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Original article

The Frequency and Association of ABCA1 (C69T) Single Nucleotide Polymorphism with Type 2 Diabetes Mellitus Among Hospital Attending Patients: A Case – Control Study

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ABSTRACT

Background and aims*. Type 2 diabetes mellitus (T2DM) accounts for the biggest percentage of the global diabetic burden and its onset and pathogenesis are complicated with multiple factors associated to the disease development. In this study we analyzed frequency and association of ABCA1 (C69T) single nucleotide polymorphism with type 2 Diabetes mellitus among hospital attending patients.* ***Methods****. Genotyping of ABCA1 (C69T) was performed using real time polymerase Chain Reaction in all participants. Genotypes were counted from all participants to determine genotype and allele frequency, and all possible genetic models were constructed. The genetic models and allele frequencies were used to determine the association of ABCA1 (C69T) SNP and type 2 diabetes mellitus using SPSS, 25.0 software.* ***Results****. The frequency of TT genotype was higher in T2DM patients 30 (27.3%) compared to 12 (12.0%). In controls, a significant association between TT vs. CC genetic model T vs. C allelic model with T2DM, (Odds Ratio (OR), 95% Confidence Interval (95%CI), OR: 2.596 [1.202 – 5.608], P 0.015 and OR: 1.632 [1.086 – 2.453], P 0.018 respectively with T2DM.* ***Conclusion****. The findings of our study show an association for ABCA1 (C69T) gene polymorphism with type 2, diabetes among hospital attending diabetic patients.*

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INTRODUCTION

Diabetes is among the major metabolic disorders, of public concerned with several associated complications, and existing as a co morbidity with a number of non-communicable disease (NCD) [1]. Distinguished and recognized by high blood glucose, impaired insulin activity and secretion usually with abnormal blood lipid profile, Type 2 diabetes (T2DM) accounts for about 95% of the global diabetic burden [2,3]. Asians pose a high prevalence of type 2 diabetes mellitus compared to other parts of the world, basically due to insulin resistance accompanied with aging, inflammation, obesity and the reduced insulin secretion among the Asian population [4].

Type 2 diabetes mellitus (T2DM) cause is still hard to understand, with multiple factors linked to the disease. Environmental and genetic factors can interact to increase the risk of disease [5]. Adenosine triphosphate binding cassette transporter 1 (ABCA1) gene belongs to ATP – binding cassette family responsible for the synthesis of trans - membrane transporter protein, playing an essential role in the secretion of cellular cholesterol and phospholipids from the cell to lipid-poor apolipoprotein A-I, creating nascent high-density lipoprotein (HDL) [6,7]. Mutations and polymorphisms in the ABCA1 gene have been known to cause Tangier disease and familial HDL deficiency [8]. Lack of a normal functioning ABCA1 either due to impaired trafficking of ABCA1 protein to plasma membrane or abnormally synthesized protein can contribute to increase in glucose intolerance and cholesterol accumulation within the pancreatic beta cells plasma membrane, which plays important roles in the pathogenesis of T2DM [9].

We hypothesized that, ABCA1 (C69T) gene polymorphism to have an association on the development of type 2 diabetes mellitus. We investigated the frequency and association of ABCA1 (C69T) rs1800977 polymorphism with T2DM through a hospital-based case – control study though the sample size was not pre – determined.

METHODS

Study design and setting

This was a case – control study, which included adult type 2 diabetic patients (cases) and healthy individuals (controls). The study was evaluated by the hospital clinical laboratory department and approved by the hospital research ethics committee. A written informed consent was obtained from all the participants upon explanation of the study nature.

A total of 110 adults 40 years and above T2DM patients attending the outpatient department (OPD) of the third affiliated hospital of Jinzhou Medical University, Jinzhou, China from March 2021 to August 2021 were included as cases and were age and sex matched with 100 healthy participants as the control group. People with family history of diabetes in control category, type 1 diabetes mellitus (T1DM), pregnant women, and, people presenting different malignancies, and other reported genetic disorders were excluded from the study.

Sample collection

Blood samples (6 ml) were collected from all participants and all investigations were performed according to protocol, observing the standard operating procedures. T2DM diagnosis was performed in accordance with the American Diabetes Association criteria. Participants with fasting blood glucose > 7.0 mmol/L and HbA1c > 6.5% were recruited as T2DM patients (Cases), whereas the control subjects had fasting blood glucose < 5.5 mmol/L and HbA1c < 5.7%. Demographic and Clinical data including age, gender, body mass index (BMI) and Fasting blood pressure were collected.

Biochemical parameters including fasting blood glucose (FBG), lipid profile (triglyceride, total cholesterol, HDL-cholesterol, and LDL-cholesterol), C- peptide and HbA1c were performed and results recorded using automated chemistry analyzers, HITACHI 7600 – 110, Cobas e 411 for C- peptide and BIO RAD D – 10 for HbA1c respectively. All biochemical analyses were performed in the hospital department of Clinical laboratory diagnosis following standard operating procedures.

DNA Extraction and genotyping

DNA was extracted from 200 µL EDTA anticoagulated whole blood using Spin column kit, Solarbio Life Science Beijing China, Catalogue No. D1800 following the kit manufacturer's protocol. The extracted DNA was cryopreserved at −80 °C for further molecular techniques. TaqMan real-time PCR technology was applied for determination of ABCA1 (C69T) rs1800977 gene single nucleotide polymorphism (SNP). The TaqMan SNP genotyping assay kit was purchased from Vazyme Biotech Co. Ltd. Nanjing, China. Catalogue No. Q811 – 01. The primer sequences for PCR were designed using primer blast software https://www.ncbi.nlm.nih.gov/tools/primer-blast/index.cgi as follows: Forward: 5′ -CAG CGC TTC CCG CGC GTC TTA −3′ ; Reverse: 5′ -CCA CTC ACT CTC GTC CGC AAT TAC −3.

The PCR process was performed through the following steps: 10µl of 2xChamQ Geno – SNP probe master mix, 1.0 µl of extracted DNA, 1.8 µl of each primer, 0.4 µl probes A and B, and nuclease-free water as prescribed in the manufacturer's protocol insert. The reaction mixtures were applied to the Bio – Rad CFX96 real time PCR instrument, as follows: pre - denaturation step (95 °C/ 30 seconds), followed by 45 cycles of denaturation (95 °C/10 seconds), then annealing/extension process (60 °C/30 seconds). Then terminal signal collection (60 ºC/30 seconds), then result analysis.

Statistical Analyses

All statistical data was analyzed using SSPS software version 25, (IBM SPSS, Inc., Chicago, IL, USA). The scale data were presented as mean ± standard deviation and Student's t test was applied for comparison between the two study groups. The nominal data were counted directly and reported as number and percentage, Chi-square $\chi 2$ was used for comparison between the study groups.

The frequencies and distributions of genotypes and alleles between the studied groups were determined and compared by Chi-square $\chi 2$ test. The Hardy-Weinberg equilibrium (HWE) of ABCA1 (C69T) rs1800977 genotypes was analyzed in the control group using the $\chi 2$ test. Binary logistic regressions were applied in determination of crude odds ratios, and corresponding 95% confidence interval (95%CI) for all proposed genetic models. We considered $P < 0.05$ to be statistically significant.

RESULTS

Characteristics of the study cohorts

The current study consisted of 110 T2DM patients and 100 healthy subjects. The T2DM group included 68 (61.8%) males and 42 (38.2%) females with a mean age of 52.30 ± 6.28 years. The healthy controls were age and gender matched with the T2DM patients (P 0.086 and P 0.449 respectively). Table 1, summarizes demographic, clinical and Biochemical data. BMI, systolic blood pressure (SBP), FBG, HbA1c, C- peptide, triglyceride, and LDL-cholesterol were statistically significantly higher in T2DM patients except diastolic blood pressure (DBP), and total cholesterol than in control group. However, HDL-cholesterol level was statistically significant lower in T2DM patients compared to healthy controls.

Table 1: Clinical, demographic and Biochemical characteristics of the study participants.

Characteristics	Cases (T2DM Patients) (n = 110)	Controls (Healthy participants) (n = 100)	P-Value
Age (years)	52.30 ± 6.28	50.74 ± 6.82	0.086
Gender (n) M/F (%)	68/42 (61.8/38.2)	60/40 (60.0/40.0)	0.449
BMI (kg/m²)	24.78 ± 3.17	23.26 ± 2.76	< 0.001
SBP (mmHg)	134.97 ± 14.31	129.93 ± 15.47	0.015
DBP (mmHg)	83.06 ± 9.24	80.72 ± 9.69	0.074
FBG (mmol/L)	9.67 ± 2.39	5.46 ± 0.29	< 0.001
HbA_1C (%)	7.55 ± 1.44	5.12 ± 0.39	< 0.001
C - Peptide (ng/ml)	2.79 ± 1.02	2.17 ± 0.67	< 0.001
TG (mmol/L)	1.85 ± 1.00	1.39 ± 0.90	0.001
TC (mmol/L)	5.05 ± 0.99	4.81 ± 0.90	0.069
LDL- C (mmol/L)	3.01 ± 0.78	2.76 ± 0.75	0.005
HDL-C (mmol/L)	1.08 ± 0.24	1.29 ± 0.39	< 0.001

BMI - Body Mass Index, SBP - systolic Blood Pressure, DBP - Diastolic Blood Pressure, n - number, FBG - Fasting Blood Glucose, TG - Triglyceride, TC - Total Cholesterol, LDL - C Low Density Lipoprotein Cholesterol, HDL - C High Density Lipoprotein Cholesterol. All values expressed as mean ± Standard deviation.

Hardy–Weinberg equilibrium

The genotype and allele distributions of ABCA1 C69T rs1800977 (Table 2.). The $\chi 2$ test showed the genotype distribution within the controls conformed to Hardy-Weinberg equilibrium $p^1 = 0.219$. Implying our sample adequately represents the studied population.

Association between ABCA1 (C69T) rs1800977 gene polymorphism and susceptibility to T2DM

The possible genetic models of ABCA1 (C69T) polymorphism were constructed and their distributions were compared between T2DM patients and control group. (Table 2) There was a statistically significant difference in the frequency of genotypes and alleles between T2DM patients and control group. The frequencies of the homozygous TT genotype and T allele were statistically significant higher in T2DM as compared to healthy controls implying increased susceptibility to T2DM associated with the homozygous TT genotype (TT vs. CC: OR = 2.596 [1.202–5.608]), (P 0.015); T vs. C: OR = 1.632 (1.086 – 2.453), (P 0.018). In addition, the recessive model also showed a statistically significant association to T2DM susceptibility OR = 2.750 (1.319 – 5.734), (P 0.007).

Table 2: Association between ABCA1 (C69T) rs1800977 gene polymorphism and susceptibility to T2DM.

Genotype	T2DM group n = 110, s (%)		Control group n= 100, (%)		HWE p[1] value	OR (95%CI)	P-Value
CC	52 (47.3)		54 (54.0)		0.219		
CT	28 (25.4)		34 (34.0)				
TT	30 (27.3)		12 (12.0)				
Genetic model							
CT vs. CC	28	52	34	54		0.855 (0.456-1.604)	0.626
TT vs. CC	30	52	12	54		2.596 (1.202 - 5.608)	0.015
T vs. C	88	132	58	142		1.632 (1.086 - 2.453)	0.018
Dominant	58	52	46	54		1.309 (0.761 - 2.253)	0.331
Recessive	30	80	12	88		2.750 (1.319 - 5.734)	0.007

HWE; Hardy Weinberg Equilibrium P[1]; HWE p value

Association between Clinical and Biochemical characteristics with ABCA1 (C69T) rs1800977 gene polymorphism in T2DM

A statistically significant association between high total cholesterol and high LDL-cholesterol levels to homozygous TT genotype as compared to the CT and the wild type (CC) genotypes (P 0.007). However, there were no significant association between HDL-cholesterol level, BMI, Triglycerides, C – peptide, Systolic and diastolic blood pressure to TT genotype individuals as compared to other genotypes in the T2DM group. (Table 3).

Table 3: Clinical and Biochemical distribution characteristics of T2DM cohort among different ABCA1 (C69T) genotype

Characteristics	Genotype CC (n = 52)	Genotype CT (n = 28)	Genotype TT (n=30)	p Value
BMI (kg/m²)	24.52 ± 3.10	25.79 ± 3.73	24.28 ± 2.56	0.715
SBP (mmHg)	135.12 ± 15.35	135.86 ± 15.26	133.90 ± 11.67	0.708
DBP (mmHg)	83.56 ± 9.84	85.46 ± 8.75	79.97 ± 7.98	0.093
C - Peptide (ng/ml)	2.71 ± 0.90	2.67 ± 1.07	3.03 ± 1.17	0.176
TG (mmol/L)	1.74 ± 0.87	1.75 ± 0.86	2.15 ± 1.29	0.093
TC (mmol/L)	4.82 ± 0.94	5.01 ± 0.74	5.48 ± 1.78	0.007
LDL-C (mmol/L)	2.86 ± 0.75	3.06 ± 0.57	3.38 ± 0.92	0.007
HDL-C (mmol/L)	1.10 ± 0.23	1.06 ± 0.23	1.08 ± 0.27	0.768

P < 0.05 Significant difference in the biochemical distribution between homozygous TT and the wild type.

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a multiplex metabolic and heritable disorder with high motility and morbidity especially due to other complications (WHO, 2019), distinguished by impaired insulin action, insulin secretion, to add in, abnormal regulation of lipid and protein metabolism usually incited by either environmental, behavioral and genetic factor or a combination of more than one factors.[5,10] Several studies have reported association between ABCA1 single nucleotide polymorphisms, leukocyte ABCA1 expression, to insulin resistance.[11,12] Not only that, ABCA1 has been implicated to have a role in the reverse cholesterol transport, implying its dysregulation may lead to cholesterol accumulation as well as glucose intolerance within the beta cells plasma membrane, which in turn contributes to the pathogenesis of T2DM [9]. Therefore, genetic variance of ABCA1 gene can moderate the progression of T2DM through a reduction in HDL production, ABCA1 gene polymorphisms may interfere with the transcription process of ABCA1, leading to lowered ABCA1 secretion which may affect glucose metabolism through regulating insulin secretion [13–15].

In the current study we investigated the frequency and association of ABCA1 (C69T) rs1800977 gene single nucleotide polymorphism with type 2 diabetes among a hospital attending patients in Lioaning province, Northern China. Despite

similar studies being conducted in different parts of China, other parts of the world, as well as in different ethnicities, the discrepancies in the results from the previous studies prompted us to conduct an association case - control study in the specific gene reference sequence. Clinical and biochemical characteristics were compared among the study groups. The average BMI, SBP, C-Peptide, TG and LDL-C, (P <0.001, 0.015, <0.001, <0.001 and 0.005 respectively), were statistically significant higher in the Type 2 diabetic patients (cases) compared to the healthy participants (controls). However, HDL-C was statistically significant low (P <0.001) in T2DM patients than in the control group. There was no significant difference in total cholesterol and diastolic blood pressure between the cases and controls.

Increased body mass index indicates increased body fat, usually a reflection of a person's diet and rate of physical exercise, the two leading environmental factors predisposing to T2DM [16]. High SBP is associated with increased risk of T2DM [17]. To add in, increased C- peptide is a sign of type 2 diabetes or insulin resistance. Likewise, lipid profile parameters were characteristic of dyslipidemia, which is a common feature of T2DM with exception of total cholesterol. In addition, previous studies reported a significantly high BMI, SBP, triglycerides, total cholesterol, LDL and HDL in T2DM patients [2,18–20]. To add in, a significantly lower HDL cholesterol was reported in T2DM patients than healthy controls [19]. However, there was no significant difference clinical and biochemical parameters reported between T2DM patients and controls [5,21].

There was statistically significant higher frequency of homozygous TT as well as the T allele in the T2MD patients as compared to their control counterparts implying that TT and T are significantly associated with the risk of T2DM (TT vs.CC, OR = 2.596 [95% CI, 1.202 – 5.608], P 0.015), T vs. C, (OR = 1.632 [95% CI, 1.086 – 2.453], P 0.018). Not only that, there is a statistically significant association between the recessive genotypic model, (OR = 2.750 [95%CI, 1.319 – 5.734], P 0.007) and T2DM patients as compared to the dominant model further proving the risk of T2DM imposed by variance in this gene. Similarly, a significant association between (C69T) rs1800977 SNP and susceptibility to type 2 diabetes was reported in Chinese population, in all possible genetic models (TT vs. CC, P < 0.001; T vs. C, P 0.005; and the recessive model, P <0.001 [2]. In addition, (C69T) rs1800977 SNP in ABCA1 gene was significantly associated with susceptibility to T2DM in the Han Chinese population, in all possible genetic models, TT vs. CC, T vs. C and the recessive P values, < 0.001, 0.006 and < 0.001 respectively [18].

To add in, ABCA1 (C69T) gene polymorphism was statistically significant associated with T2DM risk in the Egyptian population, TT vs. CC, P 0.040, T vs. C, P 0.024 and recessive model, P 0.010. Moreover, the ABCA1 TT genotype was associated with increased BMI, hypercholesterolemia, and diminished HDL which confers an increased risk of dyslipidemia and obesity [19]. Not only that, in Malaysian population, an association between ABCA1 (C69T) gene polymorphism and T2DM in TT genotype against CC, P 0.018 as well as T vs. C, P 0.005 [5]. However, a protective role of TT genotype as well as T allele of ABCA1 rs1800977 against T2DM risk was reported in Chinese Han population. Here in the TT genotype and T allele were more frequent in the control group than the cases, TT vs. CC, P 0.001, T vs. C, P 0.003 and recessive model P < 0.001 [22]. Similarly, ABCA1 (C69T) gene polymorphism was found protective against T2DM, (TT vs. CC, 0.008 and T vs. C, P 0.020) in Turkish population [20]. Furthermore, the frequency of the T allele of the ABCA1 C69T gene was significantly higher in healthy subjects compared to T2DM patients P < 0.001, and therefore the T allele may be a protective factor against T2DM in the Saudi population [23]. Moreover, no association between ABCA1 (C69T) gene polymorphism and T2DM was reported in Bangladeshi, TT vs. CC, P = 1.0 and T vs. C, P 0.414 [21].

In this study, we also found a statistically significant association between ABCA1 (C69T) gene polymorphism with high total cholesterol as well as high LDL- cholesterol which are indicators of hyperdyslipidemia, a common characteristic of T2DM. There was a significant association between TT and increased total cholesterol and LDL – cholesterol compared to CC and CT genotypes in the T2DM group, P 0.007 in each, but there was no significant difference between HDL – cholesterol and triglycerides with TT and other genotypes in T2DM group. Similarly, a statistically significant increased total cholesterol, LDL – cholesterol, T2DM patients carrying TT genotype P < 0.001. However, significantly decreased HDL – cholesterol, P < 0.001 with TT genotype in T2DM patients as compared to other genotypes was reported in the Egyptian population [19]. Whereas, HDL – cholesterol and LDL – cholesterol were significantly low in TT genotype, P > 0.05, as compared to wild type with no report about total cholesterol in Chinese Han population [2,18]. However, there was no statistically significant difference between TT genotype of ABCA1 (C69T) rs1800977 gene polymorphism and lipid profile in T2DM patients [5,20,23]. Elsewhere, significantly increased total cholesterol and LDL – cholesterol levels as well as decreased HDL - cholesterol levels in diabetic patients with ABCA1 (G1051A) single nucleotide polymorphism in Tunisian population [24]. Studies on other SNPs of ABCA1 gene in association to T2DM risk have been carried out with the following reports; ABCA1 (R219K) has been reported to be significantly associated to T2DM in different genetic models.[2, 5, 25] However, there was no significant association between ABCA1 (R219K) with types 2 diabetes.[18].

Rs4149313 and (R230C) rs9282541 were reportedly significantly associated to T2DM [2,18]. In addition, no significant association between (R230C) rs9282541 SNP and T2DM in Malaysian populations [5]. Therefore, results of the current study were consistent with some previous studies as well as having some discrepancies when compared to others. This calls for more studies with bigger samples as well as considering all possible cofounders before drawing a final conclusion on the role of ABCA1 (C69T) gene polymorphism in the pathogenesis of T2DM.

CONCLUSION

The findings of our study show an association for ABCA1 (C69T) gene polymorphism with type 2, diabetes among hospital attending patients in Northern China. Further studies with large sample size and further analysis of cofounders should be carried out on similar population before generalizing the association to the study population.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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