Biosensor Utilization in Medical Applications

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Abstract: Sensors are vital tools in the medical field and advancement in sensor technologies has given room for development of several types of sensors to meet specific medical demands. Recent advances in developing low-cost and highly efficient biosensors devices which are highly sensitive and possess great specificity have opened new scope for discovery and diagnosis through conversion of biochemical signals into measurable physicochemical signals. This chapter presents a review on the application of biosensors in the medical field. The review captures biosensor concept, principle of detection, components and its application in detection and diagnosis of diseases. Biosensors and their functions in medical field are critical aspects and their special advantage of fast response and high sensitivity makes them imperative.

Keywords: *Sensors, Biosensors, Detection, Diagnosis.*

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I. INTRODUCTION

A sensor is a device which can detect some types of input from the physical environment, respond to it by processing it and generate an output which is usually a signal that is convertible to human-readable information at the sensor location or transmitted electronically over a network for reading or further processing. There are several types of sensors, some work outside the body while others are designed to be implanted within the body. Sensors have become part of our everyday life. We use them in our homes, offices, hospitals, recreational centers, etc.

The development of reliable and sensitive molecular electronic devices is a matter of great importance in the fields like biotechnology and medicine [1]. Furthermore, in case of diagnostics, biosensors may significantly facilitate and accelerate early detection of several diseases. The monitoring of clinical treatment may also be performed via the usage of properly designed biosensors [2]. Body fluids like urine, blood, saliva, tears or sweat may be treated also as samples full of specific disease biomarkers for micro/nanotechnology-based techniques

➢ *Sensor Overview*

Three basic components of sensor have been identified:

- A sensor element
- Sensor packaging and connections
- Sensor processing hardware.

There may be extra components in some types of sensors that perform some unique functions. For example, output signal processor is added for smart sensors, magnetostrictor is an additional component for the fiber optic magnetic-field sensor which uses multiple sensors to convert a magnetic field into an electrical signal.

New technological components (Figure 1) have been added to modern sensor systems [3], this includes the following:

- Sensor element(s) and transduction material(s) which convert more than one forms of energy into other forms.
- Interconnections between elements (electrical and /or mechanical input gate).
- Output gate and interconnection

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- Modulating device which helps the sensor to adjust when there is change in the physical properties of the sample being measured.
- Calibration device which helps in the adjustment of the sensor system to enable it function accurately.
- Amplifier
- Actuators.

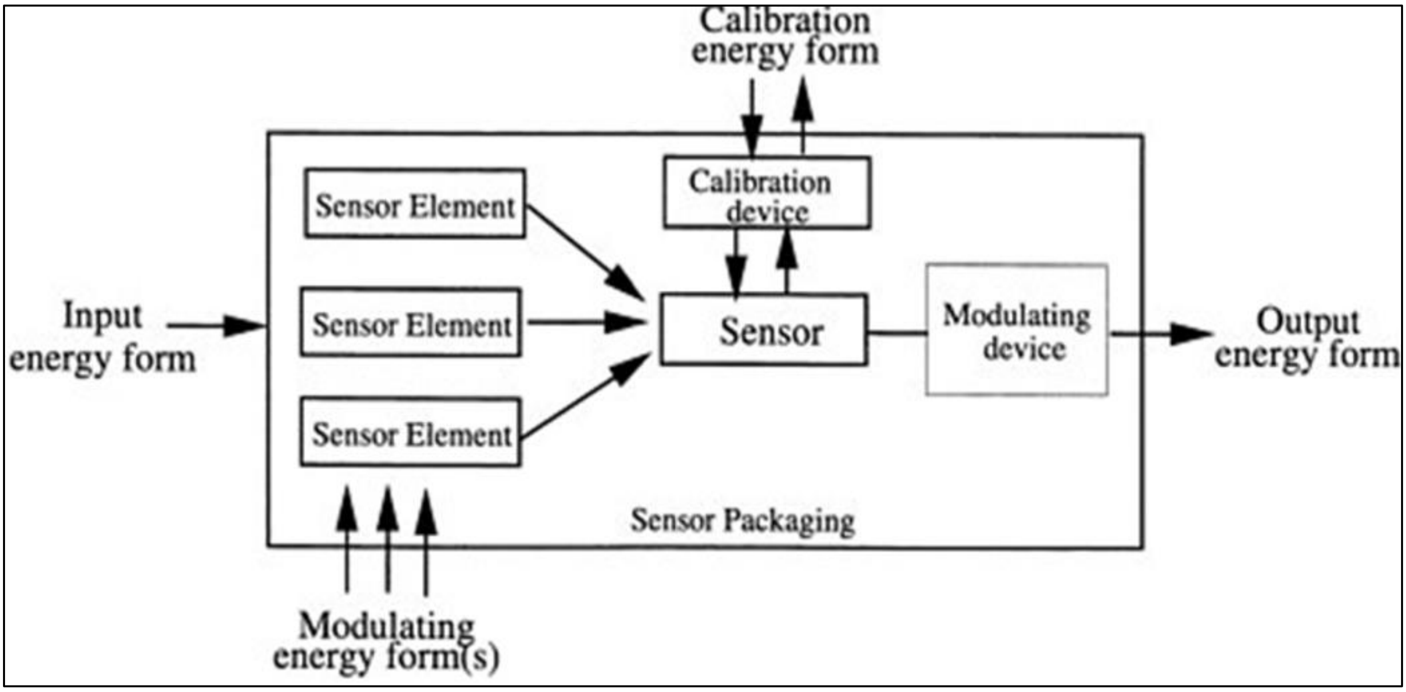

Fig 1 Anatomy of a Sensor System

II. CONCEPT OF BIOSENSOR

Biosensors are devices that depend on the specificity between cells and molecules as a means to identify and measure substances at very low concentrations [4]. They are hybrid of chemical and physical sensing technique which is one of the newly described classes of sensors [5]. A biosensor is a detecting device that uses biomolecules as the recognition element with a transducer which gives quantitative or semi-quantitative analytical data similar to the target concentration [6-8]. They are analytical devises, used for analyzing biological samples for proper understanding of their composition, structure and function. This is achieved by converting a biological impulse into an electrical signal. These particular devices that comprise of a component that recognize biological molecules are connected to signal transducers that can together give a relationship between the concentration of the analyte (or group of molecules similar to the analyte) and the response that can be measured. Several types of biosensor base on analyte exist which include microbial sensor, enzyme electrode sensor, immunosensor and DNA sensor while based on detection mode we have electrochemical, electrical, optical, mass sensitive and thermal biosensors. Examples of some sensing techniques used in biosensors are as follows:

- Fluorescence
- DNA microarray
- Surface Plasmon Resonance
- Impedance Spectroscopy
- Quartz Crystal Microbalance
- Scanning Probe Microscopy
- Surface Enhanced Raman Spectroscopy
- Electrochemical

➢ *Properties of Biosensors*

- *Linearity:*

This has to do with the single dimension of the sensor's calibration curve. To detect high concentration of the substrate, the sensor's linear value should be high.

- *Sensitivity:*

This is the acuteness of the electrode in responding to signals per the concentration of the substrate.

- *Selectivity:*

This is the ability to distinguish the signals from related chemical compounds and it should be reduced to the minimum for a correct result to be obtained.

- *Response Time:*

This is the time required to obtain 95% of the response.

➢ *Components of a Biosensor*

According to fig. 2 [13] below, the four major parts of a biosensor include the following:

- A bio-recognition element which can distinguish between the target compound and other related molecules.

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- The transducer that converts the recognized event into a quantifiable signal.
- Amplifier which is used for the amplification of the signal in other to generate a suitable electrical signal that can be measured or used.
- The signal processing system which transforms the quantifiable signal into a readable information (display unit) [9]. The biomolecules that serve as recognition elements include the following: Hormones, receptors, enzymes, antibodies, nucleic acids, microorganisms, etc [10, 11]. The five main classes of transducers are electrochemical, optical, thermometric, piezoelectric, and magnetic [12].

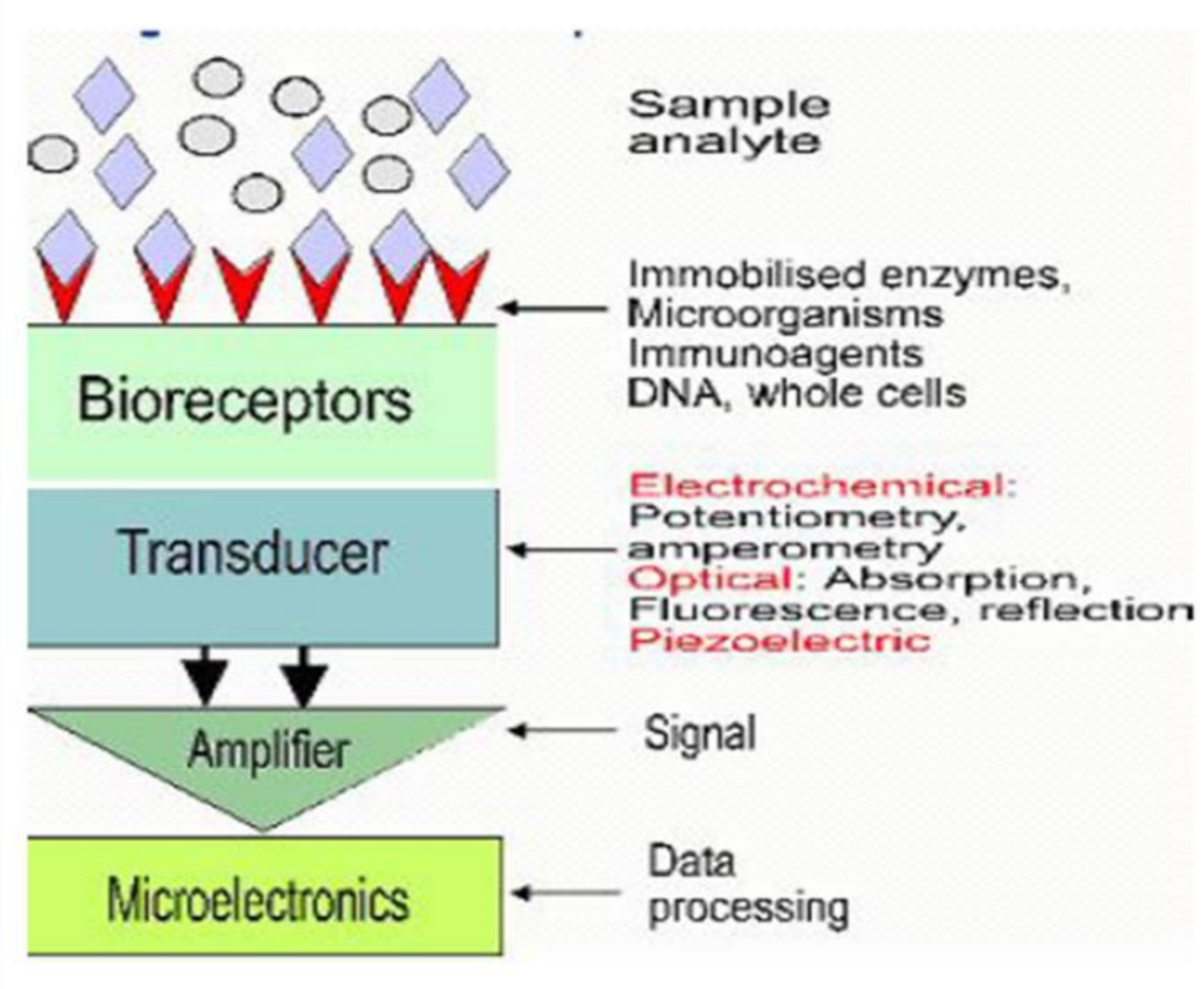

Fig 2 Components of a Biosensor

III. BIOSENSOR PRINCIPLE OF DETECTION

➢ *Photometric:*

Most of these optical biosensors operate on the principle of surface plasmon resonance (SPR) which is an evanescent wave technique. It utilizes gold as an electrode (biological element). A thin layer of gold on a glass surface with high refractive index glass usually absorbs laser light, which produces electron waves on the surface of the gold. Thus, the interaction between the target analyte and the receptor on the surface of the gold material will generate a signal which can be quantified. Some biosensors operate on the principle of laser light introduced into the fiber. The evanescent field produced at the tip of the fiber can be used to energize the analyte molecules bound to the recognition element (an antibody). The photometric detection system can be used to sense an optical signal (e.g., fluorescence) emanating from the target analyte or from the interaction between the analyte and the bioreceptor. Such laser nanosensors are also used for invivo studies of proteins and other biomarkers in living cells [13-15].

➢ *Electrochemical:*

Some biosensors operate on the catalysis of enzymatic reactions that either donate or receive electrons (the enzymes involved in such catalysis are known as redox enzymes. The

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sensor substrate in such biosensors has three electrodes –The reference electrodes, working electrode, sink electrode. The target analyte reacts with a working electrode, and generate ions which produce a potential difference that is channeled to the reference electrode to produce a signal. Auxiliary electrode / counter electrode is a part of ion source. The broad class of electrochemical sensors encompasses both Amperometri**c** devices, a very sensitivity biosensor that detects electro-active molecules present in biological test samples, and potentiometric devices, simple and sensitive and suitable for turbid samples without modification which can be used for kinetic studies [13, 17, 18]

➢ *Piezoelectric:*

These acoustic devices utilize crystal**s** that can experience an elastic distortion whenever an electric potential passes through them. The alternating current generates a wave within the crystal. The frequency of the wave generation depends on the elasticity of the crystal. When this crystal is covered with a biological element, this binding interaction between the large target analyte and the receptor will alter the frequency which will lead to the generation of a signal. The crystal used here is quartz [19]. Mass sensing devices are also illustrated by quartz crystal microbalance. Target analytes for mass sensing can be either molecular components (such as proteins or nucleic acids) or whole cells and they are majorly used in the determination of hybridized DNA, DNA-binding drugs and Glucose concentration [13, 18].

➢ *Ion Channel Switch:*

The use of ion channels has been shown to offer highly sensitive detection of target biological molecules [13, 20] by the fixation of the ion channels to tethered bi-layer membranes (t-BLM) fastened to an electrode, an electrical circuit is produced. Recognition element like antibodies can be bound to the ion channel such that the interaction of the target molecule with the recognition element regulates the flow of ion through the channel. These will lead to a quantifiable alteration in the electrical conduction that is proportionate to the concentration of the target [19]. Also a device known as enzyme field effect transistor which is mainly used to detect pH, it is designed to ascertain the Pathogenesis of Cancer (POC) in clinical environments or hospitals. It gives an exact and quantifiable test results within a reduced interval of time. [13, 17]

➢ *Thermal detection biosensors:*

These types of biosensors utilize the basic characteristics of biochemical reactions which is the generation of heat energy which consequently alters the temperature of the reactions medium. As soon as the analyte interacts with the enzyme, the heat generated as a result of the enzymatic reaction is measured and calibrated against the concentration of the analyte. The overall heat generated is proportionate to the enthalpy of the system and the number of molecules present in the reaction medium. The devices that are mostly used to measure the temperature of enzymatic reactions are called enzyme thermistors. They are commonly used to detect the presence of pesticides and pathogenic bacteria in biological samples. Its high sensitivity to thermal changes without constant recalibration, insensitivity to optical and electrochemical characteristics of the analyte are some advantages possessed by these biosensors [13, 17].

IV. MEDICAL APPLICATIONS OF BIOSENSORS

➢ *Pregnancy Test*

Many sensor technologies used in industries can be applied in laboratory diagnosis. One of them is in Pregnancy testing. In Pregnancy testing, it is usually the level of human chorionic gonadotropin (hCG), a glycoprotein hormone secreted by the placenta in pregnant women, that is being checked for. This hCG is also secreted in some gestational diseases such as trophoblastic diseases, ectopic pregnancies, germ cell tumor, etc and its function is to stimulate the production of progesterone and other steroid hormones in the corpus luteum to enhance the growth of the placental [21]. Therefore, any increase in the level of hCG in the blood or urine is a major indicator of pregnancy as well as pregnancy related diseases [22]. Hence, it became very paramount to develop a very sensitive and selective sensing device that will help to detect early increase in the level of hCG to facilitate early diagnosis of either pregnancy or these diseases. There are current lab-dependent procedures that are being used to determine the level of hCG which include: Enzyme-linked Immunosorbent assay (ELISA), Radioimmunoassay, Flouro-immunoassay etc. However, the innovative technologies like electrochemical immunosensors are laboratory-independent and imperative to enhance the substitution of existing laboratory-dependent detection systems which are bulky, time consuming, expensive and labour intensive with laboratory-independent ones. These sensors for the detection of hCG involve the use of label-free, point of care (PoC) immunosensor (antibody-assisted biosensor) to determine the level of hCG utilizing the various classes of sensitive electrodes to detect the target molecule in the analyte, placed on the sensitive upper layer of the biochips [23]. These commercially available sensors are able to determine a concentration as small as 25mlu/ml of hCG, mostly in substandard analytical conditions, which is enough to diagnose pregnancy four days before the menstrual period [23]. One novel property of these biosensors is that they are capacitive based. These capacitive biosensors have the capacity to detect the target molecule immediately in the analyte which is either in its natural form or slightly prepared and so can be applicable for point of care (PoC) diagnosis and treatment [24]. This capacitive property of these sensors is due to some alterations in some parameters like dielectric properties, charge distribution, permittivity and conductivity on the upper layer of the transducer electrodes. Therefore, alterations in these parameters can be determined if a molecular interaction has taken place between the analyte and the surface on the electrode.

➢ *Cancer Management*

Sensors are applied in the diagnosis and treatment of cancer. It is also used to monitor how cancer patients are responding to treatment. They are equally used to monitor the

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diseases progression in cancer patients and select the best treatment option according to the stage and position of the cancer [25]. Cancer can be defined as an uncontrollable growth cells as a result of excessive mutations in gene programmes that regulate cell division. This uncontrolled cell growth may lead to the development of a tumor mass which overtime becomes resistant to the body's mechanisms of regulating cell division and proliferations [26]. The earlier cancer is detected, the more chances of its treatment. Presently, most cancers are detected when they must spread to other part of the body and at this stage, it is difficult to cure or manage them. These sensors that are used in diagnosis of cancer are fabricated to sense a particular biological target by effectively transforming a biological molecule (protein, RNA or DNA) into an electrical event that can be determined and quantified.

Therefore, due to increasing cases of cancer each year all over the world, investigations concerning early cancer detection become a vital matter. Also, the possibility of cancer treatment monitoring with biosensor techniques gives hope for a personalized therapy [27]. Human breast cancer as a clonal disease, was assumed to evolve when a cell gains enough germline or somatic unusual traits and gets modified to fully exhibit malignant tendencies. Though initially, breast cancer was taken as a peculiar disease of the breast, but further research and clinical studies have shown that breast tumors are heterogeneous in nature. Thus, it has been established that each patient requires therapies that aligns to his cancer type [28-30].

- *Diagnosis of Cancer*

No single diagnostic test that can correctly diagnose cancer and it usually take some months to several years the before malignant cells can reproduce itself, forming a diagnosable tumor mass (solid tumor) or liquid tumor (leukemia or lymphoma). Since cancer or tumor biomarkers are critical for early cancer detection, early detection of the cancer biomarkers, matched with the most accurate and effective treatment for a particular cancer patient according to the cancer heterogeneity of the individual, will affect the longevity and quality of life of cancer patients. An electrochemical immunosensor which work the principle of functionalized nitrogen doped grapheme QD was designed in order to detect the cancer biomarker carcino-embryonic antigens (CEA) in human blood [31,32]. Also, direct label-free diagnosis of tumor biomarkers is an effective feature of devices called silicon nanowire sensors, which have precise antibody immobilized on them to detect the antigen of interest. Another study on nanowire showed that nanowire sensors operate in aM (attometer, 10^{-18}) to nm (nanometer, $10^{-9)}$ range and they out-perform most current methodology for detecting tumor biomarkers. A study also observed that the outstanding Limit of Detection (LoD) of 23aM attained by a nanowire memristor sensor which has a precise antibody immobilized on it to detect to the biomarker for prostate cancer, prostrate-specific antigen (PSA) outperformed the sensitivity of conventional methods for the determination of PSA level [33]. Usually, prostate cancer is always associated with elevated level of serum PSA and the use of serum PSA level determination has improved the timely diagnosis and treatment of prostate cancer [34]. Although, 20-30% cases of prostate cancer are always linked with low PSA level and which are not detected by conventional clinical PSA tests. An accurate diagnosis can be gotten in this low range of PSA level by either observing a continual increase in PSA level with time or by reducing the PSA limit of detection and this is obtainable with nanowire sensors [35].

- *Cancer Treatment*

Sensors are also applied in monitoring cancer patients to determine how the cancer cells are responding to chemotherapy drugs. These sensors can detect hydrogen peroxide inside human cells which causes Apoptosis (programmed cell death). These cancerous cells undergo several mutations which can lead to unregulated metabolism, causing abnormally high production of hydrogen peroxide [36]. Excessive production of this hydrogen peroxide can damage the cancer cells and so, they depend mostly on the antioxidant systems which detoxifies and eliminate hydrogen peroxide from cells [36]. These sensors can assist researchers to develop novel drugs that can either enhance the production of hydrogen peroxide or disable the antioxidant system. These sensing devices can equally be used to examine each patient's tumors so as to check whether such drugs could be potent against them.

➢ *Cardiovascular*

Cardiovascular diseases or coronary heart diseases are often used to refer to various health conditions affecting the heart or blood vessels. It is always associated with the accumulation of fatty deposits (plaques) inside the arteries (atherosclerosis) and or increased risk of blood cloth. These coronary heart diseases can manifest as:

- *Angina:*

This manifests as the chest pain associated with the restriction of blood flow to the heart muscles.

- *Heart Attack:*

This is where the flow of blood to the heart muscles is suddenly blocked.

- *Heart Failure:*

This is where the heart is unable to pump blood around the entire body properly.Timely detection of cardiovascular disease is essential for saving many lives, importantly for individuals having episode of heart attack. Efficient and immediate determination of cardiac muscle specific markers in the blood will assist in correct diagnosis and prognosis with early treatment of the patients.

Some cardiac-specific markers like myoglobin, B-type naturiuretic peptide (BNP), cardiac troponin1 (cTn1), C-reactive protein (CRP), interferons and interleukins can be identified using optical, acoustic, electrochemical or magnetic-based sensors [37]. Sensors can also be used to predict heart failure or heart attack possibilities by detecting when a patient condition is worsening.

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According to study, these implantable sensors can integrate a number of measurements from some activities that is going on with the patient including breathing, heartbeat, pulse rate, blood pressure, oxygen saturation, etc and put all together to give an index that is both sensitive and specific to heart failure. One of the recent innovations is the introduction of wearable sensor systems for real-time diagnosis of myocardial infarction. This type of sensor system consists of a sensor subsystem that is wearable and an intelligent myocardial infarction detecting and alerting subsystem. These two subsystems share information wirelessly through Bluetooth technology. The sensor subsystem that can be worn registers the electrical activity of the heart from the chest region and gives an electrocardiogram (ECG) trace which it sends across to the other potable intelligent subsystem which can detect the signs of heart attack [38]. This device will allow patients to be monitored from their homes or places of work and are alerted once a symptom of heart is detected. There are existing ECG monitoring systems, but they are tasking and take quite a longer period of measure the ECG signals in patients, with the attendant longer period hospitalization. Also the ECG data obtained will be sent to experts for interpretation and diagnosis. Therefore, these ECG sensors that are wearable could be very effective for direct diagnosis of cardiovascular diseases, since it can take decision on its own by mere observation irregularities in the ECG signals recorded and identifying imminient heart attack [39].

➢ *Cholesterol Detection*

Cholesterol is one of the most important animal steroids from which other steroid compounds, including steroid hormones are formed. It is also a component of biomembranes, which helps in maintaining membrane fluidity and permeability. Humans get cholesterol from food and through its hepatic biosynthsis. However, an increased level of cholesterol in the blood (hypercholesterolemia) mostly implicated atherosclerosis, myocardial infarction including other cardiovascular diseases in humans [40]. Abnormalities in cholesterol metabolism could affect the regulation of low density lipoproteins (LDL) and high density lipoprotein (HDL) which influence the development of cardiovascular diseases. There are several methods that are used to quantify the level of cholesterol contained in most food and biological samples, but they still have some limitations, in terms of low sensivity and selectivity, sophisticated instrumentation or time consumption. This is where the affordable, easy-to-use and effective cholesterol sensors are applied for easy diagnosis of hypercholesterolemia. A type of such sensors is the chemiluminescence (CL) sensors that work on the basis of the peroxidase-like activity of copper nanoclusters which is used in the determination of cholesterol content. The copper nanoclausters is the catalyst for the CL reaction between luminol and H_2O_2. This H_2O_2 is the product of the oxidation of cholesterol in the presence of cholesterol oxidase [41].

➢ *Diabetes Application:*

Diabetes mellitus as a metabolic disease is always associated with increased concentration of glucose in the blood. This increased blood glucose concentration is either as a result of reduced production of insulin by the pancreas or that the body cells do not adequately respond to the insulin secreted by the pancreas. It is of three types namely: type I or juvenile diabetes (cause by less production of insulin), type II or adult-onset diabetes (cause by cell’s inability to respond to insulin) and Gestational diabetes mellitus (GDM) which is increased concentration of glucose in the blood that is induced by pregnancy. This GDM enhances the tendency of developing type II diabetes in some women and their babies after birth and within the first 10 years of life [42]. Constant blood glucose screening has become an indispensible tool for the management of diabetes. Since sustaining the optimal blood glucose concentration is highly encouraged, some suitable and efficient glucose biosensors have equally been developed [43]. Table 1 shows some commercially available glucose biosensors with their assay method, minimum volume of sample required and the time needed for the test to be completed. The working principle of these glucose biosensors is based on the oxidation of D-glucose by molecular oxygen leading to the production of gluconic acid and hydrogen peroxide which is catalyzed by the immobilized glucose oxidase. Hydrogen peroxide is oxidized at a catalytic, classically platinum (Pt) anode leading to electron transfer. The electrode easily detects the number of electron transfers, and this electron flow is directly proportional to the number of glucose molecules present in blood [44].

Carbon nanotubes (CNTs) designed with significant structural, electronic, and optical properties offers significant opportunities in developing novel and fascinating platforms of nanotools for the detection of disease biomarkers. These novel non-invasive signal-detecting devices which are affordable and of reduced magnitude can perform better than current non-expensive blood glucose test strips. Well functionalized CNTs possess great potency in detecting the diabetes markers and to offer therapeutic solutions for both types of diabetes [45]. Several types CNT biosensor has been used effectively in monitoring the progression or reduction of glucose concentration during diabetes treatment [46-56]

➢ *Orthopaedics Application*

There is also need for the use of biosensors in orthopaedic field of studies [13, 57-62] to address some health challenges related to:

- soft tissues like tendon and ligament,
- hard tissue like bone and bone associated aliments like as osteoporosis and Paget’s disease,
- to check fracture risk and
- to check how the bone responds to treatment of bone disease

➢ *Other Applications*

Biosensor has also gained applications in detection of several other diseases and illness. For instance DNA-based biosensors are applied for the clinical to detection of direct mutations of the phenylalanine hydroxylase (PAH) enzyme, which is responsible for Phenylketonuria [63], detection of

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pathogens like bacterial agent for the fatal disease meningitis [64-66], hepatitis A and B viruses (HAV and HBV) [67-69]. Detection of the genomic DNA of *Brucella spp.* in biological samples can also be achieved using optical biosensors [70]. Cellulose fiber paper devices that are to be applied for medical examinations are also developed to enable the production of practical DNA-based biosensors [71].

Table 1 Commercially Available Glucose Biosensors [43].

Manufacturer	Brand	Assay method	Minimal sample volume (uL)	Test time (S)	Assay range (mg/dL)	Hematocrit Range (%)	Memory (results)
Abbott	FreeStyle Freedom Lite	GDH-PQQ	0.3	–5	20–500	15–65	400
AgaMatrix	WaveSense KeyNote	GOD	0.5	4	20–600	20–60	300
Arkray	Glucocard X-meter	GDH	0.3	5	10–600	30–52	360
Bayer	Ascensia Contour	GDH-FAD	0.6	5	10–600	0–70	480
Bionime	Rightest GM300	GOD	1.4	8	20–600	30–55	300
Diabestic Supply of Suncoast	Advocate Redi-Code*	GOD	0.7	7	20–600	20–60	450
Diagnostic Devices	Prodigy Autocode	GOD	0.6	6	20–600	20–60	450
LifeScan	OneTouch UltraLink	GOD	1.0	5	20–600	30–55	500
Nova Biomedical	Nova Max	GOD	0.3	5	20–600	25–60	400
Roche	Accu-Chek Aviva	GDH-PQQ	0.6	5	10–600	20–70	500

V. CONCLUSION

The application of biosensor in medical sciences offers a good platform for diagnosis and detection of diseases. Biosensor technology holds the potential to offer cost-effective, lab-independent, fast and accurate diagnosis through early detection of biomarkers in minute concentration that most laboratory procedures cannot detect. Also, the use of biosensors in monitoring the progression of some therapeutic drugs used for the treatment of some diseases can ascertain their efficacy and enhance the development of more efficient and potent drugs. The emergence of portable biosensors like the wearable and implantable biosensors has further brought health care delivery closer to the people, reduced hospital visitation and made biosensors suitable for point of care (PoC) medical attention. Hence, medical sciences have found its application very vital as more research is going on this area to further advance its utilization especially in the area of nanotechnology.

DECLARATIONS

- *Ethics Approval and Consent to Participate*
  Not applicable

- *Consent for Publication*
  Not applicable

- *Availability of data and material*
  Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

- *Competing interests*
  The authors declare that they have no competing interests.

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- *Authors' contributions*
  There was total collaboration between the authors in the execution of this study. MBA, AES and ECE conceptualized the study. MBA, ENGN and ICP did the literature searches. Authors MBA and AES wrote the first draft of the manuscript and incorporated all corrections from co-authors. The authors MBA, AES, ECE, NUB and ICP critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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