Int. J. Electrochem. Sci., 16 **(2021)** Article ID: 210719, doi: 10.20964/2021.07.52

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Mini Review

Glucose electrochemical biosensors: The past and current trends

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Received: 1 March 2021 / *Accepted:* 17 April 2021 / *Published:* 31 May 2021

Electrochemical glucose biosensors have been developed as the analytical devices for laboratory and personal use since the 1950s. Glucose oxidase is the common biorecognition part in the biosensors though the other recognition elements exist. New generations of the biosensors have emerged and various nanomaterials used for the construction of electrodes, enzyme immobilization or nanocatalyzers become popular. This review is focused on the development of glucose electrochemical biosensors. The common facts about diabetes mellitus are described and standard methods for instrumental diagnosis are introduced in this work. The glucose electrochemical biosensors are introduced and four generations of them are characterized. In the last chapter, the current experimental trends are described. In this work, actual literature is surveyed in the field of glucose biosensors as well.

Keywords: biosensor; Clark electrode; diabetes; electrochemistry; glucometer; glucose oxidase; glycemia; point-of-care; screen-printed electrode

1. INTRODUCTION

Diabetes mellitus is a serious disease with growing incidence over the world. Two basic types of diabetes mellitus are distinguished: type 1 also known as insulin dependent diabetes mellitus and type 2 also known as insulin independent diabetes mellitus [1-3]. Other types like the gestational diabetes mellitus exist as well [4,5]. Total number of people suffering from diabetes is quite high as seen from the epidemiological statistics. Probability of diabetes mellitus (namely the type 2) can be increased due to various factors like physical inactivity, smoking, obesity, age and genetic dispositions. In the United States, 9.4 % of adults suffer from a form of diabetes and the number is growing with the age as approximately 25 % of adults above 65 years are affected by diabetes [6]. In the Mexico, 20 % of medically preventable deaths can be attributed to the diabetes [7]. It is expected that the number of diabetic patients will grow four times up to 86.6 million adults by the year 2050 when compared to the state of year 2020 [8]. The highest number of the diabetic patients will come from the United States:

48.3 million in the year 2050 [9]. There is also quite high prevalence of undiagnosed and people with prediabetes [10-14].

The developed diabetes mellitus can be manifested by several symptoms like increased thirst and urination, ketonic odor of urine, blurred vision, skin and vaginal infections and longtime healing sores but the unambiguous revealing of the disease has to be done by a standard laboratory diagnostical method. Beside the first diagnosis, the methods also serve for the control of the disease progression and therapy efficacy. This review is focused on a substantial part of the methods: electrochemical assays of glucose. The electrochemical assays became of the first type of point-of-care diagnosis of diabetes mellitus and they still remain crucial for screening and control of the therapy efficacy.

2. STANDARD LABORATORY DIAGNOSIS OF DIABETES MELLITUS

Glucose level is the major hallmark of diabetes mellitus and its level is directly or indirectly measured in laboratory diagnoses. Direct assay of glucose is made in blood (glycemia) or urine (glycosuria). Glycemia levels are the standard markers for the current medicine [15-20]. Fasting glycemia is under 5.6 mmol/l in the health people and the level higher than 5.6 mmol/l but under 6.9 mmol/l point to prediabetes and the level 7 mmol/l means diabetes. Glycemia is also determined in the oral glucose tolerance test [21-23]. The oral glucose tolerance test is based on drinking of approximately 250 ml of a syrupy containing 75 grams of glucose. After two hours, the glycemia should not exceed 7.8 mmol/l in the health people, the higher-level means prediabetes and the level above 11.1 mmol/l diabetes. Nearly no glucose is presented in the urine until renal threshold for glucose is reached in the blood (approximately 10 mmol/l) and then the glucose is released into urine where it can be detected [24-27]. Various colorimetric tests for glycosuria determination exists and new types are also introduced [28-31].

The increased glycemia leads to the spontaneous reaction between glucose and various macromolecules called advanced glycation end products. Glycated hemoglobin is probably the most relevant advanced glycation end product and it is common in the current diagnoses of diabetes mellitus as a marker. The glycated hemoglobin has quite long half-life equal to half-life of erythrocytes: 28 days [32]. Comparing to the glucose, the level of glycated hemoglobin cannot be significantly influenced by a short time lasting diet or a fast or short life style change. Int the health people, glycated hemoglobin represents approximately 6 % of the total hemoglobin respective 42 mmol/mol, the prediabetes is recognized when glycated hemoglobin forms 6.0 to 6.4 % (42 – 47 mmol/mol) of the total hemoglobin and diabetes is recognized when glycated hemoglobin exceeds 6.5 % (48 mmol/mol) [33,34].

Various analytical methods can serve for the purpose of glucose or glycated hemoglobin assay. The glycated hemoglobin is typically assayed by instrumental analytical methods like liquid chromatography and/or mass spectrometry [35-39] respective capillary zone electrophoresis and/or mass spectrometry [40-43]. Immunoassays are also for option in the routine measuring of glycated hemoglobin [44-47].

The glucose assay can be also based on the instrumental analyses like chromatography and or mass spectrometry [48-50]. However, cheaper methods like spectral or voltammetry analyses based on glucose specific enzymes are common in the current laboratory praxis. Combination of glucose oxidase

and horse radish peroxidase for glucose oxidation up to products detectable by a voltammetry or spectrophotometry are used in the current praxis. The principle of the voltametric methods is described in the next chapter. Various adaptations of spectrophotometric glucose assay exist. An applicable one is based on the oxidation of glucose respective glucopyranose by glucose oxidase to gluconic acid respective gluconolactone and hydrogen peroxide. In the next step, hydrogen peroxide reacts with reduced o-dianisidine in the presence of peroxidase to water and oxidized o-dianisidine. In the final step, sulfuric acid causes pink coloration of oxidized o-dianisidine that is measurable at 540 nm. This adaptation was used and is fully described in the cited papers [51-53]. Principle of the assay is given in the figure 1. Other spectral analyses are also applicable for praxis. Various compounds reacting with hydrogen peroxide (for instance 4-aminoantipyrine and phenol) can serve for the assay purpose. The assay can be also based on other types of enzymes. For instance, assay of glucose based on two steps using mixture of hexokinase, adenosine triphosphate, oxidized nicotinamide adenine dinucleotide and glucose-6-phosphate dehydrogenase. In the first step, phosphorylation by hexokinase in the presence of adenosine triphosphate get arise of glucose-6-phosphate. In the second step, glucose-6-phosphate dehydrogenase is converted to 6-phosphogluconate by enzyme glucose-6-phosphate dehydrogenase. Oxidized nicotinamide adenine dinucleotide is reduced and this redox change is measured at 340 nm.

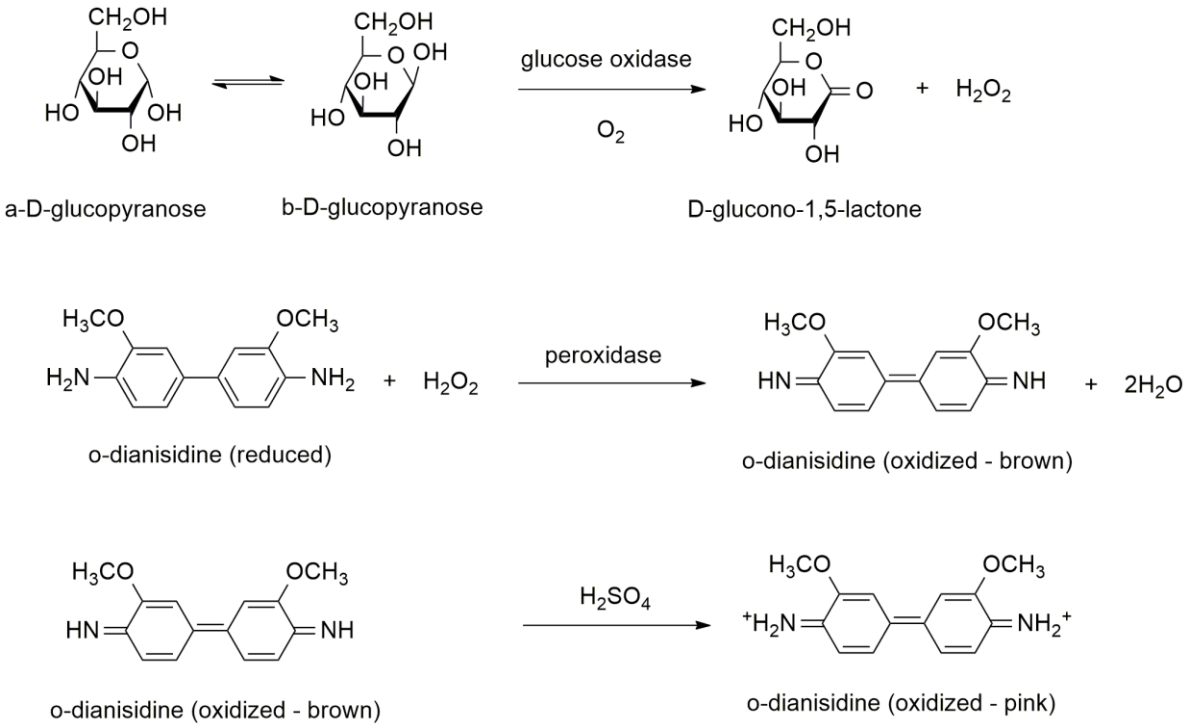

Figure 1. Principle of the spectrophotometric assay of glucose based on glucose oxidase, peroxidase and o-dianosidine.

The wearable and point-of-care tests for diabetes mellitus undergo evolution and various sensors and biosensors for wide number of markers of diabetes mellitus are developed apart of the electrochemical methods described in this review. Especially remote assays and assays of glycated

hemoglobin respective glycated plasma proteins like albumin are relevant competitors to the glucose biosensors [54-60].

3. COMMON ELECTROCHEMICAL METHODS FOR GLUCOSE ASSAY

The electrochemical biosensors for glucose assay are the oldest type of a biosensor even. The history of the glucose biosensors started with the name of Dr. Leland Clark and Cham Lyons who firstly constructed Clark oxygen electrode and then improved the oxygen electrode by adding enzyme glucose oxidase under covering membrane in the end of 1950s and early 1960s [61,62]. The biosensor composed from the platinum working and the Ag/AgCl reference electrodes, the outer dialysis membrane that covered glucose oxidase and the inner membrane permeable for oxygen. The chemical principle of the biosensor is based on three consequential reactions. In the first reaction, glucose (glucopyranose) is oxidized to gluconic acid (gluconolactone) by enzyme glucose oxidase. In the same time, enzymatic cofactor flavine adenine dinucleotide is reduced. In the second reaction, oxygen is reduced to hydrogen peroxide while flavine adenine dinucleotide is oxidized back. In the third reaction, hydrogen peroxide is oxidized by applied voltage to oxygen and electrical current is measured. The principle is summarized as figure 2. The original type of glucose biosensors based on oxygen penetration is also labeled as the first generation of biosensors. It became commercialized as Model 23A YSI analyzer by Yellow Springs Instrument Company (USA) in 1975 [63-67]. This device was intended for the use in laboratory conditions due to manufacturing price caused by the used massive platinum and silver wires, size and overall assay procedure. The first generation of glucose biosensors has the common drawbacks: interference of redox active substances presented in the blood (e.g. ascorbic acid, uric acid) and influencing of the assay when oxygen access is restricted [68].

$$glucose + GOx(FAD) \longrightarrow gluconic\ acid + GOx(FADH_2)$$
$$GOx(FADH_2) + O_2 \longrightarrow GOx(FAD) + H_2O_2$$
$$H_2O_2 \longrightarrow O_2 + 2H^+ + 2e^-$$

Figure 2. General principle of an electrochemical glucose biosensor based on flavine adenine dinucleotide (FAD) dependent glucose oxidase (GOx).

Further improvements of the glucose biosensors are based on the use of electron mediators replacing oxygen by compounds like ferrocene, ferricyanide and quinines and such biosensors typically exert lower sensitivity to interference by redox active compounds, the mediators are located in membranes that block access of possible interferents like ascorbic acid. This type of glucose biosensors is called the second generation [69,70]. The term third generation of glucose biosensor is also used in some papers and devices where direct electron transfer between enzyme and membrane/electrode happens are given here. The third generation biosensors typically use composite and nanomaterial derived parts or replaces glucose oxidase by other type of enzyme like glucose dehydrogenase that is more convenient for the direct electron transport [71-73]. The third generation of glucose biosensors can exert similar analytical properties like the second generation but the absence of the electron mediator

makes the fabrication process simpler and avoiding environmentally or health problematic materials. In some sources, the term fourth generation of glucose biosensors can be found as a further development of the biosensors. The fourth generation of biosensors are chemical sensors in true world because the enzyme (biorecogition part) of the biosensor is replaced by an artificial structure exerting similar catalytical properties including specificity like the original enzyme. For instance, CeO_2 nanostructure on CuO core shell replaced glucose oxidase in an electrochemical assay presented by Dayakar and coworkers [74]. Other materials like mesoporous metals oxides ZrO_2, SiO_2 and In_2O_3 modified graphene composite are applicable for glucose assay [75]. The fourth generation has benefit in the use of chemical origin materials that can be better for mass production and the chemically produced recognition parts can exert better uniformity and reproducibility comparing to biotechnologically prepared enzymes. On the other hand, specificity can suffer in this type of devices. The edge between the single types of biosensors is not clearly defined and the division of biosensors should be taken for estimative rather than a normatively accurate one. The fact that the biosensor can be considered as higher generation also does not mean that it will exert better analytical specifications. The evaluation of new devices should be based on critical consideration of various facts including analytical and economical specifications. The overview of the generations of glucose biosensors is given as table 1.

Table 1. Glucose biosensors generations

Generation	***Description***	***Advantage or drawbacks***	***References***
The first generation of glucose biosensors	It works on oxygen reduction to hydrogen peroxide.	Drawback: possible interference of some compounds (e.g. ascorbic acid) presented in the blood. Original wire electrodes were expensive.	[61-63]
The second generation of glucose biosensors	It uses electron mediators instead that replace oxygen in the reaction. Advanced types of membranes are also used.	Advantage: the assay is less sensitive to interferents like ascorbic acid.	[69,70]
The third generation of glucose biosensors	It is based on the direct electron transfer between enzyme and membrane/electrode – electron mediator can be replaced by conductive membrane;	It exerts similar analytical properties like the second generation, the absence of electron mediator makes the fabrication process simpler and	[71-73]

	other types of enzymes can be used.	avoiding environmentally or health problematic materials.	
The fourth generation of glucose biosensors	Enzyme in the biosensor is replaced by an artificial structure exerting similar catalytical properties including specificity like the original enzyme.	Advantage: easier mass production, better uniformity and reproducibility. On the other hand, specificity should be verified.	[74]

In the current market, glucose biosensors of the second and third generation represent a substantial part of the commercialized biosensors and similar devices [76-79]. Self monitoring and wearable devices are currently an object of commercial interest [80]. The contemporary glucose biosensors fill the requirements given for the point-of-care tests [81-86]. They are generally affordable and easy to use for the determination of glucose in the capillary blood. Though the current glucose biosensors are marketed and applicable, further improvements like better accuracy and lower sensitivity to interferences are desired.

4. THE PROGRESSION IN THE GLUCOSE BISENSORS

The discoveries of new materials, immobilization of enzymes on nanoparticles, improved manufacturing processes of electrodes and replacing of expensive materials for biosensors construction by the cheaper one makes gradually the biosensors not only more affordable but also suitable for point-of-care tests and suitable for application as a wearable technology. The discoveries published on the glucose biosensors in the last years are given in the next paragraphs. Survey of the important electrochemical glucose biosensors is given in table 2.

An enzyme free photoelectrochemical biosensor based on gold nanoparticles with $BiVO_4$ and indium tin oxide modified photoelectrode was prepared by Chen and coworkers [87]. The biosensor worked on the principle of glucose oxidation by the photoelectrode to the gluconic acid. Oxygen was contemporary reduced to hydrogen peroxide. The principle is close to the first generation of glucose biosensors but the replacement of the enzyme by nanoparticles based electrode was the main improvement of the assay. The biosensor exerted extensive linear range 1 nmol/l to 1 mmol/l and limit of detection equal to 260 pmol/l. The proved limit of detection was deeply under expected physiological concentration of glucose. The aforementioned biosensor of the fourth generation is another device developed on the basis of artificial catalyzer [74]. This worked with nanoparticles based on CuO core

shell nanostructure with CeO_2 that replaced glucose oxidase. The nanoparticles were placed on screen printed electrodes and standard voltammetry was performed. The assay run at potential +0.4 V against Ag/AgCl reference electrode and it exerted limit of detection for glucose equal to 0.019 µmol/l. The both copper and cerium participated in the electrochemical glucose oxidation but the authors proposed chemical mechanism that is based on CuO oxidation to CuOOH followed by a fast reduction combined with oxidation glucose Chemical principle of the assay is depicted as figure 3.

$$CuO + OH^- \longrightarrow CuOOH + e^-$$
$$glucose + CuOOH + e^- \longrightarrow gluconic\ acid + CuO + OH^-$$

Figure 3. Principle of the glucose oxidation by CuO core shell nanostructure with CeO_2 as described in the work by Daykar and coworkers [74].

The biosensors having immobilized glucose oxidase become advanced by use of new types of materials and immobilization procedures that make the assay more sensitive and are promising for further miniaturization and reduction of fabrication costs by save of the used material. Glucose oxidase immobilized on graphene oxide laminated glassy carbon electrode provided huge density of enzyme activity combined with a good electron transfer [88]. Such biosensor had sensitivity to glucose 46.7 µA/mmol/l/cm^{-2}. In another work, Ti3C2 nanosheets modified with poly-L-lysine and then glucose oxidase were invented by Wu and coworkers [89]. The glucose oxidase was cross linked with and the finalized electrode good analytical properties due to the improved conductivity of the electrode. Limit of detection for glucose equal to 2.6 µmol/l was achieved.

Further improvements of glucose biosensors can be based on the application of new types of electron mediators. For instance, Benjamin and coworkers synthesized electroactive disubstituted ferrocenyl ionic liquids with chloride counter anion [90]. The electron mediator allowed to detect glucose using a low potential: 0.2 V. Further research can be also focused on the alternative use of the current biosensors. In a study, uncompetitive inhibition of glucose oxidase by Cr^{6+} ions was chosen as a phenomenon that can serve for Cr^{6+} assay [91]. The researchers prepared quite standard biosensor where glucose oxidase is immobilized in a chitosan membrane placed on a cut of filter paper and then the cut on a screen printed electrode and performed amperometric assay for glucose, enzyme activity drops in the assay when Cr^{6+} presented. The biosensor exerted linear range 0.05 – 1 ppm of Cr^{6+} and limit of detection 0.05 ppm. The relative standard deviation (5.6 % was also low enough) fill the demands on a practical assay.

Table 2. Survey of the recent electrochemical glucose biosensors

Description	***Significant novelty***	***Analytical specifications***	***References***
Enzyme -free photoelectrochemical biosensor based on gold nanoparticles with $BiVO_4$ and indium tin oxide modified photoelectrode, the electrode oxidized glucose to gluconic acid and reduced oxygen to hydrogen peroxide.	Replacement of enzyme by gold nanoparticles with $BiVO_4$ with catalytic properties.	Linear range for glucose 1 nmol/l to 1 mmol/l, limit of detection 260 pmol/l.	[87]
Enzyme -free electrochemical assay, the used nanoparticles worked as an catalyzer and electron mediator in the same time.	Replacement of enzyme by CuO core shell nanostructure with CeO_2 with catalytic properties.	Applied voltage +0.4 V against Ag/AgCl reference electrode, limit of detection for glucose 0.019 µmol/l.	[74]
Glucose oxidase biosensor for glucose assay, glucose oxidase is immobilized through graphene oxide.	High density of enzyme activity per square of electrode.	Sensitivity to glucose 46.7 $\mu A/mmol/l/cm^{-2}$.	[88]
A glucose oxidase biosensor containing Ti3C2 nanosheets modified with poly-L-lysine and then glucose oxidase.	Improved conductivity of the electrode due to the use of conductive nanosheets.	Limit of detection 2.6 µmol/l for glucose.	[89]
Standard glucose biosensor based on glucose oxidase placed in chitosan membrane and using screen printed electrodes. It worked on the principle of glucose oxidase inhibition by Cr^{6+}. The chromium cations were the analyte in the assay.	Standard glucose biosensor that was used for a new analyte: Cr^{6+}.	Cr^{6+} assay: linear range 0.05 – 1 ppm of Cr^{6+} and limit of detection 0.05 ppm.	[91]

5. CONCLUSION

Though the glucose biosensors are the oldest type of biosensor even, their evolution is ongoing. The discoveries in nanomaterials combined with miniaturization of electrodes and materials saving are the major impetus for the next progression and application of the new technologies based on the wearable bioanalytical devices [92-100]. The glucose biosensors are one of the important bioanalytical devices. It is questionable whether enzymes will be replaced by artificial catalyzers in the near future since they still have technological shortcomings but gradual replacement of various materials like types of electrodes, membranes etc. is a fact that should be taken into account. On the other hand, technologies competitive to the electrochemical biosensors for glucose assay are developing as well. Especially remote assays and assays of glycated hemoglobin are relevant competitors to the glucose biosensors.

ACKNOWLEDGEMENTS
This work was supported by a long-term organization development plan Medical Aspects of Weapons of Mass Destruction of the Faculty of Military Health Sciences, University of Defence (Ministry of Defence, Czech Republic).

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