

Sugar-based electrochemical biosensors for quantification of a secreted protein in human fluids

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Summary:

Obesity is a major risk factor for Type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD), two highly prevalent metabolic disorders with substantial clinical burden. Phosphoglucose Isomerase (PGI), classically recognized as a key glycolytic enzyme, has recently emerged as a candidate biomarker for metabolic disease because of its extracellular function as a cytokine. In this study we report the development of electrochemical biosensors for the sensitive detection of PGI in plasma and evaluated their performance in high-fat diet-induced mouse models of obesity. We show that these biosensors reliably detects circulating PGI and enables monitoring of its levels in the context of diet-induced obesity. Together, these findings identify circulating PGI as a potential early biomarker of obesity-associated metabolic disorders and highlight electrochemical biosensing as a promising non-invasive approach for the early diagnosis and monitoring of obesity-driven metabolic diseases progression.

Keywords: Glyco-sensor, graphene-pyrene transducer, PGI, diet-induced obesity, Type 2 diabetes, High fat mouse.

Background, Motivation and Objective

Diabetes mellitus, a metabolic disorder marked by hyperglycemia, is a major global health challenge. It is classified into Type 1 diabetes (T1DM, ~6% of cases), an autoimmune disease destroying pancreatic beta cells; Type 2 diabetes (T2DM, ~92%), driven by insulin resistance in muscle, liver, and fat; and rare forms (~2%), including gestational diabetes, MODY, and monogenic diabetes. The surge in T2DM is closely linked to obesity, sedentary lifestyles, and genetic factors, reflecting the interplay between environment and heredity.

Globally, 436 million adults worldwide live with T2DM, with 65% also affected by metabolic-associated steatotic liver disease (MASLD). This coexistence highlights the intricate relationship between diabetes and metabolic disorders, such as cardiovascular disease, nephropathy, and fatty liver disease, which collectively increase morbidity and mortality [1,2].

Modern lifestyles—high-calorie diets, physical inactivity, and obesity—exacerbate insulin resistance and T2DM progression, posing a multifaceted public health challenge. Addressing this requires comprehensive

strategies for prevention, early diagnosis, and management of obesity and associated metabolic diseases [3].

Phosphoglucose Isomerase (PGI), classically recognized as a key enzyme of glycolysis and gluconeogenesis, is now considered as a multifunctional protein with both intracellular and extracellular activities. Beyond catalyzing glucose-6-phosphate and fructose-6-phosphate interconversion, PGI is also secreted as autocrine motility factor (AMF), influencing cancer cell migration and invasion. This dual role places PGI at the interface between metabolic homeostasis and disease mechanisms, highlighting its relevance as an attractive molecule for biomedical research [4].

PGI is implicated in several pathological conditions, including cancer, rheumatoid arthritis, and metabolic disorders. In tumors, it promotes metastasis; while in inflammatory and metabolic diseases, elevated extracellular PGI levels have been reported [4]. Its presence in plasma and urine suggests its potential as a biomarker for early disease diagnosis. Accordingly, innovative tools, such as electrochemical biosensors, are being developed to measure pathological PGI levels,

offering non-invasive approach for monitoring MASLD and T2DM [5].

This work explores the roles of PGI in health and disease, with particular focus on its diagnostic and therapeutic potential. Here, we report the development of electrochemical biosensors for sensitive PGI detection in plasma, and their application as preclinical model of T2DM in high-fat diet (HFD) mouse models, to evaluate PGI as a candidate biomarker for early diagnosis of HFD-induced metabolic disorders.

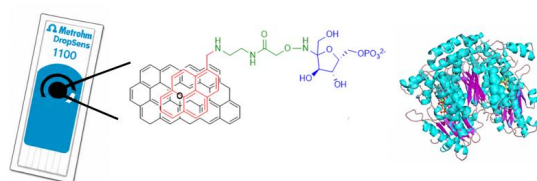


Fig. 1. Schematic representation of the biosensor: The transducer consists of a nanocomposite formed by RGO/pyrene/glucose-6-phosphate as the biomarker. The nanocomposite was synthesized, and the resulting ink was drop-casted onto a screen-printed carbon electrode (SPCE) to form the biolayer.

Description of the Method

The sensor consists of a screen-printed carbon electrode modified with graphene/pyrene biolayers covalently bound to the carbohydrate D-fructose-6-phosphate, the enzyme substrate, which serves as a bioreceptor, as described in our previous work [6].

This study was designed to investigate the temporal evolution of the biosensor response to PGI present in plasma by comparing plasma samples from control and HFD-fed mice. The HFD is known to induce a prediabetic state. Five distinct groups of plasma samples were analyzed: short-term control, long-term control, HFD for 3 days, 8 days, and 8 weeks (long-term). The experimental protocol consisted of four independent experiments per group, under strictly controlled conditions and repetition to highlight the scalability of the measures. This approach allowed for a robust assessment of how the biosensor responds over time to dietary-induced metabolic changes. The plasma are diluted with buffer at various level and then PGI concentration was measured with the electrochemical biosensors using electrochemical impedance spectroscopy. The variation of charge transfer resistance of the E-Biosensors was measured by fitting the data with equivalent circuit.

Results:

Our findings revealed a progressive, time-dependent increase in biosensor signal in plasma from HFD-fed mice, with signal intensity correlating with the duration of high-fat diet exposure. This demonstrates the biosensor's ability to discriminate normal from metabolically stressed conditions, while sensitively capturing the progressive metabolic deterioration induced by HFD.

The evaluation of PGI concentration in high-fat diet mice was conducted using a calibration curve obtained in vitro, where normal mouse plasma was doped with increasing concentrations of PGI. The results demonstrated a good correlation with previous studies [5].

Overall, these findings highlight that the biosensor is highly sensitive to dynamic changes in plasma, making it a promising tool for monitoring metabolic health and disease progression.

All results obtained will be discussed in detail during the presentation.

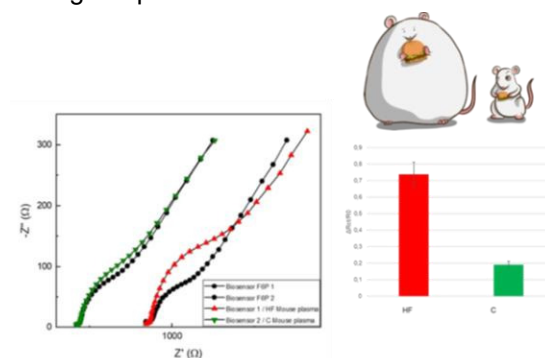


Fig. 2. Impedance characterization of the glycosensor. (Left) Nyquist plots illustrating the impedance variation for plasma samples from high-fat diet mice and control mice. (Right) Histogram showing the variation in charge transfer resistance.

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