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Systematic Review

Biosensors for Detection and Monitoring of Joint Infections

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Abstract: The aim of this review is to assess the use of biosensors in the diagnosis and monitoring of joint infection (JI). JI is worldwide considered a significant cause of morbidity and mortality in developed countries. Due to the progressive ageing of the global population, the request for joint replacement increases, with a significant rise in the risk of periprosthetic joint infection (PJI). Nowadays, the diagnosis of JI is based on clinical and radiological findings. Nuclear imaging studies are an option but are not cost-effective. Serum inflammatory markers and the analysis of the aspirated synovial fluid are required to confirm the diagnosis. However, a quick and accurate diagnosis of JI may remain elusive as no rapid and highly accurate diagnostic method was validated. A comprehensive search on Medline, EMBASE, Scopus, CINAH, CENTRAL, Google Scholar, and Web of Science was conducted from the inception to June 2021. The PRISMA guidelines were used to improve the reporting of the review. The MINORS was used for quality assessment. From a total of 155 studies identified, only four articles were eligible for this study. The main advantages of biosensors reported were accuracy and capability to detect bacteria also in negative culture cases. Otherwise, due to the few studies and the low level of evidence of the papers included, it was impossible to find significant results. Therefore, further high-quality studies are required.

Keywords: joint; infections; biosensors; electrochemical impedance spectroscopy; cyclic voltammetry; amperometry

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1. Introduction

Joint infections (JI) are worldwide considered a significant cause of morbidity and mortality in developed countries [1]. Diagnosis of JI remains challenging as no "gold standard" exists. Moreover, JI shares similar clinical aspects with other forms of arthritis [2], making the diagnostic process more difficult. Timely and proper treatment is crucial to preventing significant complications as loss of joint function, septicemia, and death [3–5]. JI can be classified in two different clinical forms: septic arthritis (SA) and periprosthetic joint infections (PJI) [6]. SA of native (non-prosthetic) joints affects approximately 13,714 per year in the United States [7]. PJI is among the most dreading complications and causes joint arthroplasty failure [8]. Due to the progressive ageing of the global population, the request for joint replacement (in particular, hip and knee) increases [9,10]. Consequently, the risk of PJI rises worldwide, with an estimated incidence of 2% in the total hip [11] and knee [12] arthroplasty.

PJI treatment is challenging and constitutes a burden for the healthcare systems. Nowadays, the diagnosis of JI is based on clinical and radiological findings as X-ray, computed tomography and magnetic resonance imaging MRI. Nuclear imaging studies are an option but are not cost-effective [13]. Serum inflammatory markers (serum erythrocyte sedimentation rate; C-reactive protein level) and the analysis of the aspirated synovial fluid (measurement of the synovial WBC count; aerobic and anaerobic synovial fluid cultures) are required to confirm the diagnosis [13].

However, a quick and accurate diagnosis of JI may remain elusive as no rapid and highly accurate diagnostic method was validated. Moreover, the combination of clinical features, radiology, serology, and culture techniques does not always provide accurate information about the existence and virulence of microorganisms in an infected joint [14–18]. The use of biosensors to detect markers of JI [19] could solve this problem.

A biosensor is a device that measures biological or chemical reactions by producing signals proportional to the concentration of an analyte in the reaction [19]. Biosensors are routinely adopted in disease monitoring or drugs and pollutants revelation [19,20]. Moreover, biosensors could also be adopted in viruses and bacteria detection [19]. These devices have been already tested for the early diagnosis of osteoarthritis [20], showing advantages in accuracy, costs, and ease of use compared to other diagnostic methods [20]. However, fewer studies explored the possible advantages of biosensors for the diagnosis of JI.

The objective of this review is to report the current knowledge about the use of biosensors in the diagnosis and monitoring of JI. Therefore, a systematic review of the literature was performed to find all the papers focused on the use of biosensors in joint infections. Moreover, a comprehensive discussion reporting the main types of biosensors was performed to provide information for possible future applications in this research field.

2. Materials and Methods

2.1. Study Selection

The following study designs were included: randomized controlled trials (RCT) and non-randomized controlled trials (NRCT), prognostic studies, prospective studies, retrospective studies, case-series, case-control, diagnostic studies, observational studies, laboratory studies and cohort studies.

2.1.1. Inclusion Criteria

Only articles published in English were screened. Peer-reviewed articles of each level of evidence according to Oxford classification were considered. Studies reporting biosensors used for the diagnosis or the monitoring of joint infections were included. Both septic arthritis and PJI were included.

2.1.2. Exclusion Criteria

Studies that include biosensors for systemic infections or did not specify the type of biosensor or using polymerase chain reaction (PCR) or bacteriophages immunofluorescence were excluded. In addition, narrative and systematic reviews were not considered eligible for this study.

2.2. Search

A systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21]. Medline, EMBASE, Scopus, CINAHL, CENTRAL bibliographic databases, Google Scholar, and Web of Science were searched using the following string: ((biosensor) OR ((electrochemical OR Electrochemical Impedance Spectroscopy OR Cyclic Voltammetry OR Amperometry OR Plasmon Resonance OR Fiber Bragg grating OR optical OR colorimetric OR fluorescence OR Quartz crystal microbalance, OR molecular) AND (sensor))) AND ((joint OR knee OR shoulder OR hip OR wrist OR elbow) AND (infection)). Keywords were used, both isolated and also

combined with their mesh terms. Additional studies were searched among reference lists of selected papers and systematic reviews.

Two of the authors (S.D.S. and C.D.N.) performed the search in June 2021, and articles from the inception of the database to June 2021 were searched.

2.3. Data Collection Process

Two independent reviewers performed data extraction (S.D.S. and C.D.N.), and differences were reconciled by mutual agreement. The reviewers used the following screening approach: title and abstract were reviewed first, then the full articles. The full text of papers not excluded was evaluated and eventually selected after a discussion between the reviewers. In case of disagreement, the third reviewer (U.G.L.) decided. The number of articles included or excluded was recorded and reported in the PRISMA flowchart (Figure 1).

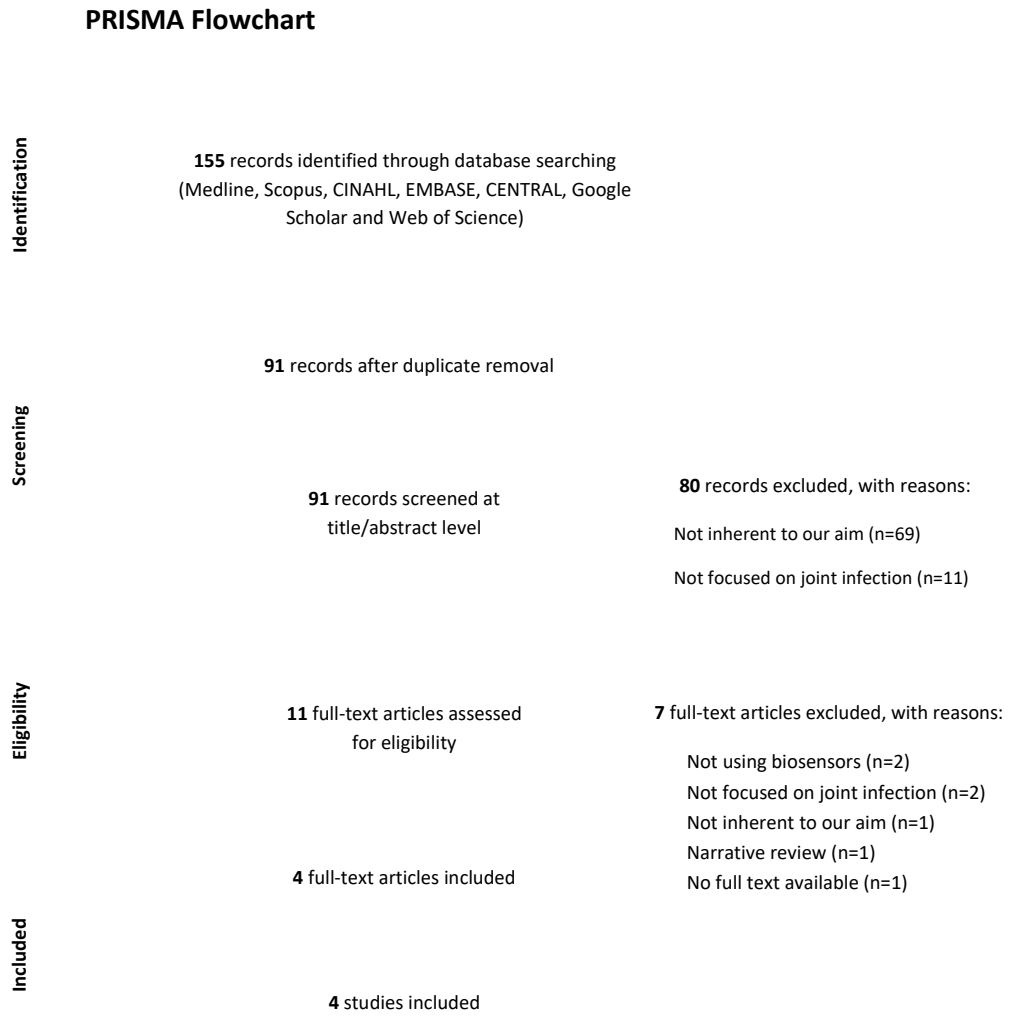

Figure 1. Study selection process and screening according to the PRISMA flow chart.

2.4. Data Items

General study characteristics extracted were: primary author, year of publication, type of study, level of evidence (LOE), journal name, sample size, joint involved, type of bacteria detected, type of infection (spontaneous or prosthetic joint infection, first implant or revision surgery), type of bacteria, biosensor used, clinical specimen, characteristic of biosensor, advantages. Biosensor types included were electrochemical sensors, optical sensors, conductometric sensors, piezoelectric sensors, and surface plasmon resonance

sensors. All the characteristics of the studies and the biosensors included are reported in Tables 1 and 2.

2.5. Study Risk of Bias Assessment

The Methodological Index for Non-Randomized Studies (MINORS) was used for quality assessment of non-randomized studies [22]. This score consists of 12 items—clearly stated aim; inclusion of consecutive patients; prospective data collection; endpoints appropriate to study aim; unbiased assessment of study endpoint; follow-up period appropriate to study aim; <5% lost to follow-up; prospective calculation of study size; adequate control group; contemporary groups; and baseline equivalence of groups and adequate statistical analyses. All the reviewers individually assessed all the items. The MINORS items were scored 0 if not reported, 1 when reported but inadequate, and 2 when reported and adequate. The ideal global score was 20 for NRCTs. The simplicity of MINORS comprising only 12 items makes this item readily usable by both readers and researchers. Slim and colleagues have already demonstrated the reliability of this score [22]. The potential risk of bias of the studies was independently assessed by the two reviewers (S.D.S. and C.D.N.). If no consensus was reached, the opinion of the senior author was decisive (U.G.L.).

3. Results

3.1. Search results

According to the PRISMA protocol, a flow-chart diagram reported the selection process of the studies (Figure 1). A total of 155 studies were found. A total of 91 studies after duplicate removal were maintained. Of that, 80 were excluded from the study through title and abstract screening because they were not inherent with our aim (n = 69) or not focused on the joint infection (n = 11). Then, 11 full-text articles were screened. Of these studies, 7 were excluded (Not using biosensors = 2; not focused on joint infection = 2; not inherent to our aim = 1, narrative review = 1, no full-text available = 1). After this process, 4 articles were eligible for this study.

3.2. Study Characteristics

No RCTs eligible for the study were found. The articles selected included 2 NRCTs (1 prospective observational study [23], 1 diagnostic study [18]) and 2 laboratory studies [24,25]. Studies were published between 2012 [23] and 2017 [25]. A total of 414 patients (172 men) were included in the review. The study by Jacovides et al. [18] reported the highest number of patients (n = 341). Knee joints were involved in three studies [18,23,25]; while the hip joint was involved only in one study [18]. In the study by Chang et al. [24] the joint involved was not specified. All the studies were performed in patients with PJI.

3.3. Use of Biosensors in the Diagnosis of JI

The most common biosensors adopted was Ibis T5000 (mass spectrometry sensor) [18,23], followed by integrated microfluidic chip (electrochemical impedance spectroscopy) [24] and magnetically assisted surface-enhanced Raman spectroscopy (MA-SERS) [25]. All the authors used joint fluid and/or tissue specimens.

All the studies reported high accuracy in joint infection monitoring and detection compared to PCR or conventional culture methods. Moreover, Rasouli and Jacovides [18,23] reported a high accuracy in joint infection diagnosis in patients with culture-negative PJI. A summary of the characteristics of the included studies is reported in Tables 1 and 2.

Table 1. Characteristics of the included studies.

Author and Year	Journal Name	Type of Study and Level of Evidence	Sample Size	Joint Involved	Primary Surgery/ Revision
Jacovides et al., 2012 [18]	The Jurnal of Bone and Joint Surgery	Diagnostic study, LOE III	341 (133 men)	Knee or Hip	PJI
Rasouli et al., 2012 [23]	The Journal of arthroplasty	Prospective observational study, LOE III	65 (33 men)	Knee	PJI
Chang et al., 2014 [24]	Lab on a Chip	Laboratory study	9 (6 men)	Not specified	PJI
Fargašová et al., 2017 [25]	Clinical Orthopaedics and Related Research	Laboratory study	4 (sex not specified)	Knee	PJI

PJI: periprosthetic joint infection, LOE: level of evidence.

Table 2. Characteristics of the biosensors.

Author and Year	Type of Bacteria	Biosensor	Clinical Specimen	Characteristics of the Biosensor	Advantages
Jacovides et al., 2012 [18]	*Candida* spp., *Streptococcus* spp., *Treponema* spp., *Peptostreptococcus* spp., *corynebacterium* spp., *Enterococcus* spp., *Staphylococcus* spp.	Ibis T5000 biosensor (PCR and Mass spectrometry)	Joint fluid and/or tissue specimens	The Ibis technique is based on the principle that microbial organisms have genomes containing sets of shared genes at various taxonomic levels and that can provide targets for detection and speciation. The broadest range primers are designed to amplify a product from an entire domain of microbial life. In contrast, more specific primers are designed to identify genera and species in major pathogenic groups, as well as genes that determine antibiotic resistance. The presence of one or more organisms, the presence of *staphylococci and/or streptococci*, and a confidence level of >0.7 for the identification of any organism had the most significant sensitivity for PJI Limitations: The sensitivity of Ibis is not high as that of conventional PCR	The Ibis looks to be a viable tool for identifying organisms in periprosthetic joint infection that is culture-negative. Its great sensitivity prevents its use as a diagnostic tool for periprosthetic joint infection at this time, as it appears to be capable of detecting organisms that are not linked with clinically significant illness. Nonetheless, we feel these data point to the complex biology of periprosthetic joint infection, and we believe they constitute true-positive results.
Rasouli et al., 2012 [23]	*Candida* spp., *Enterococcus* spp., *Staphylococcus* spp.	Ibis T5000 biosensor (PCR and Mass spectrometry)	Joint fluid	Ibis identified a pathogen with a confidence level of 0.7 or higher in a total of 36 cases. Limitations: The sensitivity of Ibis is not high as that of conventional PCR	The Ibis T5000 universal biosensor is a promising technology that has been utilized to identify a wide range of pathogens in sepsis. It has the potential to overcome the limitations of the PCR approach for PJI diagnosis. Furthermore, pan-genomic amplification may allow Ibis to detect infecting organisms that would otherwise be missed by traditional PCR.

Table 2. *Cont.*

Author and Year	Type of Bacteria	Biosensor	Clinical Specimen	Characteristics of the Biosensor	Advantages
Chang et al., 2014 [24]	*Staphylococcus* spp., *Enterobacter* spp. and *Acynetobacter* spp.	Integrated microfluidic chip (EIS)	Joint fluid	Biosensors have micro-components for liquid transportation, such as normally closed valves and pneumatically driven micro-pumps, so that samples and reagents can be regulated automatically by the integrated control system.	A new microfluidic system was developed for rapid and accurate diagnosis of PJI instead of the conventional methods for PJI diagnosis
Fargašová et al., 2017 [25]	*Staphylococcus aureus* and *Streptococcus pyogenes*	Magnetically assisted surface-enhanced Raman spectroscopy (MA-SERS)	Joint fluid	MA-SERS uses streptavidin-modified magnetic nanoparticles whose surface is functionalized with suitable biotinylated antibodies and then coated with silver nanoparticles by self-assembly.	The MA-SERS procedure is simple, versatile, inexpensive, and quick to perform. Moreover, it could be a valid alternative to Koch's culturing or colony counting methods

EIS: electrochemical impedance spectroscopy, PJI: periprosthetic joint infection, PCR: polymerase chain reaction.

3.4. Quality Assessment

All studies were NRCTs. MINORS tool was used to assess the Quality of Evidence of the included papers. These studies had a high risk of bias (<20 points on the MINORS scale). MINORS was reported in Table 3.

Table 3. MINORS score of the included studies.

Author	Clearly Stated Aim	Inclusion of Consecutive Patients	Prospective Data Collection	Endpoints Appropriate to Study Aim	Unbiased Assessment of Study Endpoint	Follow-Up Period Appropriate to Study Aim	<5% Lost to Follow-Up	Prospective Calculation of Study Size	Adequate Control Group	Contemporary Groups	Baseline Equivalence of Groups	Adequate Statistical Analyses	Total Score (. . . /24)
Chang et al., 2015	2	2	2	2	0	0	0	0	2	2	2	0	14
Jacovides et al., 2012	2	2	2	2	0	0	0	2	2	2	2	2	18
Rasouli et al., 2012	2	2	2	2	0	2	2	0	2	2	2	0	18
Fargašová et al., 2017 [25]	2	1	1	2	0	0	0	0	1	1	1	1	10

4. Discussion

This study aimed to perform a systematic review of the literature on biosensors in diagnosing and monitoring the JI. No studies assessed the utility of biosensors in the diagnosis of septic arthritis, as all the authors focused the analysis on PJI. The studies included reported high accuracy of these devices in JI detection. Compared to standard techniques (culture or PCR), the biosensors could offer a valid alternative. Two authors [18,23] reported several cases of aseptic prosthesis mobilization with negative culture. They used biosensors to find bacteria, reporting the presence of Staphylococcus spp. and Streptococcus spp. This data reveal the necessity to investigate the aseptic joint revisions to find undetectable bacteria thoroughly. However, this systematic review of the literature reveals also the lack of high-quality clinical studies (involving both humans and animals) on biosensors used for JI detection and monitoring [26–28].

Furthermore, the type of biosensors reported in the included studies was limited. Rasouli and Jacovides used a mass spectrometry sensor [18,23], Fargašová used a magnetically assisted surface-enhanced Raman spectroscopy, while Chang and colleagues used electrochemical impedance spectroscopy [24]. However, several biosensors are available; therefore, further clinical studies, including different devices, are required.

A biosensor is a device whose sensing mechanism is mediated by a biological recognition element [29]. Thus, representing a sensor as a measure chain including successive steps of sensing and transducing, the prefix Bio- is referred to as the starting point of the chain: the one interacting with the quantity to be measured. Of course, a bio-sensing element is used because of its high selectivity [30] toward the biological measurand. Besides, sensor selectivity is dependent on the other blocks of the measurement chain, which influence the performances of the final sensor device: sensitivity, resolution, limit of detection, response time. In particular, the working principle used for the sensor and the transduction mechanism also determine essential parameters for sensor usability, such as size, power consumption, and portability/wearability. This short introduction just to say as this section on sensor technology is structured: The first section is devoted to the illustration of a generic measure chain; the second subsection presents the different working principles and transduction mechanisms that can be used to realize each block of the measuring chain; the third subsection gives an overview of the available sensing materials; the last subsection focuses on the applications of the technology discussed on the core-activity treated in the paper.

4.1. Sensor Measure Chain

The more general overview of a measure chain, together with the elementary and auxiliary blocks for its functioning [31,32] is reported in Figure 2.

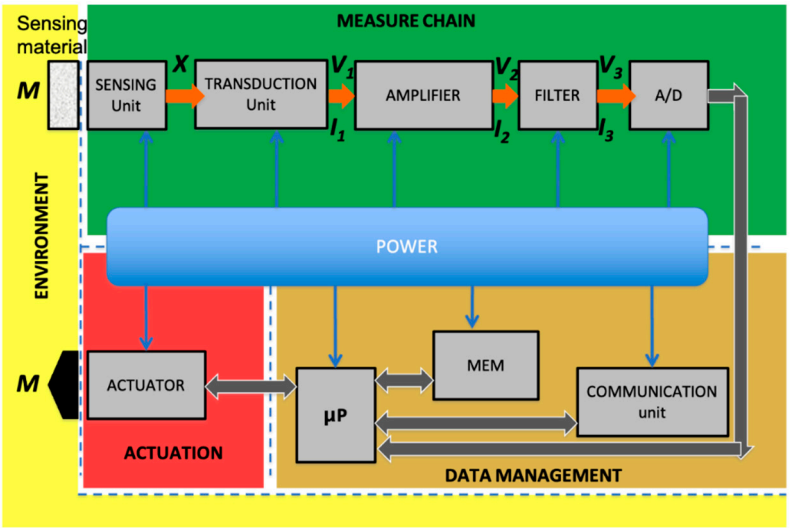

Figure 2. General overview of a sensor device. The device interacts with the environment detecting the measurand *M* and acting on it as feedback given by its quantification. The interaction takes place using the sensing material, which is the first block of the measurement chain. The sensing unit responds to the measurand *M* with an output quantity X, transduced in an electrical quantity V_1 or I_1. Often this signal is weak, and the amplifier increases its amplitude giving out the signal V_2 or I_2. The useful component of the signal V_2 or I_2 is selected in the target frequency interval (often, these two blocks are duplicated in a cascade to amplify only the selected component). Finally, the analogic signal is converted in its digital version to be more effectively elaborated, transmitted, and stored (see the data management section). A power unit supplies all the blocks.

In Figure 2, the measurement chain is composed of the blocks above mentioned. Each of the blocks of the measurement chain influences the sensitivity and resolution of the

sensor. Moreover, the type of electrical quantity (voltage, current, frequency) is determined by the type of working principle of the sensing element and the type of transducer. The other element is represented in Figure 2: the power unit, the data management blocks, and the eventual actuation unit also depend on the typology of the measurement chain's blocks, but this is a biunivocal relationship. Indeed, it is clear that some transducers ask for a higher power supply than others. However, it is also well known that the choice of digital technologies for data management could heavily influence sensor resolution. Considering medical applications in general and particularly the monitoring of joint infections, which asks easy handling of instruments for frequent examination, the power supply and the size of the sensor cannot be neglected. For the sake of simplicity, the amplification-filtering stage has been represented as a two-blocks system. It is worth noting that, very often, this double-step unit is duplicated. The transducer output signal has to be increased in amplitude, but a first amplification stage could also amplify the unwanted components of the signal in the frequency range, which are not of interest. Thus, a first amplification stage with a bit of gain (named pre-amplification) is used. Its output passes through a filtering stage, selecting the component in the frequency range of interest, which can then be amplified with a higher gain by the successive amplification stage.

4.2. Working Principles and Transduction Mechanisms

Five working principles are here described:

- Electrochemical sensors;
- Optical sensors;
- Conductometric sensors;
- Piezoelectric sensors;
- Surface plasmon resonance sensors.

This list is not exhaustive, but it is helpful to report the technologies used to monitor joint infections at state-of-the-art.

4.2.1. Electrochemical Sensors

The electrochemical sensors are composed of a cell containing the solution under measurement and at least two electrodes in contact with this solution. The chemical or biological species inside the target solution reacts with the electronic/ionic conductor interface of the electrodes (used as probe) and electric exchange charges; this exchange gives an electric output signal [33]. This output signal is directly related to the concentration of the compounds present in the solution. The nature of the output signal depends on the transduction mechanism, which could be potentiometric, amperometric, and conductometric. The most used technique in the medical field is cyclic voltammetry [34]. It consists of applying to the solution under measurement a cyclic input voltage with a particular waveform in a specific voltage range and registering the current flowing due to the applied voltage. This technique could be selective when looking for a specific compound reacting at a specific voltage. Furthermore, it could be used with a fingerprinting approach by considering all the voltammograms registered as a multidimensional pattern representing the overall solution under measurement [35]. The materials used for the electrode fabrication are metals selected for the specific reactions/compound, which has to be investigated. The most commons are Pt, Au, Ag, Cu. The electrodes could be opportunely functionalized also with biological elements.

4.2.2. Optical Sensors

The main working principle exploited by optical sensors is based on the absorption technique. This technique shows very low response time (<1 s), high and easily tunable sensitivity, selectivity, and optimal stability. The physical principle behind the adsorption is based on the fact that the light emitted by a source is partially adsorbed by the compounds present in the sample crossed by light to reach the detector. This adsorption is expressed by the Beer–Lambert Law [36].

$$I = I_0 \cdot e^{(-\alpha d)} \quad (1)$$

where I is the light transmitted through the sample under measurement, I_0 is the light incident on the sample, α is the absorption coefficient of the sample, d is the optical path-length of the cell containing the sample. Thus, the absorption coefficient α is relative to the sample characteristics [37]. The most common techniques based on this principle are non-dispersive infra-red sensors (NDIR sensors) and tunable diode laser spectroscopy (TDLS).

Fluorescence represents another widely used working principle, an optical phenomenon characterized by the absorption of photons at one wavelength and emission at a longer wavelength. Specific fluorophores (fluorescent chemical compounds that can re-emit light after excitation) can be used to detect the presence and measure the concentration of biomolecules of interest.

4.2.3. Surface Plasmon Resonance Sensors

One of the currently most used working principles is the SPR (surface plasmon resonance): it exploits the refractive index shift of a metal surface, that can be caused, for instance, by the adsorption of large biomolecules; the changes in the refractive index of the face of a metal foil is proportional to the mass of the biomolecules adsorbed on the opposite face of the metal foil, functionalized with a specific ligand. In a standard configuration, a polarized light, emitted by a LED source, is reflected by the metal surface and detected by a photodiode array: the detector will record a variation of the incident light intensity (a change of the refractive index of the metal surface) caused by the adsorption of large biomolecules on the ligand on the metal surface face opposite to the one exposed to the light.

4.2.4. Conductometric Sensors

Conductometric sensors are based on materials that change their conductivity when interacting with specific compounds or when environmental conditions, such as temperature or relative humidity, change. MOX (metal-oxide sensors) are the most common and used conductometric sensors [38], but very often, semiconductors are also used [39] or polymer doped with metal ions [40]. Considering that the varying physical quantity is the conductance, the electronic interface has to use a current flowing into the material and detect the voltage drop. This kind of readout architecture is simple and generally composed of circuits as voltage dividers, Wheatstone bridges, and differential (or instrumentation) amplifiers [32]. However, the main characteristic of MOX sensors is the tunability of their selectivity: indeed, the conductivity shift is dependent on the temperature applied to the sensing material; this temperature could be optimized for each different MOX and the target compound [41]. Therefore, the electronic interface for temperature control is more complex than the readout circuits cited above.

4.2.5. Acoustic and Piezoelectric Sensors

The working principle is based on piezoelectric materials, where the electric input is converted into acoustic waves which can travel on the surface of the sensor (surface acoustic waves, SAWs) [42], or into the sensor bulk (bulk acoustic waves, BAWs). In particular, the quartz crystal microbalances (QCMs, also called QMB: Quartz MicroBalances) are used for medical applications [43–45], due to their high sensitivity. The adsorption of the target compounds on the sensing material covering the crystal surface results in a change of the mass on the QMB and, consequently, the resonance frequency at which the QMB is oscillating. The electronic interface for QMB driving is an oscillator. Many architectures exist which are addressed to grant high stability and resolution [45]. Quartz slaces can be cut in different directions obtaining different fundamental vibration modes and frequencies, ranging from hundreds of kHz to tens of MHz. From the Sauerbrey equation [46], which rules that the frequency decreases proportionally to the mass increase, the constant factor contains the square of the resonant frequency: this suggests the great dependency of the sensitivity and resolution of QMB on the resonant frequency. For the same reason, being

the frequency range of SAW from 30 MHz to some GHz, they are often preferred when very high-resolution sensors are needed.

4.3. Sensing Materials

As described in the introduction, two typologies of sensing materials could be used: selective and non-selective. None of them is better than the other: it depends on what the sensor is designed for. For example, if the goal is a specific compound, selectivity is mandatory. On the other hand, selectivity can be tailored with a different strategy: using a biosensing element with a specific interaction mechanism with the target molecule (often named key-lock) or enhancing reactivity toward certain species by modifying material geometry. In both cases, the adsorption process of the molecules on the sensing layer is fundamental.

When the processes of adsorption and desorption of molecules onto the sensing material occur at a constant temperature, the Langmuir model is usually applied to define the kinetics and the steady-state isotherms of the coverage of the adsorbing site, under a specific hypothesis that simplified the experimental conditions with a satisfactory grade of approximation [47–50].

Thus, Langmuir isotherm is an optimal starting point for designing an effective sensing material. Due to its importance in the field, equivalent models have been developed; among them, an excellent representation for sensing material study and tailoring is exploiting an electronic circuit [51].

4.4. Focus on Joint Infections

All the working principles and transduction mechanisms reported in Section 4.2 have been used to monitor joint infections. From the point of view of sensor technology, the main characteristics have been reported in Table 4 for each application.

Table 4. Characteristics of most used sensing technologies.

Method	Technology	Cost	Where	Performances
EIS (Electrochemical Impedance Spectroscopy) [52,53]	Impedance measurement of a system linked to the AC potentials frequency	Medium/Low	Lab/Home	High
Cyclic Voltammetry [53]	Measurement of the current that develops in an electrochemical cell applying a triangular potential to the cell	Low	Lab/Home	Medium/High
Amperometry [53,54]	Measurement of the current generated on an electrode	Low	Lab/Home	Medium/High
QCM (Quartz Crystal Microbalance) [55,56]	Measurement of a mass variation by measuring the change in frequency of a quartz crystal resonator	Medium/Low	Lab	Medium
Plasmon Resonance [57–61]	Measurement of light absorption of a metal surface caused by refractive index changes	High	Lab	Very High
Fiber Bragg grating (FBG)-based optoelectronic micro-indenter [62]	Measurement of a wavelength shift	High	Lab	Medium
Dimerization-dependent red fluorescent protein [63]	Measurement of a fluorescence	High	Lab	High
Fluoro-microbeads guiding chips [64]	Measurement of a fluorescence	High	Lab	High

The limitations of this review are the lack of randomized controlled trials, the small sample sizes of the studies included, and the heterogeneity of biosensors adopted. Moreover, only English articles were included, constituting a limitation in the search string. Lastly, the quality of evidence of the studies included was low according to the MINORS; therefore, it was impossible to obtain significant conclusions.

5. Conclusions

Biosensors reported advantages in terms of accuracy compared to traditional methods in the early diagnosis and monitoring of JI. Moreover, biosensors have been proved to be helpful in the detection of bacteria in aseptic loosening. However, nowadays, only mass spectrometry sensors and electrochemical impedance spectroscopy are being used in the diagnosis and monitoring of JI. Other types of sensors are already adopted to detect biomarkers for musculoskeletal diseases. Therefore, further high-quality studies, including different types of biosensors, are required to obtain significant results regarding the utility of these devices in the diagnosis and monitoring of JI.; De Salvatore, S.; Zompanti, A.; Di Naro, C.; Grasso, S.; Casciaro, C.; Sabatini, A.; Mazzola, A.; Pennazza, G.; Santonico, M.; Denaro, V.

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