Fasting urine pH is independent of insulin sensitivity

Biruh Workeneh, Fahim Abbasi, and Gerald Reaven

ABSTRACT

Background: It has recently been suggested that a low urine pH be added to the abnormalities linked to insulin resistance. This conclusion is based on the finding of a low urine pH in individuals with clinical syndromes associated with insulin resistance and not on studies in which a direct measure of insulin sensitivity was shown to be significantly related to differences in urine pH.

Objective: To address this issue, we quantified insulin-mediated glucose uptake (IMGU) by using the insulin suppression test in 96 apparently healthy, nondiabetic individuals and defined its relation to fasting urine pH.

Design: Urine samples were collected and analyzed from a cohort of healthy subjects within a narrow body mass index range who were recruited to determine insulin sensitivity.

Results: There was an approximate 6-fold variation in values for IMGU in this population, with no relation to urine pH ($r = 0.02$). Furthermore, there was no relation between body mass index, as a surrogate estimate of insulin resistance, and urine pH ($r = 0.06$).

Conclusion: On the basis of these findings, we question the view that a low urine pH be added to the abnormalities linked to insulin resistance in low-risk populations.

INTRODUCTION

Resistance to insulin-mediated glucose uptake (IMGU) varies >6-fold in apparently healthy individuals (1), and approximately one-third of an apparently healthy population is sufficiently insulin resistant to be at increased risk of adverse clinical outcomes (2, 3). In this context, several recent reports have suggested that a low urine pH is another characteristic of insulin-resistant individuals. However, this conclusion is based primarily on the finding of a low urine pH in individuals with clinical syndromes associated with insulin resistance (4–8), not on a relation between urine pH and a direct measure of IMGU. The current study was initiated to address this debated issue and consisted of defining the relation between urine pH and a specific measure of IMGU in 96 apparently healthy individuals over an approximate 6-fold range of differences in insulin sensitivity.

SUBJECTS AND METHODS

Subjects

The study population was drawn from a database consisting of apparently healthy, nondiabetic volunteers to include individuals with a wide range of insulin sensitivity who had answered newspaper advertisements indicating their interest in studying the role of insulin resistance in human disease. The selected subjects underwent study from July 2005 to December 2007. To focus on differences in insulin sensitivity, rather than adiposity, we limited the study to participants with a body mass index (BMI; in kg/m²) ≥25.00 to ≤30.0. Excluded from the study were subjects with a clinical diagnosis of diabetes, a serum creatinine concentration >1.2 mg/dL, or who had been treated with hypoglycemic medications, drugs known to alter urinary pH, or uricosuric agents. All procedures were approved by the Stanford University Institutional Review Board.

Protocol

After fasting overnight, the subjects were admitted to the Stanford General Clinical Research Center, and IMGU was estimated by using a modification (9) of the insulin suppression test (IST) as described and validated by our research group (10, 11). Briefly, an intravenous catheter was placed in each arm: one for the simultaneous 3-h infusion of octreotide (0.27 μg · m⁻² · min⁻¹), insulin (32 μg · m⁻² · min⁻¹), and glucose (267 μg · m⁻² · min⁻¹) and one for blood draws. Plasma glucose and insulin concentrations were measured every 10 min during the 150–180-min time period and then averaged to determine steady state plasma glucose (SSPG) and steady state plasma insulin (SSIPI) concentrations. Because SSIPI concentrations are comparable in all individuals, and glucose infusion was identical, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the disposal of a given glucose load; ie, the higher the SSPG concentration, the more insulin resistant the individual (11).

Before the IST, fasting urine was collected and refrigerated at −70°C. Urine aliquots were later thawed in ice water and analyzed in a blinded fashion by using a Corning 430 pH meter (Corning Inc, Corning, NY).

Statistical analysis

The sample size ($n = 96$) was estimated to provide 80% power to reject a zero correlation if the true correlation was 0.3 and the

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The correlation was evaluated with a 2-sided test at the 5% significance level by using Kendall’s tau test to allow for non-normality. We used SAS software (version 9.1; SAS, Cary, NC) for all analyses.

RESULTS
The demographic and clinical characteristics of the study population are given in Table 1. There were more female than male participants. The experimental population had an average age of 51 y and an average BMI of 27.7. It should be emphasized that the SSPG concentration varied by \( \approx 6 \)-fold in these 96 individuals.

The relation between SSPG concentration and urine pH is illustrated in Figure 1. It is obvious that there was no correlation between these 2 variables \((r = 0.02)\). Thus, being more insulin resistant (a higher SSPG concentration) was not associated with a lower urine pH.

Similarly, the data in Figure 2 indicate the lack of an association between adiposity, as estimated by BMI, and urine pH. However, in this instance, and distinct from the values for SSPG concentration, the participants did not have either very low or very high BMI values.

DISCUSSION
The IST provides a direct measure (SSPG) of the ability of exogenous insulin to mediate disposal of an intravenous glucose load under steady state conditions in which endogenous insulin secretion is suppressed. The SSPG concentration is highly reproducible and correlates well with euglycemic clamp (gold standard) estimates in healthy subjects and patients with type 2 diabetes (9, 11).

At the simplest level, it is apparent that we were unable to show any relation between differences in insulin sensitivity and urine pH in the 96 apparently healthy, nondiabetic participants in the current study. It is more difficult to reconcile our findings with suggestions from previous publications that a low urine pH is associated with abnormalities and clinical syndromes thought to be associated with insulin resistance (4–8). However, there are 2 possible ways in which our findings might be reconciled with those of previous publications.

First, we used a single fasting urine sample that had been frozen and thawed for our measurement of urine pH. However, meticulous studies have shown that pH values of specimens stored at \(-20^\circ\)C are stable (12, 13). Because the specimens in this study were stored at \(-70^\circ\)C, it is certainly possible that the measurements we made reflected the true pH. This comment does not necessarily address the question of a 24-h urine collection as compared with a single fasting sample, but it does suggest that the data were unlikely to be confounded by falsely high pH values because of the manner in which the specimens were handled. Also, diet composition can influence urinary pH and cloud insulin resistance as a determinant. However, the present study was performed specifically to test whether fasting urine pH could be used as an effective, practical screening tool in patients who could be at risk of insulin resistance in an outpatient setting.

A more likely explanation for the apparent discrepancy between our results and previous reports concerning the relation between insulin resistance and urine pH are the differences in experimental populations. More specifically, our study group consisted of apparently healthy individuals, in contrast with patients with disease assumed to be related to insulin resistance, eg, type 2 diabetes, the metabolic syndrome, and uric acid nephrolithiasis (4–8). In addition, we quantified IMGU with a specific method, in contrast with making assumptions about the presence of insulin resistance because of the putative association between the clinical syndrome in question and the defect in insulin action or using surrogate estimates of insulin resistance. Perhaps the study that most closely approximates ours is that of Abate et al (5), who performed hyperinsulinemic, euglycemic

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
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<tr>
<td>Sex (male/female)</td>
<td>63/33</td>
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<tr>
<td>Age (y)</td>
<td>51 ± 10 (27–67)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.7 ± 1.5 (25.0–29.9)</td>
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<tr>
<td>SSPG (mg/dL)</td>
<td>157 ± 67 (41–286)</td>
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<tr>
<td>Urine pH</td>
<td>6.2 ± 0.7 (5.0–7.9)</td>
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1. SSPG, steady state plasma glucose.
2. Mean ± SD; range in parentheses (all such values).

![FIGURE 1. Relation between steady state plasma glucose (SSPG) concentrations and urine pH. A weak correlation \((r = 0.02)\) was observed between SSPG and urine pH across a broad range of insulin sensitivity \((n = 96)\).](image1)

![FIGURE 2. Relation between BMI (in kg/m²) and urine pH. BMI, within a narrow range \((25–30)\), did not correlate with urine pH.](image2)
clamps on 35 apparently healthy individuals. In contrast with our results, these authors showed a significant relation between a decrease in IMGU and a low urine pH. However, the correlation coefficient was relatively modest ($r = 0.35$), which suggests that differences in insulin sensitivity accounted for only $\approx 12\%$ of the variability in urine pH in their study population. It was also of interest to note that, although average values for IMGU in patients with uric acid calculi in their study decreased by $\approx 40\%$, the mean urine pH of the 2 groups only differed by 0.7 (6.2 compared with 5.5).

In conclusion, we were unable to discern a relation between urine pH and IMGU in 96 apparently healthy individuals. The limitations of our study have been pointed out, and we could not conclude that differences in urine pH are unaffected by the degree of insulin sensitivity. However, in light of the results of Abate et al (5) discussed above, it does appear that if decreases in IMGU per se contribute to the regulation of urine pH, the effect is relatively modest in magnitude. Finally, it must be emphasized that this formulation does not negate the possibility that the effect of clinical syndromes assumed to be related to insulin resistance might have a greater effect. Future studies should examine insulin sensitivity and its relation to urine pH under standard conditions (eg, stable metabolic diets and 24-h urine collection).

The authors’ responsibilities were as follows—BW and FA: executed the methods described and contributed to the written manuscript; and GR: supervised the procedures and contributed to the manuscript. None of the authors had any potential conflicts of interest to declare.

REFERENCES