



Carbon Nanotube Biosensor for Diabetes Disease

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Abstract

Objective: Diabetes is the major and leading cause of death, poor quality of life and organ failure which emphasizes the importance of accurate measuring of body glucose. Carbon nanotube (CNT) biosensors exhibit great sensitivity and selectivity for glucose in blood and body fluids. The most recent progresses on the development of various methods of CNT biosensors for glucose detection are summarized in this review.

Methods: For this review, online search of different sources such as PubMed, ISI and Scopus resulted in finding 34 articles correlated with CNT detector and its application in diabetes sensing.

Results: The results showed advanced methods of CNT sensor functionalization with various modifiers like polyaniline and techniques such as self-assembly layer-by-layer process. These point-of-care solution-phase nanotube biosensors have significant potency to monitor blood glucose non-invasively and eliminate painful finger prick procedure.

Conclusion: In this study, it was concluded that appropriate surface modification of CNT biosensors could play an important role in real-time diagnosis of diabetes.

Keyword: Carbon nanotube, Biosensor, Diabetes mellitus detector, Nanotechnology

Introduction

Diabetes mellitus is one of the major causes of death, poor life quality, and disability worldwide. It is caused by hyperglycemia (high blood glucose levels) and insulin shortage (1). Type 1 diabetes or juvenile diabetes, as an insulin-dependent diabetes, is an autoimmune disorder which results from a deficiency in insulin-producing beta cells of the islets of Langerhans and leads to hyperglycemia. Type 2 diabetes or adult-onset diabetes, as a noninsulin-dependent diabetes, is a metabolic disorder involving insulin resistance, also characterized by hyperglycemia. Gestational diabetes mellitus (GDM) resulting from high blood sugar level during pregnancy increases the risk of developing type 2 diabetes for women and their babies within 10 years after delivery, as well (2). Therefore, continuous and accurate glucose sensing in blood and serum is important for diagnosis, self-monitoring, and management of the disease (1). Hence, the innovation of reliable, sensitive, and low-cost biosensors for miniaturization of detection system and development of efficient sensor has significant impact on diagnosis of diabetes biomarker (3,4). Recent advent in nanomaterial sensors offers an opportunity to create portable devices with required sensitivity for non-invasive diabetes diagnosis via saliva, urine or tear. Among various types of nanomaterials, carbon nanotubes (CNTs) have been considered as the most promising materials for the

development of future devices to assist in the early sensing of hyperglycemia as the most important biomarker for both types of diabetes (5). Biosensors as selective detectors in transduction integrate the recognizable responses of immobilized biorecognition elements such as enzymes, antibodies, and antigens with their biological sensors and produce an electronically measurable signal for bioassays (6,7). According to various types of bioreceptors, biosensors can be classified as immunobiosensors, genobiosensors and enzymatic biosensors, or optical, piezoelectric, electrochemical, and thermometric biosensors according to signal transduction procedure (8). Functionalized nanoparticles with biomedical applications such as drug administration and tissue engineering have shown considerable potency to be applied in the generation of highly sensitive biosensors recently (6,9,10). The detection limits of various biomarkers like DNA, RNA and glucose have been developed by substantial improvement in nanotechnology and biosensing technology using organic materials such as CNTs and inorganic materials like gold nanostructures (11). Remarkable structural, electronic, and mechanical properties, variable conductivity, and small size, in addition to expanded active surface area make CNT a predominant choice to be applied as a host substance for nanoparticles (12,13). Tremendous sensitivity of CNTs to any miniature change such as biomolecules exposing around their immediate adjacent

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makes them an ideal sensing element for biodetectors (14). The electrocatalytic ability of CNTs affects performance of electrochemical sensors which result in ultrasensitive biosensing of biological indicators like glucose (8,15).

The review of recent and in-progress methods for design of CNT sensors that facilitate more sensitive, patient-friendly, and real-time diabetes monitoring was the aim of this study. The glucose detection performances of different CNT-based electrodes were traced in this review in both molecular and cellular levels.

Methods

Search Strategy

Online databases such as PubMed, ISI, and Scopus were searched using related keywords. Selection of articles was limited to those published between 2006 and 2016. The particular criteria and keywords of review were specified as: CNT biosensor, biosensor, diabetes disease, glucose detection, nanoparticle.

Inclusion and Exclusion Criteria

Considered criteria in our review were:

- Studies including diabetes and various biosensing methods of it
- Research articles about CNT and nanotechnology impacts on disease detection

A total of 34 related articles were summarized to illustrate our mentioned subject at last.

Data Extraction

Five main groups were organized by authors in result of studying and reviewing the articles: structure and properties, synthesis and functionalization, types, single-walled CNT (SWCNT) for diagnosis, and multi-walled CNT (MWCNT) for diabetes detection.

Results

CNT Structure and Properties

CNTs have 3-dimensional morphology and are composed of sp^2 hybridized carbon atoms assembled in a series of benzene rings rolled up (16). These tubular sheets have hollow interior layer with nanoscale diameter and nanometer-to-micron length (8). CNTs with significant electronic, optical, chemical, and mechanical properties, as well as unique physicochemical properties such as cell membrane penetration, high surface area ratio, and drug loading, surface modification, photoluminescence property, and non-immunogenicity allow label-free detection in receptor-based targeting (8,17). CNTs have considerable potency to simplify electron transfer among the electrodes and redox sites of bioreceptors without any requirements of mediator which can lead to amplification of the signal and allow label-free recognitions (17). Biomolecule immobilization, facile functionalization, and redox interfacial modulation are characteristic properties of CNTs as used in biosensor designing (18,19). CNTs are classified as 4 groups of single, double, triple, and multi-

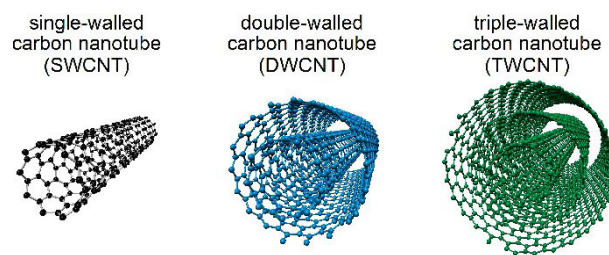


Figure 1. Schematic Representation of Single-walled Carbon Nanotubes (SWCNTs) Formed of Single Hollow Cylindrical Graphite. Double-walled carbon nanotubes (DWCNTs) composed of 2 graphene rolled cylinders; and triple-walled carbon nanotubes (TWCNTs) composed of 3 hollow cylinders of graphene sheets.

walled CNTs according to their structures which mainly affect their physical and chemical properties (Figure 1) (20).

Particularly among different types of CNTs, SWCNTs and MWCNTs with rapid electron-transfer kinetics have been simulated as the remarkable components to improve the construction of electrochemical biosensors (10,15).

SWCNTs are formed by rolling the only single hollow cylindrical graphene sheet, while MWCNTs consist of hollow cylinders formed by the rolling of several graphene layers (4,21). There are critical differences between characterizations of SWCNT and MWCNT which play an important role in controlling their performance as transducers. Catalysts are necessary for SWCNTs synthesis procedure. Their synthesis in bulk is complicated and functionalization process causes more defect. SWCNT has great distribution and its accumulation in the body is less. In comparison, MWCNT can be produced without catalyzer; thereby, being synthesized in bulk. Modification of MWCNT with functional groups results in more defect with more accumulation in the body (20).

Synthesis and Functionalization Methods of CNT

Several synthesis strategies have been introduced in the development of CNTs. The main synthetic techniques utilized for conventional CNT production are: arc-discharge method, laser ablation method and chemical vapor deposition (CVD). Arc-discharge method mainly refers to the deposition of CNT on graphite cathodes under the current in a vacuum reactor. Arc-synthesized method has straight and defect-free advantages for MWCNT preparation (22).

In laser ablation method, graphite is positioned in a vacuum furnace and laser beam with high energy irradiates, the carbon atoms of graphite, and metal catalyst, where dispositioning of carbon atoms on collector results in CNT creation (4). In CVD strategy, CNTs are generated by decomposition of the carbon gas under the high temperature to create carbon atoms on coated transition metal catalysts (Figure 2) (23). Properties such as stable structure and great absorption capacity of inner tube have significant influence on CNTs insolubility in most solvents; that is the main problem in synthesis of CNTs

for biosensors (4). Surface functionalization of CNT is essential to increase solubility, enhance biocompatibility, and reduce toxicity in biomedical applications. Covalent and non-covalent immobilization of different chemical groups such as gold, silver, platinum, graphene, glass, and silica presents conjugating opportunity with biomolecules for suitable biosensing application and amplifying the electron transfer rate (8, 13). Chemical modification of the CNTs surface has great impacts on the creation of sensitive functional groups which prevent agglomeration, improve host compatibility, and expand solubility in different solvents (23).

Various Types of CNT

CNT-based biosensors are mainly classified into chemical or physical categories (24). Amperometric, potentiometric, and impedimetric biosensors are 3 basic types of electrochemical (EC) biosensors as label-free sensing methods (25,26). An analyte immobilization on molecular sensing elements results in an electrical change in the current of amperometric, impedance of impedimetric, and voltage of potentiometric and EC biosensors (15). The CNT arrays used in EC biosensors preserve signal on bulk area and reduce noise; thus enhance signal-to-noise ratios (27). In amperometric biosensors, the analyte concentration is detected by variation in the current production in electrochemical oxidation or reduction of the redox centers of enzymes (7,10). Enzyme–CNT electrode in amperometric biosensors is fabricated by the functionalization of CNT with enzyme, as the hollow shape of CNT increases the enzyme immobilization (28). Optical, piezoresistive and calorimetric biosensors are common types of physical sensors. CNTs with great luminescence properties along with tunable near-infrared light emission in response to surrounding dielectric changes are suitable materials for optical biosensing (29). Piezoresistive biosensors have intense sensitivity to any resistance change caused by peripheral force. CNTs with excellent strength and toughness could be a remarkable candidate material for piezoresistive-based sensors (30). Lastly, calorimetric biosensors calculate the alternation of system temperature as a consequence of reactions between the immobilized biological materials and the desired objects (31).

CNT for Diabetes

A painful invasive pricking process with multiple repetitions per day contributes the immediate necessity of valuable non-invasive diabetes monitoring (5). Optimal non-invasive reading of glucose levels in serums other than blood is enhanced as a consequence of improved sensitivity and selectivity of CNTs along with their miniaturized size (2). Therefore, CNT biosensors are beneficial in protection of blood glucose levels in healthy normoglycaemic as the key purpose of both type 1 and type 2 diabetes control.

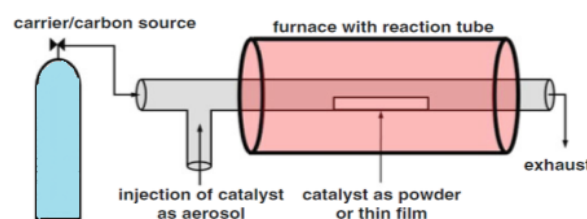


Figure 2. Schematic Representation of a Thermal CVD System With a Furnace Containing Reaction Tube and Catalyzer for Carbon Source, Decomposing Under Heat to Produce CNT.

1. SWCNT for Diabetes

Valentini et al employed an electrochemical 1-step strategy for coating polypyrrole – glucose oxidase (GOx) film on the aligned deposited SWCNT onto Au microelectrodes surface by the electrophoresis deposition process. Different analyses performed on sensor resulted in the expanded linear range of concentration from 4 to 100 mM covering the hypo- and hyper-glycemia range with a detection limit of 50 mM for glucose detection. The results showed that the thickness, surface coating, and mesoporosity of the nanocomposites widely influenced the biosensor efficiency (32).

In 2011, the analytical sensing using SWCNT transistor was developed by Hu et al for glucose recognition. Glucose-dependent current in biosensor resulted in a reliable outcome based on the variation of glucose concentration (33).

Label-free all-electronic sensing strategy was decorated by functionalization of a CNT with pyrene-1-boronic acid for D-glucose probing. A boronate anion was the result of incorporation of boronic acid with a monosaccharide-influenced nanotube immediate environment. This sensitive and selective CNT sensor monitored glucose in ultralow detection limit of 300 at usual level of glucose in blood and saliva (14).

Wang et al prepared a multifunctional glucose biosensor in 2011. The oxidized dopamine coupled with electroless silver nanoparticles was deposited on CNT for stable immobilization of glucose oxidase glassy carbon electrode. It should be highlighted that polydopamine (Pdop) adherence to a wide variety of surfaces has made it an ideal component for immobilizing biological molecules. With regard to this end, the glucose oxidase (GOD)-immobilized Ag-Pdop CNTs–modified glassy carbon electrode (GCE) with distinct redox peaks and stable electron transport rate catalyzed a reaction between GOD and glucose for oxygen reduction. Expanded enzymatic activity and affinity were observed for resultant nanocomposite sensing electrode (34).

Kang et al developed an electrochemical solution-phase SWCNT biosensor via Layer-by-layer (LBL) self-assembly of negatively charged ssDNA-SWCNTs surfaces. The results revealed that introduction of negatively charged GOD to this 3D nanostructure exhibited high linear range and promoted sensitivity. The insolubility and aggregated

affinity of SWCNT is greatly affected by ssDNA to form a uniform layer on the transducers for solution-phase SWCNT employment. The study demonstrated that the adsorption of oppositely charged films helps in fixed GOD immobilization for enhancing the stability and anti-interference capability (35).

In 2010, Wan et al studied the effect of polyaniline (PANI) on glucose sensing of CNT. A high-performance amperometric glucose biosensor was fabricated by the covalent functionalization of Chitosan-carbon nanotubes (CS-CNTs) and GOD on Au electrode modified by polyaniline (PANI), oxidative graft polymerization of aniline. The resulting Au-g-PANI-c-(CS-CNTs)-GOD biosensor with a linear response to glucose exhibited high sensitivity, stability, and reproducibility. The authors also found that PANI led to high electrocatalytic and biological performance of GOD (36).

In another research project, Cella et al developed an enzyme-free chemiresistive biosensor by phenoxy dextran and concanavalin A (ConA) modified on gold electrodes. The ConA as a metalloprotein is dimeric at low pH and tetrameric at neutral pH. Dextran with strong affinity to glucose showed the reversible binding ability to ConA. Displacement of dextran from dextran-ConA complex via glucose was followed by coupling ConA to carbohydrates, changing its isoelectric point and forming positive charge, respectively. Therefore, changeable conductivity in the system was shown as a result of ConA removal and binding to the SWCNTs. The authors concluded that this displacement-based chemiresistive probe with low detection limits provided the ability to recognize glucose in serum (37).

2. MWCNT for Diabetes

Researchers have also designed a number of MWCNT biosensors for glucose monitoring. A substrate-enhanced electroless deposition method was employed for the fabrication of non-enzymatic amperometric sensor based on a composite of cubic Cu nanoparticles and arc-synthesized MWCNTs for glucose sensing in real blood serum instead of the common GCE. As a result, improved electron transfer, increased active area, and enhanced sensitivity for glucose probing were obtained by direct anchoring of cubic Cu nanomaterials with significant catalyzed potential for glucose determination on MWCNTs (38).

Huang et al evaluated the performance of enzyme-free MWCNT glucose biosensor for low detection limit of glucose by attachment of MWCNTs and 1-dimensional ultra-long Cu nanowires (Cu NWs) hybrid on GCE. Cu nanomaterials with high electro catalytic glucose oxidation activities possess low cost and high electrical conductivity benefits. Resultant biosensor displayed rapid wide linear response for detecting glucose in human serum with low detection limit and excellent sensitivity (39).

Chen et al arranged fabrication of functional CNTs and sugar-lectin biospecific interaction for glucose probing by

MWCNT-bi-enzyme bionano-multilayer electrode. After modifying via poly (allylamine hydrochloride), positively charged MWCNTs were water soluble for coupling with negatively charged horseradish peroxidase (HRP) and ConA/GOD on functionalized electrode through 4-step LBL assembly technique. In this study, the obtained bi-enzyme sensor with catalytic link between GOD and HRP showed quick and linear amperometric response with a detection limit of 2.5-7 M for glucose in serum (17).

Discussion

The severity of diabetes as a metabolic disease depends on the amount of glucose transport in the body (40). Selective and accurate real time glucose sensing in blood and body fluids at molecular and cellular levels is vital for diagnosis of insulin shortage and hyperglycemia with regard to the role of glucose in diabetes management and diminishing its health-threatening side effects (1). Eye and kidney disorders, heart diseases, neurodegeneration, and infection vulnerability are a few examples of long-term hyperglycemia side effects (2). In addition, determination of glucose in blood and cells has significant effect in clinical cancer diagnostics; as the concentration of glucose is elevated in tumor cell (39). Therefore, development of sensitive biosensors for detecting ranges of glucose at normal level, hypo- and hyper-glycemia is a considerable challenge (32). Glucose detecting sensor recognizes the glucose by converting the glucose to gluconic acid and hydrogen peroxide in the presence of oxygen (33). Expensive enzymatic biosensor with complicated GOD-immobilizing procedure shows susceptible activity according to temperature, pH, humidity, chemical reagent, and toxic material as in contrast to free enzyme biosensor. In addition, modification of CNT-based amperometric biosensor as a combination of biomolecules and CNTs is necessary for altering the hydrophobic surface of the CNTs into a hydrophilic surface in order to be combined with enzymes (38). Thus, low-cost reproducible non-enzymatic GOD biosensor with stability and simplicity opens a promising approach to overcome these troubles (39). Point-of-care CNT-based sensors have great sensitivity to glucose in the body fluids like saliva along with blood where daily uncomfortable finger prick is eliminated by this biosensing agent. To this end, the scalable boronic acid modified CNT transistor was designed for systemic variation measurement based on the appropriate clinical amount of glucose. This point-of-care solution-phase nanotube biosensor has potency to measure the blood glucose instead of painful finger prick (14).

The significant difference in glucose sensing performance of CNT could be observed based on varied production method and various modifying compounds. For example, Kang et al applied self-assembly technique as an amplifying and low-cost strategy for developing the CNT biosensors due to its capability in controlling the layer thickness in nanometer level (35). Moreover, wan et al showed that conductive polymers such as polyaniline (PANI) enhance

the effectiveness of amperometric glucose biosensors. PANI-modified biosensor improves signal by acting as an appropriate immobilization mediator for electron transition in enzymatic reaction (36).

In this study, the suitability of modified CNT as an efficient glucose sensor for diabetes control was reviewed. These aforementioned projects exhibited new methods of using nanosensors as metabolic biomarker detectors, but each of these studies was limited to a single evaluation article. Therefore more studies are needed to obtain sufficiently trustable results for introducing new cost-effective biosensor manufacturing methods which may be effective for clinical glucose detection in the near future.

Conclusion

This review aimed to describe the current developed biosensors for diabetes monitoring in vivo or in vitro. CNTs with significant structural, electronic, and optical properties present prominent opportunities to create new and attractive platforms of nanotools for biosensing of disease markers. These new non-invasive sensing devices with low cost and miniaturized size can challenge current non-expensive blood glucose test strips. In conclusion, we found that the appropriate functionalized CNTs have great potential in detecting the diabetes markers to resolve therapeutic problems of both types of diabetes.

Competing Interests

Authors declare that they have no conflict of interests.

Ethical Issues

Not applicable.

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