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Review

Biosensing for Autoimmune Chronic Disease—A Review

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Abstract: Although relatively rare, affecting 10% of the general population, autoimmune disorders are causative linked with chronic diseases and morbidity. Control of the course of the disease is closely dependent on the ability to monitor its onset, as well as its response to treatment. In the present report, we review the progress in the development of biosensor-based approaches and related tools for the point-of-care diagnosis and monitoring of biomarkers related to several autoimmune diseases, such as myasthenia gravis, rheumatoid arthritis, multiple sclerosis, systemic erythematosus lupus, Crohn's disease, diabetes mellitus, Behcet's disease and celiac disease. Various biosensing technologies are discussed, including electrochemical, optical and mechanical ones, along with the use of advanced nanomaterials and immobilization techniques for the biorecognition elements. The need for innovative devices with unique features of rapid, low-cost, real-time detection is discussed in the context of preventing permanent (i.e., nonreversible) organ and tissue damage from chronic autoimmune diseases.

Keywords: autoantibodies; autoimmune; biomarker; biosensor; chronic disease; cytokines; microRNAs; point-of-care

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1. Introduction

Autoimmunity refers to long-term disorders that are characterized by the presence of autoantibodies that bind proteins of the human body, protein complexes or polypeptides, resulting in an autoimmune attack that is responsible for the pathogenesis of a disease [1]. Autoimmune diseases are classified into two categories: organ-specific, such as type I diabetes mellitus (DM), Graves' disease and other thyroid disorders, myasthenia gravis (MG), etc., and systemic diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis.

Systemic disorders are rather rare in the global population (overall prevalence of 1.5%), varying from 0.001% (myositis) to 0.9% (rheumatoid arthritis). A recent comprehensive epidemiology review on SLE revealed that its incidence ranged from 1.5 to 11.0 per 100,000 individuals [1]. Organ-specific autoimmune disorders are more frequent, varying from 0.004% (chronic autoimmune hepatitis) to 1.7% (psoriasis vulgaris). In general, autoimmune disorders affect about 10% of the worldwide population [2] and belong to the main causes for chronic severe disabilities and mortality, creating significant economic issues for patients and the healthcare system [3]. In many cases, serum autoantibodies (AABs) can be detected prior to the clinical onset of a disease and during the course of organ-specific diseases. They are predictive markers in healthy subjects because they can be detected years before clinical manifestations emerge and irreversible damage to the organism occur. Furthermore, autoantibodies can be used as a follow-up for monitoring disease activity in patients [4]. The medical and economic impact of autoimmune diseases is growing, and there is a continuous improvement of treatment possibilities through targeted therapies. With this in mind, autoantibody diagnostics have increased over the last decades, but there is still a gap between high-quality diagnostics and cost efficiency.

Detection of autoantibodies is mainly conducted by analytical techniques. Currently, enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF) and Western blotting are the most common traditional methods that have been developed for AAbs detection in autoimmune disorders [5]. All these techniques require specialized personnel and equipment, are time consuming and have a high cost and, in some cases, can only detect autoantibodies at high concentrations, co-occurring with permanent tissue damage, thus making their sensitivity as diagnostic methods less satisfactory [6]. Considering these limitations, it is important to develop new and reliable techniques for the detection of autoantibodies as a means to achieve early diagnosis in autoimmune diseases.

Biosensors are integrated receptor–transducer devices that combine a receptor (biochemical recognition system) and a detector (transducer), which transforms the biochemical (biological) response into a measurable output signal [7]. In 1962, Clark and Lyons introduced the first biosensor that meets this definition: an amperometric biosensor designed to monitor glucose that was called an "enzyme electrode" [8]. It was probably the first usable biosensor that led to a widespread use of electrochemical glucose sensors by patients at home and has led to a revolutionary care of patients with DM by allowing them to monitor their glucose levels at home instead of in a lab [9]. In this way, patients have more control over their disease and can achieve better management by having the option to measure glucose levels at their own convenience, more frequently and at a lower cost [10]. This is a good example of how modern glucose sensors helped achieve the current goals in the point of care (POC) with a simple measurement protocol, one that is foolproof and can be used by an untrained patient. In this case, a small portable device is used to draw a small quantity of blood sample, accompanied with test strips that are inserted into a meter that offers a readout on glucose level and provides the necessary information to the patient in a simple manner. The protocol can be more demanding in some cases, such as with immunosensors used for many types of biomolecules, that often require extra reagents and more steps and would need to be more automated and with a simple packaging suitable for POC use [11].

2. Biosensors

As mentioned, biosensors, as self-contained analytical devices, combine both a biological element and a signal transducer. The biological element is immobilized on a solid-state surface and enables a bio-specific interaction with the target analyte. The output signal caused by the binding of the analyte can be obtained by using labeled compounds or not, thus classifying the biosensors respectively as labeled and label-free types. One of the commonly used methods for labeling involves the use of enzymes, radionuclides, nanoparticles and fluorescent or electrochemiluminescent probes. There are various test formats available, including sandwich assays, competitive assays and indirect assays [12]. The primary benefit of labeled test formats is their ability to detect lower concentrations with greater accuracy, although higher operational costs are usually implied with longer assay times in comparison to most label-free test formats, which are performed without any labeled compound and are distinguished between direct and indirect assays [13].

Direct assays are a simpler and inexpensive approach, as the signal response changes when analyte molecules bind to the transducer surface with no need for further steps or reagents in the procedure. In some cases, this simplicity could be a disadvantage when dealing with complex samples, as there could be binding of other non-analyte components onto the sensor surface and a false-positive result may arise. These kinds of unwanted effects can be resolved by ensuring that a significant change in the biosensor signal response is achieved only by the binding of the analyte to the corresponding element that is immobilized on the biosensor surface or using labeled test formats where the labeled compound usually determines the final biosensor signal response.

When considering the use of a biosensor for diagnostic applications, the core question of single use or multiuse arises. It is more than the biosensor itself that needs to be considered during the development stage to create a user-friendly and reliable device. The degree of specificity is determined by the biorecognition elements used in the biosensor,

the majority of which bind with high affinity to the analyte molecules. The sensitivity is primarily influenced by the detector element that turns the biological response into a quantifiable output signal [14]. In the multiuse option, the sensing capability of the biosensor needs to be regained, and often, a regeneration step that leads to dissociating the binding between the biorecognition element and the analyte is necessary. This regeneration procedure may require additional expenses that exceed the savings that the use of multiuse biosensors provides. When considering the development of a POC-use sensor, single-use devices that are disposable are usually preferred [15], and similar considerations are applied to all system elements that come into contact with the sample provided.

One of the major challenges of creating a biosensor is to detect the disease biomarker selectively among a vast number of proteins and other elements in the sample that could potentially interfere with the analysis and the result. A patient's prognosis can be benefited by the quantification of the appropriate biomarkers for that specific disease that can be detected in tissue or body fluids [16]. Selectively detecting these biomarkers requires meticulous consideration of the efficiency of the bioreceptor itself, its immobilization on the sensors surface and the way the signal is transduced, so that the output signal can be maximized, and the response to components bound nonspecifically is minimized. In Figure 1, the historical development of biosensors for selected chronic diseases is presented.

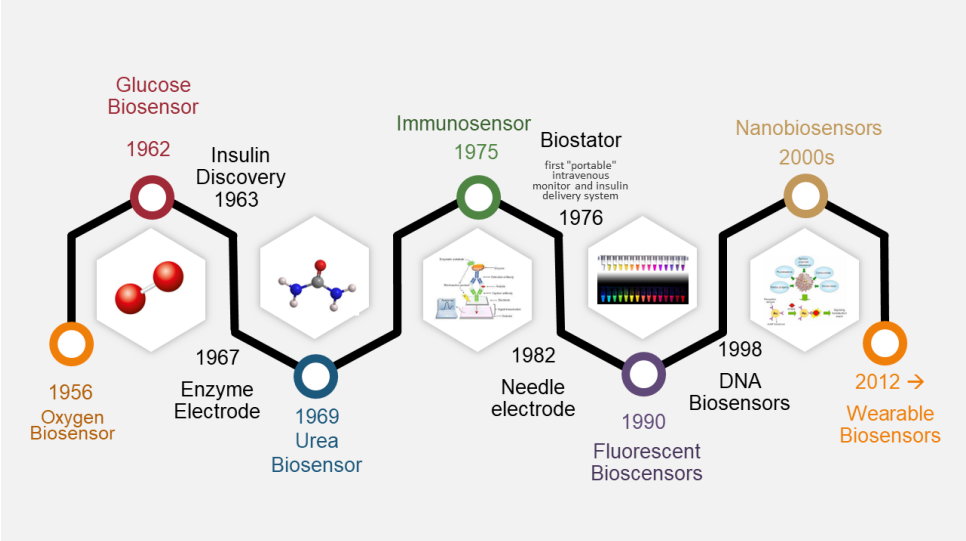

Figure 1. Biosensors development timeline.

2.1. Categories

2.1.1. Electrochemical

Due to their sensitivity, selectivity, quick response and cost effectiveness, electrochemical devices are the most common biosensors used for the early detection of disease-related biomarkers. Additionally, these biosensors have drawn a lot of interest as suitable POC tests for diagnostic purposes. Numerous nanobiosensors and electrochemical biosensors have been reported in the literature for the detection of different biomarkers in autoimmune diseases. The most frequently used techniques include amperometric, impedimetric and voltametric techniques [17–19]. Functionalized nanomaterials, such as metallic nanoparticles, conducting polymers and others, in association with electrochemical systems improved electron transfer, consequently improving the electrical signal transduction [20].

Amperometric biosensors use a fixed voltage to detect the amount of an analyte by measuring the produced current. Regarding autoimmune diseases and rheumatoid arthritis in particular, an amperometric nanobiosensor (NGP-NTiP-Thi) based on gold nanoparticles, titanium dioxide nanoparticles and thionine was designed by Li et al. in 2008 to detect macrophage migration inhibitory factor (MIF) in the serum of RA patients [21]. MIF was recognized by the IgM immunosensor in a linear relationship with the lower limit (S/N = 3)

of 0.02 ng/mL. Villa et al. in 2011 [22] created an amperometric immunosensor for the measurement of anti-citrullinated peptide antibodies (ACPAs), a possible biomarker for the diagnosis of rheumatoid arthritis. A composite made of multiwalled carbon nanotubes and polystyrene (MWCNT-PS) was used to increase the platform's sensitivity, achieving detection limits similar to those achieved with ELISA. Concerning systemic lupus erythematosus (SLE), in 2018, Fagúndez et al. [23] developed a sandwich-format electrochemical immunosensor for the anti-double-stranded DNA (anti-dsDNA) autoantibodies assay in serum samples from patients. The assay requires a total of only 30 min, and the sensor is capable of detecting 16 ng (8 μg mL^{-1}) of α-dsDNA antibodies, according to the team [23].

A potent and nondestructive approach that has lately become more widely utilized as a diagnostic tool is the electrical impedance spectroscopy (EIS) biosensor. In multiple sclerosis (MS), two label-free EIS biosensors have been fabricated. The first is a cytokine immunosensor by Bhavsar et al. (2009), designed for MS diagnosis by detecting interleukin-12 (IL-12), and results indicate that this sensor can detect IL-12 at physiological levels <100 fM [24]. In a study conducted by Derkus et al. in 2013, a label-free electrochemical impedance immunosensor to determine anti-myelin basic protein (anti-MBP) autoantibodies in patients with MS was produced. In this biosensor, the use of titaniumdioxide (TiO_2) nanoparticles resulted in a satisfactory detection range with the gelatin-MBP detection limit at 0.1528 ng mL^{-1} and gelatin-TiO_2-MBP immunosensors detection limit of 0.1495 ng mL^{-1} [25].

Regarding voltametric biosensors, they utilize a variety of techniques, including square wave voltammetry (SWV), linear sweep voltammetry (LSV), differential pulse voltammetry (DPV) and cyclic voltammetry (CV). Their high sensitivity, selectivity and cost-effectiveness and their capacity for simultaneous quantification of their targets classify them among the most extensively used and available biosensor-based approaches for the detection of specific biomarkers in autoimmune disorders. In 2017, a new nanoimmunosensor based on graphene oxide (GO)/[poly(propyleneglycol)] (pPG) nanocomposite was published by Derkus et al. for simultaneously detecting MBP and Tau proteins in MS patients using serum and cerebrospinal fluid (CSF) as samples [26]. This team, in order to achieve the simultaneous quantification of MBP and Tau proteins in CSF and serum, modified the surface of screen-printed carbon electrodes (SPCE) using amine- and GO-functionalized first-generation trimethylolpropane tris[poly(propyleneglycol)] dendrimers (pPG). MBP and Tau antibodies were immobilized using a new carrier GO/pPG nanocomposite structure for the creation of a nanoimmunosensor. The next step was to apply to the matrix a secondary antibody conjugated with carboxyl-functionalized 3.5th-generation pPG/CdS and pPG/PbS probes and to obtain a sandwich complex. Following this phase, the nanoimmunosensor was characterized and optimized using electrochemical signals of Cd^{2+} and Pb^{2+} that were created by the ionization impact of nitric acid. This suggested approach aimed to quantify simultaneously with increased sensitivity both targets, and the developed nanoimmunosensor had detection limits of 0.30 nM for MBP and 0.15 nM for Tau proteins [26].

Another autoimmune disease for which voltametric biosensors have been studied is celiac disease (CeD), an inflammatory disorder mediated by T-cells in the upper small intestine caused by consuming gluten [27]. Examples of early detection of anti-tTG antibodies in patients include the nanobiosensor developed by Gupta et al. [28], a GQD/PAMAM nanohybrid-modified AuNP embedded in MWCNT (multiwalled carbon nanotube) with a lower limit of detection of anti-tissue transglutaminase antibody at 0.1 fg per 6 μL and another nanoimmunosensor based on cyclic voltammetry developed by Neves et al. [29]. With the use of cyclic voltammetry and square wave voltammetry, the team of Bellagha-Chenchah et al. developed an electrochemical biosensor in order to detect autoantibodies against CSG114(Glc), a synthetic glycopeptide [30] with the potential to detect antibodies in patients with MS [31]. The synthetic glycopeptide was modified in order to be suitable for bioelectrochemical detection, and a lower sample volume could be used because of a series of platinum microband electrodes employed on microfluidic channels, which offer

other advantages, as well, toward the development of this type of system as a POC test device [31].

Another detection method that also has high sensitivity, fast response and low background signals is the photoelectrochemical (PEC) method [32]. This method has been studied for use in the early diagnosis of rheumatoid arthritis by the team of Pang et al., who developed a PEC biosensor based on ZnO nanorod (NR)/$CH_3NH_3PbI_3$/nitrogen-doped carbon quantum dot (NCQD) nanocomposites for rapid determination of fibroblast-like synoviocyte (FLS) cells that showed a low detection limit of 2 cell/mL [33]. Overall, biosensors based on electrochemical methods are frequently used as a tool for the early detection of autoimmune diseases because of their several advantages, including their rapid detection capability, the fact that they can be reusable and the fact that they require a low sample volume. The quantitative analysis is feasible but false-positive results can occur originating from matrix electrolytes and lack of adequate control of the response of the working electrode at higher currents [34].

2.1.2. Optical Biosensors

A compact analytical device that contains a biorecognition sensing element that is integrated with an optical transducer system is characterized as an optical biosensor, and its main objective is to produce a proportionate signal to the concentration of the analyte (the measured substance). The exploitation of the interaction of the optical field with a biorecognition element provides optical detection. As a category, they can be divided into label based and label free. The first category, label-based biosensors, involve the use of a specific label and a method (fluorescent, luminescent or colorimetric) to generate the optical signal. On the other hand, the label-free biosensors generate the signal directly by the interaction of the transducer with the sample [35]. The advantages of label-free detection can be offered by optical biosensors as well, and in the field of autoimmune diseases, the screening of biomarkers for diagnostic purposes has recently evolved. A number of studies for the detection of specific biomarkers have been conducted regarding optical biosensors.

The use of electrochemiluminescence (ECL) has advantages including high sensitivity, a wide detection range, simple controllability and a rapid response, and thus, ECL biosensors have a wide use to detect biomarkers [36]. Rheumatoid arthritis has been one of the autoimmune diseases targeted with an attempt to have early diagnosis by sensitive quantification of the anti-CCP (anti-cyclic citrullinated peptide) antibody by the team of Zhao et al. [37]. Their team developed a label-free ECL sensor that is based on asymmetric heterogeneous polyaniline–gold (PANI-Au) nanomaterial, which was incorporated with graphite-like carbon nitride (g-C3N4) in order to improve stability with a lower detection limit of 0.2 pg mL^{-1} obtained for the determination of an anti-CCP antibody. Another common and widely used optical method is fluorescence. In the case of MS, the team of Mansourian et al. [38] developed a biosensor for determining microRNA-145 as a biomarker in patients' plasma, based on fluorescent DNA-hosted silver nanoclusters (AgNCs) and hybridization chain reaction (HCR) amplification. The use of silver nanoclusters is considered to have many advantages, including simple synthesis, low toxicity, high stability and biocompatibility [39].

Fluorescence enhancement, along with surface-enhanced Raman scattering (SERS), has been applied to develop ultrasensitive bioassays. Fluorescence is enhanced in the vicinity of metals that might interact with both the stimulating laser beam and the fluorophores that are radiating. For example, a paper-based nanoplatform was created by Campu et al. for LSPR, SER and metal-enhanced fluorescence (MEF)-based multimodal biodetection [40,41]. Gold nanobipyramids (Au-BPs) were used to deposit the modulated platform with variable LSPR responses onto the cellulose fiber using a commercial pen and a plasmonic calligraphy technique. Target proteins were detected using three different sensing approaches. In order to provide portable point-of-care diagnostics, the researchers combined several LSPR, SERS and MEF nanosensors with multiplex capabilities into a single flexible and portable plasmonic nanoplatform [40].

SERS has developed into a high-throughput detection technique with a wide range of substrates [42] that can be fabricated, and clinical diagnosis [43,44] is among the possible applications of this technique [45]. As a technique with huge potential when combined with the technological progress achieved in the development of related instrumentation, vast research is being conducted around SERS, and a broad spectrum of analytical, physical and chemical applications has been proposed. The practical accomplishment of nanostructures with outstanding quality and customized morphologies, in some cases having smaller and more precisely engineered 2D and 3D nanogaps, has been one of the main driving forces behind recent advancements in SERS. These manufacturing methodologies and methods have also made it possible to produce substrates and nanotags on a wide scale with a reliable SERS response for both general and goal-oriented sensing applications.

Surface plasmon resonance (SPR) and surface plasmon resonance imaging (SPRi) are also techniques used in optical biosensors for detecting specific biomarkers in patients with autoimmune diseases. The SPR phenomenon occurs when the surface of metal is illuminated by polarized light at a specific angle (resonant angle) and electrons get excited (plasmon) when they absorb light energy. The intensity of the reflected laser beam decreases with the resonance angle, and the number of absorbed molecules on the metal surface strongly influences resonance, thus allowing for a calibration curve for a specific analyte by a resonance angle change [46,47].

These biosensors have a wide range of applications in the area of diagnosis and for measuring molecular interactions. In RA patients, the real-time detection of chemokine CXCL12 in urine samples was achieved by the development of an SPR biosensor by Vega et al. [48] using a SAM-coated gold chip covalently attached to lentiviral particles that contained CXCL4 (chemokine ligand 4) through amine coupling. In MS, there was a recent enzyme-free strategy developed with a single nanostructured enhancer of SPRi for the simultaneous multiple microRNAs assay using as a sample of patients' blood. Four microRNAs were detected in this study by Sguassesero et al. (with a limit of detection (LOD) of up to 0.5 pM) through neutravidin-coated gold nanospheres that were functionalized with biotinylated antibody against DNA/RNA hybrids [49]. This type of biosensor had been used in research for POC diagnostics regarding interferon-γ, a cytokine secreted by immune cells that can be considered an early indicator for different autoimmune disorders [50], such as Crohn's disease (CD) [51], rheumatoid arthritis (RA) [43], multiple sclerosis (MS) [50,52] and systemic erythematosus lupus (SEL) [53] that manifest with different characteristics. By immobilizing IFN-γ on the electrodes, Sipova et al. used an engineered protein that absorbed to the IFN-γ bound on the surface but mentioned that the presence and amount of IFN-γ in the solution indirectly altered the SPR signal [54,55]. As also reported by Debreczeni et al. [43], a label-free and high-throughput resonant waveguide-grating-based optical biosensor was utilized for the treatment of primary HUVEC with rC1r, the lack of which is known to contribute to the development of the severe autoimmune condition SEL. The SPR technique is very sensitive to the binding of molecules from a solution, and it is important for the nonspecific molecule binding to be eliminated. Stigter et al., in a research paper also on interferon-gamma isolation and quantification, presented that metal surfaces that were modified with dextran-mercaptoundecanoic acid showed minimum nonspecific adsorption from patients' plasma [56]. SPR biosensors are used for detecting autoimmune diseases and are a rather common optical method option because of their sensitivity, specificity, small size and cost-effectiveness [57]. Compared to conventional techniques, analyses with SPR is less time consuming and can be easily adapted to automated systems, and repetitive measurements can occur on the chip surfaces. Usually, optical sensors based on SPR need laser sources and optical components that are well aligned. Nevertheless, the possibility of small SPR sensors that are cost-effective exists, as the team of Chuang et al. presented by using cyclic olefin copolymer miniature prisms and paper in order to establish a multistep quantitative analysis that achieved an LOD of 10 pM within 30 min [57].

In general, optical biosensors, by enabling the direct, real-time and label-free detection of many different biomarkers, provide advantages over analytical techniques used for

detecting autoimmunity. Currently, they are a widespread technology, and scientists focus on improving the sensitivity and resolution of a conventional SPR, with modifications including surface plasmon resonance imaging (SPRi), long-range surface plasmon (LRSP) and localized surface plasmon resonance (LSPR) in the area of biosensing with a direction to make the technology compatible with miniaturization for portable devices [58]. A new analytical tool may emerge through their application for autoantibody detection in several autoimmune diseases, common or rarer, such as myasthenia gravis, in which patients present autoantibodies against AChR (acetylcholine receptor) and other proteins of the neuromuscular junction [59]. They may be of great diagnostic interest, as they can allow for an analysis of the serum level of the autoantibody in question and, furthermore, of its binding characteristics, making them applicable to a wide spectrum of autoimmune disorders and their serological evaluation [6].

2.1.3. Mechanical Biosensors

In interactions between biomolecules such as biorecognition, mechanical transducers may detect changes in mechanical parameters such as mass, surface stress and viscoelasticity [60]. Their complexity makes them less common and popular than optical or electrochemical biosensors. This type of biosensor can be categorized into four broad categories depending on the chemical interactions of the sensor and the analyte: (1) affinity-based assays that achieve highly selective target identification by applying high specificity between the device surface and the target, (2) separation-based assays, where spatiotemporal separation of analytes is permitted because of chemical affinities between immobilized molecules and flowing analytes, (3) fingerprint assays, where the target is identified through specific binding affinities to sensors and (4) spectrometric assays, where the target's identification is enabled through deducing its optical properties or its mass [61].

Quartz crystal microbalance (QCM) sensors are the most established ones, which are based on quartz crystal resonators [62]. They are centimeter-scale mechanical resonators that measure the mass of analytes on their surface in fluid, gas or vacuum. When the crystal is deformed with the use of the piezoelectric technique, a mass change occurs when the analyte binds to the biorecognition element that is immobilized on the crystal surface. There have been attempts to develop RA-specific peptide-coated single-walled carbon nanotube (SWCNT)-based QCM biosensors [63]. By binding an RA-specific peptide (containing citric citrulline) to a functionalized SWCNT and depositing it on a QCM sensing crystal, it was possible to identify the related autoantibodies in patients' serum. The finding demonstrated that the QCM sensor detected 34.4% more RA patients with anti-citrullinated peptide antibodies than those detected by the classic analytical method of ELISA and 37.5% more patients than microarray analysis [63].

Biology is fundamentally based on mechanical interactions. On a cellular level, mechanical forces of chemical origin control adhesion and motility, and on a molecular level, they control transport and affinity. Unique opportunities to detect forces, displacements and changes in mass from cellular and subcellular activities are provided by biological sensing in the mechanical domain [64]. Mechanical biosensors often benefit from properties that scale advantageously as physical size is decreased. Exquisite mass resolution is provided by nanoscale mechanical sensors. Nanoelectromechanical systems (NEMS) have achieved nanogram resolution in a fluid environment and zeptogramscale mass resolution when operating in a vacuum. The ability of a device's mechanical compliance to be displaced or disformed is significantly increased by uniform reduction in its dimensions [65]. One of the biggest challenges for all NEMS devices has been the development of transduction and actuation methods that are efficient, but significant advances have been made over these past years [66].

Mechanical biosensors, such as QCM, have the benefit of being very sensitive, having a large dynamic range of detection ranging from nanomolar to femtomolar ranges. Another benefit is that they are flexible enough to utilize almost any surface coating for tests [65]. The main disadvantage of mechanical biosensors is that handling samples is often cumber-

some and susceptible to measurement artifacts [3]. There are still many challenges, from integrating arrays of advanced nanosensors with conventional techniques to developing better capture agents, but developing tools capable of high-throughput studies at the level of a single cell for understanding biological systems remains the goal for developing tools that will bring advances in the field.

A schematical overview of the main biosensing approaches for the diagnosis and monitoring of autoimmune diseases is presented in Figure 2.

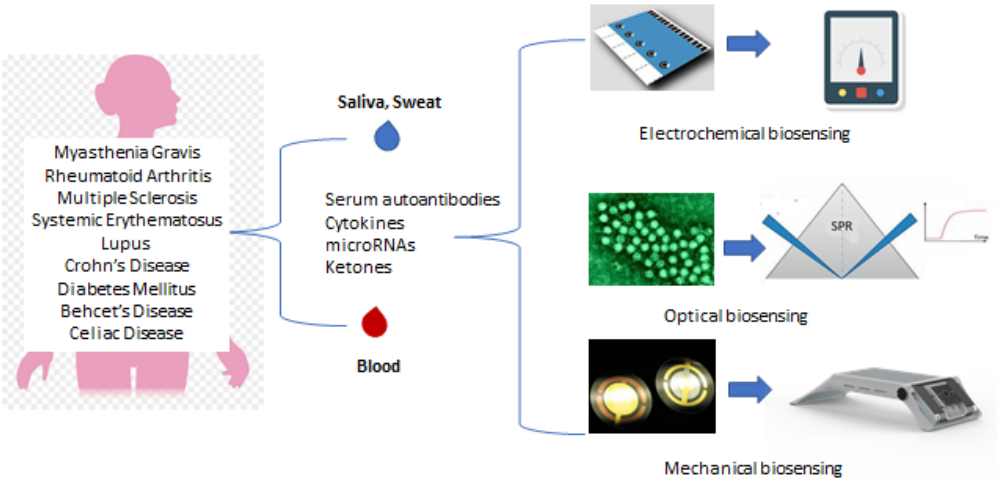

Figure 2. Overview of the main biosensing approaches for the diagnosis and monitoring of chronic and autoimmune diseases.

3. Nanomaterials in Biosensors

Nanomaterials are often used in biosensors to improve the electrical, mechanical and optical characteristics, regardless of the kind of sensor, in order to increase the detection limits [65]. The modification of the nanoparticles' physical and chemical characteristics, alterations in their size, shape or composition, is beneficial. The use of nanomaterials along with multianalyte detection and platform integration to create POC devices present a promising future for therapy monitoring and early detection of chronic autoimmune diseases. In the last years, there has been important progress in the use of nanomaterials regarding the methods of immobilization. The optimal goal with the integration of nanomaterials into immunosensors is to obtain surfaces that are nanostructured for the immobilization of antibodies or antigens, thus enhancing the biosensors' performance. High-conductivity materials, such as metallic particles, nanotubes and graphene, have electrocatalytic effects and give higher signals by improving the electron transfer [66].

Graphene is considered a "wonder material" because of its great physicochemical characteristics, including high conductivity, high surface–volume ratio and low charge-carrier resistance [67], all of which categorize graphene as an ideal candidate in order to design a transducing material. The graphene sheets have increased conductivity, and their dimensionality makes it possible for every atom to be easily exposed to environmental fluctuations, an important characteristic for a biosensor [68,69]. Another material that offers an excellent platform in biosensing are gold nanoparticles (GNPs) that have unique colorimetric properties, depending on their size, their shape and their state of aggregation [70], and they are utilized in developing electrochemical, optical and piezoelectric biosensors.

Carbon nanotubes (CNTs), an allotropic form of carbon, are also known for their excellent electrical, mechanical, thermal and electrocatalytic properties [71], and their geometry has attracted many potential biosensor applications. When they are doped with polyaniline, known for its improved redox activity, CNTs present better biosensing properties. CNTs have been utilized in dermal biosensors, paving the way for cost-effective health monitoring in a manner that is not invasive. Another material used in nanobiosensors is the covalent organic framework (COF) that has been developed from organic molecules

with covalently linked nano/microporous structures. It has a fully conjugate structure, a large surface area and one atomic-thickness dimension and, with these advantages, it has potential use in sensors and electrochemical devices [72]. Metal–organic frameworks (MOFs) have an interesting architecture and possess a large surface area with a high level of porosity; they are customizable, and they have tunable characteristics—all excellent properties for their application in biosensors [73].

4. Bioelement Immobilization

In chronic autoimmune diseases, bioelements specific for biomarkers could be immobilized through different techniques [74–76], and the method used for the immobilization is of paramount importance for the performance of the sensor. The bioelement used can be either linked via self-assembled monolayers (SAMs) or directly absorbed onto the electrode. Even though the adsorption of the bioelement is a simple procedure, a controlled orientation of the recognition element is not allowed for the proper binding of the antibody or the antigen, and therefore, it is preferred to use methods that allow an oriented and controlled immobilization. Examples of this are SAMs that, through AU-S linking, can be readily formed onto gold electrodes. A strategy could be to utilize polymer composites for linking the antibody covalently in an oriented manner [64] or by linking the antibody directly onto the electrode by electroaddressing [65]. Polymers that are employed for oriented immobilization include poly (sodium-4-styrensulfonic acid) [66] and polydopamine [18].

As support for the immobilization of the antibody, protein A or G and avidin could be used, as they have the advantages of high loading capacity and easy separation along with easy washing steps [67]. This formation of affinity interactions with a protein that is Fc-region specific is a reversible immobilization procedure and, in particular, includes noncovalent interactions [77]. This method can be used in microarray studies, as no antibody modification is required and high sensitivity can be achieved in high concentrations [78]. Immobilization can make use of the inherent affinities of biomolecules, such as lectin–sugar and antigen–antibody. The streptavidin–biotin interaction, which results in one of the strongest noncovalent forms, is the most well-known step in this approach. With several application areas, including immunology and cell/molecular biology, this interaction offers a perfect mechanism for affinity binding [79].

In enzyme immobilization, reversible methods enable the enzyme to be retrieved in mild conditions after the assay is complete. The deactivated enzyme is removed and replaced with a fresh one, and this is a benefit toward an increased cost-effectiveness of the process. In the literature, a number of reversible immobilization methods have been documented, and numerous phenomena, such as ionic binding, hydrophobic adsorption, affinity binding and ionic binding, are frequently utilized for the reversible immobilization of enzymes onto diverse substrates [80–82]. Irreversible methods include cross-linking [83,84], entrapment [83,85] and covalent binding [86].

In electrochemical biosensors, improvement of the signal-to-noise ratio can be achieved by nanoparticles of gold (Au) and zinc oxide (ZnO) [87], nanorods, graphene [88] and graphene oxide (GO) [89] that can act as electron mediators by lowering the applied potential. Immunosensors with integrated nanomaterials enhance the performance of the biosensors by achieving the goal of having nanostructured surfaces for the immobilization of the antigen or the antibody. The biocompatibility of the nanomaterials is also important to mention [90].

Multiple antibodies or aptamers can be immobilized on nanoparticles, therefore increasing sensitivity. Silica nanoparticles were employed by Taghdisi et al. to immobilize aptamers, while copper nanoparticles were utilized to immobilize aptamers, as they interact with the poly-T strand of the aptamer, increasing the fluorescent signal [91]. According to Wen et al. [92], the introduction of magnetic nanoparticles additionally makes it easier for the separation and concentration of multiple biomarker immobilization. By altering the distribution of electric fields on the particle surface, nanoparticles can enhance the localized surface plasmons, a technique demonstrated by Jeong et al., who fabricated a fiber-optic

LSPR sensor based on spherical gold nanoparticles (GNPs) for real-time label-free immunoassays of IFN-gamma and a specific antigen [93]. This technique could be examined for application on autoimmune diseases. With the purpose of IFN-gamma detection, and in order to enhance the chemiluminescent signal amplification, the team of Jiang used luminol-tagged gold nanoparticles (AuNPs); with this strategy, the aptasensor showed high sensitivity, pointing to considerable possible applications in clinical analysis [94], while Zhu et al. employed CdS quantum dots for their photoluminescent properties and their lesser toxicity in comparison to other nanoparticles that are Cd based [95]. This latter sensitive electrochemiluminescent (ECL) immunosensor possesses a three-dimensional structure nanocomposite that enhances the intensity of ECL, as it is beneficial for immobilizing primary antibodies. Secondary antibodies labeled with CdS quantum dots were used to generate ECL on a sandwich-type immunoreaction. In theory, they can be applied to monitor the biomarkers in samples in response to drug stimulation [96].

5. Chronic Diseases and Biosensors

Among the leading causes of death and of severe disability worldwide are chronic diseases. Apart from autoimmunity, which has been analyzed earlier, research has been made on biosensors regarding other chronic conditions as well. Due to the large variety of chronic diseases, examples of some of the most common ones will be provided in this article. Diabetes mellitus is a metabolic disorder that results in hyperglycemia or nerve and kidney dysfunctions that are triggered by high glucose levels and the impaired biological action or defective secretion of insulin in the patients [97]. The detection of DM currently is performed by testing the glucose serum levels, including the fasting plasma glucose test and oral glucose tolerance test [98]. Over the past few years, a new method for detection of specific blood components has been researched. Terahertz (THz)-microstructured-fiber (MSF) biosensing has a high accuracy, is a fast technique and can be supported by compact readout devices [99,100]. THz imaging and spectroscopy have become increasingly popular for in vivo applications because of the non-ionizing and non-invasive nature of THz radiation, in combination with its high sensitivity in aquatic samples.

Monitoring blood glucose levels plays a significant role in managing the disease, as mentioned, but there is also an interesting correlation between sweat glucose and blood glucose levels both in patients and in healthy subjects [101]. It has been mentioned that glucose concentrations are approximately a hundred times lower in a person's sweat than in the blood [102,103], and a precise measure of the glucose concentration in the sweat could provide a non-invasive estimation of the blood glucose levels. Another condition related to DM is diabetic ketoacidosis, caused in patients with hyperglycemia by the accumulation of ketone bodies. A dominant physiological ketone, β-hydroxybutyrate, can be detected in sweat and can be used as a biomarker for this condition [104].

Another example of a chronic autoimmune disease is Behcet's disease (BD), a rare autoimmune disorder that causes inflammation of blood vessels and tissues. Patients often experience a different odor that could be a result of the abnormal composition of their sweat, and a metabolomics analysis revealed that some metabolites could be candidate biomarkers [105]. Several of the cytokines found in sweat were thought to be connected to a number of chronic conditions. For example, interleukin-31 (IL-31) has a role in autoimmune skin conditions, such as psoriasis and alopecia [106], and is considered the most accurate predictor of all-cause mortality in older people compared to other cytokines [107]. The most significant biomarker in sweat is chloride (Cl-), which is considered a gold-standard biomarker for the diagnosis of cystic fibrosis [108].

For all these diseases that have as a common characteristic the possible biomarkers in sweat, epidermal wearable biosensors are a current technological challenge. This category of portable detection devices can be worn directly on the epidermis for in situ detection of the determined biomarkers in sweat and other body fluids. Real-time analysis of the biomarkers can be facilitated, and patients can enjoy continuous monitoring of their health that could provide sufficient information for biomedical research, clinical diagnosis and

treatment [109]. An in-depth understanding of the biochemical process of various biomarkers may be achieved though this type of monitoring and provide valuable information that will strengthen the management of chronic diseases. A variety of substrates, such as smart bandages, wristbands and textiles, have been used for the manufacture of wearable biosensors [109–111].

Despite the difficulty of integrating liquid handling and immunobiosensing devices in a wearable platform, many types of biosensors have been used for biomarker detection in sweat with electrochemical biosensors being the most commonly used method [112–114], including enzyme-based biosensors [115], aptamer-based biosensors [116] and immune-based biosensors [112]. Another option is colorimetric biosensors that, with the use of electronic equipment, capture the sensor's color changes in response to different analytes and quantify them by performing an image analysis [114,117,118]. Of course, the ultimate clinical application would be met by continuous monitoring combined with real-time sampling, as the number of biomarkers that can be monitored continuously with accuracy is still very limited.

6. Biosensors for Autoimmune Diseases Based on Antibodies, Antigens and Peptides

The vast range of autoimmune diseases and the limited knowledge of their pathogenesis leads to symptomatic medical treatments instead of curing the diseases themselves. As mentioned earlier, early diagnosis and detection of the diseases are important to reduce the severity of the symptoms and to prevent irreversible damage to tissues and organs. In most cases, serological tests conducted in laboratories are needed for disease confirmation in order to measure objectively and evaluate specific markers for each disease as an indicator of the disease's progress or its pharmacologic response. Interesting concepts have been reported toward POC diagnostics on several autoimmune diseases based on Abs and Ags.

In celiac disease (CeD) biosensors, examples for the early detection of anti-tTG antibodies in patients include the nanobiosensor developed by Gupta et al. [28] and by Neves et al. [29], as mentioned in the electrochemical biosensors section. Another team, Cosa-Garcia et al., developed a biosensor that can detect two different biomarkers, each with two isotypes (IgA AGA, IgB AGA, IgA anti-tTG and IgB anti-tTG). A nanostructured carbon–metal hybrid was used to modify screen-printed electrodes (SPE), and the antigens (AGA and tTG) were immobilized onto the electrodes in order to capture specific Abs [109]. Several examples of indirect assays regarding IgA and IgB anti-tTG have been published, such as by the team of Zhang [119], who used cyclic voltammetry, electrochemical impedance spectroscopy and differential pulse voltammetry as detection methods to develop a double-signal electrochemical immunosensor for the fast and sensitive detection of human IgG antibodies. This sensor was based on AgNPs/carbon nanocomposite (Ag/C NC) as the signal probe and a catalytic substrate was developed. This double-signal strategy was successfully implemented in the analysis of human IgG in patients' serum and could provide an effective and relatively simple method for developing other immunosensors [120]. New diagnostic tools like biosensors are needed especially in cases of common autoimmune disorders, like multiple sclerosis, a disease in which patients develop a series of autoantibodies, and their presence in biological fluids can be used as diagnosis and prognosis biomarkers [121], and rheumatoid arthritis, where early stages diagnosis is crucial for a positive outcome for the disease [122].

Another versatile tool for the creation of flexible frameworks concerning autoimmune diseases are peptides because of their capacity to assemble themselves in highly ordered structures in all three dimensions. Novel biosensors can be developed with the use of peptides, as they can modify the amino-acid sequence and, therefore, their secondary structure, optimizing in this way the interactions between adjacent peptides [57]. Short peptides offer short response time in electrochemical detection and better chemical stability and have a good biocompatibility, and they can be easily obtained by synthesis. The development of biosensors that are based on peptides instead of immunosensors or aptasensors is an increasing trend in the development of biosensors for autoimmune diseases.

In Table 1, examples are given of the most known biosensor techniques and related biomarkers for chronic disease.

Table 1. Target biomarkers and related biosensor technologies for the diagnosis and monitoring of chronic diseases (EC = electrochemical).

Disease	Target Biomarker	Biosensor Technology	Sample	LOD	Reference
Rheumatoid Arthritis	macrophage migration inhibitory factor (MIF)	EC	Human Serum	N/A	[21]
	anti-citrullinated peptide antibodies (ACPAs)	EC	Rabbit Serum/Human Serum	N/A	[22]
	fibroblast-like synoviocyte (FLS) cells	optical	-	2 cell/mL	[33]
	anti-CCP (anti-cyclic citrullinated peptide)	optical	-	0.2 pg mL^{-1}	[37]
	interferon-γ	optical	CNS Tissue	N/A	[52,53]
Multiple Sclerosis	interleukin-12	EC	-	<100 fm	[24]
	anti-myelin basic protein	EC	Human Serum	0.15 ng mL^{-1}	[25]
	miR-145	Fluorescence spectrophotometer	Human Serum	0.1 nM	[38]
	multiple microRNAs (miR-422, miR-223, miR-126 and miR-23a)	Phase shift in surface plasmon resonance imaging	Human Serum	0.55 pM–1.79 pM for the different miRNAs	[49]
	MS specific autoantibodies	SPR	Human Serum	N/A	[120,123]
Diabetes Mellitus	Glucose	EC	Sweat	3.84 μM	[124]
	Glucose	Colorimetric	Sweat	7 μM	[124]
Depression, anxiety	Cortisol	EC	Sweat	10 pM	[124]
	Cortisol	Colorimetric	Sweat	6.76 ng/mL	[124]
Celiac Disease	IgA anti-tTG IgB anti-tTG	Differential Pulse Voltammetry (DPV)	Human Serum	3.2 AU mL^{-1} 1.4 AU mL^{-1}	[125]
	IgA anti-tTG IgB anti-tTG	cyclic voltammetry (CV)	Human Serum	1.7 AU mL^{-1} 2.7 AU mL^{-1}	[126]
	Anti-tTG	Electrochemical Impedance Spectroscopy (EIS)	Serum	N/A	[75]
	anti-IgG-HRP	amperometry	Serum	390 ng/mL	[127]
	tTG	SPR	Serum	N/A	[128]

7. Discussion and General Considerations

Using biomedical equipment and biosensors in specific is an innovative method to provide personalized monitoring, disease management and treatment according to the biochemical characteristics and needs of each person, and it is expected to revolutionize medical practice. Taking into account the importance of early diagnosis, especially in autoimmune diseases that appear to have significantly growing incidence, biosensors could represent a significant alternative and a viable option to the diagnostic methods that are currently being used. Autoimmunity is currently an important health issue, as the number of cases reported is significantly increasing, and in most cases, there is no cure. Both practi-

tioners and patients would benefit from early diagnosis, as mentioned, and it is essential for proper tools to be developed. These tools need to be simple, affordable and suitable for decentralized analysis by any type of user and not only by specialized personnel.

Great advancements in immunology and molecular biology have been made, leading to a set of biomarkers for almost every chronic disease, either proteins, antibodies or peptides. Implementing POC devices able to detect these biomarkers remains the biggest challenge, especially before the manifestation of symptoms. There have been many reports of such attempts in the literature, as mentioned in this review, most of them dedicated to electrochemical biosensors that appear to be viable alternatives for developing POC tests.

The incorporation of nanomaterials and other types of chemicals and attractive bioassay formats into a biosensor's design is also important in electrochemical biosensing. Using magnetic particles for implementing bioassay configurations, combined with screen-printed electrodes, has shown that multiomic determination can be performed with simple test protocols. When it comes to integrated forms, the incorporation of nanomaterials and the modification of electrode surfaces with the appropriate chemicals are particularly significant. Whether nanomaterials are used singly or combined in hybrid nanostructures, their variety has been utilized as electrode modifiers to improve bioreceptor immobilization and charge transfer. In many cases mentioned, high sensitivity has been achieved and many strategies have turned into microfluidic devices.

Nevertheless, application on real samples is still quite limited and on a research level. Both existing biomarkers and candidate ones that have been or will be identified need to be validated exhaustively along with developed devices. It is essential for a combined effort to be made in order for the strategies mentioned to be implemented in the near future in clinical and everyday life. The advancement of the development of other strategies, as well, is essential, simultaneously with validating biomarkers and respectively developing biosensors. An option in the future could be biodevices with no reagent that could have the capacity for real-time determination at a lower cost.

8. Conclusions

Biosensors can provide a new hope for the next-generation technology of clinical diagnosis, especially if they can achieve the detection of low or even ultralow concentrations in the early stages of chronic diseases and, particularly, autoimmune ones, such as SLE or other disorders with antinuclear antibodies, like myasthenia gravis. Their ability to detect various biomolecules makes them versatile, and that is a great advantage for identifying novel biomarkers and predicting chronic diseases or monitoring a patient's progress and pharmaceutical response. Hopefully, in the future, the increased need to cure and to prevent permanent organ and tissue damage from chronic autoimmune diseases will be met by new highly sensitive analytical devices that have unique advantages of rapid, low-cost, real-time detection compared to traditional assays.

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