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MR Assessed Changes of Renal Sinus Fat in Response to Glucose Regulation in West European and South Asian Patients With Type 2 Diabetes

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Background: Ethnic differences in the progression and outcome of diabetic kidney disease (DKD) remain to be elucidated. MRI-quantified renal sinus fat volume could be a potential biomarker to help investigate the changes of DKD risk in response to glucose regulation.
Purpose: To evaluate whether the effect of glucose-lowering treatment on renal sinus fat volume differed in West Europeans (WE) compared to South Asians (SA), and whether ethnic-related difference exists regarding the effect of liraglutide on renal sinus fat.
Study Type: Retrospective.
Population: Ninety-three patients with type 2 diabetes mellitus, including 47 WE (27 males) aged 59.3 ± 6.5 years, and 46 SA (19 males) aged 54.4 ± 9.8 years.
Field Strength/Sequence: 3.0 T dual-echo fast gradient-echo pulse sequence using two-point Dixon technique with a phase-correction algorithm.
Assessment: Changes of renal sinus fat volume were measured by a radiologist (LL) with 4-years' experience, and were compared between the two ethnic groups, together with glycemic level, metabolic risk factors and renal function. The effects of liraglutide were assessed.
Statistical Tests: Normality of the data was visually evaluated by histograms and Q–Q plots. Within-group and between-group differences were analyzed using paired *t*-tests and analysis of covariance. Associations were analyzed by person's correlation and multiple linear regression models.
Results: Renal sinus fat decreased in SA patients ($\Delta\% = -7.6\% \pm 14.8\%$), but increased in WE patients ($\Delta\% = 5.0\% \pm 13.1\%$), with a significant difference between the two ethnic groups. In the WE group, the increase of sinus fat volume was significant in the placebo subgroup ($\Delta\% = 6.8\% \pm 12.5\%$), in contrast to the nonsignificant increase in the liraglutide subgroup ($\Delta\% = 3.0\% \pm 13.8\%$, $P = 0.444$).
Data Conclusion: Renal sinus fat accumulation responds differently to glucose regulation, showing a reduction in SA patients in contrast to a persistent accumulation in WE patients. A trend of less accumulation of sinus fat in WE patients receiving liraglutide has been observed.
Evidence Level: 4
Technical Efficacy: Stage 4

J. MAGN. RESON. IMAGING 2023.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.29174

Received Jul 31, 2023, Accepted for publication Oct 19, 2023.

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Diabetic kidney disease (DKD) has surpassed other causes of renal disease to become the most frequent driver of kidney failure, and is responsible for over 40% of new cases of end stage kidney disease.[1] Increased renal sinus fat volume has been found in participants with prediabetes and diabetes, indicating an early accumulation of sinus fat in the development of metabolic diseases.[2] As a special visceral fat depot in close contact with renal vasculatures, renal sinus fat was found to be associated with lower glomerular filtration rate (GFR) and increased renal vascular resistance in type 2 diabetes mellitus (T2DM).[3] Reduction of renal sinus fat has been found after weight loss in obese participants.[4] While it has been shown that strict glycemic control could delay and slow the progression of DKD, one previous study did not find a significant reduction of renal sinus fat in response to glucose-lowering treatment in a cohort of patients with mixed ethnicities with T2DM.[5,6]

Ethnic differences in the progression and outcome of DKD have been suggested by previous studies, in which South Asian patients with T2DM demonstrated a faster decline in kidney function compared to participants of European ancestry.[7,8] The South Asian population appears to have higher metabolic risks due to high total body fat percentage.[9] Since renal sinus fat is potentially linked with insulin resistance and DKD, the dynamic changes of sinus fat volume in patients with T2DM might also vary with ethnicities, which remains to be investigated.

Glucagon-like peptide-1 (GLP-1) receptor analogues have been applied to improve glycemic control in patients with T2DM and to treat obesity.[10,11] Liraglutide, a commonly used GLP-1 receptor analogue, has been shown to reduce ectopic fat accumulation including abdominal visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), hepatic steatosis and epicardial fat in patients with T2DM.[12–15] Moreover, a large clinical trial showed that liraglutide lowers the rate of development and progression of DKD.[16]

Excellent intra- and inter-rater reproducibility (intraclass correlation coefficients were 0.966 and 0.903) of the quantification of renal sinus fat volume based on MRI has been presented in a previous article.[17] Larger volume of renal sinus fat has been found in patients with T2DM than in healthy controls.[17] It was also found that sinus fat volume was positively associated with glycated hemoglobin (HbA_{1c}) and urinary albumin-to-creatinine ratio (UACR), making it a potential imaging biomarker for DKD at an early phase.[17]

The present study aimed to assess whether the treatment effects of glucose regulation on renal sinus fat differ between West European (WE) and South Asian (SA) patients, and whether ethnic-related difference exists regarding the effect of liraglutide on renal sinus fat.

Methods

Study Design and Participants

This study is an assessor-blinded secondary analysis of the randomized, double-blind, single-center clinical trial MAGNA VICTORIA studies (ClinicalTrials.gov NCT01761318, NCT02660047), containing the baseline and 26-week follow-up data of WE and SA patients with T2DM.[18,19] WE participants were enrolled between December 2013 and September 2015, while SA participants were recruited between July 2015 and September 2017. The primary and secondary endpoints included left ventricular function, HbA_{1c}, body weight, and measurements of body fat distribution (VAT, hepatic and renal triglyceride contents).[18–21] The trials were approved by the local ethics committee and performed in accordance with the revised Declaration of Helsinki. Written informed consent was obtained from all participants before the study. The trial was conducted at Leiden University Medical Center, Leiden, the Netherlands.

Patients were recruited from the outpatient clinics of Leiden University Medical Center, local hospitals, and general practices in Leiden and The Hague, and by advertisements in local newspapers. Ethnicity was defined based on self-identified and self-reported origin of both biological parents and their ancestors. South Asian descent includes South Asian Surinamese, Indian, Pakistani, Bangladeshi, or Sri Lankan origin. Inclusion criteria were initially the same for WE and SA patients, which were: age 18–69 years, body mass index (BMI) ≥25 kg/m^2, HbA_{1c} ≥53.0 and <86.5 mmol/mol (≥7.0% and ≤10.0%), blood pressure <150/85 mmHg, eGFR >60 mL/min/1.73 m^2, no history of coronary artery disease. However, the inclusion criteria for SA patients were broadened to enable sufficient enrolment, which were: age 18–74 years, BMI ≥23 kg/m^2, HbA_{1c} ≥47.5 and <96.5 mmol/mol (≥6.5% and ≤11.0%), blood pressure <180/110 mmHg, eGFR >30 mL/min/1.73 m^2, no acute coronary accident in the preceding 30 days. Main exclusion criteria were: use of glucose-lowering therapy other than metformin, sulfonylurea derivative and insulin, severe hepatic or renal disease, and any contraindications for MRI.[18,19]

Randomization and Data Collection

Enrolled patients were randomized (1:1 stratification for sex and insulin use) to receive either liraglutide (Victoza, Novo Nordisk A/S, Bagsvaerd, Denmark) or placebo for 26 weeks, in addition to metformin, sulfonylurea derivative and/or insulin.[18,19] The randomization was executed by the institutional research pharmacist. Investigators and patients were blinded to the treatment allocation. The final cohort consisted of 47 WE (aged 59.3 ± 6.5 years with 27 males) and 46 SA participants (aged 54.4 ± 9.8 years with 19 males) who were randomized to receive Liraglutide (22 WE and 21 SA) or placebo (25 WE and 25 SA). The trial flow chart is presented in

Fig. 1. Details of the enrollment of WE and SA patients have been described previously.[18,19]

At baseline and 26 weeks after treatment, participants received medical history assessment, physical examination, blood examination and MRI scans. The assessments were scheduled either in the morning or evening after ≥6 hours of fasting. HbA_{1c}, triglyceride, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were obtained from blood samples. Serum creatinine was measured from blood samples and eGFR was calculated according to the CKD-EPI equation.[22] UACR was obtained from urine samples. Detailed information of the collection of clinical data has been reported in a previous publication.[20]

MR Protocol and Measurements

A 3.0 Tesla MRI scanner (Ingenia, Philips Medical Systems, Best, the Netherlands) was used for abdominal assessments in the trials, with a dStream Torso anterior coil and a FlexCoverage posterior coil (in total up to 32 coil elements) for signal reception. In this study, renal volumes and abdominal adipose tissue were measured on the high-resolution water-fat separated images obtained by a two-point modified Dixon sequence with the following parameters[23]: repetition time 3.5 msec, first/second echo time 1.19/2.3 msec, flip angle 10°, slice thickness 4 mm with slice overlap of 2 mm, acquired matrix 300 × 205, reconstructed matrix 528 × 383, reconstructed voxel size 0.9 × 0.9 × 2 mm^3, bandwidth 1344 Hz, speed up factor 1. There were 2 blocks of the Dixon sequence covering the whole abdomen, each of which had 100 slices with a scan time of 13.5 seconds.

Renal parenchyma and renal sinus fat volumes of the left kidney were measured by a radiologist (LL) with 4 years' experience of abdominal MRI blinded to any information on the participant's identity and examination date using an open source software (ITK-SNAP 3.6.0, www.itksnap.org).[24] Renal sinus fat was defined by a straight-line tangent to the margins

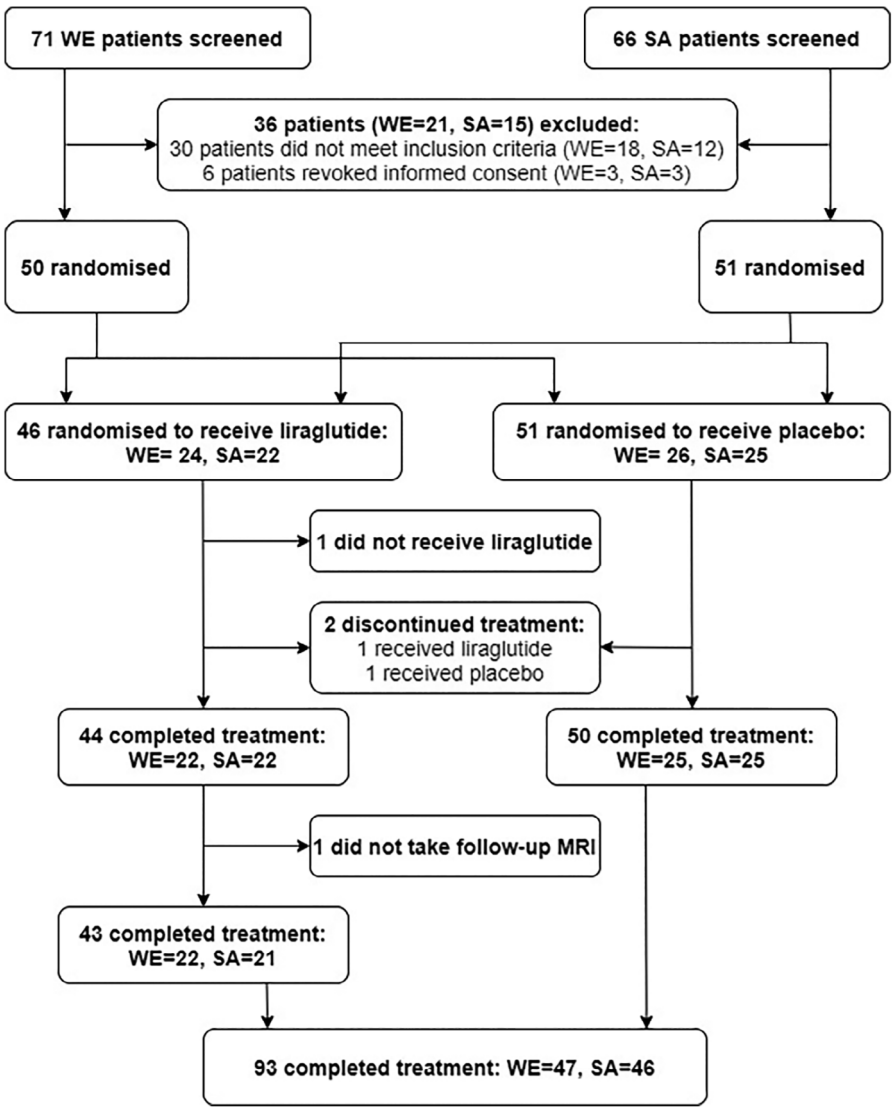

FIGURE 1: Trial flow diagram.

of parenchyma beside the renal hilum on transversal slices, and renal pelvis, calyces, vasculature and cysts were manually discarded (Fig. 2). The baseline and follow-up MRI scans were blindly measured in a random order to avoid potential bias. The difference between the follow-up and the baseline value was recorded as delta (Δ), and the percentage of delta (Δ%) represented the percentage change from the baseline value.

Abdominal VAT and SAT were measured using reformatted Dixon images with slice thickness of 10 mm and slice gap of 12 mm. VAT and SAT were semi-automatically labeled on three transverse slices at the fourth to fifth lumbar vertebrae level based on voxel intensity thresholding and were quantified as the mean area of the three slices (MASS 2015-EXP, Leiden University Medical Center, Leiden, The Netherlands).

Statistical Analysis

Statistical analyses were performed with SPSS v.26 (IBM, Armonk, NY). Normality of the data was visually evaluated by histograms and Q–Q plots. Data are presented as mean ± SD for parametric variables or as median (interquartile ranges) for non-parametric variables. 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 was reported as means (95% CI). Association between the changes of renal sinus fat volume and the changes of glucose level, renal function and metabolic characteristics were analyzed by person's correlation and multiple linear regression models. P value <0.05 was considered statistically significant.

A sensitivity analysis using ANCOVA was performed to evaluate the between-ethnicity effect on the changes of renal sinus volume with additional adjustments of all the discrepant characteristics.

Results

Baseline Characteristics

As is shown in Table 1, fasting glucose, HbA_{1c}, and kidney function were balanced between the two ethnic groups (eGFR: 93.5 ± 13.3 mL/min/1.73 m^2 vs. 93.8 ± 16.6 mL/min/1.73 m^2), despite that WE patients had larger anthropometric measurements (BMI: 32.1 ± 3.9 kg/m^2 vs. 29.5 ± 4.0 kg/m^2) and larger abdominal VAT (205.1 ± 74.2 cm^2 vs. 163.0 ± 51.3 cm^2), while SA patients were younger (54.4 ± 9.8 years vs. 59.3 ± 6.5 years) but with longer diabetes duration (17.8 ± 10.0 years vs. 10.5 ± 6.0 years). WE patients had significantly larger renal parenchyma and sinus fat volume than SA patients (188.5 ± 32.9 cm^3 vs. 152.0 ± 36.2 cm^3, 18.2 ± 6.3 cm^3 vs. 12.3 ± 7.6 cm^3).

Effects of Glucose-Lowering Treatment and the Differences Between WE and SA Patients

Table 2 lists the changes from baseline values of metabolic risk factors and renal function in each group after 26-week glucose-lowering treatment. The level of fasting glucose (WE: $\Delta = -1.1 \pm 2.2$ mmol/L, SA: $\Delta = -0.9 \pm 2.6$ mmol/L) and HbA_{1c} (WE: $\Delta = -9.5 \pm 10.3$ mmol/mol, SA: $\Delta = -7.4 \pm 10.1$ mmol/mol) significantly decreased in both groups. Significant decreases in weight (WE: $\Delta = -2.0 \pm 3.9$ kg, SA: $\Delta = -1.9 \pm 3.1$ kg) and abdominal SAT (WE: $\Delta = -11.6 \pm 37.9$ cm^2, SA: $\Delta = -15.5 \pm 37.1$ cm^2) were also observed in both groups, while the decreases in waist circumference (WE: $\Delta = 0.6 \pm 3.9$ cm, $P = 0.288$; SA: $\Delta = 99.1 \pm 10.3$ cm) and in abdominal VAT (WE: $\Delta = -3.9 \pm 30.0$ cm^2, $P = 0.379$; SA: $\Delta = -9.4 \pm 23.7$ cm^2) were significant only in the SA group (Table 2). The changes of serum creatinine and eGFR were also significantly different between WE and SA patients, with greater increase of creatinine ($\Delta = 4.2 \pm 5.8$ μmol/L) and decrease of eGFR

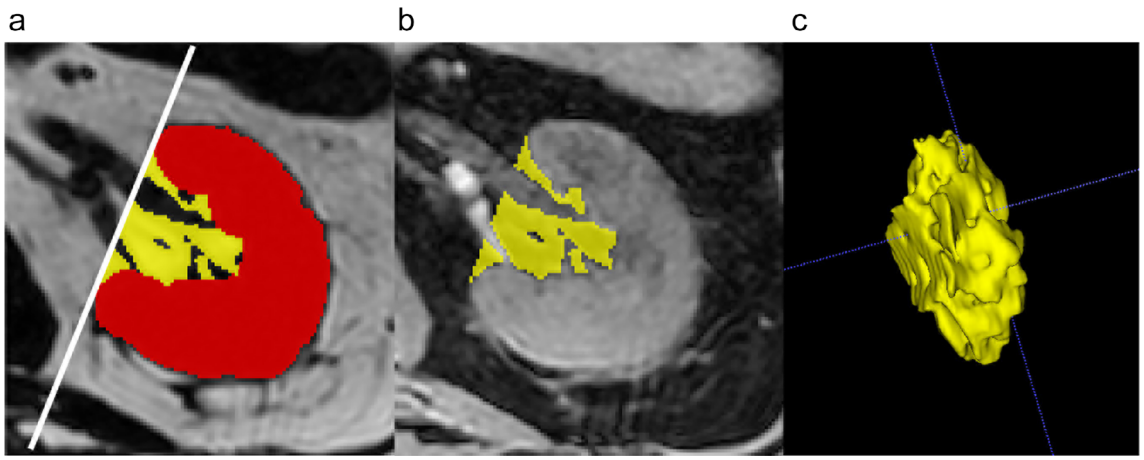

FIGURE 2: The measurement of renal sinus fat volume (yellow). (a) Renal parenchyma (red) and sinus fat were first labeled on transversal fat-only images, and sinus fat was defined by a straight line (white line) tangent to the margins of parenchyma. (b) Renal pelvis, calyces, and vasculatures were manually discarded based on the water-only images. (c) 3D reconstruction of renal sinus fat volume.

TABLE 1. Baseline Characteristics

	WE (N = 47)	SA (N = 46)
Demographic and anthropometric variables		
Age (years)	59.3 ± 6.5	54.4 ± 9.8
Sex: male (%)	27 (57%)	19 (41%)
Height (cm)	172.9 ± 8.8	164.7 ± 8.8
Weight (kg)	96.0 ± 13.5	79.9 ± 11.9
BMI (kg/m^2)	32.1 ± 3.9	29.5 ± 4.0
Waist circumference (cm)	110.0 ± 8.9	100.9 ± 9.5
Hip circumference (cm)	107.3 ± 7.6	104.2 ± 8.2
Waist-hip ratio	1.03 ± 0.07	0.97 ± 0.09
Metabolic risk factors		
Systolic blood pressure (mmHg)	141.4 ± 14.7	144.7 ± 21.7
Diastolic blood pressure (mmHg)	86.6 ± 8.8	85.6 ± 9.9
Triglycerides (mmol/L)	1.9 (1.2, 2.6)	1.3 (0.9, 2.2)
Total cholesterol (mmol/L)	4.8 ± 1.0	4.2 ± 1.0
HDL (mmol/L)	1.3 ± 0.3	1.2 ± 0.3
LDL (mmol/L)	2.6 ± 0.9	2.1 ± 0.8
Abdominal VAT (cm^2)	205.1 ± 74.2	163.0 ± 51.3
Abdominal SAT (cm^2)	347.1 ± 125.8	321.6 ± 122.7
Diabetes-related variables		
Fasting Glucose (mmol/L)	8.0 ± 2.3	8.2 ± 3.0
HbA_{1c} (mmol/mol)	65.5 ± 10.9	67.8 ± 11.4
HbA_{1c} (%)	8.1 ± 1.0	8.4 ± 1.0
Diabetes durations (years)	10.5 ± 6.0	17.8 ± 10.0
Metformin, N (%)	47 (100%)	44 (96%)
Sulfonylurea derivative, N (%)	14 (30%)	8 (17%)
Insulin, N (%)	30 (64%)	35 (76%)
Insulin dose (units/day)	44 (31, 90)	65 (44, 99)
Lipid lowering drugs: N (%)	38 (81%)	40 (80%)
Antihypertension drugs, N (%)	36 (77%)	33 (72%)
Diuretics	20 (44%)	16 (36%)
AT_2 antagonist	14 (30%)	15 (33%)
Beta blocker	5 (11%)	16 (35%)
Calcium antagonist	11 (23%)	7 (15%)
ACE-inhibitors	17 (36%)	13 (28%)
Kidney function		
Serum creatinine (μmol/L)	69.4 ± 17.7	70.6 ± 19.5

TABLE 1. Continued

	WE (N = 47)	SA (N = 46)
eGFR (mL/min/1.73 m^2)	93.5 ± 13.3	93.8 ± 16.6
UACR (mg/mmol)	0.7 (0, 0.7)	2.5 (0.5, 10.8)
Renal volume		
Parenchyma volume (cm^3)	188.5 ± 32.9	152.0 ± 36.2
Sinus fat volume (cm^3)	18.2 ± 6.3	12.3 ± 7.6

WE = West European; SA = South Asian; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; AT_2 = angiotensin 2; UACR = urinary albumin-to-creatinine ratio.

(Δ = −3.9 ± 5.6 mL/min/1.73 m^2) in WE patients than in SA patients (creatinine: Δ = 0.3 ± 8.4 μmol/L; eGFR: Δ = −0.3 ± 7.9 μmol/L) (Table 2). There was no macroalbuminuria (defined by UACR ≥300 mg/mmol) at baseline, nor after treatment. In more than half of the patients (60/93, 64.5%), UACR decreased or stabilized after treatment. However, the difference between baseline and follow-up UACR (WE: Δ = 0.03 ± 0.7, $P = 0.768$; SA: Δ = −0.7 ± 2.7, $P = 0.722$) did not reach statistical significance in both groups.

Renal sinus fat volume significantly increased in WE patients (Δ% = 5.0% ± 13.1%), while significantly decreased in SA patients (Δ% = −7.6% ± 14.8%), with significant between-group difference (mean [95% CI] = 13.8 [7.5, 20.0]%), which persisted after adjusting baseline value (Table 3). In the WE group, the increase of sinus fat volume was statistically significant in the placebo subgroup (Δ% = 6.8% ± 12.5%), in contrast to the nonsignificant increase in the liraglutide subgroup (Δ% = 3.0% ± 13.8%, $P = 0.444$). However, no additional significant effects of liraglutide as compared to placebo was observed after adjustment for baseline volume in both groups (WE: $P = 0.393$; SA: $P = 0.981$) (Table 3; Fig. 3).

Associations Between Changes of Renal Sinus Fat Volume and Changes of Glucose Control, Metabolic Alterations as Well as Renal Function

The correlation matrix of the changes in renal volumes and clinical variables is presented in Table S1 in the Supplemental Material. In multiple linear regression, the changes of sinus fat volume in response to glucose-lowering treatment were significantly associated with Δ weight ($\beta = 0.21$), Δ waist circumference ($\beta = 0.17$) and Δ HbA_{1c} ($\beta = 0.04$) after adjustment for age, sex, treatment allocation, and ethnicity (Table 4). There was no significant association between Δ sinus fat volume and Δ fasting glucose ($\beta = 0.02$, $P = 0.805$). Moreover, Δ sinus fat volume was not significantly associated with Δ VAT ($\beta = 0.005$, $P = 0.537$) or the changes of blood lipids (Δ triglycerides: $\beta = 0.22$, $P = 0.25$; Δ total cholesterol: $\beta = 0.20$, $P = 0.406$). No significant association was found between Δ sinus fat volume and the changes of renal function (Δ eGFR: $\beta = -0.005$, $P = 0.874$).

Sensitivity Analysis

After additional adjustments of age, sex, diabetes duration, baseline BMI, and abdominal VAT, the significant differences between the two ethnic groups persisted in the changes of renal sinus fat, but lost statistical significance in the changes of serum creatinine ($F = 1.475$, $P = 0.228$) and eGFR ($F = 1.338$, $P = 0.251$).

Discussion

The key finding of this study was the effects of 26-week glucose regulation on sinus fat in patients with T2DM differed between the two ethnic groups, showing a volumetric reduction in SA patients in contrast to an increase in WE patients. There was a trend of less accumulation of sinus fat in WE patients receiving liraglutide in addition to standard treatment, but did not reach statistical significance when compared with placebo.

Different Changes of Sinus Fat in the Two Ethnic Groups

There have been several cross-sectional studies suggesting the association between sinus fat accumulation and kidney injury, but longitudinal studies of the dynamic changes of sinus fat are sparse, and have been carried out in healthy or obese individuals without diabetes.[3,4,25–28] In a cohort of 278 obese participants, renal sinus fat decreased after an 18-month diet intervention.[4] On the contrary, an earlier study found that renal sinus fat volume in 40 healthy subjects increased along with the increase of VAT, but did not show significant decrease when significant decrease of VAT was observed.[27] A cross-sectional study demonstrated a gradual increase of renal sinus fat from normoglycemic to prediabetes and to diabetes.[2] The baseline analysis also demonstrated larger sinus fat volume in patients with T2DM than in healthy controls, and

TABLE 2. Effects of Glucose Regulation and the Differences Between the Two Ethnic Groups

	WE (N = 47)			SA (N = 46)			Between Group Difference[a]	
	Follow-Up	Δ	*P* Value	Follow-Up	Δ	*P* Value	Mean (95% CI)[b]	*P* Value
Weight (kg)	94.1 ± 13.9	−2.0 ± 3.9	**0.001**	78.0 ± 12.5	−1.9 ± 3.1	**<0.001**	−0.05 (−1.7, 1.8)	0.954
Waist circumference (cm)	110.6 ± 9.2	0.6 ± 3.9	0.288	99.1 ± 10.3	−1.8 ± 4.5	**0.009**	2.8 (0.9, 4.7)	**0.005**
Triglycerides (mmol/L)	1.6 ± 0.7	−0.6 ± 1.0	**0.001**	1.8 ± 1.3	−0.07 ± 1.3	0.727	−0.3 (−0.7, 0.05)	0.089
Total cholesterol (mmol/L)	4.2 ± 0.9	−0.6 ± 0.7	**<0.001**	4.1 ± 1.1	−0.1 ± 1.0	0.484	−0.3 (−0.6, 0.1)	0.152
HDL (mmol/L)	1.3 ± 0.4	0.02 ± 0.2	0.529	1.2 ± 0.3	−0.04 ± 0.1	**0.024**	0.06 (−0.01, 0.1)	0.073
LDL (mmol/L)	2.2 ± 0.8	−0.3 ± 0.5	**<0.001**	2.1 ± 0.9	0.001 ± 0.8	0.991	−0.2 (−0.4, 0.07)	0.144
Abdominal VAT (cm^2)	201.2 ± 71.7	−3.9 ± 30.0	0.379	153.6 ± 50.3	−9.4 ± 23.7	**0.010**	10.4 (−0.9, 21.8)	0.071
Abdominal SAT (cm^2)	335.5 ± 126.4	−11.6 ± 37.9	**0.041**	306.1 ± 120.6	−15.5 ± 37.1	**0.007**	5.2 (−10.2, 20.6)	0.506
Fasting Glucose (mmol/L)	6.9 ± 2.2	−1.1 ± 2.2	**0.002**	7.3 ± 2.9	−0.9 ± 2.6	**0.029**	−0.3 (−1.2, 0.6)	0.535
HbA_{1c} (mmol/mol)	56.0 ± 10.3	−9.5 ± 10.3	**<0.001**	60.4 ± 11.7	−7.4 ± 10.1	**<0.001**	−3.1 (−6.9, 0.7)	0.104
Creatinine (μmol/L)	73.6 ± 17.1	4.2 ± 5.8	**<0.001**	70.9 ± 20.0	0.3 ± 8.4	0.806	3.8 (0.9, 6.7)	**0.011**
eGFR (mL/min/1.73 m^2)	89.6 ± 13.8	−3.9 ± 5.6	**<0.001**	93.5 ± 17.3	−0.3 ± 7.9	0.765	−3.6 (−6.4, −0.8)	**0.013**
Square root of UACR	1.2 ± 1.1	0.03 ± 0.7	0.768	2.2 ± 2.7	−0.7 ± 2.7	0.075	−0.1 (−0.7, 0.5)	0.722

P values less than 0.05 are presented in boldface.
Δ = follow-up—baseline. WE = West European; SA = South Asian; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; UACR = urinary albumin-to-creatinine ratio.
[a]With adjustment for baseline values.
[b]Calculated by WE − SA.

TABLE 3. Changes of Renal Sinus Fat Volume After Glucose Regulation

	WE (N = 47)			SA (N = 46)			Between Group Difference[a]	
	Follow-Up (cm^3)	Δ%	*P* Value	Follow-Up (cm^3)	Δ%	*P* Value	Mean (95% CI) of Δ%[b]	*P* Value
Sinus fat volume	19.0 ± 6.5	5.0 ± 13.1	**0.045**	11.4 ± 7.5	−7.6 ± 14.8	**<0.001**	13.8 (7.5, 20.0)	**<0.001**
Liraglutide	19.2 ± 7.4	3.0 ± 13.8	0.444	11.0 ± 6.0	−7.7 ± 12.6	**0.004**	11.3 (1.8, 20.7)	**0.020**
Placebo	18.8 ± 5.6	6.8 ± 12.5	**0.049**	11.8 ± 8.7	−7.5 ± 16.7	**0.008**	15.7 (6.6, 24.8)	**0.001**
Between group difference[a]	Mean (95% CI) of Δ%[c]			Mean (95% CI) of Δ%[c]				
	3.3 (−4.4, 11.0)		**0.393**	0.1 (−9.1, 9.3)		**0.981**		

P values less than 0.05 are presented in boldface.
Δ% = (follow-up − baseline)/baseline × 100%. WE = West European; SA = South Asian; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; UACR = urinary albumin-to-creatinine ratio.
[a]With adjustment for baseline values.
[b]Calculated by WE − SA.
[c]Calculated by liraglutide − placebo.

baseline sinus fat volume was associated with HbA_{1c}, VAT, and blood lipids.[17] After treatment, however, the changes of renal sinus fat in response to glucose-lowering treatment significantly differed between the WE and the SA patients.

It has been reported that South Asians have higher insulin resistance than other ethnic groups at similar adiposity level, indicating more pronounced metabolic sensitivity to excessive fat accumulation.[29,30] In addition, higher VAT, impaired β-cell function, an abnormal adipokine profile and certain high-risk genetic polymorphisms have been found in South Asians compared to Caucasians.[31] Nevertheless, controversial results have been reported by studies looking at ethnic differences in the progression of DKD. Faster decline of kidney function has been reported in non-white ethnic groups than their Caucasian counterparts with universal access to healthcare in UK and the Netherlands.[32,33] However, other studies did not identify differences in the progression of DKD between South Asian and white European patients.[34–36]

This study found a reduction of sinus fat volume in SA patients in response to glucose regulation, which significantly differed from the continued accumulation in WE patients. Moreover, the difference in the changes of sinus fat persisted in the sensitivity analysis with additional adjustment of the unbalanced predispositions (age, sex, diabetes duration, baseline BMI, and abdominal VAT) of the two ethnic groups. The underlying mechanism of this difference could be multifactorial, which requires further studies to identify the key contributors to the changes of renal sinus fat after glucose regulation. However, whether a larger decrease of sinus fat indicates an improved prognosis remains to be elucidated.

In this study, the changes of sinus fat volume were not associated with the decrease of HbA_{1c}, VAT, triglyceride or cholesterol. These results suggested that renal sinus fat might be regulated by unique pathophysiological pathways that are independent from the metabolism of abdominal VAT and blood lipids. The morphological and functional heterogeneity among different anatomical fat accumulation has been observed in previous studies.[37] As a special perivascular adipose tissue, excessive renal sinus fat may contribute to kidney injury in a paracrine manner. The positive association between the changes of sinus fat volume and the changes of HbA_{1c} indicated that sinus fat might reflect a cumulative effect of glucometabolic alterations on kidneys.

The Effect of Liraglutide in Addition to Standard Treatment

A recent large clinical trial has shown that adding liraglutide to usual care resulted in lower rates of the development and progression of DKD.[16] It is presumed that GLP-1 receptor agonists induce reno-protective effects through indirect and overlapping mechanisms, including the mitigation of hyperglycemia, dyslipidemia, hypertension, and obesity.[38] There is not sufficient evidence that GLP-1 receptor agonists can attenuate glomerular hyperfiltration.[38] An earlier study found a reduction of intrarenal

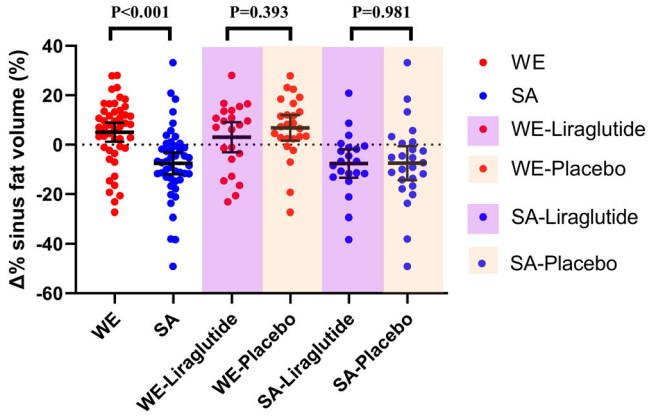

FIGURE 3: Between-group differences of the changes of renal sinus fat volume from baseline. The bars represent mean values and 95% confidence interval. All the *P* values were calculated by the analysis of covariance adjusting baseline values. Renal sinus fat volume increased in the WE patients and decreased in the SA patients. No additional effect of liraglutide was observed in comparison to placebo.

TABLE 4. Changes of Renal Sinus Fat Volume in Association With Changes of Clinical Parameters

	Δ Sinus Fat Volume (cm^3)	
Independent Variable	***β* (95% CI)[a]**	***P* Value**
Δ Weight (kg)	0.21 (0.07, 0.35)	**0.003**
Δ Waist circumference (cm)	0.17 (0.06, 0.29)	**0.002**
Δ Triglycerides (mmol/L)	0.22 (−0.15, 0.58)	0.250
Δ Total cholesterol (mmol/L)	0.20 (−0.28, 0.69)	0.406
Δ HDL (mmol/L)	−1.18 (−3.68, 1.32)	0.350
Δ LDL (mmol/L)	0.15 (−0.51, 0.81)	0.649
Δ VAT (cm^2)	0.005 (−0.01, 0.02)	0.537
Δ SAT (cm^2)	0.01 (−0.002, 0.22)	0.091
Δ Fasting Glucose (mmol/L)	0.02 (−0.15, 0.20)	0.805
Δ HbA_{1c} (mmol/mol)	0.04 (0.002, 0.09)	**0.041**
Δ Serum creatinine (μmol/L)	0.01 (−0.05, 0.07)	0.818
Δ eGFR (mL/min/1.73 m^2)	−0.005 (−0.07, 0.06)	0.874
Δ square root of UACR	−0.02 (−0.25, 0.20)	0.837

P values less than 0.05 are presented in boldface.
Δ = follow-up − baseline. VAT = visceral adipose tissue; UACR = urinary albumin-to-creatinine ratio.
[a]With adjustment for age, sex, treatment allocation, and ethnicity.

triglyceride content measured by MR Spectroscopy, with a trend of more influence by liraglutide than placebo.[39] In this study, there was a trend of less accumulation of sinus fat in WE patients receiving liraglutide, but did not reach statistical significance when compared with placebo. The nonsignificant results could be due to the short follow-up period with no onset of macroalbuminuria. Moreover, as previously reported, no added value of liraglutide was observed in the decrease of fasting glucose, HbA_{1c} or abdominal VAT in this clinical trial, making it plausible to expect nonsignificant effects on sinus fat volumes.

Clinical Relevance

Diabetic renal damage can progress in clinical silence for many years, and there has been increased recognition of non-albuminuric DKD.[40] Therefore, early biomarkers other than eGFR and UACR are needed to implement more timely strategies. DKD in T2DM is heterogeneous in nature and driven by multiple interactive factors including hyperglycemia, hypertension, dyslipidemia, obesity, insulin resistance, sodium retention, neurohormonal activation, and inflammation. These findings suggest that the change of sinus fat volume is a promising biomarker for further studies on ethnic-specific prevention and treatment of DKD.

Limitations

This study is limited by the small sample size, single magnet, single vendor, single field strength, and single center design. These results need to be validated in larger populations with longer follow-up periods in the future. Moreover, the inclusion criteria of the SA group were broader than those of the WE group, which is another limitation. Nevertheless, the conclusions are not likely to be impacted as suggested by the sensitivity analysis. Finally, nondiabetic causes of kidney injury could not be entirely excluded as kidney biopsy was not available.

Conclusion

Ethnicity-related difference might exist in the dynamic changes of renal sinus fat in response to glucose regulation in patients with type 2 diabetes mellitus. A trend of less accumulation of sinus fat in West European patients receiving liraglutide has been observed. Further studies are required to identify the key contributors to the changes of renal sinus fat in response to glucose regulation.

Acknowledgments

We express our gratitude to all individuals who participated in the MAGNA VICTORIA. We are grateful for all participating general practitioners and nurses, and the physicians and nurses of the Haaglanden Medical Center (The Hague, The Netherlands) for inviting eligible participants. This investigator-initiated study was funded by Novo Nordisk (Denmark). Novo Nordisk had no role in the design of the study, data collection, data analysis, data interpretation, or

writing of the report. Dr. Ling Lin was funded by China Scholarship Council (CSC201807720065).

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