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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—205 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—Non-invasive measurement of skin conductance strongly associated with eGFR in AA with T2D, replicating results in Hong Kong Chinese. SUDOSCAN® may prove useful as a

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low cost, non-invasive screening tool to detect undiagnosed diabetic kidney disease in populations of African ancestry.

Keywords

African Americans; diabetes; kidney disease; neuropathy; skin conductance

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.(Gin et al 2011; Yajnik et al 2012; Calvet et al 2013; 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.

Methods

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.

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.

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 and Nelder 1989) MDRD eGFR values above 120 ml/min/1.73 m^2 were winsorized at 120.(Hastings et al 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 and 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.

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, HbA1c, and UACR were similar. AA cases also had slightly higher eGFR than EA cases (p=0.023); 9% of AA and 16% of EA cases had an eGFR <60 ml/min/1.73 m^2 (p=0.039). Among controls, mean (SD) median HbA1c values were 5.79 (0.72) 5.7% in AA and 5.46 (0.29) 5.5% in EA (p<0.0001); all were below 6.5% although results likely reflect insulin resistance/metabolic syndrome in some controls. AA are known to have a slightly higher HbA1c relative to EA, given similar ambient serum glucose concentrations.(Kamps et al 2010) Non-diabetic controls in each race/ethnic group had similar age and gender distributions; UACR and percentage eGFR <60 ml/min/1.73 m^2 were also similar, although AA controls had a higher mean eGFR relative to EA controls (p<0.0001). The high mean BMI in AA with T2D reflected a small number of morbidly obese individuals; the median value is more representative. Blood pressure (BP) and anti-hypertensive medications were recorded in cases with T2D, not in controls. Among AAs and EAs with T2D, 76.9% and 83.8%, respectfully, had hypertension defined by clinical diagnosis, use of anti-hypertensive medications, or BP >140/90 mmHg. The mean (SD) systolic and diastolic BP in AAs with T2D were 130.6 (17.4) and 76.7 (11.7) mm/Hg, respectively, and 125.9 (16.5) and 73.9 (9.9) mmHg in EAs with T2D. Use of diuretics was reported by 33.2% of AA cases and 14.6% of EA cases; angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker use was reported by 46.7% of AA cases and 30.8% of EA cases.

SUDOSCAN® skin conductance measures in hands and feet were markedly lower in cases with T2D, relative to non-diabetic controls in each population ancestry (Table 2). Further, AA had significantly lower skin conductance relative to EA, when comparing AA cases with T2D to EA cases with T2D, or AA non-diabetic controls to EA non-diabetic controls.

Tables 3 and 4 display the results of analyses assessing cross-sectional relationships between eGFR and UACR, respectively, with SUDOSCAN® global skin conductance (global score reflects mean of [hands and feet]). An unadjusted analysis in AA cases revealed a significant positive association between global skin conductance and eGFR (parameter estimate (β)=3.42, standard error (SE)=1.2; $p=4.9E^{-3}$). This relationship persisted in the fully adjusted model that accounted for age, gender, BMI, and HbA1c (β=3.38, SE=1.2; $p=5.2E^{-3}$). The unadjusted analysis revealed a positive association between global skin conductance and eGFR in EA cases with T2D (β=3.3, SE=1.55; p=0.03) and EA controls; however, the effect was no longer significant in the fully adjusted model (p=0.22 in cases and p=0.39 in controls).

No evidence of association was observed between global skin conductance and UACR in cases of either race/ethnicity (Table 4). Additional analyses comparing skin conductance in AA and EA cases with T2D based on discrete categories of UACR (<30, 30–299, >300 mg/g) did not detect significant differences based on category of UACR (data not shown). Asymmetry of skin conductance in hands and feet, which may suggest a confounding etiology for abnormal skin conductance, was low and not associated with eGFR or UACR in either population of cases with T2D.

Table 5 contains results of association analyses between the cardiac neuropathy complication risk score and eGFR (cardiac neuropathy complication risk scores are investigational measures). In unadjusted analyses, this risk score negatively associated with eGFR in AA and EA cases with T2D ($p=5.2E^{-5}$ and $4.3E^{-5}$, respectively) and in EA non-diabetic controls ($p=6.6E^{-3}$). A trend was observed in AA non-diabetic controls (p=0.09). After adjusting for age, gender, BMI and HbA1c, the relationship was no longer significant in any group, although a trend persisted in AA cases with T2D (β=-4.77, SE=2.7, p=0.08).

The observation that AA had lower hand, feet, and global skin conductance relative to EA (with and without T2D) suggested that African ancestry may independently be associated with skin conductance readings, independent of peripheral nerve or autonomic nerve function. AAs are an admixed population group with approximately 80% African and 20% European ancestry. We examined the percentage of African ancestry based on a genome-wide association study that was performed on the Illumina 5M platform in AA-DHS participants to see if it correlated with skin conductance and explained population ancestry-based differences in these measurements. Although this analysis may have been underpowered, higher percentage of overall African ancestry was not associated with measured skin conductance; the correlation between African ancestry and global skin conductance in AA with T2D was 0.003, p=0.96.

Discussion

This is the first comparison of SUDOSCAN® skin conductance measures in AA and EA, including participants with and without T2D evaluated for presence of kidney disease. This electrochemical measure of global skin conductance was positively associated with kidney function in AA with T2D. Similar observations have been reported in Chinese study subjects with T2D residing in Hong Kong.(Ozaki et al 2011) Although a significant relationship was not observed between skin conductance and eGFR in EA with T2D in the fully adjusted model (p=0.22), significant association was observed in the unadjusted model and the direction of effect was consistent with that in AA. It also appears that biologically mediated differences exist in skin conductance between populations of African and European ancestry. Given the burgeoning worldwide epidemic of T2D with associated rapidly rising healthcare costs, non-invasive, rapid and inexpensive screening tools to detect early diabetic kidney disease are urgently needed, particularly in developing countries. Based on the results reported in Asian and African populations, electrochemical skin conductance may prove to be useful in this setting. As opposed to estimating GFR on blood samples and measuring UACR, non-invasive skin conductance testing results are immediately available and at far lower cost.

Ozaki et al.(Ozaki et al 2011) compared a related tool that measures skin conductance with kidney function and proteinuria in 100 Hong Kong Chinese patients with T2D. In contrast to the current study, they pre-selected 50 subjects with fairly advanced DKD and 50 with T2D lacking nephropathy. Mean eGFR and UACR in their cases were 37 ml/min/1.73 m^2 and 127.1 mg/mmol, respectively; while controls had mean eGFR 104 ml/min/1.73 m^2 and UACR 0.7 mg/mmol. This provided a dramatic contrast between study groups and allowed for the demonstration that skin conductance scores below 55 appeared to reliably predict DKD. In contrast, our EA and AA cases with T2D had higher eGFR and lower UACR (AA cases had UACR 21.1 mg/mmol and EA cases had 11.9 mg/mmol). The robust association observed between skin conductance and eGFR in AA suggests true association, as unselected AA-DHS participants were enrolled regardless of their eGFR (or UACR) and association was detectable in those with milder reductions in eGFR relative to the Hong Kong report. Additional AA and EA cases with T2D and more marked renal impairment (lower eGFR) will be required to perform a sensitivity analysis to determine a cut-off SUDOSCAN® value where screening for DKD might be advisable.

Markedly different skin conductance was observed between individuals of African and European ancestry, a finding of clinical and research importance. The effect was seen in non-diabetic controls and cases with T2D, suggesting physiologically different skin barrier function, sweat gland number, and/or pattern of innervation between populations.(Darlenski and Fluhr 2012) AA have higher skin electrical resistance than EA, reflecting increased thickness and/or adhesion of the stratum corneum (SC).(Johnson and Corah 1963) Relative

to EA, AA have higher overall lipid content in the SC,(Reinertson and Wheatley 1959) with lower ceramide concentrations.(Corcuff et al 1991) It is thought that the lower ceramide concentrations may explain higher rates of trans-epidermal water loss in the skin of African ancestry populations.(Wilson et al 1988) Finally, race/ethnicity may influence skin surface pH. After application of tape strips, skin pH falls to a greater extent in individuals of African ancestry, relative to European.(Berardesca et al 1998) Differences in sebaceous and sweat gland activity could play a role; however, this remains unknown.(Darlenski and Fluhr 2012)

There are limitations to this report. As opposed to the Hong Kong report, our participants had less advanced DKD with higher eGFR and lower UACR. This may explain the lack of an association between skin conductance and albuminuria in adjusted analyses. The association between skin conductance and eGFR in AA and Chinese subjects with T2D supports a true relationship. In addition, the consistent direction of association with eGFR in EA with T2D from this report is reassuring and a larger sample size may have demonstrated association in those of European ancestry. Nonetheless, it remains possible that an unmeasured confounding factor could potentially explain association between skin conductance and eGFR. It is also unknown whether skin conductance reflects T2D-associated or CKD-associated neuropathy, not kidney function *per se*. Adjustment for HbA1c and age (which is strongly correlated with diabetes duration) minimizes the likelihood that this was the case. However, invasive peripheral nerve conduction studies would be required to definitively resolve this question. We lack blood pressure and medication use in non-diabetic controls; as such we were unable to adjust for their effects.

This is the first report of SUDOSCAN® skin conductance measures in an African ancestry population, and the largest assessing association between measures of DKD with skin conductance. As in an Asian study, skin conductance was positively associated with eGFR in subjects with T2D. In contrast, relationships were not observed with UACR or eGFR in a European ancestry population. Future analyses will assess SUDOSCAN® skin conductance in AA and EA with more severe DKD. This may provide skin conductance values where screening for the presence of clinically significant reductions in eGFR would be recommended. Non-invasively measuring skin conductance offers hope for a low cost and portable screening test to detect DKD in populations of African and Asian ancestry.

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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						
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/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

Table 2

Distribution of conductance measures by race/ethnicity and type 2 diabetes status

SUDOSCAN® Variable	Cases with type 2 diabetes							Non-diabetic controls							Effect of Diabetes	
	African American (N=205)			European American (N=185)			P-value	African American (N=93)			European American (N=73)			P-value	P-value in AA	P-value in EA
	Mean	Med	SD	Mean	Med	SD		Mean	Med	SD	Mean	Med	SD			
Global conductance(defined as mean of hands + feet; μS)	55.05	57.5	16.34	65.51	68	14.21	<.0001	64.64	66.5	12.45	75.91	77	8.05	<.0001	0.0006	<.0001
Average Feet Conductance (μS)	62.74	70	18.91	71.69	76	15.07	<.0001	70.88	74	12.86	80.16	82	7.45	<.0001	0.0006	<.0001
Average hand Conductance (μS)	47.36	49	16.43	59.32	61	16.73	<.0001	58.4	60	15.12	71.66	72	11.41	<.0001	<.0001	<.0001
Feet Asymmetry Ratio	6.85	4	7.72	5.97	3	9.6	0.0142	4.62	3	6.31	2.42	2	2.25	0.0107	0.0065	0.0055
Average left foot conductance (μS)	63.2	70	19.27	71.78	77	15.32	<.0001	70.45	74	13.48	80.25	82	7.76	<.0001	0.0052	<.0001
Average right foot conductance (μS)	62.78	69	18.99	71.94	77	15.84	<.0001	71.85	76	12.66	80.67	83	7.31	<.0001	<.0001	<.0001
Hand Asymmetry Ratio	11.58	8	10.76	7.83	5	8.72	<.0001	6.69	5	6.23	4.64	3	4.98	0.0598	<.0001	0.0035
Average left hand conductance (μS)	48.9	49	16.81	60.41	63	17.15	<.0001	59.85	63	15.36	72.63	74	11.44	<.0001	<.0001	<.0001
Average right hand conductance (μS)	46.32	48	16.73	58.72	60	16.92	<.0001	57.42	58	15.28	71.18	72	11.77	<.0001	<.0001	<.0001
Cardiac neuropathy complication risk score (%)	45.17	45	13.48	44.62	44	13.03	0.6853	26.85	26	14.75	19.1	20	14.79	0.001	<.0001	<.0001

SD –standard deviation; Med – median; AA – African Americans; EA – European Americans

Table 3

Association between MDRD eGFR and average skin conductance

Adjustment	Race / Ethnicity	T2D status	Estimate	SE	P-value
None	AA	Control	−2.22	1.82	0.23
None	***AA***	***Case***	***3.42***	***1.20***	***4.9E-03***
None	EA	Control	7.04	3.20	0.03
None	EA	Case	3.31	1.55	0.03
Age and gender	AA	Control	−1.73	1.76	0.33
Age and gender	***AA***	***Case***	***3.10***	***1.20***	***0.01***
Age and gender	EA	Control	3.64	3.15	0.25
Age and gender	EA	Case	1.66	1.50	0.27
Age, gender and BMI	AA	Control	−1.68	1.78	0.35
Age, gender and BMI	***AA***	***Case***	***3.21***	***1.19***	***7.7E-03***
Age, gender and BMI	EA	Control	3.66	3.17	0.25
Age, gender and BMI	EA	Case	1.83	1.50	0.22
Age, gender, BMI and HbA1c	AA	Control	−1.70	1.79	0.34
Age, gender, BMI and HbA1c	***AA***	***Case***	***3.38***	***1.20***	***5.2E-03***
Age, gender, BMI and HbA1c	EA	Control	2.78	3.18	0.39
Age, gender, BMI and HbA1c	EA	Case	1.84	1.51	0.22

T2D – type 2 diabetes; SE – standard error; AA – African American; EA – European American; BMI – body mass index; HbA1c – hemoglobin A1c

Table 4

Association between urine albumin:creatinine ratio and average skin conductance

Adjustment	Race / Ethnicity	T2D status	Estimate	SE	P-value
None	AA	Control	0.10	0.10	0.34
None	AA	Case	−1.86	2.74	0.50
None	EA	Control	2.50	1.85	0.18
None	EA	Case	0.89	1.83	0.63
Age and gender	AA	Control	0.10	0.10	0.30
Age and gender	AA	Case	−2.01	2.84	0.48
Age and gender	EA	Control	3.37	1.96	0.09
Age and gender	EA	Case	0.88	1.85	0.63
Age, gender and BMI	AA	Control	0.11	0.10	0.29
Age, gender and BMI	AA	Case	−2.01	2.85	0.48
Age, gender and BMI	EA	Control	3.32	1.97	0.10
Age, gender and BMI	EA	Case	0.88	1.87	0.64
Age, gender, BMI and HbA1c	AA	Control	0.11	0.10	0.29
Age, gender, BMI and HbA1c	AA	Case	−1.49	2.84	0.60
Age, gender, BMI and HbA1c	EA	Control	3.42	2.01	0.09
Age, gender, BMI and HbA1c	EA	Case	0.96	1.87	0.61

T2D – type 2 diabetes; SE – standard error; AA – African American; EA – European American; BMI – body mass index; HbA1c – hemoglobin A1c

Table 5

Association between MDRD eGFR and cardiac neuropathy complication risk score

Adjustment	Race / Ethnicity	T2D status	Estimate	SE	P-value
None	AA	Control	−2.62	1.52	0.09
None	AA	Case	−5.77	1.43	5.2E-05
None	EA	Control	−4.79	1.71	6.6E-03
None	EA	Case	−6.74	1.65	4.3E-05
Age and gender	AA	Control	0.05	1.87	0.98
Age and gender	AA	Case	−3.90	1.62	0.02
Age and gender	EA	Control	−0.87	2.43	0.72
Age and gender	EA	Case	−2.82	1.92	0.14
Age, gender and BMI	AA	Control	0.98	2.57	0.70
Age, gender and BMI	AA	Case	−4.43	2.69	0.10
Age, gender and BMI	EA	Control	−0.91	4.61	0.84
Age, gender and BMI	EA	Case	−2.28	3.24	0.48
Age, gender, BMI and HbA1c	AA	Control	0.94	2.57	0.71
Age, gender, BMI and HbA1c	AA	Case	−4.77	2.70	0.08
Age, gender, BMI and HbA1c	EA	Control	1.01	4.67	0.83
Age, gender, BMI and HbA1c	EA	Case	−2.29	3.25	0.48

T2D – type 2 diabetes; SE – standard error; AA – African American; EA – European American; BMI – body mass index; HbA1c – hemoglobin A1c