

Demand for the Early Detection of Diabetic Risk at Annual Health Examinations and A Probable Solution

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Abstract

Despite medical examinations, the number of cases of undiagnosed diabetes has reached 17.9 million. Hence, there is a strong need for diagnostic criteria that uses proper biomarkers at annual health examinations, even in developing countries. Recently, we developed a second-generation prototype of a multimarker analysis system that facilitates a rapid assay of a single, small-volume sample for numerous biomarkers. Clinicians may be able to manage and/or advise subjects regarding their food and exercise habits before the onset of diabetes by evaluating their biomarker levels using this system. We have begun 5 years of cohort testing to evaluate these multibiomarkers.

Keywords: Diabetic risk; Insulin resistance; Biomarkers; Multimarker

Introduction

According to the International Diabetes Federation, the number of people living with diabetes was 386.7 million in 2014. The prevalence of diabetes in adults aged 20–79 years is 8.3%, and it is estimated that one in 12 people have diabetes. Despite medical examinations, the number of cases of undiagnosed diabetes has reached 17.9 million. Criteria for diagnosing diabetes includes a fasting plasma glucose (FPG) concentration of >126 mg/dL and a plasma concentration of >200 mg/dL at 120 min after an oral glucose tolerance test (OGTT). The Japan Diabetic Society classifies subjects with an FPG value of 100–109 mg/dL as high-normal in the range of glucose metabolism disorders, and it recommends that subjects with a high-normal FPG value undergo a 75-g OGTT to determine whether they are normal, borderline, or diabetic [1]. However, there is a strong need for diagnostic criteria that uses proper biomarkers at annual health examinations, even in developing countries.

Insulin resistance and homeostasis are important topics when discussing the risk of diabetes. The homeostasis model assessment of insulin resistance (HOMA-IR) and the Matsuda index were developed to quantify insulin resistance. HOMA-IR is calculated as $(\text{FPG} \times \text{fasting insulin}) \div 405$ (normal level, <1.6 and insulin resistance, >2.5, according to the Japan Diabetes Society). The Matsuda index is calculated using plasma glucose and insulin concentrations during the OGTT ($\text{Matsuda index} = 10,000 \div \text{the square root of } [\text{fasting glucose} \times \text{fasting insulin}] \times [\text{mean glucose} \times \text{mean insulin during the OGTT}]$ (0, 60, and 120 min, respectively; normal level, >3) [2]. Both glucose tolerance and insulin homeostasis are important factors in evaluating the diabetic risk and maintaining patients' health. However, as the OGTT is a time-consuming and optional test in Japan, few people undergo it each year.

Many research studies have shown that lipid metabolites, which are formed by oxidative stress, are involved in the onset of diabetes. For example, it has been reported that the formation of 9-

hydroxyoctadecadienoic acid in the erythrocyte membranes of patients with diabetes [3] and hydroxyl fatty acids that are derived from linoleic acid in low-density lipoproteins from patients with atherosclerosis [4]. Thus, metabolized lipids by oxidative stress can be a candidate biomarker for the early detection of diabetes. We have previously reported that fasting plasma levels of 10- and 12-(Z,E)-hydroxyoctadecadienoic acid (HODE), not 9- and 13-(E,E)-HODE (free radical-mediated specific products), exhibited a significant correlation with plasma levels of hemoglobin A1c, glucose, insulin secretion, and resistance index [5]. However, 10- and 12-(Z,E)-HODE alone cannot perfectly predict the risk of diabetes. A further study was performed for selecting candidate biomarkers, and it was found that fasting plasma levels of leptin and adiponectin together with insulin and glucose, which are usually measured, are sufficient for predicting the risk of diabetes when concomitantly used with 10- and 12-(Z,E)-HODE [6]. Among the biomarkers we tried (ca. 30), 10- and 12-(Z,E)-HODEs were the strongest biomarkers. They are predominantly formed by singlet oxygen-derived oxidation. Accordingly, we are proposing a new mechanism for the onset of diabetes. Briefly, due to hyperglycemia, neutrophils containing myeloperoxidase are recruited to adipose cells or β -cells, which results in the formation of singlet oxygen. This is considered the early stage of the pathogenesis of diabetes, and the normal response toward inflammation (before insulin secretion), abnormalities, and insulin resistance are observed (i.e., adaptation). These hypotheses are supported by our recent studies [7,8].

We recently developed a second-generation prototype of a multimarker analysis system, which is equipped with a CD-type microfluidic device [9] and an apparatus for measuring chemiluminescence (Figure 1). ELISA reaction is performed on the microfluidic device rapidly. This device facilitates a rapid assay of a single, small-volume sample for numerous biomarkers. Clinicians may be able to manage and/or advise subjects regarding their food and exercise habits before the onset of diabetes by evaluating their biomarker levels using this system without OGTT. We have started 5 years of cohort testing to evaluate multibiomarkers and the analysis system mentioned above. The same person (more than 100 subjects)

will be recruited and taken OGTT for 5 years consecutively. After the testing, we believe these multibiomarkers measured by the system will provide the sufficient information for detecting diabetic risk at annual health examinations.

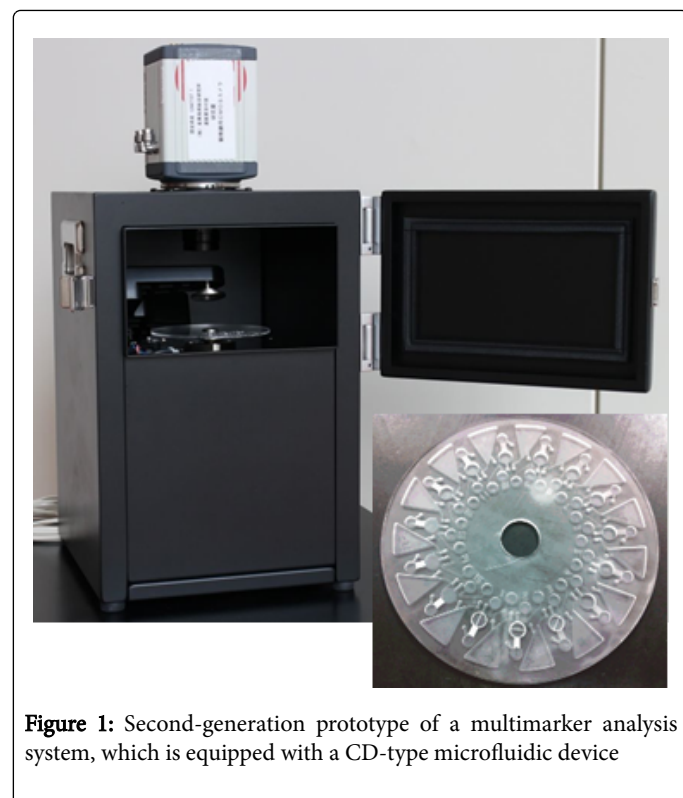


Figure 1: Second-generation prototype of a multimarker analysis system, which is equipped with a CD-type microfluidic device

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