Identification of Protein Z as a Potential Novel Biomarker for the Diagnosis of Prediabetes

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Type 2 diabetes mellitus (T2DM) has rapidly emerged as one of the major metabolic diseases in modern society [1]. Accounting for more than 90% of human cases of diabetes, T2DM has become a global health threat in both developing and developed countries worldwide. T2DM is considered to be a chronic metabolic disorder, and it is associated with hyperglycemia due to impaired insulin secretion (via pancreatic β-cell dysfunction), as well as insulin resistance in the peripheral tissues such as the liver, skeletal muscles, and fat cells [2]. Patients with T2DM have higher risks for developing severe complications such as microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (myocardial infarction, stroke) [3]. Due to the severity of the complications associated with T2DM, it is important to identify the optimal diagnostic tools for prediabetes (a state prior to the development of T2DM) before the progression of the disease.

Glycated hemoglobin (HbA1c) is currently the most universally utilized biomarker for the diagnosis of both prediabetes and T2DM [4]. Elevated HbA1c levels reflect a chronic hyperglycemic state, and are more highly associated with microvascular complications than fasting plasma glucose (FPG). Although it is a convenient biomarker for detecting prediabetes and T2DM, the usage of HbA1c has limitations due to its moderate sensitivity compared with more traditional methods, such as FPG and the oral glucose tolerance test [5,6]. Moreover, certain conditions that affect the lifespan of red blood cells themselves could impact plasma HbA1c concentrations [7]. Efforts are underway to identify more reliable and convenient biomarkers for the diagnosis of prediabetes and T2DM. Examples include metabolites (ceramide, acyl-carnitine, and high-density lipoprotein), certain classes of mi-RNAs (miR-192 and 193b), and inflammatory cytokines (C-reactive protein, interleukin 6 [IL-6], IL-18, and plasminogen activator inhibitor-1), each of which has unique advantages and limitations [8].

In the current issue of *Endocrinology and Metabolism*, Bae et al. [9] published a new article regarding the potential role of protein Z (PROZ) as a novel biomarker for prediabetes and T2DM. In this study, the authors used blood samples from groups with normoglycemia, prediabetes, and T2DM to detect specific cytokines that were significantly correlated with the disease state by using a cytokine microarray analysis. Thirty-three cytokines were differentially identified in the blood samples from the prediabetic and T2DM groups compared with the normoglycemic group, showing a strong enrichment of biological processes such as immune and inflammatory responses. Interestingly, the level of PROZ was significantly lower in individuals with prediabetes or T2DM than in the normoglycemic control group, and this finding was validated with an enzyme-linked immunosorbent assay analysis. PROZ, a plasma glycoprotein secreted from the liver [10], has been shown to inhibit

blood coagulation and to display a negative correlation with the incidence of vascular disorders [11-13], without any association with glycemia. Indeed, PROZ showed a negative correlation with FPG and HbA1c, which are markers for glycemic disorders, suggesting that it could serve as a potential novel biomarker for prediabetes and T2DM. Based on the proposed role of PROZ, it is plausible to predict that reduced plasma PROZ might be involved in the vascular complications that are associated with T2DM.

In conclusion, the study by Bae et al. [9] identified PROZ as a potential novel biomarker for diagnosing prediabetes and T2DM, which requires further validation. An analysis of a larger cohort in a longitudinal study should be conducted to monitor plasma PROZ levels. Given its potential association with vascular disorders [12,13], it is desirable to delineate the potential role of PROZ in glycemia and/or the development of vascular disorders in T2DM. Regardless, the current study provides a novel insight regarding a newly-discovered potential biomarker for prediabetes that may be helpful to reduce the risk of progression to T2DM in the future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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