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<table>
<thead>
<tr>
<th>Citation</th>
<th>American Journal of Physiology-Renal Physiology, 312(6): F992-F997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issue Date</td>
<td>2017-06-01</td>
</tr>
<tr>
<td>Type</td>
<td>Journal Article</td>
</tr>
<tr>
<td>Textversion</td>
<td>author</td>
</tr>
<tr>
<td>Relation</td>
<td>The following article has been accepted by American Journal of Physiology-Renal Physiology. After it is published, it will be found at <a href="https://doi.org/10.1152/ajprenal.00645.2016">https://doi.org/10.1152/ajprenal.00645.2016</a></td>
</tr>
<tr>
<td>DOI</td>
<td>10.1152/ajprenal.00645.2016</td>
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</tbody>
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Self-Archiving by Author(s)
Placed on: Osaka City University

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H.U., A.T., and E.I. contributed equally to this work.

Running Head: Uric acid and afferent arteriolar resistance

Key words: uric acid, inulin clearance, para-aminohippurate clearance, afferent arteriolar resistance, renal hemodynamics

Word count: 3090 words

Number of figures and tables: 2 figures and 2 tables

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Disclosure Statements: The authors have nothing to disclose.
Abstract

BACKGROUND: Hyperuricemia has been reported to affect renal hemodynamics. In a recent study, both low and high levels of serum uric acid (SUA) were found to be associated with loss of kidney function.

Objective: The goal of this study was to evaluate the relationship between SUA levels and intrarenal hemodynamic parameters in healthy subjects, utilizing plasma clearance of para-aminohippurate ($C_{PAH}$) and inulin ($C_{in}$).

Subjects and Methods: Renal and glomerular hemodynamics were evaluated by simultaneous measurements of $C_{PAH}$ and $C_{in}$ in 48 healthy subjects (54.6 ± 13.4 years). Intrarenal hemodynamic parameters, including efferent ($R_e$) and afferent ($R_a$) arteriolar resistance, were calculated using Gomez's formulae. Relationships of SUA levels with these intrarenal hemodynamic parameters were examined.

Results: In quadratic regression analysis, SUA levels had a significant, inverse U-shaped relationship with $C_{in}$ ($p < 0.0001$, $R^2 = 0.350$) and $C_{PAH}$ ($p = 0.0093$, $R^2 = 0.188$), and a U-shaped relationship with $R_a$ ($p = 0.0011$, $R^2 = 0.262$). In multiple regression analysis with normal (3.0 to 6.0 mg/dL) and mildly low or high (<3.0 or >6.0 mg/dL) SUA levels entered as dummy variables of 0 and 1, respectively, mildly low or high SUA levels were significantly and independently associated with $R_a$ ($\beta = 0.230$, $p = 0.0403$) after adjustment for several factors. ($R^2 = 0.597$, $p < 0.0001$).

Conclusions: Both mild hyperuricemia and mild hypouricemia are significantly associated with increased $R_a$, although weakly. The increase in $R_a$ in subjects with mild hyperuricemia or hypouricemia may be related to renal hemodynamic abnormalities, possibly leading to a decline in renal function.
Higher uric acid levels are well known to be associated with reduced glomerular filtration rate (GFR) (3, 12, 13, 39). In rat models, the mechanism underlying renal dysfunction induced by elevated uric acid has been explained by endothelial dysfunction, which causes a decrease in nitric oxide synthesis and a subsequent increase in resistance of the renal artery (10, 24). Glomerular ischemia can be induced by hyperuricemia in a rat model (19), and increased resistance of the renal artery and decreased renal plasma flow may occur due to hyperuricemia in humans (40). We recently found a significant association between higher serum uric acid levels and increased afferent arteriolar resistance in humans with normal renal function (37).

Hypouricemia may be a risk factor for development of acute renal failure with loin pain and patchy renal ischemia after anaerobic exercise (ALPE) induced by a non-myoglobinuric status (16). This complication may be due to the decreased antioxidant potential caused by loss of uric acid leading to kidney injury by reactive oxygen species (ROS) (22). Patchy vasoconstriction of the renal vessels may be induced by oxidative imbalance in ALPE, given the wedge-shaped distribution and reversibility (14). However, idiopathic renal hypouricemia is a rare disorder with an incidence of 0.15% in Japan (9). Thus, the cause of acute kidney injury in ALPE is unclear (15).

Kanda et al. recently found that low or high levels of serum uric acid are associated with loss of kidney function in a community-based prospective cohort study with an observational period of up to 9 years (21). Verdecchia et al. showed that serum uric acid levels have a U-shaped association with cardiovascular disease in essential hypertension (38), and Sugihara et al. found that hyper- and hypouricemia cause endothelial dysfunction (33). These data suggest that both hyper- and hypouricemia are risk factors for organ failure. However, hypouricemia is normally defined as severe at a uric acid level of <2 mg/dL, and there are no data supporting a relationship of mild hypouricemia with intrarenal hemodynamic
parameters.

In humans, it is not possible to measure glomerular hemodynamic variables directly. However, Gomez published a series of formulae for indirect evaluation of human glomerular hemodynamics (7). These formulae have been used to calculate glomerular hemodynamics in various conditions, including untreated and treated essential hypertension (7, 18), renovascular hypertension (26), primary aldosteronism (31), and supraventricular tachycardia (28). We have also utilized the formulae for evaluation of intrarenal hemodynamics in diabetic and non-diabetic subjects (34, 36). The aim of the present study was to evaluate the relationships of serum uric acid levels, including mild hyper- and hypouricemia, with intrarenal hemodynamic parameters in healthy subjects, utilizing data for clearance of para-aminohippurate ($C_{PAH}$) and inulin ($C_{in}$).

SUBJECTS AND METHODS

Subjects

The subjects were 48 healthy individuals (19 males and 29 females, age 54.6 ± 13.4 years old) who were scheduled to provide a kidney for transplantation at Osaka City University Hospital between January 2010 and March 2016. All subjects were admitted to the Urology Department of our Hospital for examinations to confirm the suitability for providing a kidney for transplantation, including oral glucose tolerance test and several blood tests, including measuring prostate specific antigen (PSA) in male subjects. All subjects underwent medical checkup by expert urologists and nephrologists, who found no urination disorder in any subject during the clearance study. PSA was normal in all of the male subjects. None of the subjects had received treatment with any drug such as antihypertensive agents. All subjects showed normal glucose tolerance. Urinalysis showed normal findings in all subjects. During the course of admissions including the present study period, all participants took hospital
food, including salt 6 g/day and protein 60-70 g/day. The clearance study, as described below, was performed in the morning after overnight fasting (approximately 12 hours of fasting). The study protocol was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (# 1444). Written informed consent was obtained from each subject.

**Measurements of $C_{in}$ and $C_{PAH}$, and calculation of intrarenal hemodynamic parameters**

Renal plasma flow (RPF) and glomerular filtration rate (GFR) were determined by the constant input clearance technique using PAH and inulin, respectively (34, 36). Continuous intravenous infusion of 1% inulin and 0.5% PAH via the antecubital vein was performed in the morning after an overnight fast, based on the method of Horio et al. (11). $C_{PAH}$ and $C_{in}$ were measured simultaneously using a simple method based on a single urine collection. In brief, subjects received 500 mL of water orally 15 min before infusion. As a priming dose of PAH and inulin, the rates of infusion were set at 300 mL/h for the first 30 min and at 100 mL/h for the remaining time. As instructed by the physicians, subjects completely emptied their bladder 45 min after the start of the test and urine was collected for measurement of urinary PAH and inulin. The urine collection period was set at 90 min to increase the accuracy of the clearance study. We did not determine whether the bladder of the subjects was emptied, i.e. through the use of an indwelling bladder catheter or ultrasonography, since the clearance study was performed according to the Japanese guidelines, as has been performed previously in several studies (11, 20, 34-37). Blood samples for measurements of serum PAH and inulin were taken at the beginning and end of the clearance period. Blood samples were obtained from the antecubital vein after an overnight fast, and serum was separated by a routine, standard clinical laboratory method within an hour. Serum uric acid and total protein were measured by standard routine clinical laboratory methods of uric acid/uricase assay and
Biuret test, respectively.

\[ \text{C}_{\text{PAH}} \text{ and } \text{C}_{\text{in}} \text{ were calculated by the UV/P method (U: concentration in urine, V: urine volume [mL/min], P: concentration in plasma) using the mean serum PAH and inulin concentrations at the beginning and end of the clearance period of 90 min. Plasma PAH and inulin were determined colorimetrically using the N-(1-naphthyl)ethylenediamine and anthrone methods, respectively, with a Corning 258 spectrophotometer (5, 6, 25).} \]

Formulae introduced by Gomez (7) for indirect assessment of glomerular hemodynamics (7, 8) were utilized. These formulae were designed for quantitative estimation of filtration pressure across the glomerular capillaries (\( \Delta P_F \)), glomerular hydrostatic pressure (\( P_{\text{glo}} \)), and afferent and efferent arteriolar resistances (\( R_a \) and \( R_e \), respectively), using measured blood pressure, GFR as measured by \( \text{C}_{\text{in}} \), RPF as measured by \( \text{C}_{\text{PAH}} \), hematocrit, and plasma protein concentrations, under the assumptions that (1) intrarenal vascular resistances can be divided into three compartments: afferent, efferent and venular; (2) hydrostatic pressures in the venules, interstitium, renal tubules, and Bowman’s space (\( P_{\text{Bow}} \)) are in equilibrium at about 10 mmHg; (3) the gross filtration coefficient (\( K_{\text{FG}} \)) is 0.0406 mL/s per mmHg per kidney; and (4) filtration disequilibrium is postulated along the glomerular capillaries (7, 8).

The Gomez formulae were calculated from the original paper as follows:

\[
\begin{align*}
\Delta P_F &= \frac{\text{GFR}}{K_{\text{FG}}} \\
P_{\text{glo}} &= \Delta P_F + P_{\text{Bow}} + \pi G \\
\pi G &= 5 \cdot (C_M - 2) \\
C_M &= \frac{TP}{FF \cdot \ln(1/(1-FF))}
\end{align*}
\]

where \( \Delta P_F \) is the filtration pressure across the glomerular capillary. \( K_{\text{FG}} \) (gross filtration coefficient) was estimated as 0.0406 mL/s · mmHg per kidney, and \( P_{\text{Bow}} \) (hydrostatic pressure in Bowman's space) as 10 mmHg. \( \pi G \) (oncotic pressure in the glomerular capillaries) can be obtained from \( C_M \) (plasma protein concentration in the glomerular capillaries).
capillaries), which is calculated from total protein concentration (TP) and filtration fraction 
(FF) (FF = glomerular filtration rate (GFR)/renal plasma flow (RPF).

From Ohm's law:

\[ R_a = \frac{(MBP-P_{glo})}{RBF} \times 1328 \]

\[ R_c = \frac{GFR/K_{FG} \times (RBF-GFR)}{1328} \]

RBF can be calculated from RPF and hematocrit (Ht), using the standard formula:

\[ RBF = \frac{RPF}{(1-Ht)} \]

In these equations, 1328 is the conversion factor to dyne · s · cm⁻⁵; GFR (glomerular filtration rate), RPF (renal plasma flow), and RBF (renal blood flow) are expressed in mL/s; and the mean blood pressure (MBP) is calculated as \((2 \times \text{diastolic BP} + \text{systolic BP})/3\). In the present study, the Gomez formulae were applied in subjects with Cin > 60 mL/min/1.73m². Ht denotes hematocrit.

**Statistical analysis**

Results are expressed as the mean ± standard deviation (SD). Correlations between two variables were examined using single and quadratic regression analyses. Multiple regression analyses were performed to evaluate relationships between general hemodynamic parameters and other clinical parameters. In the analysis, normal (3.0 to 6.0 mg/dL) and mildly low or high (<3.0 or >6.0 mg/dL) uric acid levels were entered as dummy variables of 0 and 1, respectively. All analyses were performed using StatView 5 for Windows (SAS Institute Inc., Cary, NC, USA). The level of significance was set at \(p < 0.05\).

**Results**

**Baseline characteristics**

Baseline characteristics of the subjects are shown in Table 1. The mean GFR measured by
C\textsubscript{in} was 95.8 ± 22.6 mL/min/1.73m\textsuperscript{2}, and GFR was ≥60 mL/min/1.73m\textsuperscript{2} in all subjects. The mean serum uric acid level was 4.9 ± 1.1 mg/dL, and uric acid was <7.0 mg/dL in all subjects.

Relationships between serum uric acid and renal hemodynamic parameters

Relationships between serum uric acid levels and renal hemodynamic parameters were examined in all subjects. Serum uric acid levels showed a significant negative correlation with GFR measured as C\textsubscript{in} (r = -0.390, p = 0.0061), but no significant correlation with renal plasma flow (r = 0.191, p = 0.1931) or filtration fraction (r = 0.019, p = 0.8984). Quadratic regression analysis showed that serum uric acid levels had a significant inverse U-shaped relationship with GFR measured as C\textsubscript{in} (R\textsuperscript{2} = 0.350, p < 0.0001) and with RPF measured as C\textsubscript{PAH} (R\textsuperscript{2} = 0.188, p = 0.0093) (Figure 1); a significant U-shaped relationship with R\textsubscript{a} (R\textsuperscript{2} = 0.262, p = 0.001), but not with R\textsubscript{e} (R\textsuperscript{2} = 0.0026, p = 0.5549); and an inverse U-shaped relationship with P\textsubscript{glo} with significance (R\textsuperscript{2} = 0.188, p = 0.0105).

Relationship between R\textsubscript{a}, GFR and serum uric acid was examined separately in men (n = 19) and in women (n = 29) by quadratic regression analyses. In both men and women, serum uric acid levels had a significant U-shaped relationship with R\textsubscript{a} (R\textsuperscript{2} = 0.347, p = 0.0332 in men, and R\textsuperscript{2} = 0.306, p = 0.0087 in women). In both men and women, serum uric acid levels had a significant inverse U-shaped relationship with GFR measured as C\textsubscript{in} (R\textsuperscript{2} = 0.461, p = 0.0072 in men, and R\textsuperscript{2} = 0.264, p = 0.0187 in women).

Effect of mild hyperuricemia and mild hypouricemia on renal hemodynamics

Multiple regression analyses were performed to examine independent associations of mildly low or high uric acid levels with GFR, RPF, R\textsubscript{a}, and P\textsubscript{glo}. Because uric acid levels had a relationship with several hemodynamic parameters in quadratic regression analyses,
multiple regression analyses were performed with uric acid included as an independent
dummy variable: i.e., normal (3.0 to 6.0 mg/dL) and low or high (< 3.0 or > 6.0 mg/dL) uric
acid levels were entered as dummy variables of 0 and 1, respectively. In the multiple
regression analyses (Table 2), mildly low or high serum uric acid levels (low and high) were
independently associated with GFR (β = -0.314, p = 0.0256) and RPF (β = -0.270, p =
0.0551) with borderline significance after adjustment for age, gender, body mass index, and
systolic blood pressure, in which β is standard partial regression coefficient of multiple
regression analysis. In a second multiple regression analysis (Table 2), mildly low or high
serum uric acid levels (low and high) were significantly and independently associated with
increased R_a (β = 0.230 p = 0.0403) and decrease P_glo (β = -0.259 p = 0.0838) after
adjustment of the above confounders, but not with R_e (β = -0.234 p = 0.1459).

Discussion

In this study, we examined relationships between serum uric acid levels and renal
hemodynamic parameters in healthy subjects. Quadratic regression analyses showed that
these levels had a significant inverse U-shaped relationship with GFR and RPF, a significant
U-shaped relationship with R_a, and an inverse U-shaped relationship with P_glo, but no
relationship with R_e. In multiple regression analyses, mildly abnormal serum uric acid levels
(low and high) were independently associated with GFR and RPF, and significantly and
independently associated with R_a and P_glo after adjustment for several confounders, whereas
R_e.

The relationship between uric acid and kidney disease in humans is complicated by many
confounding variables. Serum uric acid levels are associated with other risk factors for kidney
disease, such as hypertension, insulin resistance and microalbuminuria (4, 32), and potential
mechanisms underlying kidney damage by uric acid include induction of afferent arteriopathy,
inflammation, and activation of the renin-angiotensin system (4, 23). Recently, we examined
the relationship between serum uric acid and intrarenal hemodynamic parameters in humans,
utilizing the plasma clearance of para-aminohippurate (C_{PAH}) and inulin (C_{in}), and found that
higher serum uric acid levels are significantly associated with R_a in subjects with C_{in} >60
mL/min/1.73m^2 (37). Using renal biopsy samples, Kohagura et al. found that hyperuricemia
was significantly and independently associated with renal arteriolar hyalinosis and higher
grade wall thickening, which suggests that higher uric acid may cause progression of chronic
kidney disease (CKD) through an effect on arterioles (27). Weiner et al. reported that serum
uric acid is a modest independent risk factor for incident CKD in the general population (39),
and Bellomo et al. also showed that the serum uric acid level is an independent risk factor for
decreased kidney function (2). The effects of elevated uric acid on incident CKD are thought
to be due to a direct toxic effect of uric acid on the kidney, via exacerbation of hypertension
(2, 27, 39). In humans, the highest tertile of serum uric acid levels is associated with incident
kidney injury, but not with progression of kidney injury (29). However, Iseki et al. reported
that hyperuricemia is associated with progression of CKD to end-stage renal disease (13).
Our finding that mild hyperuricemia is associated with increased R_a and decreased GFR, RPF
and P_glo is consistent with these previous studies relating hyperuricemia to kidney dysfunction.
Kanda et al. recently described a U-shaped association between the risk of loss of
kidney function and serum uric acid level in healthy subjects, showing that hypouricemia
is also a risk factor for kidney dysfunction (21). Some studies have also shown that uric
acid has a U-shaped association with cardiovascular disease and endothelial dysfunction.
Sugihara et al. found that depletion of uric acid due to a loss-of-function mutation in
SLC22A12 (URAT1) causes endothelial dysfunction in hypouricemia (33). Uric acid serves
as an antioxidant in vascular endothelial cells (33) and hypouricemia is a risk factor for ALPE
induced by non-myoglobinuria. Ishikawa et al. reported exercise-induced acute renal failure
in three patients with renal hypouricemia (17). The cause of acute kidney injury in ALPE is unclear, but several hypotheses have been proposed (15). A plausible explanation is that the decreased antioxidant potential due to the reduced uric acid level leads to reduction of renal plasma flow by increased ROS (1, 30). Patchy vasoconstriction of renal vessels may then be induced by the oxidative imbalance in ALPE (14).

These reports suggest that reduction of renal blood flow is promoted by endothelial dysfunction of the kidney in patients with hypouricemia. In this study, we showed that mild hyper- and hypouricemia are both associated with decreased GFR and RPF and increased $R_a$ although weakly. The increase in $R_a$ in subjects with mildly higher or lower uric acid levels may lead to dysfunction of glomerular perfusion. To the best our knowledge, this is the first description of the relationships between serum uric acid levels and intrarenal hemodynamic parameters in healthy subjects. The mechanisms underlying our results may be associated with vasoconstriction of afferent arterioles in both mild hyper- and hypouricemia.

There are some limitations in this study. First, the measurements were performed in a relatively small number of Japanese subjects, and a large-scale study would be needed to confirm whether hyper- or hypouricemia increases $R_a$. In particular, the generalizability of the findings is not known as this was a study performed in a relatively small number of Japanese adults, which may not be relevant to other ethnicities, who may exhibit different frequencies for URAT1 mutations. Second, we did not measure renal hemodynamics directly, since this is very difficult in humans. Instead, we used Gomez’s formulae to calculate renal hemodynamics. These formulae are based on several assumptions, but many studies have validated their clinical utility (26, 28, 31, 36). Third, there could be differences in renal hemodynamics based on the mechanism underlying the low uric acid, such as diet (although, during the course of admissions including the present study period, all participants took hospital food, including salt 6 g/day and protein 60-70 g/day), or the genetic background on
the fractional excretion of uric acid and endothelial function in response to lower serum uric acid. Future studies will be needed to determine if the mechanism for low uric acid is related to the hemodynamic findings. Fourth, since we did not measure nitric oxide levels, plasma renin activity, angiotensin II levels or URAT1 gene expression/mutation, we could not determine the mechanism underlying how and to what extent the lower and higher serum uric acid levels affect renal hemodynamic abnormalities. Fifth, since, in the present study, as in the previous studies by ourselves and others (11, 20, 34-37), the bladder was not confirmed as being empty after the subjects had been instructed to completely void their bladder at the specified times, it is possible that a very small amount of residual urine might have affected the data of the clearance study. However, none of the previous studies by others or ourselves utilized methods to confirm voiding of the bladder in human subjects, i.e., by indwelling bladder catheter or ultrasonography. As such, we cannot confirm that the emptiness of the bladder was thoroughly examined at the instructed times in the present study, or in the previous studies (11, 20, 34-37). Sixth, we could not follow-up the data on the same subjects at some interval to determine the predictive value of these measurements. It is a future study needed to explore the significance of these parameters on renal dysfunction. Lastly, we did not examine the mechanisms through which $R_a$ is affected by mildly abnormal serum uric acid levels. Approaches such as comparison of renal hemodynamics in the presence of various vasoactive substances in urine and blood are needed to reveal these mechanisms.

In conclusion, the findings in this study show for the first time that mildly lower and mildly higher serum uric acid levels in healthy subjects are both significantly associated with decreased GFR and RPF, and with increased $R_a$. The increase in $R_a$ in subjects with lower or higher uric acid levels may be related to abnormalities in renal hemodynamics, and may lead to dysfunction of glomerular perfusion.
Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the reported research. This study was not funded by a grant from a funding agency in the public, commercial or not-for-profit sector.

Author contributions

H.U., A.T. and E.I. generated and analyzed the data and wrote the manuscript. H. U., A.T., E.I., S.U., S.N., J.U., K.M., M.E., T.N., and M.I. contributed to the discussion and reviewed the manuscript. H.U., A.T. and E.I. had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of the data analysis.
References


2005.


Figure Legends

Figure 1. Relationships of serum uric acid levels with glomerular filtration rate (GFR) measured by inulin clearance, renal plasma flow (RPF) measured by para-aminohippurate clearance, and filtration fraction (FF) in all subjects using quadratic regression analysis (n = 48). Serum uric acid had significant and inverse U-shaped relationships with GFR and RPF, but not with FF.

Figure 2. Relationships of serum uric acid levels with resistance of the afferent (R_a) and efferent (R_e) arterioles and glomerular hydrostatic pressure (P_glo) in quadratic regression analysis (n = 48). Serum uric acid had a significant and U-shaped relationship with R_a, no significant relationship with R_e, and an inverse U-shaped relationship with P_glo that had borderline significance.
Table 1. Clinical characteristics of the subjects

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<td>Age (years)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Mean blood pressure (mmHg)</td>
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<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<tr>
<td>Hemoglobin (g/dl)</td>
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<tr>
<td>Serum albumin (g/dl)</td>
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<tr>
<td>Serum uric acid (mg/dl)</td>
<td>4.9 ± 1.1</td>
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<tr>
<td>Plasma glucose (mg/dl)</td>
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<td>Hemoglobin A1c (%)</td>
<td>5.5 ± 0.2</td>
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<tr>
<td>Glomerular filtration rate (ml/min/1.73m²)</td>
<td>95.8 ± 22.6</td>
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<tr>
<td>Renal plasma flow (ml/min)</td>
<td>425.1 ± 144.3</td>
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<tr>
<td>Renal blood flow (ml/min)</td>
<td>699.5 ± 228.5</td>
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<td>Filtration fraction</td>
<td>0.22 ± 0.04</td>
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<td>Glomerular hydrostatic pressure</td>
<td>57.4 ± 5.5</td>
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<td>Afferent arteriolar resistance (dyne · s · cm⁻²)</td>
<td>4010.3 ± 1964.1</td>
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<tr>
<td>Efferent arteriolar resistance (dyne · s · cm⁻²)</td>
<td>2560.5 ± 823.5</td>
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Table 2. Factors associated with glomerular filtration rate (GFR), renal plasma flow (RPF), afferent arteriola resistance (R_a), and glomerular hydrostatic pressure (P_glo) in multiple regression analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GFR&lt;sup&gt;*&lt;/sup&gt;¹</th>
<th>RPF&lt;sup&gt;*&lt;/sup&gt;²</th>
<th>R_a&lt;sup&gt;*&lt;/sup&gt;³</th>
<th>P_glo&lt;sup&gt;*&lt;/sup&gt;⁴</th>
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<tr>
<td>Age (years)</td>
<td>β -0.391 p 0.0053</td>
<td>β -0.463 p 0.0019</td>
<td>β 0.365 p 0.0014</td>
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<td>Gender (male =0, female = 1)</td>
<td>0.131 p 0.3233</td>
<td>0.017 p 0.9004</td>
<td>-0.001 p 0.9936</td>
<td>-0.071 p 0.6034</td>
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<td>Body mass index (kg/m&lt;sup&gt;²&lt;/sup&gt;)</td>
<td>-0.148 p 0.2560</td>
<td>0.098 p 0.4535</td>
<td>-0.008 p 0.9389</td>
<td>0.158 p 0.2453</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>0.108 p 0.4173</td>
<td>0.218 p 0.1091</td>
<td>0.486 &lt;p&gt;0.0001</td>
<td>0.186 p 0.1815</td>
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<td>Uric acid (mg/dl) *&lt;sup&gt;5&lt;/sup&gt;</td>
<td>-0.314 p 0.0256</td>
<td>-0.270 p 0.0551</td>
<td>0.230 p 0.0403</td>
<td>-0.259 p 0.0838</td>
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<tr>
<td>R² / p</td>
<td>0.370 / p 0.0012</td>
<td>0.358 / p 0.0017</td>
<td>0.597 / &lt;p&gt;0.0001</td>
<td>0.315 / p 0.0057</td>
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</tbody>
</table>

*¹ GFR (mL/min/1.73m<sup>²</sup>): glomerular filtration rate measured by inulin clearance
*² RPF (mL/min): renal plasma flow measured by para-aminohippurate clearance
*³ R_a: afferent arteriolar resistance
*⁴ P_glo: glomerular hydrostatic pressure
*⁵ Dummy variables: 0 for uric acid 3.0 to 6.0 mg/dL, and 1 for uric acid <3.0 or >6.0 mg/dL
Figure 1

- GFR (mL/min/1.73m²) vs Uric acid (mg/dL)
  - \( R^2 = 0.350 \)
  - \( p < 0.001 \)

- RPF (mL/min) vs Uric acid (mg/dL)
  - \( R^2 = 0.188 \)
  - \( p = 0.0093 \)

- FF vs Uric acid (mg/dL)
  - \( R^2 = 0.012 \)
  - \( p = 0.7652 \)
Figure 2

**Uric acid (mg/dL) vs. Afferent Arteriolar Resistance**

- \( R^2 = 0.262 \)
- \( p = 0.0011 \)

**Uric acid (mg/dL) vs. Efferent Arteriolar Resistance**

- \( R^2 = 0.026 \)
- \( p = 0.5549 \)

**Uric acid (mg/dL) vs. \( P_{glo} \)**

- \( R^2 = 0.183 \)
- \( p = 0.0105 \)