

## Recent advances in biosensor technology in assessment of early diabetes biomarkers



Armin Salek-Maghsoudi<sup>a,b,1</sup>, Faezeh Vakhshiteh<sup>c,1</sup>, Raheleh Torabi<sup>a,d</sup>, Shokoufeh Hassani<sup>a</sup>, Mohammad Reza Ganjali<sup>e,f</sup>, Parviz Norouzi<sup>e,f</sup>, Morteza Hosseini<sup>g,h</sup>, Mohammad Abdollahi<sup>a,b,f,\*</sup>

<sup>a</sup> Toxicology and Diseases Group, Pharmaceutical Sciences Research Center, Tehran University of Medical Science, Tehran, Iran

<sup>b</sup> Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Science, Tehran, Iran

<sup>c</sup> Nanotechnology Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>d</sup> Laboratory of Nanobiosensor, Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran

<sup>e</sup> Center of Excellence in Electrochemistry, University of Tehran, Tehran, Iran

<sup>f</sup> Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran

<sup>g</sup> Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, Iran

<sup>h</sup> Medical Biomaterials Research Center, Tehran University of Medical Sciences, Tehran, Iran

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### ABSTRACT

Discovery of biosensors has acquired utmost importance in the field of healthcare. Recent advances in biological techniques and instrumentation involving nanomaterials, surface plasmon resonance, and aptasensors have developed innovative biosensors over classical methods. Integrated approaches provided a better perspective for developing specific and sensitive devices with wide potential applications. Type 2 diabetes mellitus is a complex disease affecting almost every tissue and organ system, with metabolic complications extending far beyond impaired glucose metabolism. Although there is no known cure for Type 2 diabetes, early diagnosis and interventions are critical to prevent this disease and can postpone or even prevent the serious complications that are associated with diabetes. Biomarkers for type 2 diabetes are useful for prediction and intervention of the disease at earlier stages. Proper selection of biomarkers that represent health and disease states is vital for disease diagnosis and treatment by detecting it before it manifests. In this respect, we provide an overview of different types of biosensors being used, ranging from electrochemical, fluorescence-based, nanomonitor, SPR-based, and field-effect transistor biosensors for early detection and management of diabetes with focus on prediabetes. In the future, novel non-invasive technologies combined with blood and tissue-based biomarkers will enable the detection, prevention, and treatment of diabetes and its complications long before overt disease develops.

### 1. Introduction

One of the most important healthcare challenges is the worldwide growing prevalence of type 2 diabetes (T2D). The disease is characterized by the insensitivity to insulin, known as insulin resistance (García-Jiménez et al., 2016). The etiology of insulin resistance is multi factorial and arises from numerous physiological stresses including genetics, physical inactivity, obesity, diet, medications, environmental toxicants, stress, and endocrine disturbances that all may result in disturbances of secretion of insulin (Khan et al., 2017; Hodjat et al., 2017; Johnson and Olefsky, 2013; Maqbool et al., 2016a; Mostafalou et al., 2012; Pakzad et al., 2013). The role of some famous environmental toxicants such as benzene (Bahadar et al., 2014a, 2015a,

2015b), xylene (Niaz et al., 2015), styren (Niaz et al., 2017a, 2017b), arsenic (Bahadar et al., 2014b; Khan et al., 2017), lead (Mostafalou et al., 2015), and mercury (Maqbool et al., 2014, 2016b, 2017) have been confirmed in the recent years. Many individuals with T2D are diagnosed after appearing several complications, which begin early in the progression from normal glucose tolerance to diabetes. The disease is a highly common disorder, as it directly impacts the quality of life of individuals. Diabetes health care spending accounts for more than billion dollars annually, including medical bills, medication, blood glucose assays, work loss and etc (Farshchi et al., 2014; Nichols et al., 2016). These observations indicate that early identification and management of individuals with a risk of T2D is necessary to reduce both the incidence of disease and its complications (Narayan et al., 2011;

\* Corresponding author.

E-mail addresses: Mohammad@TUMS.Ac.Ir, Mohammad.Abdollahi@UToronto.Ca (M. Abdollahi).

<sup>1</sup> These authors contributed equally to this work.

Hosseini and Abdollahi, 2013). Several studies have been conducted in the management of diabetes, such as administration of antioxidants (Rahimi et al., 2005; Tabatabaei-Malazy et al., 2013), development of new drugs, transplantation of isolated insulin producing cells, and clinical practice guidelines (Association, 2017; Tabatabaei-Malazy et al., 2016; Vakhshiteh et al., 2013). Multiple laboratory tests are used for the diagnosis and management of patients with T2D. The blood glucose concentration and HbA1c are the major diagnostic criteria for T2D and patient monitoring. It has long been known that more than 50 genes are involved in the performance of pancreatic  $\beta$  cell, insulin action, glucose metabolism, or any other circumstances that enhance the risk of T2D and these genes would be necessary to predict disease development. However, the outcome for candidate genes have been contradictory due to conflicting findings that probably related to small sample sizes, dissimilarities in T2D susceptibility across ethnic groups, differences in environmental exposures, and interactions between gene and environment. Hence, only few candidate genes were identified, including PPAR $\gamma$ , ABCC8, KCNJ11, and CALPN10 (Murea et al., 2012). The polygenic nature of T2D is complicated with loci affecting gluconeogenesis, glucose transport, and insulin homeostasis that lead to difficulties in predicting the incidence of diabetes. These limitations; however, can be overcome by considering multiple biomarkers for the prediction of T2D (Keating, 2015). The commonly available protein biomarker-based approaches utilized for the detection of T2D include enzyme-linked immunosorbent assay (ELISA), Western blot, enzyme immunoassay (EIA), and radioimmunoassay mass spectrometry. However, these techniques are burdened with a number of limitations such as availability, complexity, requiring modern infrastructure and equipment with skilled personnel, costly materials, and cost of time from testing to diagnosis (Cork et al., 2013; Parkash and Hanim Shueb, 2015). Biosensors can solve some of these problems. Biosensors are among the novel detection technologies in biomedical sciences defined as a single device platform that detects targets via biochemical reactions and transduces these reactions to electrical, thermal, or optical signals. These systems offer some advantages such as rapid detection, portability and patient flexibility (Hassani et al., 2016; Okafor et al., 2014). So far, the majority of designed biosensors for diabetes has focused on analysis of blood glucose and other biological fluids. In the current study, we have carried out an overview to identify biomarkers involved in impaired glucose tolerance and insulin resistance that results in prediabetes and ultimately T2D. Development of biosensors for early diagnosis of T2D would help to prevent or delay onset of the disease. Thus, we summarize the candidate biomarkers for early stage detection of prediabetes as well as the recent advances in development of biosensors for those biomarkers over the last decade. Eventually, we suggest critical biomarkers that have to be considered as potential targets for developing highly sensitive biosensors for T2D.

## 2. Biosensing technology

The classical approaches for analytical experiments, such as high performance liquid chromatography, GC, ELISA, or EIA offers quantitative data but qualitative. Moreover, extensive processing time, trained personnel requirements, as well as restriction in quantity of samples to be analyzed concurrently are regarded as additional negative points of old-fashioned methods. Hence, biosensor-based devices were introduced to advance presently detecting approaches, which offer several advantages such as high sensitivity and selectivity to its target, rapid processing period, friendliness, easy to implement, and being cost-beneficial. Biosensors have also improved processing steps and variability in signal transduction by incorporating biological and chemical sensing approaches (Kumar et al., 2015). Table 1 summarized a comparison between the characteristics of conventional methods and biosensing approaches.

**Table 1**  
Comparison of traditional analytical and biosensing techniques.

Biosensor	Pros	Cons
	Fast real-time detection Cost-effective Transportable Simple practice High sensitivity Controlled sample preparation Reusable Fewer organic solvent Specificity	Restricted commercial application
Conventional analytical techniques	Pros Sensitivity	Cons Long time procedure Costly Laboratory monitoring Skilled laboratory staff High-tech apparatus
	Specificity	Extended sample Preparation Not reusable Raised organic solvent Feeding

## 3. Classification of biosensors

### 3.1. Electrochemical biosensors

An electrochemical biosensor transforms the interaction between a biomolecule and target to an electric current or potential. Among several available biorecognition elements, enzymes are the major substrate owing to their specific binding ability as well as biocatalytic activity (Grieshaber et al., 2008). Various classifications have been introduced for electrochemical biosensors according to the signal property, which quantify the biological fluctuations in solution through potential, charge accumulation, current, conductance, or impedance. Generally, electrochemical biosensors have been categorized into amperometric, impedimetric, potentiometric, and conductometric biosensors. The sensitivity and selectivity of electrochemical biosensors principally linked to the biorecognition portion. The sensitivity is influenced by the conductivity of the materials as well. The transducer has an electrochemical feature which is thoroughly proportionate to the properties of electrode. Electrochemical biosensors are much suitable for miniaturization with well-matched sensitivity, simplicity, cost-effectiveness, and quickness.

### 3.2. Amperometric biosensors

Amperometric biosensors are among the most widespread types of biosensors, which principally quantify the current fluctuations prompted through an interaction between biosensor recognition element and the target, such as an enzyme or protein. The principle of amperometric biosensor for the target residue detection relies upon the potential or current caused by changes in the activity of recognition element before and after interaction with a target molecule (Grieshaber et al., 2008; Schuhmann, 1995). The remarkable advantage of this transducer is being low-priced as well as being very sensitive. In addition, application of disposable electrodes allows the system to exclude the requirement of repeated calibrations (Velasco-Garcia and Mottram, 2003).

### 3.3. Potentiometric biosensors

Basically, a potentiometer quantifies the changes in the potential variations in an electrochemical reaction generated across an ion-selective film separating two solutions at practically zero current flow.

Such a potential formed following the enzyme catalytic interaction or by the interaction between antibody and antigen. With reference to biomarkers detection, sensors could be classified as ion-selective pH (ISE) or pH-sensitive field-effect transistors (pH-ISFET) (Jaffrezic-Renault, 2001). Several state-of-the-art potentiometric sensors are commercially available that can be miniaturized by innovative technologies based on silicon or thick-film (Koncki, 2007). The sensitivity of the system was improved recently by receptors found upon fluorescence technology, which joined a biomarker attached to the surface of polystyrene substance and a pigment that is sensitive to pH changes. The system has led to the detection of biomarker at the minute levels (Grieshaber et al., 2008). Generally, lower detection limits are feasible by amperometric tools rather than potentiometrics.

### 3.4. Impedimetric biosensors

The impedimetric system senses the changes of electron transfer resistance at the interface between the electrode and the solution upon recognition element and target binding (K'Owino and Sadik, 2005); therefore, permitting recognition of biomolecules easily, directly, and rapidly (Koncki, 2007). The ion sensitive and the enzyme field-effect transistors (ISFET and ENFET), which were formerly classified into potentiometric group, have been recently presented as impedimetric biosensors. The ISFET has been established as the earliest miniaturized silicon-based chemical sensor in order to measure ion concentrations in a solution (Dzyadevych et al., 2006; Monošik et al., 2012). The ENFET-based biosensors perform similar to the pH-sensitive FETs in which the concentration of hydrogen ions during an enzymatic reaction is proportional to the concentrations of substrate. False positive outcomes associated with the electrolytes regarded as the foremost drawback of these biosensing devices (Pohanka et al., 2008).

### 3.5. Conductometric biosensors

Conductometric strategies measure the total variations of the ionic strength of a solution following a biological/chemical interaction. Conductometric devices are capable of being manufactured by low-priced thin-film technology with the capacity to exclude unwanted interferences (Jaffrezic-Renault and Dzyadevych, 2008). Enzyme-based conductometric approaches are well-recognized devices, which determine the conductivity alternations of a solution amongst electrodes during the interaction. These devices have exceptional applications in biomarkers platforms (Chouteau et al., 2005; Dzyadevich et al., 1994; Dzyadevych et al., 2005).

### 3.6. Immunosensors

Immunosensors are biosensing devices working based on ligand similarity that measure biochemical contacts between antibodies and antigens on the transducer outward. The immunosensor is performed on the basis of the affinity of the antibody (Ab) for a unique spot of the target analyte. The efficacy and reliability of these sensors mainly rely on the specificity, regenerability, stability and sensitivity of the Ab. Immobilization of the Ab on the firm surface provides the opportunity of reusing the system, which necessitate the dissociation of the covalent linkage between Ag and enzyme from the Ab-immobilized surface repeatedly to sustain the system specificity and activity (Kandimalla et al., 2004).

### 3.7. Optical biosensors

In optical biosensors the output transducer signal that is quantified is light. An optical biosensor is capable to sense a preferred target through association of an illumination supply, optical transducer system, and detecting component. The interaction of target and receptors, immobilized on the transducer surface, leads to a variation

in refractive index, which subsequently detected and quantified based on transducer illuminations. Various optical biosensing approaches are categorized into absorption spectroscopy, light, fluorescence and surface-plasmon resonance (SPR) and so on. The benefits of these systems are real-time examination with no need for pre-treatment or large bulk samples.

### 3.8. The fluorescence biosensors

The fluorescence-based devices sense the fluorescence emission of the target, which labeled with fluorescent tags. In fact, fluorophore absorbs the light or electromagnetic radiation frequency and emits it at visible range. The significant benefit of these devices is the high sensitivity of the detection limit (Schäferling, 2016).

### 3.9. SPR-based biosensors

In SPR-based biosensing approaches, SPR occurs when a certain wavelength of light imposed on a metal layer. The evanescent wave from total internal reflection (TIR) stimulates a combined oscillation of free electrons, which pass through the surface of the metal and subsequently produce a resonance that could be detected. SPR is an appropriate approach for investigating Ab/Ag, nucleic acid, and analyte/receptor interactions. Some metal NPs have been widely recognized for optical localized surface plasmon resonance (LSPR) properties, such as gold and silver, in which the NPs electrons capable of producing a collective fluctuation (Jokar et al., 2016). This LSPR property leads to the alternation in the color of NPs solutions which are optically measurable.

### 3.10. Mass-based biosensors

Detecting instruments based on mass-based biosensors quantify tiny modifications in resonance frequencies of surface, which are directly associated to the changes in mass.

### 3.11. Piezoelectric biosensors

These biosensors are based on the coupling of the bioelement with a piezoelectric material. In these instruments the piezoelectric component, which vibrates in response to the electric field, is joined to a recognition element. Some materials are more frequently employed in piezoelectric devices such as Ceramics (Ramadan et al., 2014). There is a growing attention in the application of piezoelectric devices, since it was recognized that many possibilities for molecular sensing can be obtained once a suitable recognition layer or a molecule is covered on the crystal. Piezoelectric transducers regarded as practical detectors for real-time observation with simplicity in monitoring the biomolecular interactions; however, lack of appropriate specificity and sensitivity during calibration regarded as drawbacks of these biosensors (Marrazza, 2014).

### 3.12. Nucleic acid-based biosensors

#### 3.12.1. DNA-based biosensors

DNA biosensing devices rely based on a single strand nucleic acid (ssDNA) probe, which directly arrested at the transducer surface to quantify particular interactions through different kinds of signal transduction. DNA-based electrochemical devices are more commonly used compared to other available forms. These biosensors work based on the initial construction of a layer of DNA followed by hybridization, and subsequent production of a transformed electrical signal. In DNA biosensors, the signal transduction directly paired to sequence recognition (Teles and Fonseca, 2008; Vercoutere and Akeson, 2002). These instruments were introduced to identify genetic disease, infections, DNA damage. The system offers a rapid and rather inexpensive

substitute to old-fashioned approaches. Nucleic acid recognition elements seem to be superior to enzymes and antibodies as they are capable of being easily manufactured for numerous practices.

### 3.12.2. Aptasensors

Aptamers are specific single-stranded DNA or RNA fragments that bind to various target molecules with high affinity and specificity. These fragments are artificial ssDNA or RNA fragments chosen through the systematic evolution of ligands by exponential enrichment (SELEX). The aptasensors are a combined system of nucleic acids and electrochemical or optical biosensors, which monitor the interactions between aptamers and the target molecule (Mehrvar and Abdi, 2004; Sassolas et al., 2012; Yan et al., 2011). Aptamers are similar to monoclonal antibodies owing to high specificity for their ligands. Moreover, aptamers exhibit several appropriate features as paralleled to traditional antibodies, including prolonged shelf life, small size, and chemical stability. The prominent properties of aptamers have introduced a patent application in biosensing technology with enhanced detection limits, selectivity, and sensitivity (Song et al., 2008; Verma and Bhardwaj, 2015).

## 4. Nanomaterials

Nanotechnology and nanomaterials (NMs) have been intertwined in the manufacture of several biosensing devices owing to their outstanding physicochemical properties. Nanomaterials have prevailed over the difficulties of little selectivity and sensitivity of previous techniques (Marx et al., 2004). Nanomaterials have demonstrated the potential to be utilized in a variety of biomarker detection platforms, including graphene-based nanocomposites, carbon nanotubes (CNTs), and metal and magnetic NPs. Metal NPs and CNTs have exhibited outstanding biocompatibility and conductivity and enhanced electron transfer kinetics, respectively (Ramnani et al., 2016) whilst magnetic NPs have facilitated the separation and purification methods (Hayat et al., 2013).

## 5. Molecularly imprinted polymers

These synthetic polymers are affinity-based recognition elements that have a desired characteristic to recognize biological systems. The polymer encompasses particular apertures that are compatible to corresponding functional moieties (Haupt, 2001). This property has paid off the limitations of usual recognition elements regarding the signal transduction (Jenkins et al., 2001). Experimentally, the template molecule is absorbed either covalently or non-covalently to the functional monomers to shape a primary composite. The composite subsequently stabilized in an extremely cross-linked polymer medium through additional polymerizations within porogenic solvent. Template molecule was then eliminated to make the recognition polymer.

### 5.1. NMs-based sensors with different structures

The electrode structure is an important aspect that impacts the implementation of non-enzymatic sensors. Pt (Chen and Holt-Hindle, 2010; Sun et al., 2015), Au (Xiao et al., 2011) and Pd (Lu et al., 2011) are nanostructured metals that are extensively applied due to their great electrocatalytic properties. Along with monometallic, bimetallic or trimetallic structures, including PtNi (Gao et al., 2011), PtRu (Xiao et al., 2009), PtPd (Sun et al., 2016), PtAuPd (Xiao et al., 2010), CuAg (Xiao et al., 2010), and PdAu (Shen et al., 2015) have introduced with enhanced sensing performance as a result of their bifunctional and electronic properties. In nanocatalyst development, economic issues considered as the main concern (Miao et al., 2014; Rahman et al., 2010). Transition-metal catalysts have attracted significant attention due to low-priced, well-regulated morphologies, and high electrocatalytic activity (Mho and Johnson, 2001; Salimi and Roushani, 2005).

Enhancement in electrocatalytic activity and nanocatalysts stability is achievable by immobilizing nanocatalysts on active supports such as CNT or graphene, which offer great surface area and abundance active sites. Hence, preserve stability throughout the electrochemical examination.

## 6. Candidate biomarkers for prediabetes and the associated biosensing approaches

### 6.1. Organokines Biomarkers

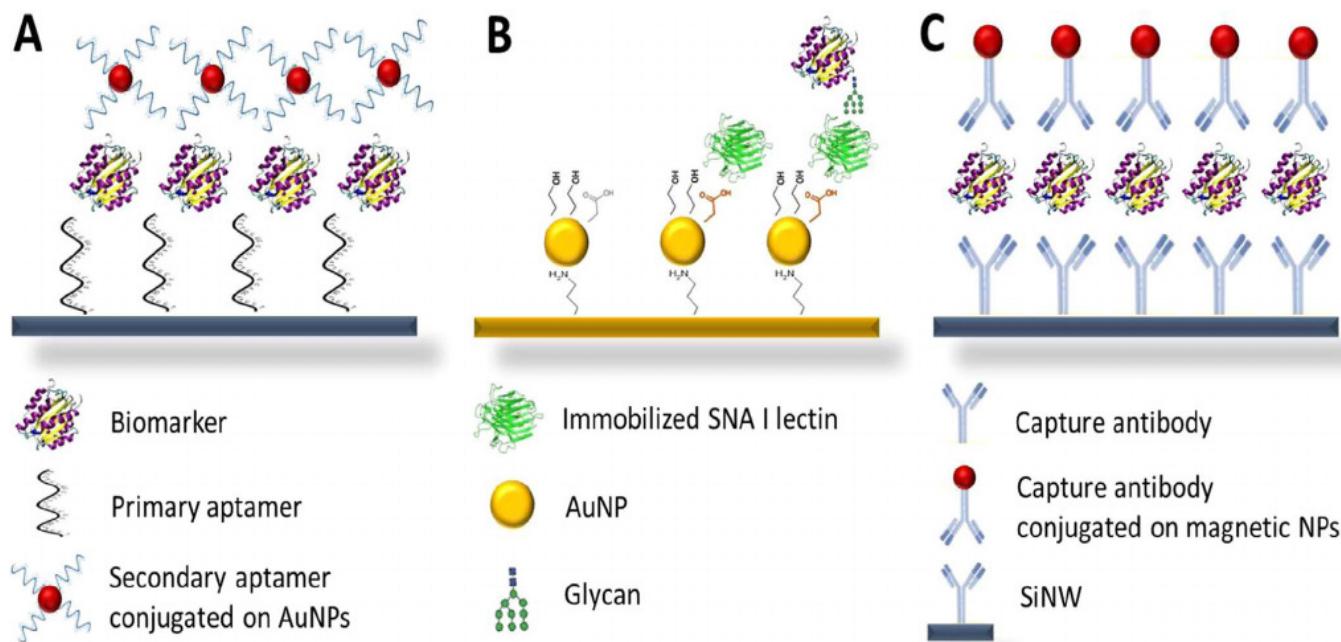
Organokines are mainly secreted from their respective tissues (e.g. adipokines from adipose tissue and myokines from muscle), which affect metabolism through autocrine, paracrine, and endocrine activity. Cardiokines and hepatokines are other classes of organokines that have been identified. In this section, the role of organokines in progress of insulin resistance and prediction of T2D will be discussed.

#### 6.1.1. Adipokines as biomarkers of insulin resistance

The growing incidence of obesity is closely related to the increased occurrence of T2D. Adipose tissue as a highly active metabolic and endocrine organ regulates lipid and glucose metabolism and produce a wide range of cytokines called adipokines (Zhang and Zhang, 2009). Obesity dysregulates adipokines secretion and leads to dysregulation of insulin as well as insulin sensitivity. Thus, the alternation in secreted adipokines profile is associated with insulin resistance and obesity, which makes adipokines as promising candidate biomarkers for the screening, diagnosis, and therapeutic monitoring of obesity, insulin resistance, and prediction of T2D recurrence (Jung and Choi, 2014), and can be determined by quantifying the blood circulating levels (Antuna-Puente et al., 2008). A number of adipokines such as adiponectin, retinol binding protein-4 (RBP4), adipocyte fatty acid-binding protein (A-FABP), leptin, vaspin, and chemerin have been indicated to be engaged in insulin resistance development (Jung and Choi, 2014). Adiponectin is an abundant 244-amino acid plasma protein that primarily produced in adipose tissue and involved in metabolism of lipid and glucose; particularly, in the regulation of insulin resistance (Ojeda et al., 2015; Thanakun et al., 2014). Typical adiponectin concentration in plasma varies from 5.0 to 30 mg mL<sup>-1</sup> (from 0.17 to 1.0 mmol/1), which represents 0.01% of total blood proteins (Brazaca et al., 2016). The adiponectin acts as a metabolic regulator by acting through adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). The interaction between the adaptor protein and AdipoR1 appear to initiate adiponectin-mediated signaling and downstream events, including fatty acid oxidation and gluconeogenesis (Hug et al., 2004). Lower levels of serum adiponectin lead to declining fatty acid oxidation in the liver and skeletal muscles which causes insulin resistance. These events ultimately raise the blood glucose and subsequently lead to T2D (Mao et al., 2006). Currently, ELISA kits are the common methods to quantify adiponectin; however, the procedure and the related analysis are time-consuming. Recently, novel biosensor for point-of-care application with nanomolar detection limit was designed (Brazaca et al., 2016; Ojeda et al., 2015). Ojeda et al. (2015) reported an electrochemical immune sensor for adiponectin detection. This platform consists of screen printed carbon electrodes (SPCEs) changed with functionalized double walled carbon nanotubes (DWNTs) for antibody immobilization. The prepared adiponectin immune sensor exhibited good reproducibility, excellent storage stability, and selectivity in comparison with the existing ELISA kits. The retinol binding protein 4 (RBP4) is a 201-amino acid peptide, which highly expressed in adipose tissue in mature, lipid laden adipocytes. RBP4 acts as a retinol (vitamin A) transporter in the blood stream from the liver to the peripheral tissues (Jabbari et al., 2015). Serum level of RBP4 is linked to obesity and insulin resistance by impairing insulin action within adipose tissue, muscles, and liver (Kotnik et al., 2011). Over expressed RBP4 in fat tissue down regulates production of glucose transporter 4 (GLUT4) in

adipocytes membrane, which leads to a decline in the uptake of glucose from the blood. Increasing RBP4 levels in serum also stimulates liver synthesis of gluconeogenic enzyme and phosphoenolpyruvate carboxykinase (PEPCK), which impairs muscular insulin signaling, and alters insulin sensitivity partly via modification in the quantity of tyrosine-phosphorylated insulin receptor substrate-1 (IRS1) and activation of PI3K (Yang et al., 2005). Measurement of urinary RBP4 is known as a functional biomarker to determine the risk of insulin sensitivity and T2D. Lee et al. (2008) established a novel SPR-based SELEX based on a single stranded aptamer that has been recognized for detection of RBP4 with high affinity. This SPR-based biosensing platform demonstrated a detection limit of 75 nM. The enzyme-linked antibody-ssDNA aptamer sandwich (ELAAS) platform was developed to distinguish adipokines RBP4, visceral adipose tissue-derived serpin (Vaspin) and nicotinamide phosphoribosyltransferase (Nampt/visfatin) for T2D identification. In this system, combination of aptamer and antibody applied, in which aptamers were functioning as arresting probe while HRP-linked polyclonal antibodies involved in production of signal. Linear range of detection for RBP4 reported to be between 78 ng mL<sup>-1</sup> to 5 µg mL<sup>-1</sup>. By utilizing aptamers as capturing probes, the sensitivity of the method enhanced in comparison to that of an SPR system with similar detection limits in comparison with the western blot approach for RBP4 detection. This method reported to be simple, reproducible, and highly sensitive (Lee et al., 2012). Vaspin is a member of adipokines that widely expressed in visceral fat tissue (Blüher, 2012). Increased serum concentration of vaspin is associated with increased fat mass (Wada, 2008). The precise role of vaspin on glucose dysregulation in humans is not well understood. However, the tissue expression and elevated plasma levels of vaspin is associated with obesity, insulin resistance, and carbohydrate tolerance. Vaspin regulates glucose tolerance by producing antiapoptotic, proliferative, and protective signals in endothelial cells by binding to GRP78/voltage-dependent anion channel complex during endoplasmic reticulum (ER) stress in obesity and diabetes. Vaspin also protects endothelial cells via inhibitory effects on NF-κB (Dimova and Tankova, 2015). In the early stages of diabetes, the increased vaspin production is involved in the process of carotid plaque formation. Formation of new carotid plaque is common in patients with T2D and is a main risk factor in cardiovascular disease (CVD) (Lundman et al., 2005). Studies confirmed the positive association between vaspin and CVD via carotid stenosis. The associations between vaspin levels and obesity, severe insulin resistance, and the development of T2D have been demonstrated; therefore, vaspin may serve as a new biomarker (Dimova and Tankova, 2015). Administration of vaspin to animal models of obesity has been demonstrated a significant recovery in hyperglycemia and decline in food intake. Thus, it involves in the management of hyperglycemia and obesity (Bluher, 2012). Lee et al. (2012) developed an ELAAS assay for early detection of T2D, capable to detect vaspin from 39 ng mL<sup>-1</sup> to 2.5 g mL<sup>-1</sup> with a detection limit of 39 ng mL<sup>-1</sup>. In 2015, Ahmad Raston and Gu, developed two different aptamers with distinctive binding sites on vaspin using graphene oxide-based systematic evolution of ligands by exponential enrichment (GO-SELEX). Later, the researchers designed a sandwich-type SPR based aptasensor by applying one of these aptamers as capture probe and another as reporter probe. While the biotinylated capture aptamers immobilized on SPR gold chip, the reporter aptamers were conjugated with AuNPs to enhance the detection of target (Fig. 1A). In presence of vaspin, the sandwich system completed and the responses analyzed using SPR instrument. This platform demonstrated a detection limit of 3.5 ng mL<sup>-1</sup> (78 pM), which revealed an improved sensitivity of about 114-fold compared to that of the single aptamer system. The linear range of detection for vaspin was reported to be 0.1–7 ng mL<sup>-1</sup>, which is in the physiological range of interest. Thus, the AuNPs strongly could increase sensitivity of the system (Ahmad Raston and Gu, 2015). Ahmad Raston et al. (2017) developed a sensitive and highly selective biosensor using this cognate aptamer duo system with a new lateral flow strip assay (LFSA). The detection limit for this LFSA platform was demonstrated to be 0.137 nM

and 0.105 nM in the buffer and spiked human serum condition, respectively. The LFSA system demonstrated a simple and effective strategy for vaspin detection. Leptin is a hormone of 167-amino acids, which primarily produced in adipose tissue (Münzberg and Morrison, 2015). Leptin performs several roles in endocrine and immune systems such as, hematopoiesis, wound healing, and glucose homeostasis. The level of leptin is relative to body fat and is closely associated with obesity (Paspala et al., 2012). This association is due to a direct relationship between the circulating leptin levels in obesity, hyperplasia, and hypertrophy (Jung and Choi, 2014). The leptin signaling is transmitted by the Janus kinase, signal transducer and activator of JAK-STAT transcription pathway (Münzberg and Morrison, 2015). It also involved in the PI3K and ERK-1/2 regulations as supposed to be the main mechanism involved in obesity (Paz-Filho et al., 2012). There were some attempts for screening leptin by biosensing approaches (Chen et al., 2010; Hidaka et al., 1999). He et al. (2013) reported two chemiluminescent immunosensors to identify human leptin using hemin/G-quadruplex DNAzymes to improve the detecting signals. The system composed of nucleic acid artificial enzymes with peroxidase representing activity as catalytic amplifier that has been utilized in several biosensors. Easier functionalization and higher stability against hydrolysis are some of their benefits over natural enzymes. According to the mentioned study, ultrasensitive immunosensor based on chemiluminescent reactions displayed great sensitivity and selectivity indicating a limit of detection of 1.9 pg mL<sup>-1</sup>. Later in 2015 the group achieved a lower limit of detection of 0.3 pg mL<sup>-1</sup> using hemin/G-quadruplex DNAzymes and Fe<sub>3</sub>O<sub>4</sub>/polydopamine (PD)/Au NPs (He et al., 2015). Dong et al. (2014) established a novel extremely delicate sandwich immunosensor to measure serum leptin using glassy carbon electrodes altered with single-walled carbon nanotubes/chitosan film. Single-walled carbon nanotube (SCNTs)/chitosan (CS) composite have exhibited outstanding mechanical, biological, and photoelectric features and extensively used in construction of electrochemical biosensors. The fat tissue-secreted protein, chemerin is involved in adipocyte differentiation and stimulates lipolysis. The protein is primarily produced as prochemerin and subsequently activated by the serine proteases through cleavage of C-terminus during inflammation and coagulation (Li et al., 2014). Many clinical studies have shown the association between chemerin and insulin sensitivity, obesity, inflammation, and other metabolic disorders. Chemerin reported to contribute to inflammation, oxidative stress, vascular insulin signaling, and vascular dysfunction in diabetes- and obesity-related diseases (Neves et al., 2016). Serum concentrations of chemerin are elevated in obese, insulin-resistant, and inflammatory states by activating immune cells, stimulating macrophage linkage to fibronectin and vascular cell adhesion molecule-1 (VCAM-1). Attracting immune cells in turn alters insulin sensitivity and glucose uptake in skeletal muscle and adipocytes. Chemerin was also associated with the parameters of T2D including BMI, TG levels, and blood pressure (Ali and Al Hadidi, 2013). It has been proposed that chemerin might be regarded as a beneficial detector marker for insulin sensitivity prior to beginning of metabolic disorders (Park et al., 2015) though there is no report for biosensor-based detection of this marker. Adipocyte fatty acid binding protein (A-FABP), adipocyte P2 (aP2) or FABP4, is expressed by lipocytes and considered as adipocyte differentiation marker. The biological activity of A-FABP is to bind to hydrophobic ligands and thus facilitating their moving to the particular compartments in the cell (Furuhashi et al., 2014). Increased circulating A-FABP levels are observed in obese individuals. Numerous studies have suggested the role of A-FABP in supporting insulin resistance and impaired insulin action through its pro-inflammatory properties associated with lipopolysaccharide-induced inflammation by a direct response loop formed with a signaling cascade of JNK/c-Jun (Hoo et al., 2017). A-FABP promotes insulin resistance and hypertriacylglycerolemia by stimulating the TNF-α production in adipose tissue and induction of lipolysis (Kralisch and Fasshauer, 2013). A-FABP also affects systemic inflammation by increasing NF-κB activity leading to inflammatory responses



**Fig. 1.** (A) Schematic illustration of a typical sandwich format biosensor based on primary and secondary aptamers conjugated on gold nanoparticle (AuNPs). (B) Basic structure of lectin biosensor fabrication and recognition using layer-by-layer approach (from left to right): formation of a linker layer on a gold surface; deposition of AuNPs and formation of a second layer on AuNPs, activation of carboxyl group and subsequent covalent attachment of SNA I lectin and ultimately application of the lectin biosensor in the biorecognition of a glycoprotein fetuin-A. (C) Illustration of the fabrication and performance of silicon nanowire (SiNW) transistor as an immunosensor using captured antibody conjugated on magnetic nanoparticles.

such as cytokines and pro-inflammatory enzymes productions (Choi et al., 2011). Therefore, the importance of FABP4 in predicting insulin resistance and its association with adiposity and obesity represent FABP4 as a candidate biomarker for insulin resistance and obesity (Park et al., 2015). However, no statement for biosensor-based detection of this marker has been reported. Apelin is a novel adipokine secreted from adipocytes. In obesity and insulin-resistance condition, apelin concentration is raised. Apelin involved in glucose homeostasis and improve glucose tolerance and utilization by increasing the peripheral glucose uptake in skeletal muscle, adipocytes, and myocardial tissue. Apelin exerts its effects through insulin-independent pathways by stimulation of the AMP-activated protein kinase (AMPK) pathway. These results suggest the importance of apelin as a biomarker for predicting T2D (Castan-Laurell et al., 2011). Biosensor-based detection of apelin has not been reported yet.

#### 6.1.2. Hepatokines as biomarkers of insulin resistance

The liver does contribute to the metabolism of lipid and glucose by releasing proteins into the blood stream, named as hepatokines. These proteins, including Fetuin-A and Fibroblast growth factor 21 (FGF21) indicated new insight into the association of the liver in insulin resistance and the associated diseases (Choi, 2016). Fetuin-A (a2-HS-glycoprotein) is a hepatokine released into the blood stream. Fetuin-A is an important element of ordinary and pathological courses such as vascular calcification, insulin resistance, breast tumor cell proliferative signaling, and keratinocytes migration (Mori et al., 2011). High serum concentrations of fetuin-A were observed in individuals with fatty or inflamed liver (Yilmaz, 2012). Therefore, high serum fetuin-A level is related to accumulation of hepatic fat, which is related to increased risk of T2D (Dabrowska et al., 2015). Further, there is a strong relationship between fetuin-A and the degree of insulin resistance. In liver and muscle, the protein inhibits the insulin receptor tyrosine kinase that leads to insulin signal transduction inhibition and insulin resistance. Furthermore, fetuin-A binds to toll-like receptor 4 (TLR4) and functions as a potential endogenous ligand, which results in inflammation

and insulin resistance (Pal et al., 2012). Besides, fetuin-A represses adiponectin production, which further leads to improved insulin resistance. Therefore, it is considered as a beneficial candidate biomarker of obesity, insulin resistance, and T2D (Park et al., 2015). There are some reports regarding to quantification of this marker, using biosensing approaches (Table 2). Bertok et al. (2013) presented an ultrasensitive electrochemical lectin based biosensor for detection of fetuin-A down to attomolar (aM) concentration using gold NPs and self-assembled monolayers (SAMs). Initially, a linker layer (NH<sub>2</sub>-terminated alkanethiol-AT) was formed on AuNPs and subsequently coated with SAM comprising of 11-mercaptopoundecanoic acid and 6-mercaptophexanol. Finally, biorecognition of fetuin accomplished through carboxyl group activation and lectin adhesion. Note that lectins are proteins that recognize and bind specifically to the carbohydrate part of glycoproteins (Fig. 1B). Lectin-based biosensors are regarded as a typical analytical device in glycomics. By the formation of SAMs as a linker to deposit lectins on the outward of gold NPs as biorecognition element, the surface loading capacity for lectin has been increased. The detection limit for this biosensor was reached to 1 aM. Nagaraj et al. (2010) developed another lectin-based biosensor called "NanoMonitor". This ultrasensitive diagnostic platform performed rapid label-free analysis of fetuin with great sensitivity. NanoMonitor technology comprised of a chip made of silicon with a row of gold electrodes establishing numerous sensor sites and functioned on the basis of electrochemical impedance spectroscopy. Upon binding of fetuins to lectins at every nanowell, an electrical disturbance takes place and further leads to a variation in the impedance. The sensitivity and specificity of NanoMonitor was about 1 pg mL<sup>-1</sup> and showed the broad linear range (< 1 pg mL<sup>-1</sup> to > 10 ng mL<sup>-1</sup>). Human fibroblast growth factor 21 (FGF21) is a plasma protein composed of 181 amino acid, which have been received attentions as a central element in both lipid and glucose metabolism. The FGF21 is formed primarily in the liver, adipose tissue, skeletal muscles, and pancreas (Park et al., 2015). It has been shown that FGF21 enhances skeletal muscle glucose uptake by its antilipolytic effect and promotes insulin sensitivity in the liver

**Table 2**  
Biosensing approaches for Organokine biomarkers detection.

Biomarker	Type of assessment	Sensing platform	Transduction type	Sensor features	Reference
Adiponectin	Predictive	Immunosensing approach for adiponectin using reduced graphene oxide carboxymethylcellulose hybrid as electrode scaffold	Electrochemical Electrochemical impedance spectroscopy (EIS)	LOD: 61 ng mL <sup>-1</sup> LR: 0.5–10 µg mL <sup>-1</sup> RSD: 5.2–5.9% LOD: 7.0 nmol L <sup>-1</sup> LR: 0.025–0.750 µmol L <sup>-1</sup>	(Arenas et al., 2016)
	Predictive	Immobilized adiponectin transmembrane receptors on gold electrode surfaces by using 3-mercaptopropionic acid (3-MPA)	Electrochemical Cyclic Voltammetry (CV) and EIS	LOD: 7.0 nmol L <sup>-1</sup> LR: 0.025–0.750 µmol L <sup>-1</sup>	(Brazaca et al., 2016)
	Predictive	Immuno-sensor using screen printed carbon electrodes (SPCEs) altered with functionalized double walled carbon nanotubes (DWCNTs)	Electrochemical (CV)	LOD: 14.5 ng mL <sup>-1</sup> LR: 0.05–10.0 ng mL <sup>-1</sup> RSD: 6.1–6.8%	(Ojeda et al., 2015)
Vaspin	Predictive	A streptavidin-coated 96-well plate was used for aptamer immobilization	Enzyme-linked antibody aptamer sandwich (ELAAS) with optical (colorimetric) assay	LOD: 78 ng mL <sup>-1</sup> LR: 39 ng mL <sup>-1</sup> LOD: 19 ng mL <sup>-1</sup>	(Lee et al., 2012)
RBP4	Predictive	A cognate aptamer duo and gold-nanoparticle (AuNPs)	Optical (SPR)	LOD: 3.5 ng mL <sup>-1</sup>	(Ahmad Rastan and Gu, 2015)
Nicotinamide phosphoribosyl transferase (Nampt/visfatin)	Predictive	Vaspin ssDNA aptamer- immobilized on a gold chip	Optical Surface plasmon resonance (SPR) Optical (observed by naked eye)	LOD: 75 nM	(Lee et al., 2008)
Vaspin	Predictive	Lateral flow strip assay (LFSA) based on pair of aptamers-functionalized AuNPs	Optical (SPR based immunoassay) Electrochemical (EIS)	LR: 0.137–25 nM	(Ahmad Rastan et al., 2017)
Fetuin A	Predictive	KOH-treated gold (Au)-coated SPR chip Gold nanoparticles	Label-free lectin biosensor Electrochemical (EIS)	LOD: 0.7 ng mL <sup>-1</sup> LOD: 1 aM	(Vashist et al., 2014) (Bertoli et al., 2013)
Glycoproteins	Predictive	Nanoporous alumina membrane that forms a high density of nanowell on top of each gold electrode	LOQ: 1 pg mL <sup>-1</sup> LR: 1 pg mL <sup>-1</sup> –10 ng mL <sup>-1</sup>	(Nagaraj et al., 2010)	
Glycan (Oligosaccharide chains attached to protein)	Predictive	Immunosensor with Au-Pyrrole Propyl Acid-Polypyrrole Nanocomposite 96-well plates containing anti human Leptin monoclonal antibody and hemin/G-quadruplex DNAzymes as signal amplifier	Electrochemical (impedance spectroscopy) Optical (Chemiluminescent (CL) immunoassay)	LOD: 10 ng mL <sup>-1</sup>	(Chen et al., 2010)
Leptin	Diagnosis and Prognosis	Functional superparamagnetic Fe3O4/PD/Au nanocomposites nanocomposite	Optical (Sandwich chemiluminescence immunosensor)	LOD: 0.3 pg mL <sup>-1</sup> LR: 1.0–800 pg mL <sup>-1</sup> RSD: 3.6%	(He et al., 2015)
	Diagnosis and Prognosis	Silica surface of the sensing chip and triethoxysilane derivatives for chip modification	Optical (waveguide-mode sensor)	LOD: 100 ng mL <sup>-1</sup>	(Tamura et al., 2013)
	Diagnosis and Prognosis	Carbon nanotubes/chitosan membrane modified electrodes	Electrochemical (Amperometric immunosensor)	LOD: 30 pg mL <sup>-1</sup> LR: 0.05–500 ng mL <sup>-1</sup>	(Dong et al., 2014)
IL-6	Diagnosis and Prognosis	Silicon nanowire (SiNW) and (FeCo)Si nanoparticles	Electrochemical (potentiometric)	LOQ: 5 pM LR: 75 fM	(Jiang et al., 2013)
	Diagnosis and Prognosis	Surface of the combination tapered fiber-optic biosensor (CTFOB) CTFOB probe Sensor chips surface	Optical (fluorescence) Sandwich immunoassay Optical (SPR)	LOQ: 5 pM LR: 5 pM–500 pM LOD: 1.3 ng mL <sup>-1</sup>	(Kapoor and Wang, 2009)
	Diagnosis and Prognosis	Graphene Oxide	Electrochemical (amperometric field effect transistor (FET))	LOD: 4.7 pg mL <sup>-1</sup>	(Chou et al., 2010)
	Diagnosis and Prognosis	Graphene Oxide post-treatment using atmospheric ethanol by Chemical Vapor Deposition (CVD)	Electrochemical (amperometric)	LOD: 1.53 pg mL <sup>-1</sup> LR: 4.7–18.8 pg mL <sup>-1</sup>	(Huang et al., 2013)
	Diagnosis and Prognosis	ZnO/SiO <sub>2</sub> /Si surface	Microelectromechanica (surface acoustic wave)	LOD: 2.27 fg	(Huang et al., 2015)
					(Krishnamoorthy et al., 2008)

\*LR: linear range, LOD: limit of detection, LOQ: limit of quantification, RSD: relative standard deviation.

(Emanuelli et al., 2014). Elevated FGF21 concentrations in serum have been related to insulin resistance and hemoglobin A1c (HbA1c) (Xiao et al., 2015). Recent studies have demonstrated a distinct alteration in serum FGF21 level in T2D. It has also found that an increase in circulating FGF21 take place prior to the incidence of overt diabetes. Therefore, this makes the FGF21 as a strong predictive biomarker of diabetes and prediabetes (Chen et al., 2011). Nevertheless, there have been no reports for biosensor-based detection of this marker.

#### 6.1.3. Myokines as biomarkers of insulin resistance

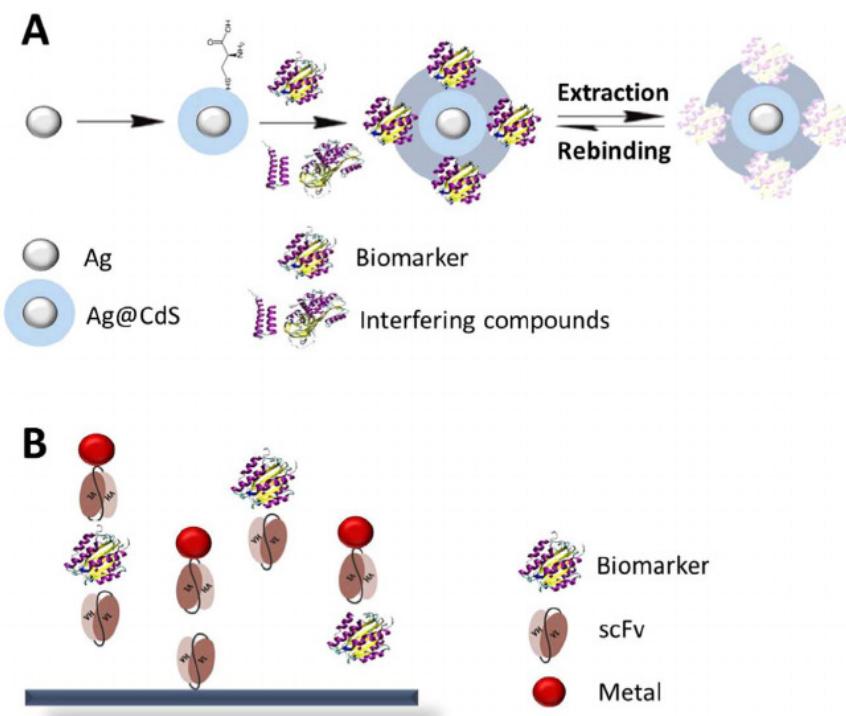
Muscles similar to adipocyte tissue can act as a secretory organ. Myokines are factors that released by skeletal muscles with autocrine, paracrine, and endocrine effects. These factors increase glucose uptake and fat oxidation (Pratesi et al., 2013). In addition, myokines increase glucose production in the liver in the course of exercise, in adipose tissue lipolysis, and probably exert an inhibitory consequence on tumor development. Furthermore, it has been demonstrated that these factors improve insulin secretion and glycemia (Schnyder and Handschin, 2015). Myokines, such as Interleukin-6 and Myostatin are also known biomarkers for insulin resistance and T2D (Pedersen and Hojman, 2012). Interleukin-6 (IL-6), a pro-inflammatory cytokine, is a myokine positively related to inflammation and obesity-linked insulin resistance. IL-6 activates several genetic factors, including IRS, AP-1, and NF- $\kappa$ B in hepatocytes and adipocytes and promotes both localization and general inflammatory reactions to arbitrate insulin resistance (Ansari et al., 2008; Pedersen and Hojman, 2012). Several mechanisms appeared to be involved in insulin resistance induced by IL-6. These include c-Jun NH2-terminal kinase1/2 (JNK1/2) activation, suppressor of cytokine signaling3 (socS3) mRNA accumulation, as well as raising tyrosine-protein phosphatase non-receptor type 1 (PTP1B) activity. These data indicate the feasibility of IL-6 as a biomarker (Nieto-Vazquez et al., 2008). Currently, Western blotting and ELISA are the common methods for detection of IL-6. To achieve a low-cost, facile, and real-time quantification of IL-6, some attempts have been recently made to introduce sensitive sensors (Table 2). Jiang et al. (2013) employed a novel silicon nanowire (SiNW) transistor with highly homogen (FeCo)Si NPs, to achieve precise and fast measurement of IL-6 in unprocessed human serum (Fig. 1C). The FeCo nanoparticles have higher magnetization levels than common magnetic nanoparticles ( $\text{Fe}_2\text{O}_3$  and  $\text{Fe}_3\text{O}_4$ ); however, severe oxidation issue makes it incompatible with human body. In this study, a unique approach for the development of (FeCo)Si core-shell assembly to coat iron-cobalt material was presented. The optical features of NPs have not been influenced by coating due to its transparency. The prepared NPs act as a label and SiNW functions as a sensor. Capture antibodies are immobilized on SiNWs. Then different doses of specific biomarkers were added and incubated. The immune sandwiches were completed by the addition of functionalized magnetic nanoparticle antibodies. Current-voltage curves of the transistor were then measured and shown to be proportional to the biomarker concentration. This novel method was capable to detect IL-6 between 75 pm to 50 pM, which represents the high sensitivity of this sensor. Huang et al. (2013) designed an electrical graphene oxide-based amperometric field-effect transistor (FET) biosensor, which can sense clinical relevant quantities of 4.7 pg mL<sup>-1</sup>. In 2015, the group improved the detection limit down to 1.53 pg mL<sup>-1</sup> (Huang et al., 2015). Krishnamoorthy et al. (2008) reported an achievement in reaching to the detection limit down of femto-gram levels (2.27 fg) with extended linearity by developing a novel ZnO/SiO<sub>2</sub>/Si guided shear horizontal surface acoustic wave (SH-SAW) biosensor.

Myostatin is a recently identified negative regulator of muscle growth acting through inhibiting the proliferation and differentiation of myoblasts (Ríos et al., 2002). It also exerts direct influence on insulin-stimulated metabolism, adiponectin expression in the circulation, and insulin sensitivity and metabolism (Allen et al., 2011). Myostatin inhibition indicated to have several benefits on improvement

of insulin sensitivity and in the pathogenesis of T2D, thus, circulating myostatin levels could be a potential biomarker for the disease (Wang et al., 2012) whilst no biosensor-based practice has been reported till now.

#### 6.2. Protein biomarkers

In addition to the above organokines, a number of other protein biomarkers have been introduced which will be further discussed. These include ferritin, cathepsin D, c-reactive protein, glucagon-like peptide-1, plasminogen activator inhibitor-1, and interleukin-1 receptor antagonist. Ferritin, a hallow globular protein consisting of 24 subunits, is the main protein that binds non-heme iron within every cell type (Massover, 1993). Ferritin with a molecular mass of 450 kDa regarded an iron reservoir protein in the spleen, liver, and skeletal muscle. Ferritin releases iron in the presence of superoxide anion or any other reducing agents (Decker and Welch, 1990). Iron is critical for numerous physiological roles; however, unnecessary concentrations have been associated with dyslipidemia (Ramakrishnan et al., 2002) and metabolic syndrome (Sheu et al., 2003). In addition, iron has been recognized to catalyse the development of reactive oxygen species (ROS) (Puntarulo, 2005). A number of probable mechanisms have been offered in contribution of raised ferritin in the progress of T2D. Elevated blood levels of ferritin reveals the raised iron stores in the line to develop T2D through intrahepatic oxidative stress. An elevated level of ferritin has been demonstrated to benefit identifying of persons at high risk of T2D and prediabetes (Kunutsor et al., 2013). One of the best biosensor for detection of ferritin was introduced in 2016 by Yen et al. The group established a real-time biosensor using a horn-like poly-SiNW FET system. A detection limit of 50 pg mL<sup>-1</sup> for ferritin in microfluidic system was achieved. Patra et al. (2015) designed extremely delicate dual sensor (electrochemical and optical) using Ag@CdS-MIP modified PGE for ultra-trace sensing of ferritin at ( $\mu\text{g L}^{-1}$ ). Initially, Ag@CdS was altered by cysteine derivatives to facilitate polymerization occurrence on the NPs core shell surface (Fig. 2A). The polymerization was completed by activator regenerated by electron transfer-atom transfer radical polymerization (ARGET-ATRP) technique at the outward of vinyl silane altered pencil graphite electrode. The fluorescence and the electrochemical properties were enhanced following the application of the mixture of Ag and CDs in a single design. The technique was effectively practiced to examine plasma samples. Cathepsin D (Cat D) is an aspartyl-family endoprotease, produced as a glycosylated preprotein with a molecular mass of 52-kDa. The protein then changed into an active two-chained (34 and 14 kDa) enzyme (Faust et al., 1985). The main functions of cathepsin D consist of intracellular protein balance and extracellular matrix collapse (Masson et al., 2010). Elevated free fatty acid and glycation end products have been introduced in prediabetic state and demonstrated to improve cathepsin D release (Grimm et al., 2012; Tan et al., 2011). Cathepsin D has a role in obesity and chronic fat tissue inflammation as a mediator (Grimm et al., 2012). As indicated in two cohort studies of non-diabetic community residents, the protein serves as a potent biomarker of insulin resistance (Nowak et al., 2016). Gorodkiewicz and Regulska (2010) reported a SPR-based instrument for aspartyl cathepsins, such as cathepsin D. The biosensor contained pepstatin immobilized on an amine-modified gold surface and activated with N-hydroxysuccinimide (NHS) and N-Ethyl-N-(3-dimethylaminopropyl) carbodiimide (EDC). The sensor dynamic response range was reported to be 0.25–1 ng mL<sup>-1</sup> with the limit of detection of 0.12 ng mL<sup>-1</sup>. The c-reactive protein (CRP) is a main acute-phase plasma peptide, defined as the one whose blood levels rises or drops by as a minimum of 25% during the course of inflammatory diseases (Husain and Kim, 2002; Volanakis, 2001). CRP is a 224 aminoacids protein and molecular weight of 25.1 kDa synthesized by hepatocyte. Quite a few studies have suggested to the role of inflammation in the development of glucose imbalance. For instance, the relationship between raised concentra-



**Fig. 2.** (A) Synthetic process of the selective imprinted sensor based on Ag@CdS-MIP modified PGE for biomarker detection. (B) Schematic representation of the construction of recombinant antibody based immunosensor for particular biomarker detection. In the presence of biomarkers, distance from the electrode surface differs and therefore variable electrochemical response will be produced.

tions of inflammatory indicators, such as high sensitivity C-reactive protein and IL-6, has been proven with the risk of development of T2D (Grossmann et al., 2015; Shoelson et al., 2006). Data obtained from two large-population based Asian cohorts indicated that the raised CRP levels have an association with prediabetes (Pradhan et al., 2003; Sabanayagam et al., 2011). In 2012, an indication for the direct link of elevated high-sensitivity CRP levels with prediabetes, characterized by IFG and IGT, among the Indian population was reported (Jaiswal et al., 2012). In the recent years, numerous biosensors have been designed for CRP detection. One of the interesting biosensing methods for CRP detection reported by O'Reilly et al. (2015) wherein combined recombinant Ab technology with electrochemiluminescence (ECL) was introduced to produce a powerful assay to quantify CRP at the fg level. Recombinant scFv (single chain fragment variable) Abs with a strong attraction for monomeric CRP was immobilized on a Pt electrode surface (Fig. 2B). The bound CRP was sensed by the similar recombinant scFv Ab fragment attached to the luminescent metal probe. Novel methods for detection of protein biomarkers in biological samples with biosensing technology have been shown in Table 3.

Glucagon-like peptide-1 (GLP-1) is a 30-amino acid hormone generated in response to food ingestion in the intestinal epithelial endocrine L-cells (Holst, 2007; Kieffer and Francis Habener, 1999). The primary 37-amino acid peptide is produced and subsequently changed by prohormone convertases to form active GLP-1<sub>7–37</sub> and GLP-1<sub>7–36</sub> amide (Holst, 2007). GLP-1 is powerful insulin secretagogues, motivating release of insulin and inhibiting glucagon secretion in a glucose dependent fashion (Nauck et al., 1993). Previous studies have shown conflicting results with a GLP-1 concentration in normal, decreased, and increased levels in prediabetes and diabetes. The low GLP-1 level was reported to relate to a risk of T2D while positively correlated with milder obesity and better insulin sensitivity (Lastya et al., 2014; Færch et al., 2015). Zhang et al. (2012) investigated the serum GLP-1 levels in Chinese people with prediabetes and newly diagnosed diabetes through the oral glucose tolerance test (OGTT). According to the results, the total GLP-1 levels and its response to

glucose reduced considerably in IFG+IGT group in comparison with isolated IFG or IGT individuals. Osborne et al. (2016) designed a dual-monoclonal sandwich immunoassay particular for GLP-1, in which streptavidin capture biosensor tips utilized for arresting biotinylated GLP-1. The reported detection limit of this method was 3 ng mL<sup>-1</sup>. Plasminogen activator inhibitor 1 (PAI-1), a serine protease inhibitor (serpin), is a 50-kDa single-chain glycoprotein representing around 10% of the plasma proteins (Gils and Declerck, 2004). In blood, PAI-1 occurs in two main active and latent forms. The latent PAI-1 is functionally inactive whilst the active PAI-1 efficiently suppresses target proteases (Blake et al., 2009). All serpins are made of 400 residues with a molecular weight of 38–70 kDa (reliant on glycosylation levels). The PAI-1 containing 379 or 381 amino acids (Gils and Declerck, 2004) and regarded as the main blocker of the fibrinolysis. The main function of PAI-1, which is inhibition of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), caused a decrease in plasmin formation. Elevating levels of PAI-1 change the balance of hemostasis to thrombosis, which in turn raises the CVDs. Elevated PAI-1 level in plasma was observed in individuals with T2D (Damare et al., 2014). A considerable number of additional observational studies reported the associations of PAI-1 with T2D (Eliasson et al., 2003; Kanaya et al., 2006; Kitagawa et al., 2006; Soares et al., 2010). The plasma PAI-1 level was improved in individuals with HbA1c of 5.7–6.4% without IFG or IGT and in individuals with IFG/IGT, proposing higher risk for upcoming diabetes and cardiovascular disorders (Xu et al., 2011). Yarmolinsky et al. (2016) accomplished a comprehensive review and meta-analysis of observational studies investigated the relation between PAI-1 and T2D. The results supported the link between PAI-1 and T2D. Interleukin-1 receptor antagonist (IL-1ra) is a pro-inflammatory mediator, which is frequently recognized as pro-inflammatory cytokines and/or chemokines resulting in inflammation in their particular tissues where they are produced (Larsen et al., 2007). Several features are indicated in the production of these pro-inflammatory mediators (Akash et al., 2013). Interleukin 1 $\beta$  (IL-1 $\beta$ ) is a potent pivotal pro-inflammatory cytokine that is implicated

**Table 3**

Biosensing approaches for protein biomarkers detection.

Biomarker	Type of assessment	Sensing platform	Transduction type	Sensor features	Reference
Ferritin	Predictive	Gold surface of sensor chip	Optical (SPR immunosensor)	LR: 0.2–200 ng mL <sup>-1</sup>	(Chou et al., 2004)
	Predictive	Cotton thread immunoassay device combined with gold nanorod (GNR) reporter probe	Electrochemical Anodic stripping voltammetry (ASV)	LOD: 1.58 ng mL <sup>-1</sup> LR: 5–5000 ng mL <sup>-1</sup> RSD: 8.6%	(Song et al., 2017)
	Predictive	Horn-like polycrystalline-silicon nanowire	Electrochemical (Conductometric) field-effect transistor	LR: 50–500 ng mL <sup>-1</sup>	(Yen et al., 2016)
	Predictive	Iron-oxide nanoparticles (IONPs)	Optical (Photonic Crystals)	LOD: 26 ng mL <sup>-1</sup> RSD: 13.1%	(Peterson et al., 2014)
	Predictive	Gold nanoparticle trimer probe in combination with dry-reagent cotton thread immunoassay tool	Optical	LOQ: 10 ng mL <sup>-1</sup> LR: 10–20,000 ng mL <sup>-1</sup> RSD: 7.9%	(Mao et al., 2015)
	Predictive	Imprinted Ag@CdS core shell NP	Electrochemical/Optical	LOD: 0.65 µg L <sup>-1</sup> LR: 1.99 – 23.43 mg L <sup>-1</sup> /	(Patra et al., 2015)
				LOD: 1.3 µg L <sup>-1</sup> LR: 4.0–91.0 mg L <sup>-1</sup>	
Cathepsins	Predictive	Gold chips and Immobilization of pepstatin A	Optical Surface Plasmon Resonance Imaging (SPRI)	LOD: 0.12 ng mL <sup>-1</sup> LR: 0.25 – 1.0 ng mL <sup>-1</sup>	(Gorodkiewicz and Regulska, 2010)
CRP	Prognosis	Gold electrodes	Electrochemical (EIS immunosensor)	LOD: 176 pM LR: 0.5–50 nM	(Bryan et al., 2013)
	Prognosis	Gold interdigitated (GID) electrodes	Electrochemical (non-Faradaic impedance spectroscopy)(NFIS)	LOD: 100–500 pg mL <sup>-1</sup> RSD: 13%	(Qureshi et al., 2010)
	Prognosis	Magnetic beads	Electrochemical (differential pulse voltammetry) (DPV)	LOD: 0.2 mg L <sup>-1</sup>	(Centi et al., 2009)
	Prognosis	ARChip Epoxy	Optical (Fluorescence)	LOQ: 1 µg L <sup>-1</sup> LR: 0.001–100 mg L <sup>-1</sup>	(Pultar et al., 2009)
	Prognosis	Magnetic beads	Magnetic immunosensor	LOQ: 25 ng mL <sup>-1</sup> LR: 25 ng mL <sup>-1</sup> – 2.5 µg mL <sup>-1</sup>	(Meyer et al., 2007)
	Prognosis	Au microwire electrode	Electrochemical impedance spectroscopy (EIS)	LR: 3.125–25 mg L <sup>-1</sup>	(Songjaroen et al., 2016)
	Prognosis	2-methacryloyloxyethyl phosphorylcholine (MPC) polymer	Mass-based surface acoustic waves (SAW)	LOD: 10 mg L <sup>-1</sup>	(Pomowski et al., 2015)
	Prognosis	Nanoelectrode array with patterned vertically aligned carbon nanofibers	Electrochemical Cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS)	LOD: 90 pM	(Gupta et al., 2014)
	Prognosis	Immune cell	Optical	LOD: 0.04 mg L <sup>-1</sup>	(Hwang et al., 2016)
	Prognosis	Electrochemical probe	Electrochemiluminescence (ECL)	LOD: 1 fg mL <sup>-1</sup> LR: 0.1 – 10 mg L <sup>-1</sup>	(O'Reilly et al., 2015)
	Prognosis	Au film and Au nanoparticles (AuNPs)	Optical (SPR)	LOD: 10 pM	(Wu et al., 2016)
	Prognosis	Plastic optical fibre	Optical (SPR)	LOD: 0.009 mg L <sup>-1</sup>	(Aray et al., 2016)
	Prognosis	Cobalt-based commercial amorphous ribbon	Giant magnetoimpedance (GMI)	LOQ: 1 ng mL <sup>-1</sup> LR: 1–10 ng mL <sup>-1</sup>	(Yang et al., 2015)
	Prognosis	Eu-NPs and carboxylate-modified polystyrene microparticles	Optical Chemiluminescence (CL)	LOD: 0.03 µg mL <sup>-1</sup> LR: 1–30 µg mL <sup>-1</sup>	(Huttunen et al., 2016)

\*LR: linear range, LOD: limit of detection, LOQ: limit of quantification, RSD: relative standard deviation.

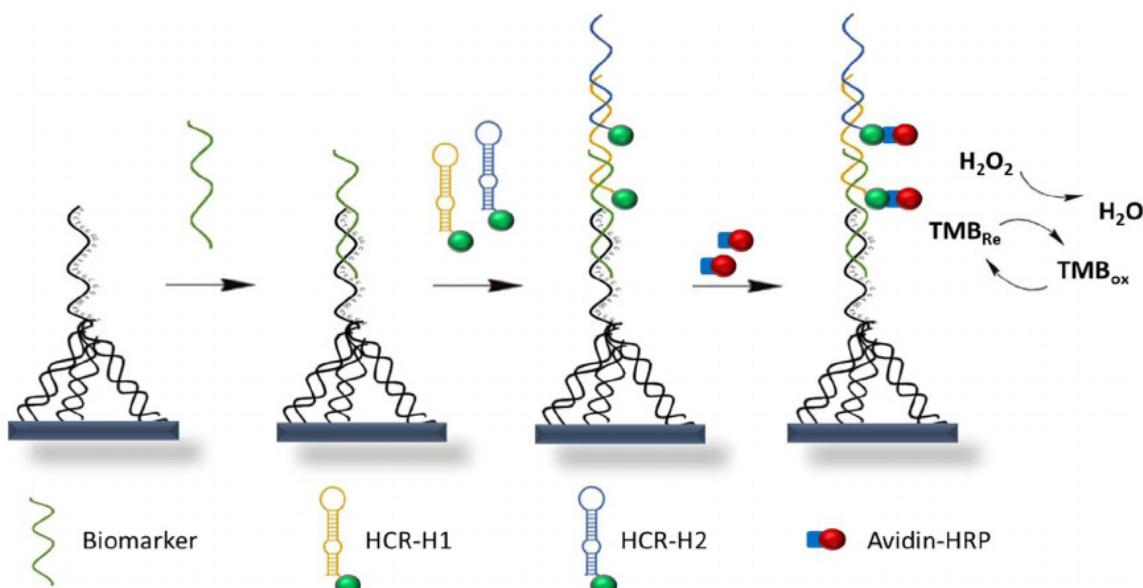
in the development of chronic inflammatory illnesses such as T2D and cardiovascular diseases (Dinarello, 2011). IL-1 $\beta$  signaling is blocked by IL-1Ra, a naturally occurring regulator of interleukin 1 (IL-1) cytokines. IL-1Ra attaches to the IL-1 receptor and thereby avoids binding

of both IL-1a and IL-1b, which are related cytokines (Herder and Donath, 2015). Chronic subclinical inflammation mostly the role of IL-1 $\beta$  is assumed to be pivotal in the process though the etiology of T2D is multifaceted. IL-1 $\beta$  has been connected in the pathology of Type 1

**Table 4**

Plasma miRNA alterations associated with T2D.

Methodology	miRNAs Detection	Reference
Serum analysis of 56 individuals related to diabetes with qPCR technique	miRNA-30d, miRNA-124a, miRNA-146a, miRNA-375, miRNA-124a, miRNA-29a, miRNA-9	(Kong et al., 2011)
Blood analysis of 265 individuals related to the metabolic syndrome with microarray Technology	miRNA-320a, miRNA-192, miRNA-150, miRNA-27a, miRNA-192	(Karolina et al., 2012)
Plasma analysis of 800 individuals from the Bruneck cohort study with microarray technology	miRNA-15a, miRNA-223, miRNA-29b, miRNA-126, miRNA-28-3p	(Zampetaki et al., 2010)



**Fig. 3.** Schematic diagram of DNA sensing by use of an electrochemical biosensor. The device was designed by merging the tetrahedron-structured DNA probes and hybridization chain reaction (HCR) extension. Probes are arrested on a 3D matrix. The synergistic effect of tetrahedral probes and HCR improves the sensitivity of detection.

**Table 5**

Novel Biosensor for detection of circulating microRNAs.

Type of Assessment	Sensing Platform	Transduction Type	Sensor Features	Reference
Prognosis	Gold electrode	Isothermal-electrochemical	LOD: 1 fM LR: 2 fM to 2 pM	(Ren et al., 2013)
	Gold sensor surface	Mass-based (Piezoelectric)	LOD: 4 fM	(Johnson and Mutharasan, 2012)
	Au film and Gold nanoparticle (AuNPs) Indium tin oxide (ITO)	Optical (SPR) Electrochemical (EIS)	LOD: 8 fM LOD: 2 fM LR: 5 fM to 2 pM	(Wang et al., 2016) (Gao et al., 2013)
	Gold surfaces and combination of DNA tetrahedral platform and HCR amplification	Electrochemical	LOD: 10 aM	(Ge et al., 2014)

\*LR: linear range, LOD: limit of detection.

diabetes (T1D) and T2D (Donath et al., 2008; Skeldon et al., 2014). IL-1 $\beta$  stimulates pancreatic tissue damage and insulin resistance in muscle and white adipose tissue and other insulin-sensitive tissues (Dinarello and van der Meer, 2013; Masters et al., 2011). An improved local  $\beta$ -cell secretion of IL-1 $\beta$  relative to IL-1Ra is supposed to increase T2D (Dinarello and van der Meer, 2013; Masters et al., 2011; Meier et al., 2002). Raised plasma IL-1Ra levels were introduced in individuals with fatness (Meier et al., 2002), decreased glucose tolerance (Ruotsalainen et al., 2006) and metabolic syndromes (Salmenniemi et al., 2004). Slow rises in IL-1Ra levels were similarly indicated in prediabetic to diabetic individuals (Grossmann et al., 2015).

## 7. Future perspective: novel biomarkers for prediabetes prediction

### 7.1. Mannose

Mannose is not an essential nutrient; it can be produced in the human body from glucose, or converted into glucose. D-Mannose ( $C_5H_{11}O_5CHO$ ) termed as D-mannoseis, D-mannopyranose, and semimannose. The liver has been described a key tissue for mannose ingestion. Hence, changed liver utilization of mannose could cause alterations in its plasma levels (Davis and Freeze, 2001). Lee et al. (2016) quantified the blood mannose concentrations in the lean and overweight individuals in two cohorts and reported that detected mannose status was superior in the obese individuals. Insulin receptors may also be affected by abnormal glycosylation leading to rise in liver tolerance to insulin.

Therefore, mannose identified as a unique blood mediators in clarifying the alteration in obesity-independent insulin resistance. These outcomes could facilitate timely management of obese individuals who are at risk of developing comorbidities related to insulin resistance, including T2D (Holmes, 2016; Lee et al., 2016).

### 7.2. Circulating microRNAs

MicroRNAs (miRNAs) are small endogenous RNAs of 21–25 nucleotides that function as translational repressors by partially coupling to the 3' untranslated region (3'UTR) of target mRNAs (Rodriguez et al., 2004). These small RNAs not only regulating gene expression in the cells, a number of them are found in blood and other organs. Normally, levels of circulating miRNAs varied from 200 aM. to 20 pM. (Arroyo et al., 2011; Vickers et al., 2011). miRNA-based regulation is implicated in disease etiology and has been suggested as biomarkers for a several disorders such as T2D. Note that miRNAs present in extracellular fluids in highly stable forms (Table 4). In recent years, biosensor technology has been widely improved for detection of circulating microRNAs.

Recently, an ultrasensitive sensing device for microRNA detection was designed by merging the tetrahedron-structured DNA probes and hybridization chain reaction (HCR) extension (Ge et al., 2014). Interestingly, ato-molar levels of limit of detection was achieved. Briefly, DNA probes were self-assembled on the surface of gold electrode. These probes function as a framework to arrest DNA identifier probes in order to enhance the tendency to undergoing

chemical reaction and convenience. The signal was amplified by HCR and the HCR derived nicked double helices HCR applied to arrest several HRP enzymes to intensify the ending produced signals via hydrogen peroxide decomposition. This strategy solely relies on DNA polymerization and have several advantages, including being inexpensive, programmable, and facile (Fig. 3). Other novel biosensors for detection of circulating microRNAs have been shown in Table 5.

### 7.3. $\alpha$ -Hydroxybutyric acid

$\alpha$ -hydroxybutyric acid ( $\alpha$ -HB) is an organic acid derivative of  $\alpha$ -ketobutyrate ( $\alpha$ -KB) (Sari et al., 2017), which formed by catabolism of amino acid and glutathione anabolism, and processed to propionyl-CoA and carbon dioxide.  $\alpha$ -HB was reported to be relevant to additional glutathione demand and disrupted mitochondrial energy metabolism and demonstrated to originate from hepatic glutathione stress. This supports the indication that increased  $\alpha$ -HB may possibly relate to raising oxidative stress in the insulin resistance and prediabetic states (Lord and Bralley, 2008). Gall et al. (2010) reported that increased levels of  $\alpha$ -HB occurred by providing additional  $\alpha$ -KB substrate from elevated cysteine anabolism. Based on the mentioned study and the global screening data, a considerable rise of both  $\alpha$ -KB and cysteine was observed with increased insulin resistance. Elevated concentrations of  $\alpha$ -HB in a cohort study supports the possibility that an increased NADH/NAD<sup>+</sup> ratio favors reduction of  $\alpha$ -KB to  $\alpha$ -HB. Moreover,  $\alpha$ -HB demonstrated to be increased in T2D individuals and animal models of T2D (Salek et al., 2007; Silva et al., 2001). In 2016,  $\alpha$ -HB was reported as a selective biomarker for decreased glucose tolerance and prediabetes state, independent of age, sex, BMI, and fasting glucose as determined for the European population cohorts (N = 4053 subjects without diabetes) (Cobb et al., 2016). Meanwhile, to determine the precise role of  $\alpha$ -HB in prediabetes further studies are required.

## 8. Conclusion

According to the official statistics about the prevalence of T2D diabetes, the disease accounts for one of the most important issues concerning global health. The rapid progression of the disease, which associated with the individual genetics and lifestyle, is rapidly spreading around the word. Meanwhile, a rapid and easy-to-use technology to adequately detect biomarkers is highly valued in order to deal with the outbreaks and the progression of the disease. Biosensor technology has demonstrated great capabilities for disease identifications. As indicated in the current paper, multiple studies have been performed to introduce proper biomarkers and to design diagnostic biosensors with appropriate mechanisms to improve the detection limits for T2D. Numerous biomarkers for diabetes and prediabetes have been introduced in recent years. Along with advances toward identification of innovative biomarkers, there have been several studies for introducing novel biosensing platforms associated with these markers. Many of these biomarkers, on the contrary, have not been investigated through biosensing approaches. The technology can offer a rapid and sensitive platform for early diagnosis of T2D compared to currently-applied methods which are often expensive and lack the required sensitivity. Thus, moving toward fundamental investigation and commercialization of biosensors to provide faster, more adequate, low-cost, and point-of-care tools would be essential.

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