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Skin microvascular function and renal hemodynamics in overweight patients with type 2 diabetes: A cross-sectional study

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Abstract

Objective: Diabetic kidney disease is a microvascular complication of diabetes. Here, we assessed the association between skin microvascular function and renal hemodynamic function in a cohort of well-phenotyped adults with type 2 diabetes (T2D).

Methods: We included 81 overweight/obese adults (age: 62 ± 8 years; BMI: 32 ± 4 kg/m^2) with well-controlled T2D and no renal impairment. Skin microvascular function was assessed by nailfold capillary density in rest and after arterial occlusion (ie, peak capillary density). Renal hemodynamic functions (ie, measured glomerular filtration rate [mGFR], effective renal blood flow [ERBF], filtration fraction [FF], and effective renal vascular resistance [ERVR]) were assessed by combined inulin and para-aminohippurate clearances and blood pressure measurements.

Results: Skin capillary density was 45 ± 10 capillaries/mm^2 at baseline and 57 ± 11 capillaries/mm^2 during post-occlusive peak; mGFR averaged 108 ± 20 ml/min. In multivariable regression analyses, positive associations between capillary density during post-occlusive peak and mGFR (β = 0.224; p = 0.022) and ERBF (β = 0.203; p = 0.020) and a positive trend for hyperemia and mGFR (β = 0.391; p = 0.053) were observed, while a negative association for post-occlusive capillary density with ERVR (β = −0.196; p = 0.027) was found.

Conclusion: These findings indicate that microvascular dysfunction in overweight adults with T2D is associated with lower mGFR and ERPF and higher ERVR. We hypothesize that increased renal vascular resistance may contribute to glomerular dysfunction due to impaired renal perfusion.

KEYWORDS
capillary recruitment, diabetic kidney disease, measured GFR, microvascular dysfunction, renal hemodynamics, type 2 diabetes

Abbreviations: BMI, Body Mass Index; BSA, Body Surface Area; DCCT, Diabetes Control and Complications Trial; DKD, Diabetic Kidney Disease; ERBF, Effective Renal Blood Flow; ERPF, Effective Renal Plasma Flow; ERVR, Effective Renal Vascular Resistance; ESKD, End-Stage Kidney Disease; FF, Filtration Fraction; GFR, Glomerular Filtration Rate; HbA1c, Glycated Hemoglobin (A1c); HOMA, Homeostatic Model Assessment; IFCC, International Federation of Clinical Chemistry; MAP, Mean Arterial Pressure; PAH, Para-aminohippurate; RAAS, Renin-Angiotensin-Aldosterone System; RED, Renoprotective Effects of Dapagliflozin in Type 2 Diabetes; RENALIS, Renal Effects of DPP-4 Inhibitor Linagliptin in Type 2 Diabetes; ROS, Reactive Oxygen Species; SAFEGUARD, Safety evaluation of adverse reactions in diabetes; Pleiotropic Effects of Incretin Based Therapies.

1 | INTRODUCTION

Type 2 diabetes (T2D) leads to microvascular and macrovascular complications that cause profound morbidity and mortality, and put a huge burden on health-care systems worldwide. Diabetic kidney disease (DKD), characterized as declined glomerular filtration rate (GFR) and/or increased urinary albumin excretion due to diabetes, affects approximately 40% of people with T2D.[1] DKD is the main cause of end-stage kidney disease (ESKD) worldwide and abundant evidence indicates that DKD may independently contribute to the pathogenesis of cardiovascular disease (CVD) and lead to all-cause mortality.[2] DKD has a complex and multifactorial pathogenesis, involving metabolic and hemodynamic pathways, with impaired renal hemodynamic function now being recognized as an independent contributor. Impaired hemodynamic function may become manifest as glomerular hyperfiltration (increased whole-kidney GFR) which occurs usually in the early phases of DKD, and contributes to kidney damage, while single-nephron hyperfiltration may occur in later stages of the disease in people with low or normal GFR.[3] In addition, impaired hemodynamic function and autoregulation could render the kidney to hypoxic damage at lower perfusion pressure.

Endothelial cells play a key role in vascular tone and homeostasis, amongst others through the production of various hormones and paracrine signals.[4] By secreting factors such as nitric oxide, endothelin, thromboxane A2 and prostaglandins, the microvascular endothelium regulates vasodilation and vasoconstriction, thereby controlling effective renal plasma flow (ERPF) and glomerular filtration rate (GFR), together with hormones of the renin-angiotensin system (RAS) and processes such as tubuloglomerular feedback.[3] Impaired microvascular endothelial function is a common finding in people with T2D and DKD.[5] Endothelial dysfunction and DKD may be linked in various ways: 1) reduced glomerular barrier function due to increased capillary wall permeability contributes to albuminuria, 2) renal inflammation caused by endothelial-derived pro-inflammatory factors induces nephron loss and 3) capillary rarefaction due to impaired angiogenesis may lead to renal hypoxia.[6,7] Finally, impaired renal microvascular endothelial function could also result in impaired renal hemodynamic function. However, the relationship between these variables remains unstudied. We therefore studied the interaction between microvascular function and gold-standard assessment of renal hemodynamic function. We assessed microvascular function by capillary nailfold microscopy, where we counted capillary density in the baseline state and after post-occlusive hyperemia. The recruitment of capillaries under these conditions has been validated as a marker for endothelial function and was previously shown to be impaired in people with T2D [8] and linked to the microvascular complications retinopathy,[9] neuropathy [10] and DKD.[11]

2 | MATERIALS AND METHODS

2.1 | Study design and population

This cross-sectional study assessed renal hemodynamic and microvascular function in overweight adults with T2D. We combined baseline measurements of three completed randomized clinical trials which aimed to assess the renal hemodynamic effects of new-generation glucose-lowering drugs in adults with T2D: 1) SAFEGUARD (Safety evaluation of adverse reactions in diabetes; Pleiotropic Effects of Incretin Based Therapies) [NCT01744236], 2) RENALIS (Renal Effects of DPP-4 Inhibitor Linagliptin in Type 2 Diabetes) [NCT02106104] and 3) RED (Renoprotective Effects of Dapagliflozin in Type 2 Diabetes) [NCT02682563]. These studies have been described in detail elsewhere and were conducted at Amsterdam UMC, location VUMC, between April 2013 and September 2018.[12–14] Complete inclusion- and exclusion criteria were published previously.[15] In short, overweight (BMI of 25–40 kg/m^2) Caucasian men and postmenopausal women aged between 35 and 75 years with T2D were recruited by advertisement in local newspapers. Patients were on a stable dose of metformin and/or sulfonylurea for at least 3 months prior to inclusion. Patients were excluded if they used diuretics which could not be stopped during the study, had a history of malignancy or pancreatic disease, active liver disease, current urinary tract infection or active nephritis, renal impairment (defined as an eGFR <60 mL/min/1.73 m^2), a neurogenic bladder or if they had a history of cardiovascular disease in the past 6 months. NSAIDs and glucose-lowering drugs other than metformin and/or sulfonylurea were not allowed. All three studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. All patients provided written informed consent before participation.

2.2 | Study protocol

Participants adhered to an average sodium intake of 9–12 grams or 150–200 mmol per day and a protein intake of 1.5–2 g/kg per day from 48 hours prior to the study visit to reduce diet-induced variation in renal physiology and refrained from smoking. After an overnight fast, participants drank 500 ml of water to stimulate diuresis and delayed all medication except for a morning dose of metformin. Patients were admitted at the Clinical Research Unit (CRU), and medical history and medication were recorded. Body weight, height and BMI were obtained. A venous cannula was placed in both forearms, one for infusion of test substances and one for blood sampling, to measure HbA1c, plasma glucose, albumin and creatinine concentrations. After 15 minutes of acclimatization, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate were measured in triplicate by an automated oscillometric device (Dinamap; GE Healthcare, Little Chalfont, U.K.) at the brachial artery of the non-dominant arm, and the average of the last two was taken.

2.3 | Capillary Videomicroscopy

Microvascular function was assessed using skin capillary videomicroscopy, performed in a quiet, temperature controlled room with participants in supine position as previously described.[16] We assessed capillary density, by quantification of constantly perfused capillaries of the dorsal skin of the distal phalange of the third finger,

and capillary recruitment by quantification of perfused capillaries during a post-occlusion measurement. To visualize the capillaries a 3.2X objective (Zeiss 2.3/0/07) was used with a total system magnification of 99x, linked to a laptop running CapiScope software version 3.90 (KK Technology, Honiton, UK) for image recording and analysis. Capillaries were visualized 3.0 mm proximal to the terminal row of capillaries in the middle of the nailfold, where the investigator selected 2 region of interest of 1 mm^2 skin area. Capillary density (mean of two fields) was measured under two conditions. First, baseline capillary density was measured during a two minute recording. Baseline capillary density was defined as the number of continuously erythrocyte-perfused capillaries per 1 mm^2 skin and was counted for 15 seconds. Then, maximal capillary recruitment (peak capillary density) was assessed after 4 minutes of arterial occlusion. Arterial occlusion was applied using a miniature cuff at the base of the investigated finger inflated to supra-systolic pressure (300 mmHg) for 4 minutes. Directly after release of the cuff, all (continuously and intermittently) perfused capillaries were counted for 15 seconds. Images were stored and were analyzed offline for this study by two investigators (EJB and MMS) who were blinded to participants' clinical characteristics. Intra-observer CV was 5.6% for baseline capillary density and 4.8% for peak capillary density, while inter-observer CV was 6.2% for baseline capillary density and 8.7% for peak capillary density.

2.4 | Renal protocol

A renal function protocol was performed with infusion of inulin and PAH to measure GFR and ERPF, respectively as described (13,14). The protocol started with a loading dose of 45 mg/kg body weight inulin (Inutest, Fresenius Kabi Austria, Graz, Austria) and 6 mg/kg body weigh PAH sodium (20%, Merck Sharp & Dohme International, Merck, Whitehouse Station, NJ, USA). Thereafter, maintenance infusion was started at 22.5 mg/min for inulin (target plasma concentration 250 mg/l) and 12.7 mg/min for PAH (target plasma concentration 20 mg/l). For study 3 ('RED'), some alterations to the tracers dosing were made (based on plasma and urinary levels of inulin/PAH from studies 1 and 2): bolus PAH 3 mg/kg, continuous infusion of PAH 5.3 mg/min, continuous infusion of inulin 11.25 mg/min based on high plasma and urine tracer levels in studies 1 and 2. Such alteration does not alter the measured clearance rates, as these are only changed by changes in GFR and ERPF themselves. Following a 90 min equilibration period, urine was collected by spontaneous voiding every 45 min and blood samples were collected before and after each urine collection.

2.5 | Calculations of renal hemodynamic functions

GFR and ERPF were calculated from inulin and PAH clearances, respectively, based on timed urine sampling, and the average of the two consecutive urine collection periods was used for analysis as described.[14,15] In short, GFR was calculated as (urine inulin concentration x urine flow) / plasma concentration of inulin. ERPF was calculated as (urine concentration of PAH x urine flow) / plasma concentration of PAH.[14,15] Effective renal blood flow (ERBF) was calculated as ERPF/(1 − hematocrit), filtration fraction (FF) as GFR/ERPF, and effective renal vascular resistance (ERVR) as MAP/ERBF. BSA was estimated using the Mosteller formula.

2.6 | Biochemical measurements

Blood determinations were performed using conventional assay methods by the Department of Clinical Chemistry in the VUmc as described.[14] Heparin-plasma and urine samples were used to assess inulin and PAH by colorimetric assay after preparation with p-dimethylamino-benzaldehyde for inulin and trichloroacetic acid and indole-3-acetic acid for PAH.[14]

2.7 | Statistical analyses

Data are presented as mean ±standard deviation, median [interquartile range] or as numbers with percentages. Correlations between baseline characteristics, capillary density and renal parameters were first assessed using the non-parametric Spearman correlation coefficient (given that most variables had a non-Gaussian distribution). Since we on forehand expected body composition to be associated with both capillary and renal measurements,[17,18] both BSA and BMI were included in these correlation analyses. Because of the hypothesis-generating nature of this study a Bonferroni correction was not performed in order to reduce the risk of type 2 errors. Subsequently, linear regression models were designed with renal measurements as dependent variable and capillary measurements as independent variables. Effect modification was assessed for sex and use of RAAS blockers by adding several interaction variables to this model, a p-value ≤0.1 for interaction terms was considered statistically significant. Three multivariate linear regression models were used to assess covariate-adjusted relations, between renal hemodynamic function parameters and baseline capillary density, peak capillary density, and hyperemia (peak capillary density corrected for baseline capillary density), while correcting for sex, age, BMI, fasting blood glucose levels, and diabetes duration. As a calculated % of hyperemia was too inconsistent (CV%: 46), hyperemia was operationalized in the regression model as the peak capillaries corrected for the baseline capillaries. Analyses were performed using SPSS version 26 and a two-sided p-value ≤0.05 was considered statistically significant.

3 | RESULTS

3.1 | Population characteristics

Baseline characteristics of the participants are shown in Table 1. A total of 81 T2D patients were included in this analysis. In general, participants were male (78%), overweight, with well-controlled

diabetes and normal kidney function (average mGFR 108 ml/min), although some individuals had micro-albuminuria. The majority of participants was treated with a RAAS inhibitor. Additional kidney hemodynamic parameters are summarized in Table 1.

3.2 | Associations between baseline characteristics and capillary density

The mean capillary density at baseline was 44.7 capillaries/mm^2 and mean peak capillary density was 57 capillaries/mm^2. Table 2 shows the associations between baseline characteristics and capillary density, where BMI was negatively associated with baseline capillary density. Regarding associations between baseline characteristics and kidney hemodynamic function, age, and female sex were associated with lower GFR and ERBF, while age was positively associated with ERVR. Fasting glucose levels were positively associated with GFR and ERBF. Diabetes duration was associated with FF. While both BSA and BMI were positively associated with GFR and ERBF, and negatively with ERVR, only BMI was negatively associated with baseline capillary density. HbA1c and urinary albumin-to-creatinine ratio (UACR) and use of RAAS inhibitors showed no significant associations with baseline or peak capillary density or any of the renal hemodynamic function parameters. Thus in variable analysis, BMI, age, sex, and diabetes duration were chosen as independent variables.

TABLE 1 Baseline characteristics of the included 81 adults with type 2 diabetes

Male sex, *n* (%)	63 (77.8)
Age, years	62.1 ± 7.6
Body mass index, kg/m^2	31.7 ± 4.1
Current smoker, *n* (%)	16 (19.8)
Diabetes duration, years	7.8 ± 5.2
HbA_{1c}, %	7.3 ± 0.7
HbA_{1c}, mmol/mol	56.2 ± 7.2
Fasting plasma glucose, mmol/L	8 (7.25–9)
Urine albumin/creatinine (mg/mmol)	0.93 (0.45–2.82)
Systemic hemodynamic parameters	
Systolic blood pressure, mm Hg	135.9 ± 14.4
Diastolic blood pressure, mm Hg	78.1 ± 7.4
Mean arterial pressure, mm Hg	98.5 ± 9.2
Heart rate, bpm	65.6 ± 8.6
Medication	
Metformin use, *n* (%)	78 (96.3)
Antihypertensives, *n* (%)	52 (64.2)
RAAS inhibitor use, *n* (%)	49 (60.5)
Microvascular measurements	
Baseline capillary density, n/mm^2	44.7 ± 10.0
Peak capillary density, n/mm^2	57.0 ± 11.3
Renal hemodynamics	
GFR, ml/min	108.2 ± 19.5
ERPF, ml/min	571 ± 127
ERBF, ml/min	985 ± 234
ERVR, mm Hg/L/min	0.109 ± 0.028
FF, %	19 ± 2.2

Note: Data are shown as percentage (%), mean±SD, or median (interquartile range).

Abbreviations: ERBF, effective renal blood flow; ERPF, effective renal plasma flow; ERVR, effective renal vascular resistance; FF, filtration fraction; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; RAAS, renin-angiotensin-aldosterone system.

3.3 | Relations between capillary density and renal hemodynamics in multivariable analyses

We next assessed relations between capillary density and renal hemodynamic function (Table 3). No significant associations were found between baseline capillary density and renal hemodynamic function. Peak capillary density was positively associated with mGFR.

(β = 0.244; p = .022) and ERBF (β = 0.203; p = .020)), while it was negatively associated with ERVR (β = −0.196; p = .027). Capillary hyperemia (peak capillary density corrected for baseline capillary density) showed a trend toward a statistically significant association with mGFR (β = 0.391; p = .053) in the covariate-adjusted model. Effect modification by sex or use of RAAS blockers was not observed (Appendix S1). Finally, a sensitivity analysis was conducted to assess differences between the three different study protocols (SAFEGUARD, RENALIS, and RED) by including the study protocol in the statistical model. This analysis showed no influence of the different protocols on the observed associations.

4 | DISCUSSION

This is the first study to investigate the relation between microvascular function, assessed by skinfold capillary videomicroscopy, and gold-standard measured renal hemodynamic function in adults with type 2 diabetes. After correcting for confounders (including BMI, age, sex, glucose levels and duration of T2D), we observed a positive relation between peak capillary density and mGFR and renal perfusion and a positive trend between hyperemia and mGFR. Peak capillary density was negatively associated with renal vascular resistance. These findings may strengthen the hypothesis that microvascular dysfunction contributes to impaired renal function by contributing to renal hemodynamic dysfunction.

We used capillary videomicroscopy to quantitatively measure constantly perfused capillaries during the baseline measurements. In addition, we performed functional post occlusion measurements. The magnitude of capillary recruitment that occurs after arterial occlusion provides information on both anatomical (maximum number of capillaries) as well as functional (reflects capillary recruitment)

TABLE 2 Associations between selected baseline characteristics and baseline and peak capillary density

Variables	Baseline capillary density	Peak capillary density	GFR	ERBF	ERVR	FF
Age	0.018	0.036	**−0.425****	**−0.505****	**0.533****	0.202
Sex	−0.043	−0.057	**−0.334****	**−0.267***	0.208	−0.023
Diabetes duration	0.026	0.023	−0.027	−0.163	0.142	**0.245***
Mean arterial pressure	0.072	0.011	−0.043	−0.046	**0.294****	0.028
Body mass index	**−0.265***	−0.209	**0.246***	**0.324****	**−0.323****	−0.187
Body surface area	−0.051	−0.047	**0.558****	**0.532****	**−0.515****	−0.105
HbA1c	0.146	0.138	0.095	0.134	−0.079	−0.122
Fasting plasma glucose	0.043	0.013	**0.275***	**0.254***	−0.149	−0.135
Urine ACR	−0.194	−0.089	0.183	0.043	−0.032	0.056
Use of RAAS inhibitors	−0.169	−0.135	0.076	0.048	−0.146	−0.057

Note: Data show Spearman correlation coefficient *r*; the *p*-value is indicated with an asterisk (*$p < 0.05$, **$p < 0.01$) when statistically significant. The non-parametric Spearman was chosen because of the non-Gaussian distribution of the capillary measurements, GFR, age, T2DM duration, and urine ACR, and the dichotomous variable 'sex'.

Abbreviations: ACR, albumin/creatinine ratio; HbA1c, glycated hemoglobin; RAAS, Renin-Angiotensin-Aldosterone System.

TABLE 3 Multivariate associations between GFR, ERBF, ERVR, and FF and baseline and peak capillary density and hyperemia (peak capillary density corrected for baseline capillary density)

Baseline capillary density	GFR (ml/min)	ERBF (ml/min)	ERVR (mm Hg/L/min)	FF
Model 1: Baseline capillary density	0.133 [$p = .236$]	0.138 [$p = .219$]	−0.099 [$p = .381$]	0.022 [$p = .845$]
Model 2: Model 1 + BMI, sex, age, diabetes duration, glucose	0.155 [$p = .122$]	***0.172 [p = .055]***	−0.139 [$p = .124$]	0.003 [$p = .979$]
Peak capillary density				
Model 3: Peak capillary density	0.183 [$p = .102$]	0.146 [$p = .194$]	−0.131 [$p = .245$]	0.091 [$p = .418$]
Model 4: Model 3 + BMI, sex, age, diabetes duration, glucose	***0.224 [p = .022]***	***0.203 [p = .020]***	***−0.196 [p = .027]***	0.047 [$p = .656$]
Hyperemia				
Model 5: Peak corrected for baseline capillary density	0.401 [$p = .218$]	0.107 [$p = .648$]	−0.192 [$p = .416$]	0.313 [$p = .184$]
Model 6: Model 5 + BMI, sex, age, diabetes duration, glucose	***0.391 [p = .053]***	0.239 [$p = .187$]	***−0.326 [p = .075]***	0.195 [$p = .381$]

Note: The independent variables were GFR (ml/min), ERBF (ml/min), ERVR (mm Hg/L/min) and FF. Data shown are standardized coefficients (β) and [*p*-value].

Statistically significant associations are in bold and italic.

properties.[19] This is reflected as well in the small differences between the models in our analysis for the peak capillary density (models 3,4) and hyperemia (models 5,6). However, we think that due to statistical limitations, such as reduced power (due to an extra variable included in the model), and increased measurement error (by including two capillary density measurements), the statistics seem somewhat weaker for hyperemia. Therefore, we hypothesize that the current relation between peak capillary density and hyperemia with renal parameters represents an association with the total anatomical amount of skin capillaries and represents an association with endothelial function.

The (micro)vascular endothelium lines the entire vascular tree. It has become clear that these cells do not merely form a passive barrier, but have unique functions that are important for vascular biology.[20] Diabetes-associated endothelial dysfunction has been put forward as a driver of DKD through several mechanisms.

Endothelial cells are crucial regulators of vascular tone Endothelial dysfunction has been linked to impairments in skeletal

muscle perfusion and a role for impaired insulin signaling has been postulated. While insulin normally causes vasodilation through increased NO secretion, it may also induce vasoconstriction by stimulating endothelin-1 expression in people with obesity and diabetes.[21] Altered concentrations of other circulating metabolites and hormones, may also contribute to overall microvascular constriction in people with diabetes.[21] endothelial cells are also involved in renal autoregulation as similar endothelial-derived factors crucially contribute to the regulation of renal perfusion and glomerular pressure.[3] Given the role of renal hemodynamic dysfunction in DKD, the link we found between endothelial and renal hemodynamic function expands on this pathway and is of importance. Other mechanisms by which dysfunctional endothelial cells may contribute to DKD include 1) reduction of barrier function barrier function to protein filtration, which contributes to leakage of albumin into urine, damaging the kidney; 2) increased low-grade inflammation through secretion of endothelial-derived cytokines in the kidney [22]; 3) impaired angiogenesis leading to nephron-loss and kidney hypoxia.[6,7,23] However, these topics were beyond the scope of current study. Interestingly, using the same technique as in present study, skin capillary recruitment during post-occlusive peak reactive hyperemia, increased the risk for albuminuria.[11]

We observe a positive relation between peak capillary density and mGFR and a trend for hyperemia and mGFR. In contrast, ERVR was associated with lower peak capillary nailfold density, indicating systemic microvascular constriction, including the renal circulation. This constricted state hampers adequate renal perfusion and may put the kidney at risk for hypoxia.

Our study has a number of strengths and weaknesses. Strengths include gold-standard quantification of renal hemodynamic function using inulin and PAH in a relatively large group of individuals that were extensively phenotyped. Second, nailfold video capillaroscopy was used and validated for microvascular assessment in many studies including people with obesity and T2D [8,17] in the past. Some limitations of this study are also worth mentioning. We describe associations between renal hemodynamic and microvascular function and therefore causality cannot be assessed. Our group was quite homogenous with respect to ethnicity and only included T2D patients on oral glucose-lowering therapy. This makes extrapolation to other populations limited. Also, we obtained an indirect measurement of endothelial function in the skin. It would be interesting to see whether other markers of endothelial function (e.g. flow-mediated dilation) yield similar results. Finally, we did not measure potential endothelial-derived metabolites or hormones that could link endothelial function to impaired renal hemodynamic function, such as NO metabolites.

4.1 | Perspective

Our findings indicate that lower capillary density as measure for microvascular dysfunction in overweight/obese adults with T2D is associated with lower mGFR, and with higher ERVR. The observed increase in ERVR may contribute to glomerular dysfunction due to impaired renal perfusion and could put the kidneys at risk for hypoxia. Confirmatory, hypothesis testing studies are now required to corroborate this hypothesis.

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CONFLICT OF INTEREST

No relevant conflicts related to the present manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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