Effect of glucose regulation on renal parenchyma and sinus fat volume in patients with type 2 diabetes

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Research letter

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To the editor

Kidney enlargement and sinus fat accumulation have been found in patients with type 2 diabetes mellitus (T2DM) and are associated with increased risk of diabetic kidney disease (DKD) [1, 2]. Strict glycemic control has been shown to delay and slow the progression of DKD [3]. However, it remains uncertain whether renal parenchyma volume and sinus fat volume decrease after glucose-lowering treatment.

Previously, we found larger renal parenchyma volume and greater sinus fat volume in patients with T2DM than in healthy controls based on magnetic resonance imaging (MRI) [4]. We also found that sinus fat volume was positively associated with glycated hemoglobin (HbA1c) and urinary albumin-to-creatinine ratio (UACR), making it a potential imaging biomarker for DKD at an early phase [5]. We present here the follow-up study aiming to assess whether renal parenchyma volume and sinus fat volume decrease after 26 weeks of intensive glucose-lowering therapy in patients with T2DM, and whether liraglutide, a glucagon-like peptide-1 (GLP-1) receptor analogue, has added effect on renal volumes in addition to standard treatment.

This study is an assessor-blinded secondary analysis of the randomized, double-blind, single-center clinical trial MAGNA VICTORIA studies (ClinicalTrials.gov NCT01761318 [5], NCT02660047 [6]), in which 93 patients with T2DM were randomized to receive liraglutide (n = 43) or placebo (n = 50) for 26 weeks in addition to metformin, sulfonylurea derivative and/or insulin. At baseline and 26 weeks after treatment, participants had medical history assessment, physical examination, blood examination and MRI scans. Renal parenchyma volume and sinus fat volume were measured on the high-resolution water-fat separated images (Fig. 1) obtained by a 3.0 Tesla MRI scanner (Ingenia, Philips Medical Systems, Best, the Netherlands). Detailed information of the MRI protocol and clinical data collection has been reported in our previous publications [4–6]. All statistical analyses were performed with SPSS v.25 (IBM, Armonk, NY). Within-group differences were assessed using paired t-tests. Between-group differences were analyzed using analysis of covariance (ANCOVA) with adjustment for the baseline values, and the effect size was reported as means (95%CI). Linear regression models were constructed to analyze the associations between renal volumes and clinical characteristics.

After 26-week glucose-lowering treatment, renal parenchyma volume decreased with statistical significance, while renal sinus volume did not change in the whole cohort (Table 1). The level of fasting glucose and HbA1c significantly decreased in the whole cohort. Significant decreases in weight, waist circumference, triglycerides, total cholesterol, low density lipoprotein, abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue were also observed. The decrease in parenchyma volume was positively associated with the deceases in fasting glucose, HbA1c and abdominal VAT, which persisted after adjustment for age, sex, treatment allocation and ethnicity.

Subgroup analysis showed that the decrease of parenchyma volume was statistically significant in the liraglutide group and larger than that in the placebo group. However, no additional effects of liraglutide as compared to placebo on parenchyma volume was observed after adjustment for baseline volume. Nor was the effect on sinus fat volume.

Kidney enlargement can be found from the onset of diabetes due to expanded nephron size, particularly hypertrophy of the proximal tubule [7]. Both obesity and hyperglycemia can induce glomerular hyperfiltration through various cytokines and growth factors, which leads to nephromegaly. On the other hand, nephromegaly increases filtration surface area per glomerulus and exacerbates hyperfiltration. Our findings indicate that the decrease of renal parenchyma volume in response to the glucose-lowering treatment in T2DM might reflect the comprehensive benefits associated with lowered glucose level and reduced abdominal VAT. The improved glucose control and the loss of VAT may reduce the secretion of neurohormonal stimuli and ameliorate glomerular hyperfiltration, thus lead to the decrease of renal parenchyma volume.

Our baseline analysis demonstrated larger sinus fat volume in patients than in healthy controls, and baseline sinus fat volume was associated with HbA1c, VAT and blood lipids [4]. After treatment, however, sinus fat volume remained unchanged despite the significant decrease of HbA1c, VAT, triglyceride and cholesterol. These results suggest that the metabolism of renal sinus fat and the general abdominal VAT might not be synchronous, which adds further evidence for the morphological and functional heterogeneity among different anatomical patterns of fat accumulation.

In conclusion, renal parenchyma enlargement in T2DM can be potentially reversed by glucose-lowering treatment. Our findings suggested that renal parenchyma volume is a promising biomarker to monitor the hyperfiltration and hypertrophy of the kidneys in the development of DKD. On the other hand, renal sinus fat in patients with T2DM might be regulated by unique pathophysiological pathways that are independent from the metabolism of abdominal VAT and blood lipids. However, these results need to be validated in larger populations with longer follow-up periods in the future.

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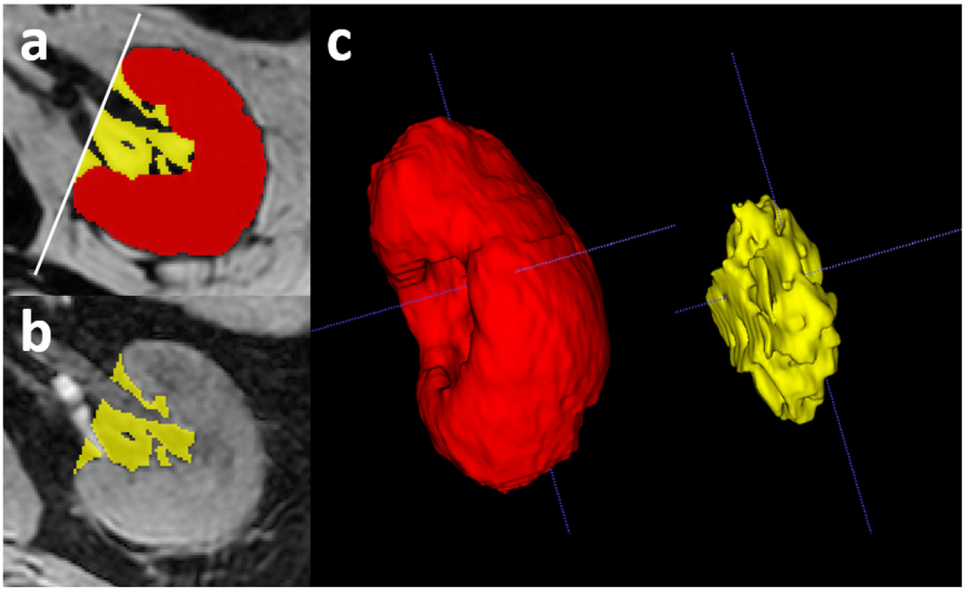

Fig. 1. The measurements of renal parenchyma volume (red) and sinus fat volume (yellow). Renal parenchyma was labelled on transversal fat-only images (a), and renal sinus fat was defined by a straight line (white line) tangent to the margins of parenchyma. Renal pelvis, calyces and vasculatures were manually discarded based on the water-only images (b). Renal parenchyma and sinus fat volume were calculated by summating the labelled voxels (c).

Table 1
Effects of glucose regulation on renal volumes and clinical characteristics.

	Baseline	Follow-up	Δ (follow-up − baseline)	*P* value*
Renal volumes				
Parenchyma volume (cm^3)	170.4 ± 39.0	168.3 ± 39.1	−2.1 ± 7.6	0.009
Sinus fat volume (cm^3)	15.3 ± 7.5	15.2 ± 7.9	−0.1 ± 2.2	0.748
Clinical characteristics				
Weight (kg)	88.1 ± 15.1	86.1 ± 15.4	−2.0 ± 3.5	< **0.001**
Waist circumference (cm)	105.5 ± 10.3	104.9 ± 11.3	−0.6 ± 4.3,	0.196
Triglycerides (mmol/L)	1.7 (1.1, 2.6)	1.3 (1.0, 2.1)	−0.3 ± 1.2	**0.014**
Total cholesterol (mmol/L)	4.5 ± 1.0	4.2 ± 1.0	−0.3 ± 0.9	< **0.001**
HDL (mmol/L)	1.2 ± 0.3	1.2 ± 0.3	−0.01 ± 0.17	0.564
LDL (mmol/L)	2.3 ± 0.9	2.2 ± 0.8	−0.2 ± 0.7	**0.019**
Abdominal VAT (cm^2)	184.3 ± 67.0	177.7 ± 66.2	−6.6 ± 27.1	**0.021**
Abdominal SAT (cm^2)	334.5 ± 124.2	321.0 ± 123.7	−13.5 ± 37.3	**0.001**
Fasting Glucose (mmol/L)	8.1 ± 2.7	7.1 ± 2.6	−1.0 ± 2.4	< **0.001**
HbA_{1c} (mmol/mol)	66.6 ± 11.2	58.2 ± 11.2	−8.5 ± 10.2	< **0.001**
Creatinine (μmol/L)	70.0 ± 18.5	72.2 ± 18.5	2.3 ± 7.4	**0.004**
eGFR (mL/min per 1.73 m^2)	93.7 ± 14.9	91.5 ± 15.6	−2.1 ± 7.0	**0.004**
Square root of UACR	2.0 ± 3.1	1.7 ± 2.1	−0.3 ± 2.0	0.100

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; UACR, urinary albumin-to-creatinine ratio.
* *P* value calculated by paired *t*-test.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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