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Relationship between Serum 1,5-anhydroglucitol, as an Indicator of Postprandial Glycemic Control, and Serum Uric Acid, Considering the Renal Threshold for Glucosuria in the Elderly

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Postprandial hyperglycemia is an independent risk factor for cardiovascular disease-related morbidity and mortality, not only in diabetes mellitus (DM) but also in impaired glucose tolerance. Postprandial glycemic levels have been difficult to monitor, but recently 1,5-anhydroglucitol (1,5-AG) levels have proven to be beneficial for this purpose.

In humans, 1,5-AG, a 1-deoxy-glucopyranose, is a major and abundant polyol, of which 90% is derived from ingested food, and little is produced from glycogen in the liver. Nearly all 1,5-AG is reabsorbed in normoglycemia, but the reabsorption rate decreases in proportion to the degree of hyperglycemia above the renal threshold for glucosuria, which is 160 to 180 mg/dL. Glucosuria appears if the level of blood glucose rises above this level. The renal reabsorption of 1,5-AG is competitively inhibited by glucosuria. The 1,5-AG level appears to be well suited for monitoring glucose homeostasis in subjects with near-normoglycemia or with postprandial hyperglycemia without fasting hyperglycemia. However, few studies have shown a relationship, which remains controversial, between the serum 1,5-AG level and the age or sex of nondiabetic subjects. Therefore, we investigated the effects of sex and age on serum 1,5-AG levels in nondiabetic subjects. This study has demonstrated that the serum 1,5-AG concentration tends to decrease with age and is significantly correlated with age in both males and females. Moreover, the serum 1,5-AG concentration tends to be higher in males than in females, but this sex difference decreases with age. The 1,5-AG level is less sensitive for identifying postprandial hyperglycemia in elderly women with near-normoglycemia, partly because they have a higher renal threshold for glucose[1].

Lifestyle changes in recent years have led to concerns about not only postprandial hyperglycemia, but also hyperuricemia. Serum levels of UA are related to urethritis and to several more serious conditions, such as kidney disease, hypertension, DM, metabolic syndrome, and cardiovascular disease. Furthermore, increased serum UA levels after menopause suggest that estrogen promotes UA excretion in the kidneys. A previous study has shown that estradiol suppresses levels of urate transporter 1 (URAT1), a urate reabsorptive transporter, in the mouse kidney[2].

In the relationship between the levels of uric acid and glucose metabolism, a previous study has found that both serum UA levels and the frequency of hyperuricemia increase with moderately increasing levels of HbA1c (6.0%–6.9%) and then decrease as levels of HbA1c increase further, due to the uricosuric effect of glucosuria[3].

Another previous study has found a positive correlation between serum UA and 1,5-AG levels in subjects with type 2 DM (mean age, 51.7±7.0 years)[4], and another study has shown a positive correlation between serum UA and 1,5-AG levels in men with normal glucose tolerance (mean age, 58.4±7.7 years)[5]. However, to our knowledge, no previous study has examined the relationship between serum UA and 1,5-AG levels in elderly subjects or in women without DM. We examined the relationship between serum levels of UA and 1,5-AG in elderly men and elderly postmenopausal women with and without DM, by means of multivariate analysis[6]. We have reported that in elderly subjects the serum 1,5-AG level is an independent factor associated with serum UA levels, in the nondiabetic state, as in DM[6].

The renal common reabsorption system of 1,5-AG and uric acid is in the renal proximal tubule. Both URAT1 and URATv1 have been identified as UA transporters[7–10]. In the future, we would like to investigate the relationship between serum levels of UA, 1,5-AG, sex hormones, and tubular damage markers. Furthermore, we would like to investigate the relationship between serum UA and postprandial hyperglycemia using a continuous glucose measurement system in diabetes.

Now, an SGLT2 inhibitor is being evaluated for use in Japan. Such SGLT2 inhibitors are ameliorative agents that have a novel mechanism of action that differs from that of other oral hypoglycemic agents in diabetes. In clinical studies, it will be important to investigate the renal threshold for glucosuria.

References

1. Ouchi M, Oba K, Yamashita H, et al.: Effects of sex and age on serum 1,5-anhydroglucitol in nondiabetic subjects. Exp Clin Endocrinol Diabetes 2012; 120: 288–295.
2. Takiue Y, Hosoyamada M, Kimura M, Saito H: The effect of female hormones upon urate transport systems in the mouse kidney. Nucleosides Nucleotides Nucleic Acids 2011; 30: 113–119.
3. Choi HK, Ford ES: Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels—the Third National Health and Nutrition Examination Survey. Rheumatology (Oxford) 2008; 47: 713–717.
4. Gotoh M, Li C, Yatoh M, Iguchi A, Hirooka Y: Serum uric acid concentrations in type 2 diabetes: its significant relationship to serum 1,5-anhydroglucitol concentrations. Endocr Regul 2005; 39: 119–125.
5. Koga M, Murai J, Saito H, et al.: Close relationship between serum concentrations of 1,5-anhydroglucitol and uric acid in nondiabetic male subjects implies common renal transport system. Clin Chim Acta 2009; 410: 70–73.
6. Ouchi M, Oba K, Aoyama J, et al.: Serum uric acid in relation to serum 1,5-anhydroglucitol levels in patients with and without type 2 diabetes mellitus. Clin Biochem 2013; 46: 1436–1441.
7. Enomoto A, Kimura H, Chairoungdua A, et al.: Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 2002; 417: 447–452.
8. Anzai N, Ichida K, Jutabha P, et al.: Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. J Biol Chem 2008; 283: 26834–26838.
9. Anzai N, Endou H: Urate transporters: an evolving field. Semin Nephrol 2011; 31: 400–409.
10. Nakanishi T, Ohya K, Shimada S, Anzai N, Tamai I: Functional cooperation of URAT1 (SLC22A12) and URATv1 (SLC2A9) in renal reabsorption of urate. Nephrol Dial Transplant 2013; 28: 603–611.