Effect of urinary glucose concentration and pH on signal intensity in magnetic resonance images

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Abstract

Purpose With advances in anti-diabetes drugs, increasing numbers of patients have high urinary glucose concentrations, which may alter magnetic resonance (MR) signal intensity. We sought to elucidate the effect of urinary glucose concentration and pH on transverse relaxation and MR signal intensity.

Materials and methods The transverse relaxation rate ($R_2$) was measured in samples with different glucose concentrations (in vitro) and in the urinary bladder of seven patients with diabetes and nine healthy volunteers (in vivo). The glucose concentration and pH in the in vitro samples and urine were measured. The signal intensity ratio of the bladder to adjacent tissues was obtained on T2-weighted imaging (WI), T1WI, and MR urography (in vivo). To clarify the effect of pH further, the urine of two healthy subjects was adjusted with acid and/or base to obtain various pH values (ex vivo).

Results $R_2$ increased significantly with high glucose concentrations in the in vitro study. In the in vivo study, high glucose concentration ($p < 0.001$) and low pH ($p = 0.005$) were significantly associated with high $R_2$. $R_2$ was higher ($p = 0.002$) and the signal in maximum-intensity projection images of MR urography was lower ($p = 0.005$) in patients with diabetes than in healthy subjects. Ex vivo study revealed that a decrease in pH in acid portion resulted in increased $R_2$.

Conclusion High concentrations of urinary glucose and low pH both enhance transverse relaxation, which, in turn, causes low signal intensity in urinary bladder on long echo time (TE) images, such as MR urography. Radiologists should be aware of this phenomenon when interpreting abnormally low-intensity bladders on long TE images.

Keywords Magnetic resonance imaging · Magnetic resonance urography · Transverse relaxation · Urinary glucose · Urinary pH

Introduction

In general, fluid is hyperintense on T2-weighted images (T2WI) and hypointense on T1-weighted images (T1WI). Fluids that show intermediate to low signal intensity on T2WI are considered to contain protein or blood, such as T2WIs of paranasal sinusitis or ovarian tumors.

We encountered a patient with diabetes in whom urine in the bladder resulted in intermediate signal intensity on T2WI. The patient was receiving sodium–glucose
cotransporter 2 inhibitor treatment, and dipstick urinalysis was negative for occult blood in urine and urinary protein while strongly positive for urinary glucose.

Urinary glucose concentration is high in patients with diabetes and can be much higher in those treated with sodium-glucose cotransporter 2 inhibitors. The sodium-glucose cotransporter protein conveys nutrients into the cells. Sodium-glucose cotransporter 2, a type of sodium-glucose cotransporter found only in the kidney, reabsorbs 97% of glucose at the proximal convoluted tubules [1]. Accordingly, inhibition of sodium-glucose cotransporter 2 effectively lowers hyperglycemia by inhibiting glucose reabsorption in the kidneys, thus, increasing glucose excretion in the urine.

The glucose molecule has five unstable hydroxyl protons, with a weighted average chemical shift difference of 1.44 ppm at 22 °C [2]. Owing to chemical exchange between hydroxyl protons and the bulk water proton pool, glucose enhances transverse relaxation [2]. Yadav et al. reported the effects of glucose concentration and pH on the transverse relaxation rate ($R_2$) in glucose solutions and in a in vivo mouse experiment [2]. However, the effect of these factors on signal intensity of urinary bladder, which is of clinical relevance, has not been investigated.

Intake of sodium-glucose cotransporter 2 inhibitors increases urinary glucose concentration and may result in low signal intensity of the urinary bladder on T2WI. Accordingly, this study aimed to elucidate the effect of urinary glucose concentration and pH on transverse relaxation and MR signal intensity.

**Materials and methods**

**In vitro experiment**

**Sample preparation**

A 50% glucose solution (Fuso Yakuhin Kogyo, Osaka, Japan) was diluted with physiological saline (Otsuka Pharmaceutical, Tokyo, Japan) to target concentrations of glucose solutions of 0, 50, 100, 200, 300, 500, and 700 mM. Then, the pH of the diluted glucose solutions was adjusted to pH 6 by adding dilutions of 0.1 mol/L hydrochloric acid (Kanto Chemical, Tokyo, Japan) and/or 0.01 mol/L sodium hydroxide (Kanto Chemical).

**MRI examination and analysis**

Each prepared solution was placed into a 7-mL tube (Insepack II-D, Tokuyama Sekisui, Shunan, Yamaguchi, Japan) and imaged using a 3-T clinical MR imaging (MRI) scanner (SIGNATM Architect, v28, GE Healthcare, Milwaukee, WI, USA) with an AIRTM anterior array coil (GE Healthcare). The tubes were placed in a container filled with warm water to be maintained near body temperature. The tube temperature was 37 °C before scanning and 41 °C after scanning. T2 mapping was performed using the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence with the following parameters: repetition time (TR), 2000 ms; echo interval, 25 ms; number of acquired echoes, 12; echo time (TE), 25–300 ms (25 ms × 12); field-of-view (FOV), 200 × 200 mm; matrix, 128 × 160; slice thickness, 5 mm; number of slices, 1; bandwidth (BW), 15.6 kHz; and acquisition time, 5 min 24 s.

The images were then transferred to a workstation (Advantage Windows VolumeShare 7, GE Healthcare). Signal intensity was measured in a 60 mm² region-of-interest (ROI) on the images of each tube. $R_2$ was calculated as the slope between the logarithm of the signal intensity and TE using the least-squares method (Microsoft Excel, Microsoft, Redmond, WA, USA). Glucose concentration (JCA-ZS050™, JEOL, Tokyo, Japan) and pH (PICCORO + ™, Hanna Instruments Japan, Chiba, Japan) were measured after MRI examination.

**In vivo experiment**

**Subjects**

This study was approved by the ethics committee of our institution (19,521). After receiving an explanation of the procedure, seven patients taking sodium-glucose cotransporter 2 inhibitors (two men and five women; age range 39–72 years) and nine healthy subjects (nine men; age range 22–24 years) provided written consent for participation in the study. The experiment period was from July 16, 2020 to December 16, 2021.

**MR examinations**

All MR examinations were performed during the time period of 12:00–13:00 using the same MRI equipment and coil as in in vitro scans, with the following sequences: T2WI (fast recovery fast spin echo; TR 4100 ms; TE 82.3 ms; FOV 240 × 240 mm; matrix, 400 × 320; slice thickness, 5 mm; BW 62.5 kHz), T2 mapping (TR 2000 ms; echo interval, 25 ms; number of acquired echoes, 12; TE 25–300 ms; FOV 240 × 240 mm; matrix, 128 × 160; slice thickness, 5 mm; number of slices, 1; BW 15.6 kHz), T1WI (liver acquisition with volume acceleration; TR 8.5 ms; TE 2.7 ms; FOV 280 × 280 mm; matrix, 256 × 160; slice thickness, 5 mm; BW 142.9 kHz), and MR urography (3D breath hold fast recovery fast spin echo; TR 1800 ms; TE 630 ms; FOV 360 × 324 mm; matrix, 256 × 160; slice thickness, 3.6 mm; BW 83.33 kHz). In addition, apparent diffusion coefficient was measured on diffusion-weighted
imaging ($b=0, 1000 \text{ s/mm}^2$; TR 7500 ms; TE 68.8 ms; FOV 240×240 mm; matrix, 128×128; slice thickness, 10 mm; BW 250 kHz) acquired in five patients and in all healthy subjects.

**Urinalysis**

The pH (PICCORO+™, Hanna Instruments Japan) as well as the protein and glucose concentrations (JCA-ZS050™, JEOL) were measured in urine collected immediately after MRI examination. The number of red blood cells per high-power field was counted in five patients and in all healthy subjects. Urinary blood concentration was measured in four patients and in eight healthy subjects (JCA-ZS050™, JEOL). Although it was confirmed that it was not hematuria with the naked eye, additional measurements were taken to determine more quantitatively whether it was hematuria.

**Image analysis**

To determine the optimal region in the urinary bladder for ROI placement, the means and standard deviations of signal intensities in six ROIs were measured on T2WI in four individuals. These ROIs were located at right ventral, center ventral, left ventral, right dorsal, center dorsal, and left ventral region in the urinary bladder. Comparison of coefficient of variation between the ventral three ROIs and dorsal three ROIs revealed that it was significantly larger in the ventral group, indicating that the signal heterogeneity was larger in the ventral portion of the bladder. Among three ROIs in the dorsal portion, based on the fact that the ureteric jet can be observed at center dorsal region in clinical practice, all bladder ROIs were placed in the right dorsal corner.

$R^2$ was calculated in the same manner as in the in vitro experiment (ROI area 94–105 mm$^2$). The apparent diffusion coefficient of urine in the bladder was calculated from the images acquired at $b=0$ and $b=1000 \text{ s/mm}^2$ (ROI area 96–105 mm$^2$). To evaluate the signal intensity of the bladder, a ROI was placed in the bladder (ROI area 98–105 mm$^2$) and iliopsoas (98–104 mm$^2$) on T1WI, in the bladder (98–101 mm$^2$) and pararectal fat (98–101 mm$^2$) on T2WI, and in the bladder (495–508 mm$^2$) and cerebrospinal fluid in the thecal sac at the L3–L4 level (100–108 mm$^2$) on a maximum-intensity projection (MIP) image of MR urography (Fig. 1). Contrast ratios were calculated as (signal intensity in the bladder)/(signal intensity of iliopsoas, fat, or thecal sac). The above measurements were performed by one board-certified radiologist and one radiologic technologist independently.

**Ex vivo experiment**

**Sample preparation**

To investigate the effect of pH on MRI signals further, the pH of the urine of two healthy subjects (ex vivo #1 and #2) was adjusted to pH 4.5–7.5 by adding hydrochloric acid and/or sodium hydroxide as in the in vitro study. Strong acids and bases were used in this process to minimize the dilution of urinary components. MRI examination was performed as in the in vitro study.

**Statistical analysis**

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Spearman’s rank correlation was used to evaluate the effects of glucose concentration on $R^2$ in vitro study. The intraclass correlation coefficients (ICCs) were used to evaluate inter-rater agreement. The agreement was classified as poor (ICC < 0.40), fair (ICC = 0.40–0.59), good (ICC = 0.60–0.75), or excellent (ICC > 0.75). Unless poor agreement was observed, the mean value of these two measurements was used in further analysis. In the in vivo study, Spearman’s rank correlation was used to evaluate the
effects of glucose concentration and pH on $R_2$. Moreover, the Mann–Whitney $U$ test was used to compare $R_2$ and the signal intensity ratios between patients and healthy subjects. Statistical significance was set at $p < 0.05$.

**Results**

**In vitro experiment**

Figure 2 shows representative T2WI of the in vitro simulated samples of urine. Signals decreased with increasing glucose concentration and longer TE. Figure 3 shows the relationship between glucose concentration and $R_2$ in the in vitro and in vivo measurements. $R_2$ increased with increasing glucose concentration in vitro. Spearman’s rank correlation revealed significant positive correlation ($p < 0.001$) in the in vitro experiment.

**In vivo experiment**

ICCs revealed good agreement between Rater 1 versus Rater 2 (0.99 in $R_2$, 0.92 in apparent diffusion coefficient, 0.72 in T1WI, 0.85 in T2WI, 0.99 in MR urography). Based on these analyses, the mean value of two raters was used for further analysis.

Spearman’s rank correlation of all participant (seven patients plus nine healthy subjects) revealed significant positive correlation between glucose concentration and $R_2$ ($p < 0.001$) (Fig. 3) and also revealed significant negative correlation between pH and $R_2$ ($p = 0.005$) (Fig. 4).

Urinalysis showed the highest protein concentration was 57.37 mg/dL. It also showed that the highest blood volume was 454 ng/mL. The number of red blood cells of this case was 5–10 per high-power field.

$R_2$ (Fig. 5a) and contrast ratios on MR urography (Fig. 5b), T1WI (Fig. 5c), and T2WI (Fig. 5d) were compared between the patients and healthy subjects using the sample: glucose concentration, pH
I: 22.22 mM, 5.7
II: 77.78 mM, 5.7
III: 72.22 mM, 6.5
IV: 144.44 mM, 6.4
V: 277.78 mM, 6.2
VI: 466.67 mM, 6.2
VII: 655.56 mM, 6.2
VIII: 5%glucose (277.78 mM), unknown temperature: 37–41°C

Fig. 2 T2 mapping of samples of different glucose concentrations. Representative T2 mapping images were acquired with an echo time (TE) of 25, 100, and 200 ms for various glucose concentrations (I–VII). (VIII) Additional plastic tubes of 5% glucose solution (277.78 mM) (Otsuka Pharmaceutical, Tokyo, Japan) were added to stabilize the sample tubes.
Mann–Whitney U test. Of note, $R_2$ was significantly higher in the patients than in healthy subjects ($p = 0.002$). In addition, the MR urography contrast ratio was significantly lower in the patients than in healthy subjects ($p = 0.005$). However, there was no significant difference in the other imaging metrics, such as the apparent diffusion coefficient, between the patients and healthy subjects ($T1WI$, $p = 0.92$; $T2WI$, $p = 0.71$; apparent diffusion coefficient, $p = 0.70$).

Figure 6 shows representative T1WIs and T2WIs and the MIP of MR urography obtained in a patient and a healthy subject.

Ex vivo experiment

The results of the ex vivo study are presented in Fig. 4. Lowering pH by adding small amount of hydrochloric acid and/or sodium hydroxide was performed in three steps for each subject. Among six steps, one step, ex vivo #1 from pH 7.55 to 6.50, traversed neutral line (pH7) and $R_2$ slightly decreased. The other five steps in acid portion were associated with increase in $R_2$.

Discussion

Glucose concentration and pH affect urinary $R_2$ and signal intensity on T2WI

In this study, we showed that high urinary glucose concentration and low urinary pH increased the $R_2$ value and could cause a signal loss on heavily T2WI. Even in conventional T2WI, a low signal might occur when the TE is set to 100 ms at a urinary glucose concentration of approximately 460 mM (approximately 10%; Fig. 2). Notably, low signal intensity in the bladder on T2WIs does not necessarily have pathological significance.

Mechanisms by which glucose enhances transverse relaxation

In the present in vitro study, $R_2$ increased as glucose concentration increased to 650 mM. This is in concordance with the findings of previous report that increase of glucose concentration from 0 to 20 mM is associated with linear increase of $R_2$ [2]. Generally, the transverse relaxation of water protons in an aqueous solution containing carbohydrates and proteins is enhanced compared with that in pure water because of the exchange of protons between different states of chemical shift [3]. Chemical shift of hydroxyl protons of glucose at $−14^\circ C$ ranges in 6.03–8.07 ppm [4]. A weighted average chemical shift difference between the protons of the hydroxyl group of glucose and the protons of water is 1.44 ppm at 22 $^\circ C$ [2]. Therefore, chemical exchange leads to a phase difference among the protons, which enhances transverse relaxation, thereby reducing the signal intensity [2].

The effect on transverse relaxation per unit concentration of solute (transverse relaxivity), $r_{2ex}$ $(s^{-1} \text{mM}^{-1})$, can be obtained from the following equation [2]:

$$r_{2ex} = \frac{k_{ex}P_B\Delta\omega^2}{k_{ex}^2 + \Delta\omega^2},$$

(1)

where $k_{ex}$ is the chemical exchange rate, $P_B$ is the number of exchangeable solute protons for 110 M proton atoms in 1 L of water, and $\Delta\omega$ is the chemical shift difference. Transverse relaxivity peaks when $k_{ex} = \Delta\omega$. Glucose has the following parameters: $k_{ex} = 4600$ s$^{-1}$ (at $37^\circ C$), $P_B = 5$ mM, and $\Delta\omega = 1.44$ ppm (at $22^\circ C$) [2]. Glucose has been reported to
In addition to glucose, urine contains various other components, such as urea, creatine, ammonia, and uric acid. Urea, which has the highest concentration and is thought to be related to transverse relaxation, has four exchangeable protons, a chemical exchange rate of $k_{ex} = 4.60$ (1/s), and $\Delta \omega = 1.0$ ppm at pH 7.37 and 37 °C [5]. Figure 7 shows that urea does not satisfy $k_{ex} = \Delta \omega$; therefore, its transverse relaxivity is small. In the quantitative analysis of Eq. (1), the relaxivity of urea, $r_{2ex(urea)}$, was $1.1 \times 10^{-2}$ times that of glucose, $r_{2ex(glc)}$, thus, it was not involved in the signal reduction of urine.

Similarly, the transverse relaxivity of eight renal metabolites (alanine, choline, citric acid, creatine, lactate, lysine, myoinositol, and taurine) was determined using Eq. (1). The transverse relaxation rate (s⁻¹) was calculated by multiplying the transverse relaxivity (s⁻¹ mM⁻¹) by the concentration (mM). The rates were low, mainly because of their low $k_{ex}$ and low urine concentrations. Indeed, the transverse relaxivity and concentration of myoinositol, which has the highest relaxivity among the eight renal metabolites, are approximately 0.6 times and 0.6 times those of glucose in normal urine, respectively [2, 5].

Thus, in the urine, only glucose has a $k_{ex}$ almost equal to $\Delta \omega$. The fact that the $k_{ex}$ of glucose is higher than that of other carbohydrates is responsible for its enhanced transverse relaxation.
Effect of pH on transverse relaxation

In this study, \( R_2 \) of healthy subjects varied from 0.76 to 2.69, even though their urine samples contained little glucose. The in vivo results of urine from each subject showed that low pH was significantly associated with high \( R_2 \).

The rate of chemical exchange can be expressed by the following equation [3]:

\[
k_{\text{ex}} = k_1 [\text{H}_3\text{O}^+] + k_2 K_w /[\text{H}_3\text{O}^+] + k_3 [\text{H}_2\text{O}],
\]

where \( k_{\text{ex}} \) is the rate constant of the chemical exchange of the solution and \( K_w \) is the solubility product of water. When a solution is acidic, the first term on the right side becomes dominant, and when it is alkaline, the second term on the right side becomes dominant. The third term remains nearly constant under physiological conditions. According to this equation, an acidic pH increases the chemical exchange rate \( k_{\text{ex}} \) and eventually the transverse relaxivity of the sample in most solutes. The mechanism that causes \( R_2 \) to increase as the urine becomes more acidic can be explained as shown in Fig. 7. Many renal metabolites (except glucose), such as urea, have \( k_{\text{ex}} \) much lower than \( \Delta\omega \), as shown in Fig. 7 [5]. As \( k_{\text{ex}} \) increases, the transverse relaxivity of urea moves to the left side of the graph in Fig. 7. Similar to urea, the transverse relaxivity of other renal metabolites is expected to increase with decreasing pH. Although the effect of individual solutes is small, the summation of the individual solutes increases the overall relaxation rate of the urine due to decreased pH.

The results of this study suggest that urinary pH is a factor that determines the signal intensity on T2WI. The urine becomes acidic due to strenuous exertion or diet [6, 7]. Generally, meat-containing meals make the urine acidic, while a diet of fruits and vegetables makes it alkaline [6, 7]. To obtain good MR urography, it is preferable to avoid strenuous exertion and meat before examination.

Fig. 6 Magnetic resonance images obtained in a patient and in a healthy subject. a T1-weighted imaging (T1WI), b T2-weighted imaging (T2WI), c maximum-intensity projection images of magnetic resonance (MR) urography. Upper row: images of a patient receiving sodium-glucose cotransporter 2 inhibitor treatment (urinary glucose concentration, 532.27 mM); lower row: images of a healthy subject (urinary glucose concentration, 0.05 mM). The urinary bladder and other urinary tracts could be visualized on MR urography in the healthy subject but not in the patient (arrows on 1-c and 2-c). The signal intensity of the urinary bladder on T1- and T2WI appears normal at first glance; however, when compared with the signal of fluid in the hip joint (arrows on 1-b and 2-b), that in the bladder of the patient is somewhat lower.
Other factors that may cause low signal on T2WIs

A low signal in urine on T2WIs could be mistaken for pathological findings, such as high protein levels or hemorrhage.

Protein

The transverse relaxivity of bovine serum albumin is 7.6 mM\(^{-1}\) s\(^{-1}\) at 14.1 T [8] and 6.3 mM\(^{-1}\) s\(^{-1}\) at 3 T (our unpublished data). Under an assumption that all proteins are albumin (molecular weight 66,000 Da), the healthy value of protein in the urine (0.1 g/L) [9] would correspond to \(1.5 \times 10^{-3}\) mM of albumin concentration; if the transverse relaxivity is 7 mM\(^{-1}\) s\(^{-1}\), \(R^2\) would be \(1.1 \times 10^{-2}\) s\(^{-1}\), indicating a negligible effect on the transverse relaxation. In another estimation with the same assumptions, \(R^2\) of 1.0 s\(^{-1}\) corresponds to 8.58 g/L of protein, indicating a nephrotic state. None of the patients or healthy subjects in this study had such a high urinary protein level.

Hemorrhage

\(R^2\) of blood at 3 T can be obtained using blood oxygen saturation (Y), hematocrit value (Hct), and the CPMG echo interval (\(τ_{\text{CPMG}}\)) [10]. The partial pressure of oxygen in urine is approximately 40 mmHg [11], which corresponds to approximately \(Y = 0.8\) according to the hemoglobin saturation curve [12]. With the parameters of \(Y = 0.8\), Hct = 0.4, and \(τ_{\text{CPMG}} = 20\) ms, \(R^2\) is reported to be \(T_2 = 100\) ms (\(R^2 = 10\) s\(^{-1}\)) [13]. Assuming that blood is diluted by one-tenth in hematuria and the \(R^2\) value is also 1/10, the equivalent \(R^2\) of the hematuria is 1.0 s\(^{-1}\). This corresponds to gross hematuria because 0.1% blood is sufficient to identify hematuria with the naked eye [14]. None of the patients or healthy subjects in this study had a high amount of blood in their urine.

Viscosity of urine

There was no significant difference in the apparent diffusion coefficient among five patients and nine healthy subjects, suggesting that \(R^2\) was not affected by viscosity in this study.

Limitations

A limitation of our study was the small number of subjects. During the COVID-19 pandemic, it was difficult to recruit patients with diabetes. Nevertheless, a clear tendency was revealed in this study. Since the number of subjects in this study was small, it is thought that better results would be obtained if the experiment is conducted with a larger number of subjects.

Under ideal conditions, control subjects should be age- and sex-matched to the patients. Healthy ranges of urinary ingredients do not change according to age or sex, and factors other than glucose concentration and pH within the healthy range do not affect transverse relaxation; thus, using only young men as the healthy controls might have no adverse effect on the results.
Conclusions

In patients with diabetes taking sodium-glucose transporter 2 inhibitors, high urinary glucose concentrations can lead to decreased signals in the bladder and urinary tract on T2WIIs with long TE, such as MR urography. Low pH can also decrease the signal intensity on T2WI. Therefore, while interpreting the low signal on T2WI, the history of sodium-glucose transporter 2 inhibitor use should be checked before diagnosing proteinuria or hematuria. To obtain good MR urography, measures should be taken to avoid strenuous activity or intake of certain foods.

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Availability of data and materials The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest All the authors disclose no relevant conflicts of interest.

Ethics approval This study was approved by the Ethics Committee of our institution (19521). All the procedures performed in this study were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Written informed consent was provided by all participants.

Consent for publication Written informed consent was provided by all participants.

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