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Glycated hemoglobin-detection methods based on electrochemical biosensors

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ABSTRACT

Diabetes is a group of heterogeneous disorders with the common elements of hyperglycemia and glucose intolerance because of insulin deficiency, impaired effectiveness of insulin action or both. The best marker for long-term glycemic control is whole-blood glycated hemoglobin (HbA1c), since its levels correspond to the long-term progression of diabetes without short-term fluctuations in the behavior of glucose. Currently, common laboratory methods to recognize glycated proteins are high-performance liquid chromatography, immunoassay and electrophoresis. The accuracy and the precision of A1C assays at least match those of glucose assays. Consequently, the International Expert Committee (with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation) decided that the A1c assay should be recognized as the primary method for diagnosing diabetes. In this review, we look at electrochemical biosensors for the detection of glycated proteins developed in recent years.

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1. Introduction

Diabetes mellitus is a public health problem worldwide. This metabolic disorder arises from insulin deficiency and hyperglycemia, and is reflected in blood-glucose concentrations higher or lower than the normal range of 80–120 mg/dL (4.4–6.6 mM). The disease is one of the leading causes of death and disability in the world. The complications of battling diabetes are numerous, including higher risks of heart disease, kidney failure, or blindness. Such complications can be greatly reduced through stringent personal control of blood glucose. The diagnosis and the management of diabetes mellitus thus require tight monitoring of blood-glucose levels. Accordingly, millions of diabetics test their blood-glucose levels daily, making glucose the most commonly tested analyte [1,2].

Diagnosis and management of the disease require tight monitoring of blood-glucose levels for a number of purposes:

- it provides a quick measurement of blood-glucose level at a given time;

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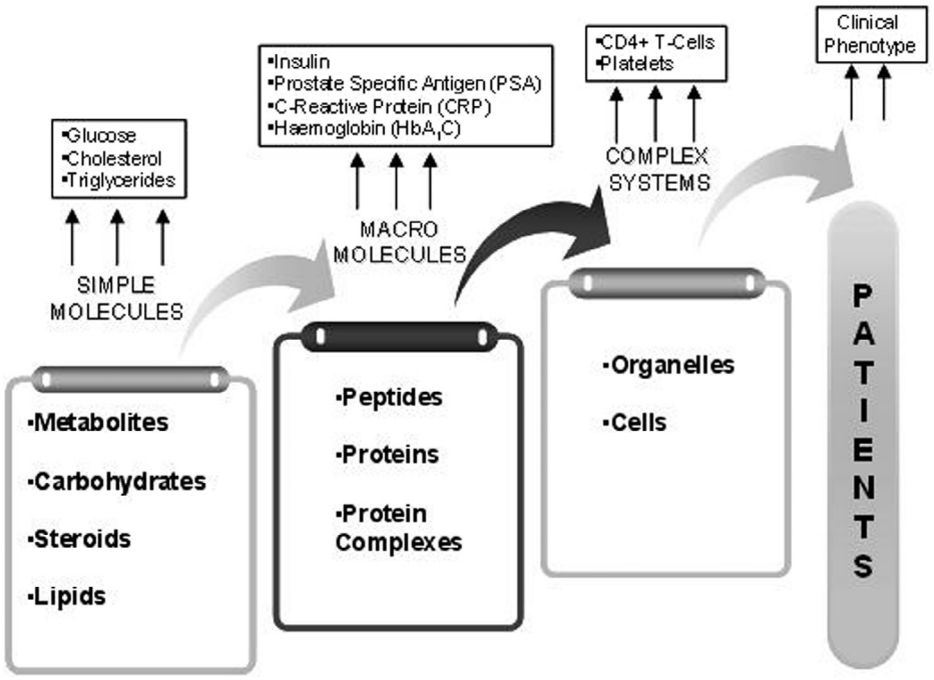

Fig. 1. Classification of biomarkers [9].

- it determines if a diabetic person has a high or low blood-glucose level at a given time;
- it demonstrates the links between lifestyle, medication and blood-glucose levels; and,
- it helps diabetics and diabetes health-care teams make changes to lifestyle and medication that will improve blood-glucose levels [3,4].

Since Clark and Lyons proposed in 1962 the initial concept of glucose-enzyme electrodes [5], we have witnessed tremendous effort directed toward the development of reliable devices for diabetes control. Different approaches have been explored in the operation of glucose-enzyme electrodes. In addition to diabetes control, such devices offer great promise for other important applications, ranging from bioprocess monitoring to food analysis. The great importance of glucose has generated an enormous number of publications, the flow of which shows no sign of diminishing. Yet, in spite of the many impressive advances in the design and the use of glucose biosensors, the promise of tight diabetes management has not been fulfilled. There are still major challenges in achieving clinically-accurate, continuous glycemic monitoring connected to closed-loop systems aimed at optimal insulin delivery. Such feedback response to changes in the body chemistry has broader implications for the management of different diseases. The management of diabetes thus represents the first example of individualized (personalized) medicine.

The direct recognition of blood proteins as biomarkers could benefit a number of scientific and clinical applications, such as drug research and environmental monitoring [6], early disease diagnosis and treatment [7]. A biomarker is a characteristic indicator of a biological phenomenon or state (e.g., a high plasma-glucose concentration could indicate potential diabetes, so glucose is a biomarker as an indicator for diabetes) [8]. There are different types of biomarker, ranging from small molecules (e.g., glucose and cholesterol) to complex systems (e.g., organelles and cells), as shown in Fig. 1.

Currently, the biomarker market has two main areas – discovery and detection. Biomarker discovery represents the largest area of application for biomarkers. Because of the limited availability of new biomarkers, biomarker discovery is expected to complete its late growth stage and attain maturity in 2015 [9,10]. However, biomarker-detection research is currently in its nascent stage with significant progress in the development of diagnostics and therapeutic guidance [9]. The trend in the biomarker market is shifting from biomarker discovery to biomarker detection. The market size for biomarkers is forecast to increase from $22.3 billion in 2014 to ~$34 billion by 2017 [11]. One of the important applications of biomarker detection, which recently attracted increased attention from researchers and physicians, is the use of glycated proteins for the early diagnosis and treatment guidance of diabetes [12,13].

Diabetes has become one of the most widespread and serious diseases all over the world. The global market for diabetes drugs and devices accounted for $41.9 billion in 2010 and is expected to attain a market size of $114.3 billion in 2016 with a high annual growth rate of 18.2% [14].

Since diabetes is directly attributed to a high plasma-glucose concentration, the diagnosis of diabetes depends on the observation of symptoms of hyperglycemia and the detection of higher casual plasma-glucose concentrations. However, hyperglycemia symptoms usually vary among individuals and the plasma-glucose concentration can fluctuate frequently during normal activities (e.g., digestion and exercise) [15]. Usually, a conventional point-of-care (POC) invasive-type device is used to assess the plasma-glucose concentration. This measurement needs to be performed several times a day, which can bring considerable physical pain, so other diagnosis methods, which are more reliable and require fewer measurements, could increase patient compliance and lead to health-care savings.

In the past decade, the use of glycated proteins has been suggested as a standard laboratory measurement for diabetes diagnosis and control assessment. Among different blood proteins, glycated hemoglobin (HbA1) is the most widely-studied glycated protein for diabetes control. HbA1 is made up of HbA1a, HbA1b, and HbA1c, depending on the attachment of different sugars. HbA1c is the primary protein used for glycemic control, involving a non-reversible process of attaching D-glucose to a specific amino-terminal site of