

Protein ingestion can significantly affect glucagon secretion along with blood urea nitrogen alteration in type 1 diabetes

We have read with great interest the article by Kawamori *et al.*¹ showing that dysregulated glucagon secretion, with respect to plasma glucose (PG) in patients with type 1 diabetes, persists for a year. The positive correlation between glucagon and blood urea nitrogen (BUN) levels was also consistently observed after 1 year. Consequently, they suggested constant dysregulation of glucagon is associated with altered amino acid metabolism in type 1 diabetes. However, they did not show the influence of meal ingredients on glucagon. To date, there is no direct evidence on whether amino acid homeostasis is altered in relation to glucagon secretion in type 1 diabetes patients.

Recently, we examined the relationship among glucagon, BUN, PG and the amount of nutrients in a patient with type 1 diabetes, and found that protein ingestion altered glucagon and BUN levels. The patient was a 16-year-old girl with type 1 diabetes, diagnosed with tyrosine phosphatase-related islet antigen 2 antibodies at 8 years-of-age. Her endogenous insulin secretion was depleted. We measured her glucagon levels using dual-antibody sandwich enzyme-linked immunosorbent assay every 2 months for 16 months. We recorded the time of blood collection (3.7 ± 0.5 h) and the estimated composition of the last meal. The data on one visit were excluded for analysis, because the sampling time (9 h after meal) was physiologically different. The serial clinical and laboratory data, and contents of the last meal before blood

sampling are presented in Table S1 and S2, respectively. She had reduced her carbohydrate intake (and increased protein intake) at her own discretion during this period. Of the laboratory values, glucagon showed a significant, positive correlation with BUN ($r = 0.920$, $P = 0.003$; Figure 1a). Even if partial correlation with correction for PG was carried out, a significant positive correlation was observed ($r = 0.929$, $P = 0.007$). There was no correlation between glucagon and PG, liver transaminase, glycated hemoglobin, glycoalbumin, creatinine, and lipid values (Table S3). Of the amount or composition of nutrients, the amount of protein showed a tendency for a positive correlation with glucagon ($r = 0.714$, $P = 0.071$), and a significant, positive correlation with BUN ($r = 0.776$, $P = 0.040$), respectively (Figure 1b,c). There was no correlation between glucagon or BUN and the amount of carbohydrate or lipid, and each nutrient composition (% of total energy; Table S3).

Glucagon has important regulatory effects on urea synthesis kinetics, the final step in the catabolism of amino acids, which is enhanced by protein intake^{2,3}. Therefore, our observation indicates that the positive association between glucagon and BUN levels seen in patients with type 1 diabetes in the previous study¹ might have been affected by protein ingestion at least in part. In addition, Kondo-Ando *et al.*⁴ recently showed that a low-carbohydrate high-protein diet by staple change increases postprandial glucagon in type 2 diabetes patients. Similarly, dysregulated glucagon secretion with respect to glucose responds to protein in patients with type 1 diabetes, although it is unknown whether the response is physiologically appropriate.


When considering glucagon regulation, attention should be paid to protein intake, even in patients with type 1 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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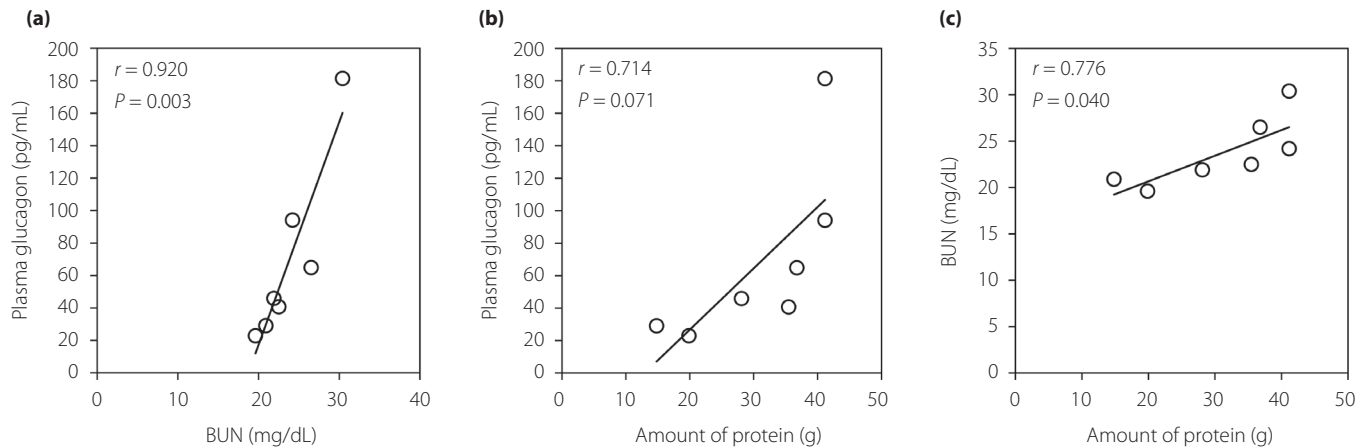


Figure 1 | The correlation of (a) blood urea nitrogen (BUN) and (b) the amount of protein with plasma glucagon, and (c) the correlation of the amount of protein with BUN from serial data with a different type of diet (normal or low-carbohydrate protein-rich) in the patient with type 1 diabetes.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Serial clinical and laboratory data of the patient.

Table S2 | Estimated content of meals, and the amounts of carbohydrate, protein and lipid, and their energy excluding some seasoning and condiments before the blood examination.

Table S3 | Results of Pearson's univariate tests in the serial data for patient with type 1 diabetes ($n = 7$).