

A multi-marker approach for improved glycemic management in diabetes mellitus

Abstract

Tight glycemic management is recognized as the guiding principle when treating diabetes mellitus, but decisions about medical intervention based on glucose measurements alone suffice but are inadequate in all circumstances. Continuous and multi-marker monitoring of other metabolic biomarkers such as insulin and glucagon are vital to providing the physician with a more comprehensive view of the condition. While there are many preexisting continuous glucose monitoring systems and ongoing developments toward an artificial pancreas, there is a lack of molecular recognition elements capable of continuous detection of insulin and glucagon. As researchers are developing appropriate molecular recognition elements for such, a parallel approach on developing disposable, discrete multi-marker sensors can occur concurrently. Using multi-sensor arrays and electrochemical impedance spectroscopy, a glucose-insulin-glucagon test strip can be developed to provide a more accurate and complete picture of glycemic states, successfully achieving tighter glycemic management.

Keywords: diabetes mellitus, multi-marker, continuous monitoring, glycemic control, electrochemical impedance spectroscopy

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Abbreviations: SMBG, self-monitoring of blood glucose; CGMS, continuous glucose monitoring systems; APS, artificial pancreas systems; MREs, molecular recognition elements; EIS, electrochemical impedance spectroscopy

Introduction

Tight glycemic control has been the goal of care for people with diabetes¹ as achieving near-normal glucose levels has been shown to reduce the risk of microvascular disease.²⁻⁴ Traditionally, people with diabetes are instructed to check their glucose consistently using self-monitoring of blood glucose (SMBG) technologies and make appropriate modifications to their medical intervention according to experience, empirically derived algorithms, and lifestyle. However, there are many challenges throughout the process including an increased risk of hypoglycemia when attempting to reach tighter glucose control. In addition, there is also a lack of ability to effectively account for multiple simultaneous life-style choices (e.g., exercise, alcohol ingestion, accurate carbohydrate counting) when deciding insulin boluses. These challenges all contribute to variability and unpredictability of daily glucose control. Unfortunately, sporadic measurement of glucose alone is insufficient to reach the goal of tight glycemic control, as it is merely a biomarker that reflects a series of complicated metabolism process. Given the discussed limitations there is a continued effort to improve glycemic management. Continuous monitoring and multi-marker detection are instrumental in achieving better management of the condition.

Continuous monitoring, specifically, continuous glucose monitoring systems (CGMS) have been commercially available for years, and are commonly used in conjunction with subcutaneous insulin infusion devices (aka “insulin pumps”) for improved disease management. Some systems also have the capability for automatic threshold suspense features to pause insulin delivery to avoid hypoglycemia. Although these technologies have provided assistance to people with diabetes in making medical dosage decisions, they are still “open loop” devices, which require the user to make their own decisions about glycemic management. Fortunately, “closed-

looped” insulin delivery devices - so called artificial pancreas systems (APS)-are currently being introduced to further automate the glycemic management process (e.g. Medtronic’s Guardian 3).⁵⁻¹⁰ However, the fundamental problem of insulin delivery based solely on glucose levels remains unsolved. Levels of other markers such as glucagon, endogenous insulin and beta hydroxybutyrate are not being consulted prior to insulin delivery, yet are vital physiological factors that affect the glucose metabolism. To achieve a truly closed-loop system capable of tight glycemic control, a continuous multi-marker approach is inevitable.

Normal glucose homeostasis is determined by interactions between glucose, insulin and glucagon. However, current technologies only rely on glucose data to make therapeutic decisions. Insulin bolus calculators do not account for the total amount of insulin in the body, but only how much insulin has been delivered. Insulin infusion has been recognized as a frequent source of hyperglycemia, accounting for 61.9% of the reported incidents.¹¹ Moreover, the complex algorithms that drive APS insulin delivery depend only on glucose as well,⁵⁻¹⁰ having a 40% chance of both insulin overdosing and underdosing.¹² On average, the insulin infusion set fails after 5.3 days with a false positive rate of 0.3/day.¹³ The CGM sensors themselves, also contribute to mismanagement. The most common source of error for CGM is pressure-induced sensor attenuation (PISA). While PISA can be detected at a 88.34% accuracy by the included algorithm, it still presents a significant source of error for the glucose sensor.¹⁴ CGM’s accuracy can also be disturbed by meals and exercising.¹⁵ Besides mechanical or electrochemical failures of the AP, all of these potential errors are the result of relying solely on glucose detection. The ability to measure insulin, glucagon and glucose simultaneously would enhance current insulin delivery devices by providing a direct measurement of existing hormone levels on board, while diverting the risk of an algorithm built solely on glucose. Individual insulin-glucagon-glucose dose-response relationships could be determined, permitting the inclusion of algorithms to measure all three parameters for optimal glucose control. In addition, combining all three sensor capabilities into a single platform with eventual continuous monitoring

capabilities could reduce the hardware footprint needed for future APSs. By monitoring these three major biomarkers simultaneously, a closer and more comprehensive view of metabolism in diabetes mellitus can be studied. Once proven, additional biomarkers such as beta hydroxybutyrate, C-peptide and other biomarkers should also be included.

Detection of minute changes in insulin and glucagon requires a sensitive detection mechanism. Among many sensitive detection techniques, optical and electrochemical approaches are most commonly used. However, optical approaches face limitations caused by fluctuations in pH and temperature making their application in biological media undesirable. Electrochemical sensors, however, are more robust to pH and temperature changes, more sensitive, inexpensive, and are already employed in current CGMs and blood glucose test strips. Many researcher groups have already developed electrochemical insulin sensors capable of detecting insulin within physiological ranges and in complex medium.^{16–19} While there has been development toward the continuous detection of insulin²⁰ and glucagon²¹ in purified solution, appropriate molecular recognition elements (MREs) capable of continuous detection of the two hormones have yet been developed. Proper MREs are required to achieve the specificity required for detection in complex medium. Typical glucagon and insulin antibodies have been employed to develop disposable and discrete measurement sensors,¹⁹ but due to the mechanism of irreversible binding to the respective analyte, they are not feasible for continuous detection. Currently there is effort toward the genetic modification of MREs to enable their functionality on a continuous platform,^{22,23} but it is far from ready for commercialization. This limitation prevents the development of continuous multi-marker detection platforms, but permits discrete measurements of all markers of interest in a single sample, analogous to the current SMBG sensor. A glucose-insulin-glucagon disposable sensor can still provide a more comprehensive picture of glycemic status than glucose alone while maintaining the patient-familiar practice of SMBG using disposable test strips.

Much work has been done toward the achievement of multi-marker detection, including the development of mathematical models to provide detailed insight into simultaneous monitoring of glucose, insulin, and glucagon.²⁴ Multi-marker detection is currently achieved through the use of multiple sensors or sensor arrays. For example, simultaneous detection of glucose and insulin was demonstrated using a needle-like glucose sensor and an insulin sensor²⁰ bundled together. An alternative is a single-electrode multi-marker sensor approach using electrochemical impedance spectroscopy (EIS). EIS stimulates the electrochemical cell using an alternating voltage across a wide range of frequencies. It was previously reported that each biomarker can be detected at an optimal frequency at which the impedance response best correlates to target analyte change.²⁵ Using the optimal frequency approach, EIS insulin and glucose sensors have been developed,^{19–25} and additionally, simultaneous detection of 2 biomarkers on the same sensor surface was also proved possible.²⁶ Given the wide-ranging advancements discussed previously, an electrochemical glucose-insulin-glucagon disposable test strip is indeed within reach, and holds promise of achieving improved glycemic management.

Conclusion

In summary, glucose values alone are not enough to achieve tight glycemic control for diabetic patients. A continuous, multi-marker approach on important metabolic biomarkers such as insulin and glucagon are necessary to obtain vital metabolic information for improved glycemic management. While CGMs and APS have evolved

drastically, they have yet to include insulin and glucagon sensors in the final device. Electrochemical detection of insulin and glucagon has been shown possible, but the lack of proper MREs capable of continuous detection will not achieve the required specificity to work in complex medium. While there is development toward appropriate MREs for continuous detection of insulin and glucagon, disposable glucose-insulin-glucagon sensors can be developed using either multi-sensor array approach or single electrode EIS approach. The technical advancements discussed within provide promise toward a multi-marker approach for enhanced glycemic management.

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Conflict of interest

Author declares that there is no conflict of interest.

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