had altered interior and exterior subchondral bone components and that there were substantial spectral changes between OA and healthy individuals (p 0.001). The phosphate band (954 and 966 cm⁻¹), amide I (1668 and 1685 cm⁻¹), and shoulder (941
Advantages and disadvantages of vibrational spectroscopy

Each vibrational spectroscopy technique has its advantages and disadvantages. Near-infrared (NIR) spectroscopy has a great penetration depth but can only transmit the cartilage's entire spectrum signal. The condition of the articular cartilage can be assessed arthroscopically using NIR spectroscopy, which can provide whole spectral signals. Its advantages are quick, precise, nondestructive, and labor-saving. The disadvantages are its wide band, considerable spectral overlap, and a masked distinctive peak. Infra-red (IR) spectroscopy detects several cartilage components and is capable of high-speed imaging. It is fast, precise, and non-destructive; it reflects information on most of the joint's organic matter. Limitations of this technique are limited sample size, complicated band, and low sensitivity. Raman spectroscopy reflects OA physiological changes at the molecular, cellular, and tissue levels and is a fast, straightforward, weak water signal that reflects biological signals. However, the optical system and fluorescence interference can both have an impact on the Raman scattering area.

CONCLUSION

Osteoarthritis is a degenerative condition that affects an increasing number of people globally and does not yet have a specific medical cure. Early diagnosis can successfully stop the progression of OA, lowering patient pain levels and treatment costs. One of the promising diagnostic modalities for detecting early OA is vibrational spectroscopy, which consists of three types: near-infrared (NIR), infrared (IR), and Raman spectroscopy, which is fast, non-destructive, and inexpensive. Early OA can be detected by analyzing the synovial fluid spectrum changes in articular cartilage and subchondral bone using spectroscopy. The NIR spectroscopy reflects the stretching and bending vibrations of C-H, N-H, and O-H bonds with wavelengths between 12,500 and 4000 cm$^{-1}$. The IR spectroscopy analyzes the structural alterations in the (4000–400 cm$^{-1}$) range brought on by the transition between molecules’ vibrational and rotational energy levels. Raman spectroscopy reflects the vibrational data between molecules using the Raman scattering technique.

REFERENCES


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