Association of Protein Z with Prediabetes and Type 2 Diabetes (*Endocrinol Metab* 2021;36:637-46, Yun-Ui Bae et al.)

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We would like to thank Pascreau et al. for reading our article carefully and thoroughly [1] and for providing interesting data from their research. As Pascreau et al. indicated, our findings are compatible with the other results that they mentioned [2]. We agree that the association of protein Z (PROZ) and type 2 diabetes mellitus (T2DM) is uncertain in patients with vascular complications. Since few studies have investigated PROZ and T2DM, accurate information on PROZ in the context of glucose dysmetabolism is currently limited. As mentioned in our article, PROZ was not found to be involved in the regulation of inflammatory [3], immune [4], and cell proliferation response pathways [5] related to glucose dysmetabolism in our bioinformatics analysis. Further studies are necessary to elucidate the hidden mechanism of PROZ in prediabetes and T2DM. When the role of PROZ in glucose dysmetabolism becomes clearer, its potential as a biomarker for prediabetes and T2DM will be ascertained.

Our study, however, had some differences from that of Pascreau et al. We mainly focused on identifying this cytokine as a potential biomarker of prediabetic status. We first checked fold changes in PROZ, and then evaluated PROZ levels in different subjects with normoglycemia, prediabetes, and T2DM. These two results showed consistent trends in PROZ levels. Our data also had some differences in the analyzed groups compared to the data mentioned by Pascreau et al. and the study by Heeb et al. [2]. We selected subjects with newly diagnosed T2DM in the cytokine microarray analysis and validation of PROZ. Most of our subjects did not have microvascular and macrovascular complications related to T2DM. The data provided by Pascreau et al. and the study by Heeb et al. [2] showed PROZ levels in subjects who had experienced ischemic stroke. We assume that these differences in the analyzed groups might contribute to differences in PROZ levels. Although a small number of subjects with cardiovascular disease (CVD) were included in our validation group (there were 0, 2, and 6 subjects with CVD in the normoglycemia, prediabetes, and T2DM groups, respectively), there were still significant differences in PROZ levels among the groups after excluding subjects with CVD. PROZ levels were lower in subjects with prediabetes (1,491.90±378.40 pg/mL) and T2DM (1,562.21±451.73 pg/mL) than in subjects with normoglycemia (1,864.07±450.83 pg/mL) after excluding subjects with CVD ($P<0.001$). Additionally, there were some differences in the PROZ levels of healthy subjects between our results and other studies [2,6]. We suggest that these gaps in the mean values of PROZ across studies might be influenced by

ethnic differences across populations. Therefore, large-scale and diverse population-based studies are needed to investigate the potential of PROZ as a marker of glucose dysmetabolism.

The letter from Pascreau et al. is valuable for understanding our article. We deeply appreciate their comments, which have enriched our study.

CONFLICTS OF INTEREST

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

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