

ORIGINAL

Association of urine acidification with visceral obesity and the metabolic syndrome

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Abstract. Urine acidification is induced by metabolic acidosis which is associated with a high intake of protein-rich diet. The purpose of this study was to investigate the relationship of urine acidification with visceral obesity and the metabolic syndrome. We recruited 1,051 male subjects who underwent health examinations at the Health Care Center in Kinki Central Hospital. Subjects who were treated for hypertension, dyslipidemia, diabetes mellitus, and hyperuricemia and had the past history of chronic liver disease, chronic kidney disease and cancer, were excluded in this study. All subjects were administered to urine pH, blood and physical examinations. Lower urine pH was associated with higher serum urea nitrogen which reflects high intake of protein-rich diet, whereas it had no relation to serum creatinine. Lower urine pH was also associated with an increase in waist circumference, homeostasis model assessment-R, fasting plasma glucose, HbA1c, serum triglyceride, serum uric acid and with a decrease in high density lipoprotein cholesterol. Urine pH was not associated with mean blood pressure. Urine acidification is a characteristic of visceral obesity and the metabolic syndrome. High intake of protein-rich diet may contribute urine acidification, which is associated with various metabolic abnormalities in visceral obesity.

Key words: Urine acidification, Metabolic acidosis, Metabolic syndrome, Hyperuricemia

IT has been known that the composition of the diet affects acid-base balance in the body. Remer *et al.* showed that high intake of protein-rich diet was metabolized to yield free sulfuric acid, which induced metabolic acidosis and urine acidification [1, 2]. High dietary protein intake and the associated metabolic acidosis have been shown to adversely affect bone health in humans because of increased excretion of urinary calcium [3, 4]. Likewise, an excessive protein intake could be associated with other pathological conditions.

The metabolic syndrome is characterized by visceral obesity causing insulin resistance, elevated blood pressure; and dyslipidemia, which is a common basis of cardiovascular diseases [5]. Although the exact mechanism remains unclear, one possible explanation is that

the increased cortisol production induces visceral obesity and insulin resistance [6], and thereby may promote the metabolic syndrome [7]. It is known that metabolic acidosis relates an increased cortisol production from adrenal glands.

The epidemiologic study has established a close link between the elevated levels of serum uric acid and the increasing prevalence of the metabolic syndrome [8]. The elevated levels of serum uric acid are associated with increased cardiovascular morbidity and mortality in the US adult population [9]. These results suggested that hyperuricemia is one of components of the metabolic syndrome.

The purpose of this study was to investigate the relationship of urine acidification with visceral obesity and the parameters of the metabolic syndrome in men.

Materials and Methods

Subjects

We initially recruited 1,503 male subjects who under-

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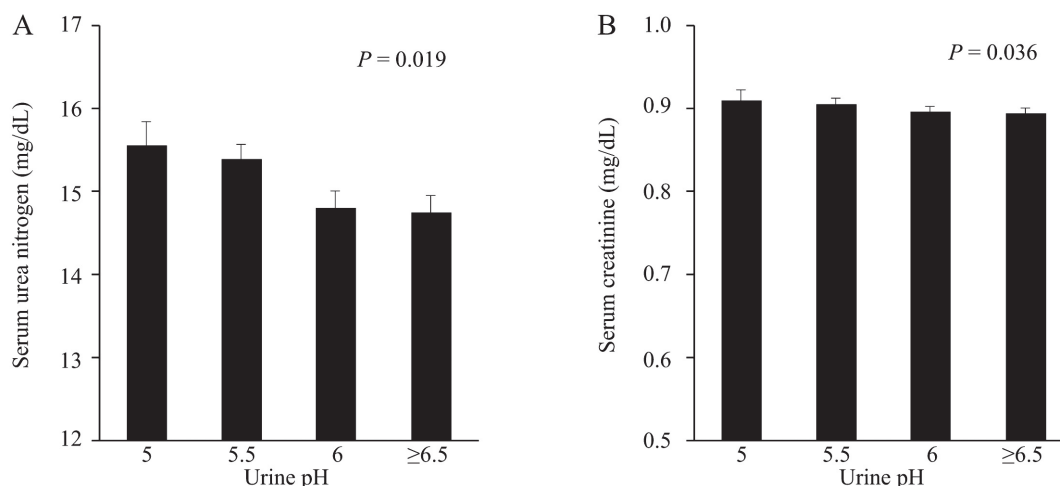


Fig. 1 Correlation of urine pH with serum urea nitrogen (A) and serum creatinine (B). Values are means \pm SE.

went health examinations at the Health Care Center in Kinki Central Hospital between May and October 2006. Additional 257 male subjects were recruited in August 2008 in order to measure morning serum cortisol levels. Subjects who were treated for hypertension, dyslipidemia, diabetes mellitus, and hyperuricemia and had the past history of chronic liver disease, chronic kidney disease, cancer and more than 10 mg/L of high sensitivity C-reactive protein (hsCRP) were excluded in this study. There were 1,051 male subjects who satisfied the above inclusion criteria. The institutional committee approved the protocol of this study, and all participants gave their informed consent.

Measurements

Blood pressure was measured with an automated sphygmomanometer HEM-906 (Omron, Tokyo, Japan) while after 5 min of rest. Mean blood pressure was calculated by (systolic blood pressure - diastolic blood pressure) / 3 + diastolic blood pressure. Blood samples were obtained after an overnight fast and urine was corrected midstream in the first void of the morning. Serum hsCRP was determined by latex-enhanced immunonephelometry on a BN II Analyzer (Dade Behring, Marburg, Germany). The range of determinants was 0.05–10 mg/L. Intra- and inter-assay coefficients of variation were 4.7 and 2.9%, respectively [10]. Plasma glucose, insulin, HbA1c, high density lipoprotein cholesterol (HDL-C), serum triglyceride, serum uric acid, serum urea nitrogen, serum creatinine, serum cortisol and urine pH were determined by standard laboratory assays. Insulin resistance was estimated by the homeostasis model assessment-R (HOMA-R) [insu-

lin at baseline (pmol/L) \times plasma glucose at baseline (mmol/L)]/135 [11].

Statistical analysis

Urine pH was divided into 4 groups (group 1, pH 5 (12%); group 2, pH 5.5 (39%); group 3, pH 6 (25%); group 4; pH \geq 6.5 (24%)). Relationship between these groups and clinical parameter (serum urea nitrogen, serum creatinine, body mass index (BMI), waist circumference, HOMA-R, serum triglyceride, HDL-C, fasting plasma glucose, HbA1c, mean blood pressure, serum uric acid, serum cortisol) was tested by ANOVA. Data are presented as mean \pm standard error (SE). These analyses were performed using a StatView computer program (version 5.0, Abacus Concepts, Berkeley, CA, USA). Statistical differences were considered to be significant at $P < 0.05$.

Results

Subjects

In this study, 1,051 male subjects were enrolled. The average age was 50.4 ± 0.3 years. BMI was 23.9 ± 0.1 kg/m² and waist circumference was 84.2 ± 0.2 cm.

Relationship between urine pH and urea nitrogen

We examined the relationship of urine pH with serum urea nitrogen and serum creatinine. Lower urine pH was associated with higher serum urea nitrogen which reflects high intake of protein-rich diet ($P = 0.019$), whereas it had no relation to serum creatinine ($P = 0.36$) (Fig. 1).

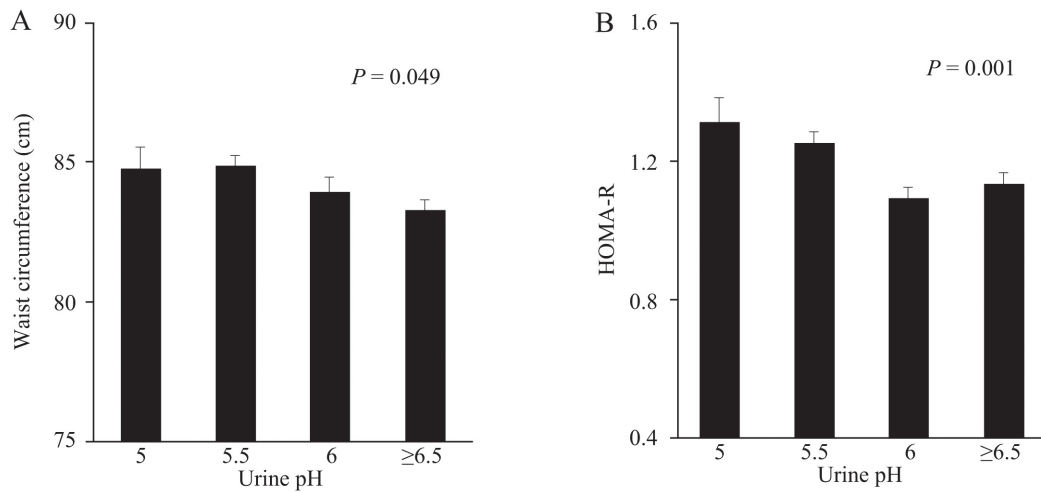


Fig. 2 Correlation of urine pH with waist circumference (A), and homeostasis model assessment-R (HOMA-R) (B). Values are means \pm SE.

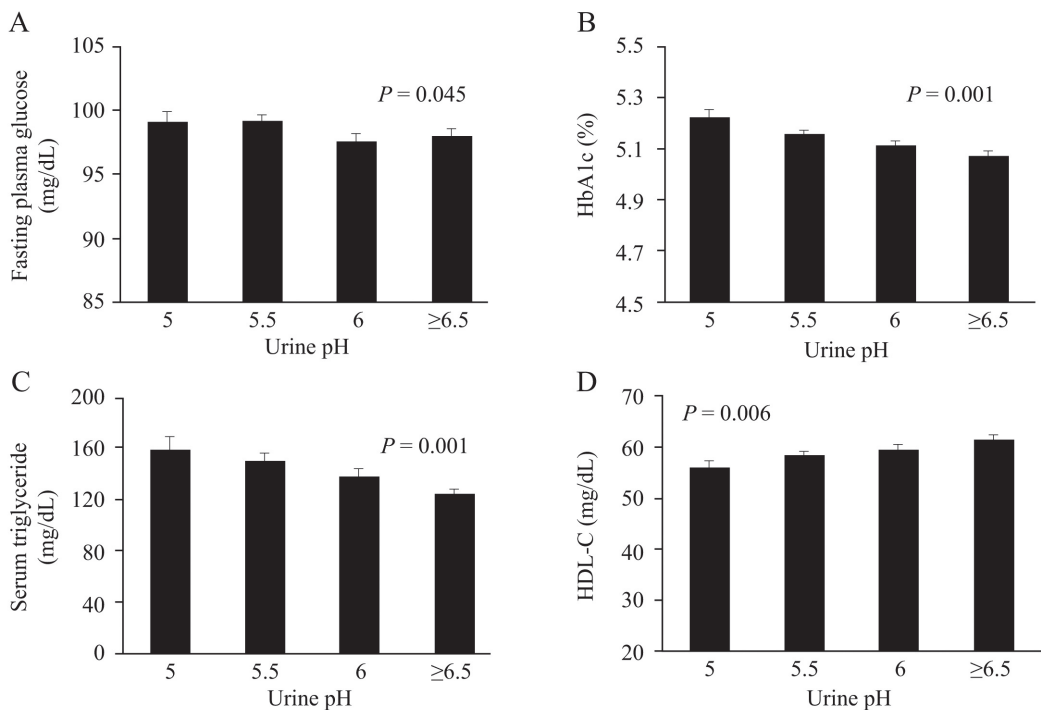


Fig. 3 Correlation of urine pH with fasting plasma glucose (A), HbA1c (B), serum triglyceride (C) and high density lipoprotein cholesterol (HDL-C) (D). Values are means \pm SE.

Relationship between urine pH and the parameters of the metabolic syndrome

Lower urine pH was associated with an increase in waist circumference which is a key feature for the metabolic syndrome ($P = 0.049$) and HOMA-R as an index of insulin resistance ($P = 0.001$) (Fig. 2). Lower urine pH was also associated with an increase in BMI ($P = 0.022$) (data not shown).

Regarding glucose and lipid metabolism, lower urine pH was associated with an increase in fasting plasma glucose ($P = 0.045$), HbA1c ($P = 0.001$), serum triglyceride ($P = 0.001$) and with a decrease in HDL-C ($P = 0.006$) (Fig. 3).

Urine pH was not associated with mean blood pressure ($P = 0.09$) although blood pressure is one of the criteria for the metabolic syndrome. Lower urine pH

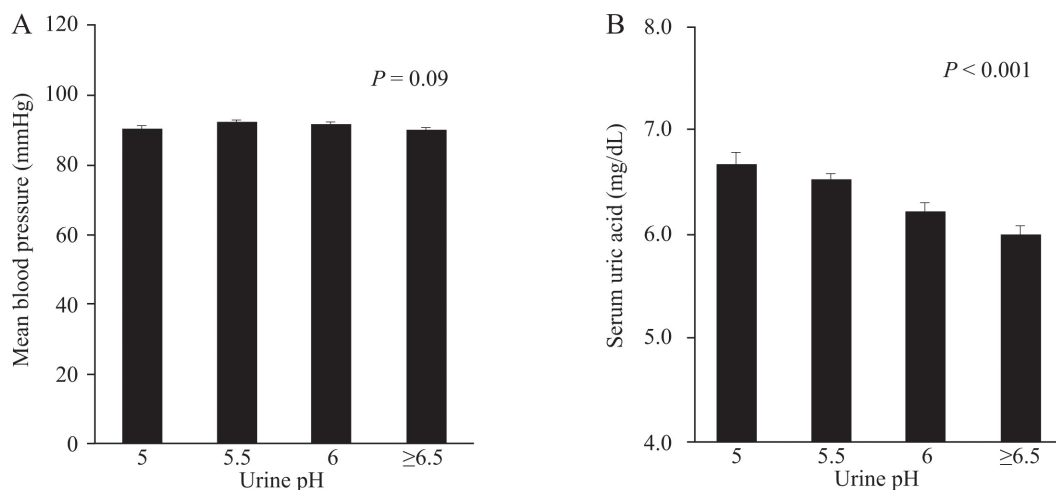


Fig. 4 Correlation of urine pH with mean blood pressure (A) and serum uric acid (B). Values are means \pm SE.

was also associated with an increase in serum uric acid ($P < 0.001$) (Fig. 4).

Relationship between urine pH and serum cortisol

In 257 male subjects whose serum cortisol levels were measured, there was no significant relationship between urinary pH and serum cortisol levels ($P = 0.74$) (data not shown).

Discussion

The levels of serum urea nitrogen positively correlate with the amount of the dietary protein intake. We showed that lower urine pH was associated with higher serum urea nitrogen, whereas it had no relation to serum creatinine. This result indicates that the excess of dietary protein intake induces urine acidification. The urine acidification reflects metabolic acidosis which occurs by the consequence that methionine and cysteine are metabolized to yield free sulfuric acid. Remer *et al.* found that 24-h urinary excretion of cortisol was significantly lower on the low protein diet than the normal protein diet. They suggested that the dietary protein intake modulated the HPA axis [12]. The effects of neutralization of dietary acid load (equimolar amounts of sodium and potassium bicarbonate substituted for sodium and potassium chloride) in healthy subjects were studied by Maurer *et al.* 24-h urinary excretions of cortisol and its metabolites were significantly lower when the bicarbonates were administered [13]. These reports indicate that the metabolic acidosis by high intake of protein-rich diet increases

ACTH release and a consequent increased production of cortisol and aldosterone. These adrenal hormones up-regulates the expression of glutaminase in kidney tubules, which evolves ammonia as a buffer for acid excretion [14-16].

In our study, waist circumference and HOMA-R as an index of visceral obesity and insulin resistance respectively reflected urine acidification. We also showed that other parameter of the metabolic syndrome such as fasting plasma glucose, serum triglyceride and HDL-C were significantly associated with urine acidification. Our results indicate that metabolic acidosis caused by high intake of protein-rich diet may promote visceral obesity and insulin resistance, inducing the metabolic syndrome. As its mechanism, we consider that increased cortisol production may play an important role in mediating between metabolic acidosis and visceral obesity. However, we failed to demonstrate the relation between urinary pH and serum cortisol levels. Therefore it cannot be concluded that the association of urine acidification with the metabolic syndrome was owing to the increased cortisol production in conditions of high intake of protein-rich diet. Measurements of daily urinary cortisol levels or salivary cortisol levels in order to avoid circadian variation of serum cortisol levels and variations of corticosteroid binding protein levels in individuals, may yield different conclusions. Unfortunately, however, we could not measure these variables in this study. Further studies are needed to clarify the reasons by which urine acidification is associated with various metabolic abnormalities in visceral obesity.

The proposed mechanisms for insulin resistance

leading to hypertension are the intrinsic ability of insulin to cause salt and water reabsorption in the kidney [17] and the activation of the sympathetic nervous system by insulin [18], resulting in expanded plasma volume. However, our study did not find any correlation between urine pH and mean blood pressure. Insulin also has the effect of vasodilatation through the production of vasodilator nitric oxide by endothelial cells

[19]. Insulin resistance in our study was not severe. These reasons might affect the relationship between urine pH and mean blood pressure.

In conclusion urine acidification is a characteristic of visceral obesity and the metabolic syndrome. High intake of protein-rich diet may contribute urine acidification, which is associated with various metabolic abnormalities in visceral obesity.

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