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Acute hyperglycemia increases renal tissue oxygenation as measured by BOLD-MRI in healthy overweight volunteers

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ABSTRACT

Aim: Animal studies have suggested that acute hyperglycemia induces transient renal hypoxia and kidney damage, yet this has not been tested in humans. Therefore, we assessed in human subjects the effect of acute hyperglycemia on renal tissue oxygenation as measured with blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI).
Methods: In this single center prospective interventional study, healthy overweight subjects were recruited. BOLD-MRI was performed before and immediately after the intravenous administration of 0.15 g/kg of glucose in a 20% solution under standard hydration and fasting conditions. $R2^*$ maps were analyzed using the twelve layer concentric objects (TLCO) technique, a semi-automatic procedure which divides the kidney parenchyma in 12 equal layers at increasing depth. $R2^*$ is a measure of local desoxyhemoglobin concentrations, with high $R2^*$ values corresponding to low oxygenation.
Results: Nineteen overweight subjects were enrolled (age 37 ± 10 years, BMI 28.9 ± 3 kg/m^2, HbA1c 5.4 ± 0.3%, 57.9% women): 5 were glucose intolerant, none had diabetes. The mean glycemia rose from 4.5 ± 0.3 mmol/l to 9.0 ± 0.9, 8.9 ± 0.7, 7.7 ± 0.6 and 6.8 ± 0.8 mmol/l at respectively 1, 10, 20 and 30 min after IV glucose. Circulating insulin levels quadrupled. The mean $R2^*$ values decreased significantly in all kidney layers, irrespective of glucose intolerance. The lower BMI, the larger the decrease in $R2^*$(spearman's r = 0.41, p = 0.035).
Conclusion: These data show that acute hyperglycemia decreases the $R2^*$ signal in humans, suggesting an acute increase in renal tissue oxygenation. The precise mechanism of this observation remains unknown, and whether this phenomenon also occurs in patients with diabetes needs additional studies.

1. Introduction

Diabetic nephropathy has become the main cause of end-stage renal disease (ESRD) in many countries due to the increasing incidence in type 2 diabetes. Although nephroprotective treatments have improved with better glycemic and blood pressure control, epidemiological studies show that stage 3 chronic kidney disease (CKD) has not decreased in subjects with diabetes [1], and that subjects with type 1 diabetes and macroalbuminuria progress to ESRD at the

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same rate as twenty years ago [2]. For this reason, experts around the world are calling for a better characterization of kidney disease in diabetes and for the exploration of other pathological pathways.

Experimental studies have shown that chronic renal hypoxia may be one of these pathways and contributes to the progression of diabetic nephropathy (chronic hypoxia hypothesis) [3,4]. Several factors can theoretically cause renal hypoxia in diabetes, including oxidative stress, altered renal hemodynamics, increased glomerular filtration rate (hyperfiltration), tubular hypertrophy and increased active transport of electrolytes [4]. Animal studies have demonstrated that cortical and medullary hypoxia are present in diabetes [5]. According to some, acute hyperglycemia causes renal tissue hypoxia [6], whereas other studies emphasize the role of oxidative stress in the pathophysiology of diabetic nephropathy, independently of circulating glucose levels [7]. Whether acute hyperglycemia leads to renal tissue hypoxia in humans is currently unknown.

Blood Oxygenation-Level Dependent MRI (BOLD-MRI) enables non-invasive assessment of renal tissue oxygenation in humans [8–11]. BOLD-MRI uses the paramagnetic properties of desoxyhemoblobin. Increases in its outcome value $R2^*$ (apparent relaxation rate, expressed as sec^{-1} or Hz) correspond to higher local deoxyhemoglobin levels and thus lower oxygenation, assuming that blood pO_2 is in equilibrium with tissue pO_2. Hence, high $R2^*$ levels correspond to low oxygenation and vice versa.

Several studies have used BOLD-MRI to measure renal tissue oxygenation in patients with diabetes. One study reported that subjects with diabetic nephropathy have a decrease in medullary $R2^*$ compared to healthy volunteers, suggesting increased medullary oxygenation [12]. In another study, cortical and medullary $R2^*$ values were higher in diabetes, thus rather supporting the hypoxia hypothesis [12]. However, these studies did not explore the influence of acute blood glucose changes and changes in HbA1c on the BOLD-MRI signal. In previous studies we reported a positive correlation between blood glucose measured just before MRI and cortical $R2^*$ levels in subjects with [13] or without diabetes [14]. This correlation was strongest for blood glucose levels above 7 mmol/l, suggesting that hyperglycemia is negatively associated with renal tissue oxygenation. This observation could actually provide an explanation for the discrepancy in results of previous studies, since blood glucose levels were not systematically measured before image acquisition. However, the described relationship between $R2^*$ and glycemia was based on cross-sectional analyses, which limit causal inferences, and needed confirmation using an interventional protocol.

The aim of this interventional study was therefore to assess whether acute changes in blood glucose levels lead to changes in renal $R2^*$ values as a proxy of renal tissue oxygenation.

1.1. *Subjects and methods*

This was a single center study performed in the Nephrology and Hypertension division at the University Hospital of Lausanne. All subjects were recruited through the display of posters in the region of Lausanne. Overweight subjects (BMI > 25 kg/m^2) with a positive familial history of diabetes (defined as having at least one parent or sibling with diabetes) and normal kidney function (estimated glomerular filtration rate (eGFR) > 60 ml/min/1.72 m^2) were enrolled in this study. Subjects with diabetes were not recruited as the main goal was to examine the effects of acute hyperglycemia on renal $R2^*$ levels independently from chronic hyperglycemia and antidiabetic therapy. We also excluded subjects with significant comorbidities such as documented cardiac disease, documented liver disease, renal malformations, kidney diseases or documented renal artery stenosis and a history of organ transplantation. Other exclusion criteria were compromised life expectancy, anemia, psychiatric illness, pregnancy or breastfeeding and chronic drug therapy. Subjects with a blood donation 2 months before the MRI investigation day, contraindications to MRI-imaging such as claustrophobia or presence of an implanted metallic device were also excluded. After explaining the nature and purpose of the study, a written informed consent was obtained. The protocol was approved by the local institutional review committee (Ethical Committee of the Canton de Vaud, Switzerland) and registered as clinical trial (clinical trial.gov, NCT02346149).

1.2. *Study protocol*

Once subjects had signed the informed consent, a complete physical examination was performed, including renal ultrasound to exclude kidney abnormalities. We also performed an oral glucose tolerance test (OGTT) with 75 g of glucose and measured HbA1c for classification according to the ADA criteria [15].

If subjects met criteria for diabetes, they were excluded from further participation. Subjects with a normoglycemic profile or impaired glucose tolerance (IGT) continued the study. Because sodium intake can influence the BOLD-MRI $R2^*$ signal [16], 24 h urinary collections were collected the day prior to the study visit to assess sodium intake. The day of the study visit, enrolled subjects started at 8 am with an oral hydration protocol at home (oral water load of 3 ml/kg followed by 1 ml/kg every hour) that was continued until 12am. Upon arrival in our service at 11 am, a complete physical examination was repeated. Blood pressure was measured five times according to the guidelines of the European Society of Hypertension with a validated Omron 705IT oscillometric device [17]. One venous catheter was placed into each arm (one for blood sampling and one for IV glucose administration). Thereafter, they were escorted to the Radiology Department. Baseline blood sampling was performed once installed in the MRI, followed by the first BOLD MRI. An intravenous bolus of 0.75 ml/kg glucose 20% (containing 200 g/l of glucose) was administered over 5 min. Subsequently, four BOLD-MRIs were performed, respectively 1, 10, 20 and 30 min after the IV administration of glucose; after each BOLD-MRI, blood was drawn for dosage of glycemia and insulin levels.

1.3. *Acquisition and analysis of BOLD-MRI images*

The principles and acquisition of BOLD-MRI have been published by our group in more detail previously [18]. In brief, BOLD-MRI uses the paramagnetic properties of deoxyhemoglobin to assess cortical and medullary oxygenation.

Magnetic resonance (MR) images were acquired using four coronal slices on a 3 T-whole-body MR system (Magnetom Prisma Fit, Siemens Healthcare SA, Erlangen, Germany). The volunteers were installed in head first-supine position on the table, and the images were acquired through the combination of the 32 channels spine coil and the 18 channels body array coil. Twelve $T2^*$-weighted images were recorded for each coronal slice within a single breath-hold of 16.6 s (in expiration) with a modified Multi Echo Data Image Combination sequence (MEDIC) for BOLD analysis with the following parameters: repetition time (TR) 65 ms, echo time (TE) 6–52.2 ms (equidistant echo time spacing of 4.2 ms), radiofrequency excitation angle 30°, field of view (FOV) $400 \times 400\ mm^2$, voxel size $0.8 \times 0.8 \times 5\ mm^3$, slice thickness 5 mm, slice distance 5.5 mm, bandwidth 331 Hz/pixel, matrix 256×256 (interpolated to 512×512).

The analysis of MR images was done using the Twelve Layer Concentric Objects (TLCO) technique as described previously in more detail [19]. In brief, the circumference of the total kidney parenchyma is defined manually, with special care to exclude the pelvis and the calyxes. Two boundaries are defined: the external boundary corresponds to the cortical side and the internal to the medullary side. The depth between the external and internal boundary can be expressed as a percent of the total parenchymal thickness, the external boundary being at depth 0% and the internal boundary at depth 100%. Longitudinal curves can be computed throughout the kidney at any fixed depth with a mean $R2^*$ value for each level of depth in order to represent the evolution of $R2^*$ levels from the outer to the inner border. Depths at 0–30% (layer 1–3) correspond to mainly cortical tissue and those between 60 and 90% (layer 8–10) to mainly medullary tissue.

2. Statistics

STATA 14.0 (StataCorp, College Station, TX) was used for statistical analyses. All values are expressed as mean ± SD, median (interquartile range) or percentage, as appropriate.

A physicist specialized in MRI research (B.M.) and blinded for baseline characteristics analyzed the BOLD-MRI data. The $R2^*$ values corresponding to renal deoxyhemoglobin content were expressed as means ± standard deviation (SD) for each kidney layer. Intravenous glucose-induced changes in $R2^*$ are shown for the outer, cortical layers (layer 1–3), for the inner, more medullary layers (8–10), and for all layers pooled together (mean change in $R2^*$). Changes in $R2^*$ were expressed as absolute changes or as percentage. Reproducibility of the TLCO analysis has been demonstrated previously [19].

Analysis of variance (anova), Student's *t*-test or χ^2 test were used as appropriate to compare trends of quantitative or qualitative variables at different acquisition time-points. Correlations between two quantitative variables were estimated with spearman's test and linear regression analysis. P values below 0.05 were considered as significant.

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline characteristics of the participants. Twenty-seven subjects were screened, and 19 could be included. Two were excluded because of previously unknown diabetes; at renal ultrasound screening, two had cysts, and one an atrophic left kidney; one subject had disturbed liver function tests, and one had an eGFR < 60 ml/min/1.73 m^2 and one claustrophobia, leaving 19 subjects for participation. Mean age of included participants was 36.7 ± 9.8 years and 11 out of 19 (57.9%) were women. Fourteen had a normoglycemic profile and 5 had impaired glucose tolerance.

3.2. Changes in baseline characteristics after IV glucose:

Table 2 summarizes the mean $R2^*$, plasma glucose and insulin levels at baseline (T0), 1 min (T1), 10 min (T2), 20 min (T3), and 30 min (T4) after the intravenous glucose bolus.

Glucose administration induced a significant increase in plasma glucose level (p trend (anova) <0.001) peaking after 1 min (T1) at 9.0 ± 0.9 mmol/l. After a stable period between T1 and T2, glucose decreased between T2-T3 (p < 0.01) and T3-T4 (p < 0.01). Plasma insulin also increased significantly (p trend <0.001) with a peak at T1 (34.5 ± 16.1 mmol/l) followed by a regular decrease (see Fig. 1).

The mean renal $R2^*$ (mean of all layers) decreased significantly after IV glucose (p trend 0.008); the largest difference was seen between T4 and baseline (ΔT4T0, $-1.1 \pm 0.68\ sec^{-1}$ (p < 0.01). The decrease in mean $R2^*$ occured quickly and was already noticed one minute after glucose injection (T1) compared to baseline (ΔT1T0 = $-0.6 \pm 0.58\ sec^{-1}$, p = 0.0003). However, the change in mean $R2^*$ between T3 and T4 was small and not significant (ΔT4T3= $-0.04 \pm 0.48\ sec^{-1}$, p = 0.7).

Decreases of $R2^*$ were found in each layer, as shown in Fig. 2. The largest decrease was reached after 30 min (T4) (ΔT4T0: all p values <0.015). Decreases in $R2^*$ over time were observed in both cortical and more medullary layers (p anova respectively 0.006 and 0.03), although the change in $R2^*$

Table 1 – Baseline characteristics of the participants.

N	19
Sex (% female)	57.9
Age (years)	36.2 ± 9.8
Non-smoker (%)	63.1
Body Mass Index (kg/m^2)	29.2 ± 2.5
Systolic blood pressure (mmHg)	121 ± 15
Diastolic blood pressure (mmHg)	76 ± 15
Pulse rate (beats/min)	71 ± 9
Creatinine (μmol/l)	75.4 ± 16.1
eGFR (ml/min/1.73 m^2)	101.4 ± 15.7
Fasting glucose (mmol/l)	4.6 ± 0.5
HbA1c (%)	5.4 ± 0.3
Hemoglobin (g/l)	140.2 ± 8.4

Values are expressed as mean (±Standard Deviation) or percentage, as appropriate.

Table 2 – Changes in glycemia, insulin and mean R2* level (all layers of both kidneys combined) after intravenous injection of glucose.

	T0	T1 (+1 min)	T2 (+10 min)	T3 (+20 min)	T4 (+30 min)
R2* (sec^{-1})	23.4 ± 1.2	22.8 ± 1.4*	22.6 ± 1.5*	22.3 ± 1.3*	22.3 ± 1.3
Plasma glucose (mmol/l)	4.5 ± 0.3	9.0 ± 0.9*	8.9 ± 0.7	7.7 ± 0.6*	6.8 ± 0.8*
Plasma insulin (mmol/l)	6.4 ± 4.6	34.5 ± 16.1*	25.9 ± 12.6*	19.5 ± 5.8*	15.6 ± 4.7*

p trend (anova) <0.05.
* p t-test vs baseline (t0) < 0.05.

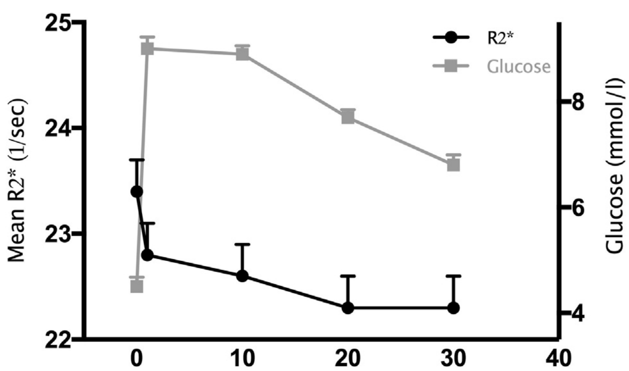

Fig. 1 – illustrates global mean R2* (defined as the mean R2* value of all twelve layers together at each time point) and glucose level variation in time (x-axis, minutes).

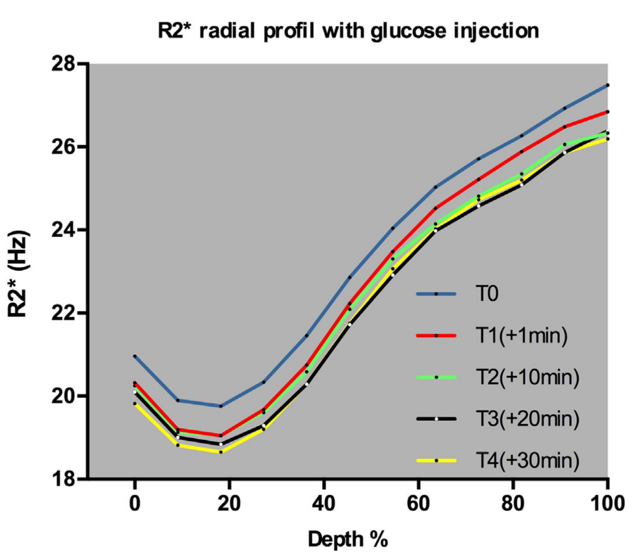

Fig. 2 – illustrates the R2* values of each layer at baseline and after IV glucose administration. Layers 1–3 correspond to cortical layers, whereas layers 8–10 correspond to medullary layers. R2* curves were downshifted after glucose administration, suggesting increased oxygenation. R2* difference between baseline (T0) and T4 was statistically significant for each layer (p < 0.01, Student's paired t-test).

between T0 and T4 was slightly but not significantly lower in the cortex than the medulla (−5.4 ± 3.3% versus −4.0 ± 3.6%, p = 0.09).

There was no significant change in renal volume after the administration of glucose: the renal length was unchanged (11.2 ± 1.3 cm before and 11. 3 ± 1.5 cm after IV glucose (p = 0.42), whereas the volume, expressed as the number of pixels present in the total renal parenchyma analyzed was 5274 ± 1151 before versus 5132 ± 1034 after IV glucose (p = 0.07).

Urine glucose concentration after IV glucose was measured in three participants. Urine glucose concentration was 0.23 ± 0.06 mmol/l after 15 min and reached its maximum of 1.16 ± 1.0 mmol/l (corresponding to 0.07 mmol/min) thirty minutes after IV glucose (T4).

3.3. *Associations between glucose-induced changes in R2* and other factors*

Mean renal R2* values correlated inversely and significantly with plasma glucose levels (all values at all timepoints combined: spearman's r = −0.21, p = 0.043). The change in glycemia was also inversely correlated with the change in R2* between baseline (T0) and T4 (r = −0.48, p = 0.038). In univariate linear regression analysis a similar negative association was found (regression coefficient β = −0.46, −95% CI −0.79 to −0.11p = 0.012), that remained significant after adjustment for age and sex (regression coefficient β = −0.38, 95% CI = −0.73 to −0.031, p = 0.035).

There was a significant association between BMI and the glucose-induced change in mean R2* (r = 0.41, p = 0.03): the higher BMI, the smaller the decrease in mean R2* (Fig. 3).

In univariate regression analysis, the glucose-induced change in mean R2* was also associated with BMI, but not with age, sex, eGFR, circulating insulin levels or 24 h urinary sodium excretion (see Table 3). Of note, the participants with a BMI above the median (>29.1 kg/m²) were older, more often male, had higher HbA1 and lower eGFR (see Suppl. Table 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2019.03.009.

When stratifying according to glucose status (normal vs prediabetes), the decrease in mean R2* was slightly lower in prediabetes than in normal subjects, but this was not statistically significant ($-0.40 \pm 1.11\ sec^{-1}$ vs $-1.23 \pm 0.78\ sec^{-1}$, p = 0.08).

4. Discussion

The main finding of this study is that acute changes in plasma glucose influence renal R2* levels and should therefore be

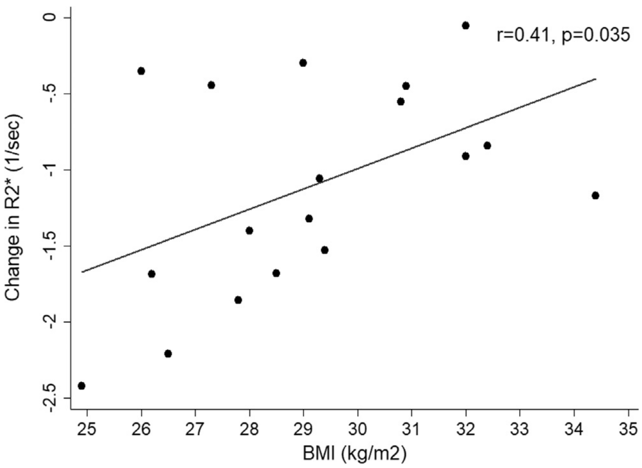

Fig. 3 – Body mass Index (BMI) versus glucose-induced change in R2*: higher BMI resulted in smaller decreases in R2* after IV glucose.

taken into account when performing renal BOLD-MRI. The higher plasma glucose levels, the lower was renal $R2^*$, suggesting an increase in tissue oxygenation. The decrease in $R2^*$ occured both at the outer and inner layers of the renal parenchyma, indicating that the effect of glucose takes place in the cortex and medulla.

To the best of our knowledge, this is the first study that assessed the influence of an IV bolus of glucose on renal tissue oxygenation as measured with BOLD-MRI in humans. The acute decrease in $R2^*$, suggesting an acute increase in renal oxygenation, contrasts with previous observational studies in humans that reported positive associations between glycemia and cortical $R2^*$ levels, both in patients with and without diabetes [13,14]. On a larger scale, our finding appears to be in disagreement with the generally accepted concept that chronically elevated glucose levels in patients with badly controlled diabetes are associated with adverse renal outcome, and also with the recent finding that chronic cortical hypoxia is associated with faster decline in renal function and end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD) [20]. However, the major difference between the above mentioned studies and the present one is that in all previous studies, measurements were performed in steady state situations with relatively stable blood glucose levels. Moreover, this study was performed in healthy overweight volunteers in order to avoid interference of glucose-lowering medication: thus, one cannot ascertain that acute hyperglycemia also increases renal tissue oxygenation in patients with diabetes or CKD.

Table 3 – Univariate linear regression analysis of factors possibly associated with the glucose-induced change in R2* (outcome variable). The higher BMI, the smaller the decrease in R2*.

	Regression coefficient β	p
Age (per year)	0.03	0.068
Sex (female vs male)	−0.07	0.84
Body mass Index (per kg/m2)	0.13	**0.03**
eGFR (per ml/min/1.73 m^2)	0.007	0.96
Baseline Insulin (per mmol/l)	0.038	0.49
Change in Insulin (per mmol/l)	0.003	0.91
24 h Sodium excretion (per mmol)	0.005	0.80

There are several potential explanations for our observation, although they should all be interpreted with caution, as renal hemodynamics were not measured. This study should therefore be considered as a hypothesis-generating pilot study, that may stimulate further research, but that does not provide answers for all the observations.

In theory, tissue oxygenation improves either by increases in oxygen delivery (renal perfusion) or by decreases in consumption (mainly oxygen-consuming tubular reabsorption of electrolytes). However, in the kidneys, an increase in renal plasma flow (RPF) doesn't necessarily lead to an improvement in oxygenation, as increases in RPF at a constant filtration fraction will also lead to increases in filtered sodium, which will on its term increase oxygen-consuming tubular transport [21]. In the literature, the impact of high glucose levels on renal hemodynamics appears to be heterogeneous. In a study by Christiansen et al conducted in healthy volunteers, glomerular filtration rate (GFR) increased whereas RPF did not change after IV glucose [22]. This should merely result in a decrease in oxygenation. In contrast, a more recent study in obese subjects (some with impaired glucose tolerance) reported a decrease in GFR and RPF after IV glucose administration [23]. If the decrease in GFR was larger than the change in RPF, this could result in an increase in oxygenation. As we did not measure GFR and RPF, we cannot confirm nor reject this hypothesis. Future studies could integrate other techniques such as arterial spin labelling (ASL) in the same MRI session to answer this question. ASL enables the measurement of regional (cortical and medullary) blood flow without the use of contrast product and is approaching clinical use [24].

As expected, the administration of IV glucose was followed by an immediate and steep increase in circulating insulin levels. Insulin has several effects on renal functions. Hyperinsulinemia results in time- and dose-dependent increases in renal plasma flow and decreases proximal tubular sodium reabsorption [25]. Insulin also lowers gluconeogenesis; hence, as gluconeogenesis is oxygen-consuming and takes partly place in the kidneys, the rise in insulin may increase oxygenation [21]. However, we did not find any association between circulating insulin-levels and $R2^*$ values, rendering this explanation less likely.

Of interest, the glucose-induced change in $R2^*$ was associated with BMI, but not with age, sex, prediabetes status or circulating insulin levels. The lower the BMI, the larger the glucose-induced change in $R2^*$. Nevertheless, it is difficult to interpret this finding, as those with the highest BMI were also oldest, had lower eGFR, higher HbA1c and were more often women. Due to the modest sample size of our study, we cannot adjust for all these variables, and larger studies are needed to clarify the underlying mechanisms.

The last possible explanation is a measurement artifact. Hyperglycemia may induce a partial volume effect affecting the recorded signal. Indeed, previous studies have shown that hyperglycemia increases plasma volume up to 10% [26]. The impact on plasma volume may be more prominent during acute changes in glycemia than during chronic variations in blood glucose. However, we did not find a change in MRI-assessed renal volume, which argues against this possibility.

As mentioned, all these explanations are hypothetical and should be interpreted with the greatest caution, as we did not measure GFR nor RPF. Other limitations of our study are its small sample size, the short duration of hyperglycemia, the relatively small rise in glycemia obtained after IV glucose and the absence of patients with diabetes.

Nevertheless, we believe that our data clearly demonstrate that acute changes in glycemia influence $R2^*$ values. Therefore, glycemia should be measured before each BOLD-MRI. Further studies in patients with diabetes are necessary to assess whether similar changes in $R2^*$ occur in this population.

Declarations of interest

The authors declared that there is no conflict of interest.

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