



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 read with interest the paper of Bae et al. [1] suggesting that plasma levels of protein Z (PROZ), a vitamin K dependent factor [2] could be a marker for the early detection of prediabetes. Indeed, they observed lower levels of PROZ in patients with type 2 diabetes mellitus (T2DM) or in prediabetic patients, and suggested that a cut-off of 1,484 pg/mL and of 1,404 pg/mL PROZ could identify prediabetic and T2DM patients, respectively. As PROZ deficiency was previously identified as a risk factor for ischemic stroke [3,4], we systematically measure PROZ (Zymutest protein Z, Hyphen, Neuville sur Oise, France) in patients with proven ischemic stroke, as well as fasting glucose and hemoglobin A1c (HbA1c) by capillary electrophoresis (Sebia, Lisses, France). From November 2012 to June 2016, these parameters were available for 421 (171 females, 250 males, median age 51 years). Of them, 34 (8%) were previously diagnosed with T2DM. We observed that median PROZ levels were similar between diabetic and in non-diabetic patients (2,295 and 1,958 pg/mL, respectively; $P=0.209$). According to the French guidelines we also divided diabetic patients into two groups: patients with correct glycemic control (HbA1c <7%) and patients with uncontrolled diabetes (HbA1c \geq 7%). The median PROZ levels were similar between the two groups (2,270 and 2,330 pg/mL, $P=0.807$). Considering the threshold

of 1,404 pg/mL of PROZ proposed by Bae et al. [1] to discriminate diabetic from normoglycemic patients, 110 (26.1%) patients from our series were classified as diabetics, nine of the 34 known diabetics (26.5%) being correctly classified by this approach. Lastly, we studied PROZ variations according to the levels of HbA1c as defined by the American Diabetes Association [5]. As it can be seen in the Table 1, PROZ levels were significantly higher ($P<0.05$) in diabetic than in normoglycemic patients. This was already described by Heeb et al. [4], who observed, unexpectedly, higher PROZ levels in diabetic patients with stroke than in stroke patients without T2DM. Therefore, both studies, on larger populations of patients, do not confirm the association of T2DM with PROZ deficiency, at least in patients with vascular complications. These conflicting results could be due to the large unusual Gaussian distribution of PROZ [2], requiring the inclusion of an elevated number of patients in order to avoid biased results.

CONFLICTS OF INTEREST

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

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Table 1. Variations of Median Plasma PROZ, FG, TG According to the HbA1c Level in Patients with a Previous Ischemic Stroke

	No.	PROZ, pg/mL	FG, mmol/L	TG, mmol/L
Normoglycemic (HbA1c <5.7%)	263	1,940 (1.375–2.472)	4.9 (4.6–5.4)	1.17 (0.83–1.5)
Prediabetes (HbA1c 5.7%–6.5%)	122	2,129 (1.294–2.815)	5.6 (4.9–6.1) ^a	1.68 (0.98–1.92) ^a
Diabetes (HbA1c >6.5%)	36	2,234 (1.497–3.133) ^b	7.9 (6.6–10.5) ^{a,c}	1.94 (1.09–2.87) ^{a,d}

Values are expressed as median (interquartile range).

PROZ, protein Z; FG, fasting glycemia; TG, triglyceride; HbA1c, hemoglobin A1c.

^a $P < 0.001$ vs. normoglycemic; ^b $P < 0.05$ vs. normoglycemic; ^c $P < 0.001$ diabetes vs. prediabetes; ^d $P < 0.05$ diabetes vs. prediabetes.

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