



Original Research Article

Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha (PPARGC1A) Polymorphism Linked With Microalbuminuria in Hypertensive Haitian Americans with Type 2 Diabetes

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ABSTRACT

Aim: To explore the relation of *PPARGC1A* polymorphism with microalbuminuria in hypertensive Haitian American adults with type 2 diabetes (T2D).

Methods: Haitian Americans, ages >30 years, with and without T2D were recruited for a cross-sectional, case-control study using community based sources, and advertisements. Urinary albumin concentrations of 0.18 mg/L were used as a cut off for microalbuminuria (Yes). Real-time PCR amplification was performed using TaqMan allelic discrimination assay for genotyping rs3774907 Single Nucleotide polymorphism (SNP) of *PPARGC1A* gene from whole genome DNA isolated using QIAamp DNA Blood mini. Using SPSS 20, logistic regression analysis assessed the contribution of rs3774907 in microalbuminuria adjusted for age, sex, BMI and smoking status.

Results: The risk for hypertensive Haitian Americans with T2D to have microalbuminuria was much lower with 'C' allele of *PPARGC1A* polymorphism (OR=0.35, $p=0.031$) than common allele 'T' (OR=2.88, $p=0.272$) suggesting protective effect of minor allele for rs3774907 SNP.

Conclusions: Our findings suggest the contribution of rs3774907 in susceptibility of microalbuminuria in hypertensive Haitian Americans with T2D. In future, larger replicative studies in several ethnicities should examine the relationship observed in this study to validate the role of *PPARGC1A* in microalbuminuria.

Keywords: *PPARGC1A*, rs3774907, T2D, microalbuminuria.

INTRODUCTION

Microalbuminuria (MA) defined as urinary albumin excretion greater than normal but lower than 300 mg/day, is associated with cardiovascular risk, irrespective of the diabetes status. [1-3] The prevalence of microalbuminuria varies in different ethnicities, populations of African

origin being at highest risk amongst Caucasians and Polynesians. [4] Additionally, the prevalence of type 2 diabetes (T2D) is also the highest (13.2%) among populations of African origin but no data is available on Haitian Americans exclusively. [5] Several studies have reported microalbuminuria to be a strong predictor of cardiovascular

complications and kidney diseases, particularly in individuals with T2D.^[1,6,7] The high odds of microalbuminuria in Haitian Americans with T2D and poor glycemic control have been reported.^[8] The risk for developing T2D and poor glycemic control increases with elevated urinary albumin excretion. Microalbuminuria is not the causative agent of cardiovascular events but is rather a marker for increased risk.^[9] Several environmental factors have been implicated with the high rates of microalbuminuria, but hypertension and systolic blood pressure (BP) association has been seen across the ethnicities.^[4,10] Hypertension increases glomerular hydrostatic pressure, accelerating urinary albumin excretion and accelerating microalbuminuria.^[11] Elevated glomerular hydrostatic pressure could very well be an indicator of endothelial dysfunction, resulting in leakage of albumin and other macromolecules of blood into the vascular wall, thereby initiating atherosclerosis.^[11] Common genetic markers predisposing one to both high BP and microalbuminuria could also be at play.

Predictive markers for microalbuminuria, including genetic ones, are now being under the close scrutiny of scientific community. Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (*PPARGC1A*) is located on chromosome 4. The protein expressed by this gene, PGC1- α is involved in mitochondrial biogenesis via transcriptional regulation of nuclear respiratory factor (NRF).^[12,13] Vascular endothelial growth factor-1 (VEGF-1) expression is also regulated by PGC-1 α .^[14] In individuals with hypertension, mitochondrial content of endothelial cells is reported to be lower.^[15] PGC1- α expression is also lower in diabetes.^[16] Several epidemiological studies have linked *PPARGC1A* polymorphisms with hypertension, carotid atherosclerosis, and

coronary artery disease, proposing its involvement in development of vascular disease.^[17] The region in which the *PPARGC1A* gene is located, chromosome 4p15.1, has been reported to be linked with high BMI,^[18] microalbuminuria,^[19] hypertension,^[20] and elevated systolic blood pressure^[21] in other studies. The associations observed with other SNPs of *PPARGC1A* gene could in fact be due to effect by any neighboring SNPs. The single nucleotide polymorphism rs3774907 located in intron of chromosome 4 at position 23829862. The C>T base substitution has been explored for its association in non-alcoholic fatty liver^[22] but exploration studies for this SNP with any biomarkers involved with T2D is lacking. Haitians have similar diabetes care and outcomes as African Americans but fewer microvascular or macrovascular complications.^[23] This study was therefore designed to explore the relation of *PPARGC1A* polymorphism with microalbuminuria in hypertensive Haitian American adults with T2D.

MATERIALS AND METHODS

Study population

Participants, ages >30 years, were recruited for a cross-sectional study conducted with Haitian Americans with type 2 diabetes. Recruitment of participants was done using invitational flyers, community-based sources and advertisements. The participants self-reported the presence of type 2 diabetes which was further confirmed with laboratory tests using American Diabetes Association criteria. Individuals were classified as having T2D if fasting plasma glucose concentration was ≥ 126 mg/dl or use of insulin or diabetes medication was reported. Participants were instructed to refrain from smoking, consuming any food or beverages except water, and engaging in any heavy physical activity for at least eight hours prior to their

blood collection. Participants were explained protocol of the study and an informed voluntary consent in English or Creole was obtained prior to the commencement of the study. This study was approved by the Institutional Review Board at Florida International University. Individuals with any other chronic condition, pregnancy or lactation, were not eligible for participation.

Socio-demographics

Validated questionnaire was used to collect information on demographics such as age, gender, and smoking history. Data on T2D status (yes/no), duration of T2D, medication use (for diabetes, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), and family history of T2D was collected using validated questionnaire by trained staff.

Anthropometric measurements and medical assessment

A SECA balance scale was used to measure both height and weight (Seca Corp, US) which were later used to calculate body mass index (BMI) in $\text{kg}/\text{height in m}^2$. Additionally, waist circumference (WC) to the nearest 0.1 cm was measured horizontally with a non-stretchable measuring tape placed midway between the 12th rib and iliac crest at minimal respiration and was used to determine central obesity (male = 102 cm/ female = 88 cm). Blood pressure (BP) measurement was repeated two times using a random zero sphygmomanometer (Tycos 5090-02 Welch Allyn Pocket Aneroid Sphygmomanometer, Arden, NC, USA) and a stethoscope (Littmann Cardiology, 3M, St Paul, MN, USA) in participants after a 15-minute rest while sitting. Presence of hypertension was established if participant had either systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg or they were using antihypertensive agents (AHA).

Blood collection

Twenty ml of venous blood was collected from each participant after an overnight fast (at least 8 hours) by a certified phlebotomist. Glucose levels in serum were quantified using hexokinase methods. Whole blood was used to measure A1C using Roche Tina Quant method (Laboratory Corporation of America, LabCorp, FL). Automatic chemical analyzer was employed to determine high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol (TC) values.

Urinary albumin and Microalbuminuria

Albumin levels in fresh, single-voided, first morning urine samples were quantitated by a semiquantitative assay (ImmunoDip, Diagnostic Chemicals Limited, Oxford, CT, USA) according to validated methods published by Davidson et al ^[24] to assess urinary albumin and microalbuminuria status. The ImmunoDip dipstick fulfilled the requirements from the National Academy of Clinical Biochemistry (NACB) as a screening tool to detect microalbuminuria. In this study, urinary albumin concentrations of 0.18 mg/L were considered as a cut off for microalbuminuria (Yes) according to vendor (ImmunoDip, Diagnostic Chemicals Ltd) which corresponded to albumin: creatinine ratio 0.30 $\mu\text{g}/\text{mg}$ values.

DNA isolation and Real-time TaqMan-based genotyping

Whole blood genomic DNA was isolated and tested for quality using QIAamp DNA Blood mini kit (Qiagen, Hilden, Germany) and 2000c nanodrop spectrophotometer (Thermo Scientific, USA), respectively. Real-time PCR amplification on BioRad CFX96 real time PCR instrument using commercially available TaqMan allelic discrimination assay (Life Technologies Inc, Carlsbad, CA)

was performed for Single Nucleotide Polymorphisms (SNPs).

Quality Control and Internal validity

All biochemical parameters measured in study had <10% of both intra- and inter-assay coefficient of variations (CVs). Both cases and controls were derived from same study base. To ensure reproducibility and reliability of genotyping method, 10% of the DNA samples were duplicated during genotyping.

Statistical analysis

All statistical analyses were performed using SPSS 20 (SPSS, Inc., Chicago, IL, USA). A P-value of <0.05 (two-tailed) was considered statistically significant. The genotype frequencies for rs3774907 SNP was tested for Hardy-Weinberg's equilibrium (HWE). Genetic associations for rs3774907 were assessed using both the dominant (CC+CT vs TT) as well as recessive (TT+CT vs CC) genetic model. These models were employed to detect recessive effects of the rare allele (C) and dominant effects of common allele (T) respectively. Student's t-test and Chi-squared test were used to compare demographic and clinical information between individuals with and without type 2 diabetes, for continuous and categorical variables respectively. Logistic regression was employed to assess the relationship of SNP and hypertension with binary outcome for case-control status (Microalbuminuria= Yes / No) before and after adjusting for potential confounding factors such as age, sex, BMI, and smoking status among Haitian Americans with T2D. The interaction between hypertension and rs3774907 SNP was also included in the model of logistic regression analysis for rs3774907 and hypertension with microalbuminuria in Haitian Americans with type 2 diabetes. Logistic regression analyses was then performed for the likelihood of microalbuminuria by rs3774907 among

hypertensive Haitian Americans with type 2 diabetes only before and after adjusting for confounders (age, sex, BMI and smoking status).

RESULTS

The general characteristics by microalbuminuria status are shown in Table 1. In the present study, genotype call rates for rs3774907 SNP were greater than 95%. The minor allele frequency of C allele was found to be 0.410 in individuals with microalbuminuria as compared to 0.246 in individuals without microalbuminuria (Table 1). The genotype frequencies for TT/CT/CC in individuals with microalbuminuria were 10/26/3 and in without microalbuminuria the frequencies were 39/29/3. Individuals with microalbuminuria had higher proportion of C allele than the individuals without microalbuminuria who had higher proportion of T allele (P=0.013).

No statistical difference in BMI (P=0.482), sex (P=0.231), smoking status (P=0.215), waist circumference (P=0.374) and proportion of individuals with hypertension (P=0.226) was found between individuals with microalbuminuria (cases) and those without microalbuminuria (controls). The levels of triglycerides (P=0.143), total cholesterol (P=0.268), FPG (P=0.262) or LDL-C (P=0.070) were not statistically different between individuals with and without microalbuminuria. However, the microalbuminuria group had higher SBP (P=0.001) and DBP (P=0.026), A1C (P=0.013) and HDL-C (P=0.039).

As shown in Table 2, the logistic regression analysis for rs3774907, shows unadjusted odds ratios indicating that the individuals with T2D and CC and CT genotype were 0.28 times as likely as those with TT genotype for rs3774907 to have microalbuminuria (P=0.004). After controlling for the effect of age, sex, BMI,

smoking status, the Haitian Americans with T2D and CC and CT genotype remained steady at 0.29 times as likely as individuals with T2D and genotype TT to develop microalbuminuria (P=0.006). On the contrary, the individuals with T2D were 1.84 times as likely to have microalbuminuria if they had TT or CT

genotype of rs3774907 compared with those with CC genotype (P=0.47). The risk decreased to OR= 1.71 when adjusted for confounding variables; age, sex, smoking status, BMI (P=0.53). However, the results were not statistically significant for TT+CT model. Hypertension was not significantly associated with microalbuminuria (Table 2).

Table 1. Characteristics of study population by Microalbuminuria status

Variables	With Microalbuminuria (n=39)	Without Microalbuminuria (n=71)	P-value	
Age	59.49±9.62	58.04±10.46	0.478	
Sex, Female	20 (51)	28 (39)	0.231	
BMI (kg/m ²)	29.01±4.79	29.77±5.80	0.482	
Waist circumference (cm)	98.85±12.75	101.01±11.85	0.374	
SBP (mm of Hg)	159.13±26.89	142.25±23.20	0.001	
DBP (mm of Hg)	94.58±13.28	88.75±12.82	0.026	
Smoke, Y	4 (10)	3 (4)	0.215	
Total cholesterol (mg/dl)	195.62±43.04	186.92±36.98	0.268	
Triglycerides (mg/dl)	113.33±60.83	99.00±40.63	0.143	
Log TG	1.99±0.17	1.96±0.18	0.335	
HDL-C	50.46±14.09	56.90±16.15	0.039	
LDL-C	122.44±37.49	110.24±30.97	0.070	
FPG (mmol/L)	176.87±75.40	156.66±98.89	0.262	
A1C (%)	9.28±2.77	7.96±2.56	0.013	
Log A1C	0.94±0.12	0.88±0.12	0.008	
Hypertension, Y	33 (84)	53 (72)	0.226	
rs3774907	TT (%)	10 (25)	39 (55)	0.013
	CT (%)	26 (67)	29 (41)	
	CC (%)	3 (8)	3 (4)	
MAF	C	0.410	0.246	

Note: Data were expressed as mean ± SD for continuous variables or N (%) for categorical variables. BMI= body mass index; WC= waist circumference; Log TG= log transformed triglyceride; FPG= fasting plasma glucose; A1C= hemoglobin A1C; HDL-C=high-density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAF=minor allele frequency.

Table 2. Logistic regression analysis for rs3774907 and hypertension with microalbuminuria in Haitian Americans with type 2 diabetes.

Parameter	Unadjusted OR	95% CI		P-value	Adjusted OR	95% CI		P-value
CC+CT vs TT	0.28	0.12	0.68	0.004	0.29	0.12	0.67	0.006
Hypertension	1.79	0.62	5.17	0.274	1.99	0.63	6.25	0.238
Hypertension *rs3774907	-	-	-	-	3.21	0.23	43.59	0.381
TT+CT vs CC	1.84	0.35	9.71	0.47	1.71	0.32	9.19	0.533
Hypertension	1.85	0.66	5.15	0.237	2.08	0.68	6.33	0.197
Hypertension *rs3774907	-	-	-	-	0.35	0.13	0.93	0.035

Note: Controlled variables included in the logistic regression analysis were age, sex, BMI, smoking status, type 2 diabetes. Hypertension* rs3774907 is the interaction term between the two variables included in the statistical model. CI= confidence interval; OR= odds ratio

In Table 3, likelihood of microalbuminuria in hypertensive Haitian Americans with T2D is shown by presence of rs3774907 alleles. The hypertensive individuals with T2D and CC and CT genotype of rs3774907 were 0.351 times as likely as TT genotype to

have microalbuminuria (P=0.031) after adjusting for age, sex, BMI and smoking status. On the other hand, the adjusted risk for microalbuminuria increased to 2.882 times in hypertensive Haitian Americans with T2D and TT +CT genotype (P=0.272).

Table 3. Likelihood of microalbuminuria by rs3774907 among hypertensive Haitian Americans with type 2 diabetes.

Parameter	Unadjusted OR	95% CI		P-value	Adjusted OR	95% CI		P-value	
rs3774907	CC+CT vs TT	0.33	0.13	0.85	0.022	0.35	0.13	0.91	0.031
	TT+CT vs CC	2.55	0.40	16.13	0.320	2.88	0.43	19.0	0.27

Note: Controlled variables included in the logistic regression analysis were age, sex, BMI, smoking status, type 2 diabetes. CI= confidence interval; OR= odds ratio.

DISCUSSION

This study investigated the relationship of rs3774907 SNP of the *PPARGC1A* gene with microalbuminuria in hypertensive Haitian Americans with T2D. As anticipated, individuals with microalbuminuria had higher blood pressure and A1C. Surprisingly no difference was seen between with and without microalbuminuria groups for BMI, waist circumference, cholesterol, or triglycerides. Despite higher blood pressure the reason why no difference in lipid profile was seen in microalbuminuria group except HDL-C being higher in individuals with microalbuminuria, is not clear. Interestingly, the minor allele frequency for rs3774907 (C) was higher in individuals with microalbuminuria than without microalbuminuria, suggesting some interaction of this allele with microalbuminuria.

Microalbuminuria is frequently observed in individuals with hypertension.^[25] We tested the effect of this association in either of the two alleles for the SNP rs3774907. Upon testing, the risk for hypertensive individuals to have microalbuminuria was much lower with allele 'C' of rs3774907 SNP than allele 'T' in this study sample of Haitian Americans with T2D. The interaction however was never before examined in Haitian American population, despite African origin populations being at high risk of microalbuminuria development.

Microalbuminuria patients usually show elevated blood pressure, compared to patients without microalbuminuria along with atherogenic lipid profile.^[25] Same relationship was observed between microalbuminuria and some of the atherogenic factors; blood pressure but not cholesterol, or triglycerides, in this study consisting of Haitian Americans. This correlation is well documented to be the

manifestation of endothelial dysfunction, reported in hypertension due to the involvement of endothelial cells in permeability and blood pressure control.^[26] Recent studies have recognized mitochondrial influence in endothelial function due to its involvement in multiple cellular processes. The complex process of mitochondrial content is based on the delicate equilibrium between selective mitochondrial degradation and mitochondrial biogenesis. Mitochondrial biogenesis is regulated primarily by *PPARGC1A* expressed PGC1- α , through activation of nuclear respiratory factor (NRF).^[27,28] In addition, PGC1- α regulates glucose and lipid metabolism as well as vascular endothelial growth factor-1 (VEGF-1) expression and thus it stimulates angiogenesis.^[29] The importance of PGC1- α in angiotensin induced hypertension was established by a recent study.^[30,31] The influence of PGC1- α on elevated blood pressure and thus hypertension could be a major determinant of microalbuminuria.

There are several limitations to the study. The small sample size with cross sectional design could have been a factor in inability to see few statistically significant interactions. Second, small sample size is may lead to false positive results thereby affect the reliability of our findings Only one variant for the gene *PPARGC1A* was chosen to test the association with microalbuminuria in this study population. Haplotype based analysis should be therefore performed in further studies by assessing other variants within the regulatory region of *PPARGC1A* gene. As type 2 diabetes is a multifactorial disease, environmental factors must be included in such studies to get comprehensive analysis. Ethnic specific case-control studies generally have intrinsic bias due to possible genetic heterogeneity among cases and controls. This study however recruited both

cases and controls from the same geographical region for Haitian Americans.

CONCLUSIONS

This is the first study that examined rs3774907 relation to microalbuminuria with hypertension in Haitian Americans with T2D. As it is an exploratory study, additional larger studies however are warranted to confirm the contribution of *PPARGC1A* gene polymorphisms in susceptibility of hypertension and microalbuminuria in Haitian Americans.

Abbreviations

SNPs: Single nucleotide polymorphisms; *PPARGC1A*: Peroxisome proliferator- activated receptor, gamma, co-activator 1 alpha; T2D: Type 2 Diabetes; SD: Standard deviation; OR: Odds ratio; CI: Confidence interval.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AC designed the study, carried out the laboratory work, analyzed the data and drafted the manuscript. TL guided the statistical analysis and revised the manuscript. GZ contributed in recruiting participants and collecting demographic and anthropometric data. JL revised the manuscript. FH provided funds, whole blood samples, and data on anthropometrics, biochemical parameters and as well as revised the manuscript. All authors read and approved the final manuscript.

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