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Relationships between electrochemical skin conductance and kidney disease in Type 2 diabetes☆,☆☆

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ABSTRACT

Background: SUDOSCAN® non-invasively measures peripheral small fiber and autonomic nerve activity using electrochemical skin conductance. Since neuropathy and nephropathy are microvascular Type 2 diabetes (T2D) complications, relationships between skin conductance, estimated glomerular filtration rate (eGFR), and urine albumin:creatinine ratio (UACR) were assessed.
Methods: Two hundred five African Americans (AA) with T2D, 93 AA non-diabetic controls, 185 European Americans (EA) with T2D, and 73 EA non-diabetic controls were evaluated. Linear models were fitted stratified by population ancestry and T2D, adjusted for covariates.
Results: Relative to EA, AA had lower skin conductance (T2D cases $p < 0.0001$; controls $p < 0.0001$). Skin conductance was also lower in T2D cases vs. controls in each population ($p < 0.0001$, AA and EA). Global skin conductance was significantly associated with eGFR in AA and EA with T2D; adjusting for age, gender, BMI, and HbA1c, positive association was detected between skin conductance and eGFR in AA T2D cases (parameter estimate 3.38, standard error 1.2; $p = 5.2E^{-3}$), without association in EA T2D cases ($p = 0.22$).
Conclusions: Noninvasive measurement of skin conductance strongly associated with eGFR in AA with T2D, replicating results in Hong Kong Chinese. SUDOSCAN® may prove useful as a low cost, non-invasive screening tool to detect undiagnosed diabetic kidney disease in populations of African ancestry.

1. Introduction

There is an urgent need to develop low cost, non-invasive screening tools to identify patients with diabetic kidney disease (DKD), particularly those residing in poor and developing nations. Rates of Type 2 diabetes (T2D) are rapidly increasing and strict blood pressure control and use of renin-angiotensin system (RAS) blocking agents slow DKD progression and reduce cardiovascular disease (CVD) mortality in patients with DKD (Brenner et al., 2001). As such, early diagnosis of DKD remains critical.

Patients with DKD often have additional co-existing diabetes-related microvascular complications, including retinopathy and neuropathy. SUDOSCAN® (Impeto Medical, Paris France) is a patented device that non-invasively measures sweat gland dysfunction employing electrochemical skin conductance (reverse iontophoresis and chronoamperometry) and is useful for assessing peripheral small fiber and autonomic nerve function and cardiovascular autonomic neuropathy (Calvet, Dupin, Winiecki, & Schwarz, 2013; Gin, Baudoin, Raffaitin, Rigalleau, & Gonzalez, 2011; Yajnik, Kantikar, Pande, & Deslypere, 2012; Yajnik et al., 2013). To date, SUDOSCAN® measures of skin conductance have not been reported in populations of African ancestry, nor have relationships been assessed with kidney function and proteinuria in European Americans (EA) or African Americans (AA) with T2D.

This report evaluated SUDOSCAN® measures of skin conductance in AA and EA, with and without T2D. Cross-sectional relationships between skin conductance, estimated glomerular filtration rate (eGFR), and urine albumin:creatinine ratio (UACR) were assessed.

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2. Methods

2.1. Patient Populations

Participants with T2D were recruited from unrelated African American-Diabetes Heart Study (AA-DHS) and EA Diabetes Heart Study (DHS) participants at the Wake Forest School of Medicine (WFSM) (Bowden et al., 2010; Divers et al., 2013). Participants in both studies denied having end-stage kidney disease (renal replacement therapy or prior kidney transplant). In an attempt to exclude subjects with Type 1 diabetes, T2D was diagnosed in patients whose disease onset began after 25 years of age if AA or 30 years of age if EA, without history of diabetic ketoacidosis or treatment with insulin alone for more than one year after initial diagnosis. All cases with T2D were actively receiving blood sugar lowering medications, oral agents and/or insulin. Those treated with diet-alone were excluded.

Unrelated AA and EA non-diabetic controls were recruited from employees, patients, and patient relatives treated at Wake Forest Baptist Medical Center. Hemoglobin (Hb) A1c values were <6.5% in controls and all denied taking blood sugar lowering medication or knowledge of diabetes. Population ancestry was self-reported in all cases and controls. Ancestry proportion estimates were also available in AA T2D cases. All cases and controls provided written informed consent and this study was approved by the Institutional Review Board at the WFSM.

Serum electrolytes, blood urea nitrogen, creatinine (kinetic Jaffe method), HbA1c (high pressure liquid chromatography method), urine albumin, and urine creatinine were measured on the day of the visit in all participants (LabCorp; Burlington, NC). The 4-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR.

2.2. Measurement of SUDOSCAN® scores

SUDOSCAN® skin conductance was measured during the study visit as an assessment of sweat gland dysfunction (Khalfallah et al., 2010). All subjects were tested in a temperature controlled room in the Wake Forest Clinical Research Unit under identical conditions and ambient temperature. In brief, electrochemical skin conductance was measured through reverse iontophoresis (extraction of chloride ions from the abundant sweat glands on palms and soles) and chronoamperometry. After cleaning both palms and soles with a moist towel, they were placed on two large-area stainless steel electrodes that had been disinfected with Surfa'Safe® (Laboratoires Anios; Lille-Hemmes, France). Subjects were asked to remain still for the approximate 2 minute test period. Electrodes were connected to a computer that recorded time/ampere curves as gentle stimulation was applied in a graded fashion via low voltage direct current (<4 volts) on the anode, generating a voltage through reverse iontophoresis on the cathode proportional to the flow of sweat gland chloride ions. The skin conductance, i.e., the ratio between current generated and the constant voltage applied, was measured (microsiemens, μS) between anode and cathode. Values were computed for skin conductance in each palm and each sole, and as a measure of asymmetry between the two hands and the two feet. Mean global skin conductance was computed as 0.5*(reflecting [right + left hand]/2 + [right and left foot]/2) in each participant and used in the main analysis. Relationships between SUDOSCAN® cardiac neuropathy complication risk score, based on conductance values and demographic data, and renal parameters were also evaluated.

2.3. Statistical analyses

Descriptive summary statistics were computed separately by T2D status and race/ethnicity. Unadjusted comparisons of the distribution of observed conductance and other demographics variables were performed between race/ethnicity by T2D status, and between T2D affected and unaffected individuals after stratifying by race/ethnicity. These comparisons were based upon the Wilcoxon two-sample test, a non-parametric test known to be robust to deviations from the normality assumption.

Generalized linear models (GLM) were fitted to test for associations between global skin conductance and kidney function measures (McCullagh & Nelder, 1989). MDRD eGFR values above 120 ml/min per 1.73 m^2 were winsorized at 120 (Hastings, Mosteller, Tukey, & Winsor, 1947). The Box-Cox method was applied to identify the appropriate transformation best approximating the distributional assumptions of conditional normality and homogeneity of variance of the residuals (Box & Cox, 1964). These methods suggested taking the logarithm of UACR. MDRD eGFR was raised to the power 1.5 and served as the outcome in the fitted models. We ran an unadjusted model to test for association between UACR and MDRD eGFR followed by adjusted models that successively included age, gender, HbA1c and body mass index (BMI) as covariates. Analyses were run stratified by race/ethnicity and by T2D status to protect against the potential confounding effect of diabetes and race/ethnicity.

3. Results

Study visits were performed between February 14, 2012, and March 29, 2013. Table 1 contains demographic data in the 390 cases with T2D (205 AA; 185 EA) and the 166 non-nephropathy controls (93 AA; 73 EA), by population ancestry. AAs with T2D were younger than EA with T2D; however, diabetes duration, gender distribution,

Table 1
Demographics and lab characteristics of the study sample, by race/ethnicity and Type 2 diabetes status.

Variable	Cases with Type 2 diabetes							Non-diabetic controls						
	African American (N = 205)			European American (N = 185)			p value	African American (N = 93)			European American (N = 73)			p value
	Mean	Median	SD	Mean	Median	SD		Mean	Median	SD	Mean	Median	SD	
Age (years)	59.84	60.39	9.62	62.9	63.59	11.00	0.0054	44.4	46	11.62	45.28	47	13.84	0.4265
Female (%)	50.00%			45.00%			0.391	55.00%			53.00%			0.8564
BMI (kg/m^2)	50.17	34.01	213.5	34.03	33.52	6.44	0.6662	31.01	30.48	7.05	27.29	25.23	6.38	0.0006
Diabetes duration (years)	14.44	12.24	8.81	14.01	11.78	9.15	0.1624	NA			NA			
HbA1c (%)	7.85	7.40	1.8	7.67	7.3	1.59	0.4309	5.79	5.7	0.72	5.46	5.5	0.29	<.0001
Serum creatinine (mg/dl)	1.03	0.98	0.35	0.93	0.87	0.32	0.0002	0.88	0.85	0.19	0.88	0.86	0.16	0.7655
MDRD eGFR <60 (%)	9.00%			16.00%			0.039	0.00%			1.00%			0.259
MDRD eGFR (ml/min per 1.73 m^2)	87.95	87.97	20.65	82.7	83.46	22.56	0.023	104.7	107.2	14.6	88.98	88.82	16.09	<.0001
UACR >30 (%)	34.00%			34.00%			0.9938	4.00%			3.00%			0.5938
UACR (mg/g)	184.7	10.11	631.3	100.9	10.98	350.4	0.9369	7.34	3.29	11.85	21	3.35	127.3	0.548

SD, standard deviation; BMI, body mass index; HbA1c, hemoglobin A1c; MDRD, Modification of Diet in Renal Disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio.