RESEARCH PAPER

Occurrence of G allele at rs1800976 of ABCA1 gene in North Indian population (Haryana) confers increased susceptibility to atherosclerotic complications in diabetic individuals

Ms. Vikas Kumari[1], Mrs. Nisha Khola[2], Mr. Rajan Sharma[3], Ms. Monika Lamba[4], Ms. Priti Devi[5], Mrs. Geeta Dhiman[6], Dr. Jasbir Singh[7*]

[1]PhD scholar, Kurukshetra University, Haryana 136119, India. Email: vikasmulodia1997@gmail.com
[2]PhD scholar, Kurukshetra University, Haryana 136119, India. Email: kholanisha5@gmail.com
[3]PhD scholar, Kurukshetra University, Haryana 136119, India. Email: rajansharma6675@gmail.com
[4]PhD scholar, Kurukshetra University, Haryana 136119, India. Email: monikalamba2018@gmail.com
[5]PhD scholar, Kurukshetra University, Haryana 136119, India. Email: pritimalik0117@gmail.com
[6]PhD scholar, Kurukshetra University, Haryana 136119, India. Email: geetadhiman7791@gmail.com
[7*]Professor, Kurukshetra University, Haryana 136119, India. Email: jasbirdhanda@gmail.com

***Corresponding author: Dr. Jasbir Singh, Professor, Kurukshetra University, Haryana 136119, India**
Email: jasbirdhanda@gmail.com

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ABSTRACT

Background

Type 2 diabetes mellitus (T2DM), and coronary artery disease (CAD) are metabolically related lesions with dyslipidemia and the deficiency of cholesterol transportation. ABCA1 is a key gene in HDL metabolism, and its polymorphisms could act as cardiometabolic risk factors.

Objective

The study needed to examine how ABCA1 (rs1800977 and rs1800976) polymorphisms relate to T2DM and CAD, as well as to both in a North Indian cohort.

Methods

Case control study was done on 600 participants (controls, T2DM, CAD, T2DM+CAD; n=150 each). PCR-RFLP was used to carry out genotyping. Statistical tests were chi-square tests, odds ratios (ORs), and haplotype analysis.

Results

There was no significant relationship with rs1800977. Conversely, the association between the two diseases (CAD and T2DM+CAD) with the association of a strong association with the frequency of G allele and the GG genotype was observed in the case of rs1800976 (OR=3.11 and 2.58, respectively; $p<0.05$). The high triglycerides and low HDL-C were associated with risk genotypes, and CG and TG were haplotypes of risk.

Conclusion

The polymorphism at the site (rs1800976) was greatly linked to higher forms of CAD and T2DM+CAD indicating that the site could serve as a genetic marker of cardiometabolic risk.

Keywords: ABCA1 gene polymorphism, rs1800976, Type 2 diabetes mellitus, Coronary artery disease, Genetic susceptibility, Lipid metabolism.

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1. Introduction

"Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that is associated with persistent hyperglycaemia caused by insulin resistance and defective functions of pancreatic 8 cells. Over the past several decades, the burden of T2DM in the world has grown significantly, and the International Diabetes Federation estimates that there were about 537 million adults with diabetes living in 2021, and this number will grow to about 783 million by 2045" [1]. Diabetes is also another major cause of death in the world according to the findings of the World Health Organization, which claims that about 1.5 million deaths are caused by diabetes every year [2]. Rapid urbanization, sedentary living with growing cases of obesity have been key factors that have led to the growth in the prevalence of T2DM, especially in the developing nations like India [3].

Both microvascular and macrovascular complications are closely linked with T2DM, the most prominent cause of mortality and morbidity of which are cardiovascular diseases (CVDs). The

most prevalent form of CVD in diabetic patients is the coronary artery disease (CAD), which greatly affects the decrease in life expectancy [4]. As it has been shown in epidemiological studies, people having T2DM are two to three times more likely to develop CAD than non-diabetic people are [5,6]. T2DM and CAD co-occurrence result in adverse clinical outcomes caused by interactions between hyperglycaemia, insulin resistance, dyslipidaemia, and chronic inflammation [7].

CAD is a multifactorial and complicated disease involving the genetic, metabolic, and environmental factors. The main pathological process underlying CAD is atherosclerosis which starts with the endothelial dysfunction due to hyperglycaemia, oxidative stress, and dyslipidaemia [8]. It is then succeeded by the deposition and oxidation of the low-density lipoprotein (LDL) cholesterol in the wall of the arteries that trigger inflammation and the formation of the foam cells [9]. The progressive growth of the plaque, increase of smooth muscle cells, and subsequent rupture of the plaque are some of the factors that lead to the acute coronary events including myocardial infarction [10].

The dyslipidaemia is critical in the "development of T2DM and CAD. Diabetic dyslipidaemia is a condition of increased triglycerides, high levels of small dense LDL particles and low levels of high-density lipoprotein cholesterol (HDL-C) [11,12]. The protective effects of HDL-C include reverse cholesterol transport, antioxidant and anti-inflammatory effects", and, as such, the propensity to atherosclerosis is diminished [13]. Thus, lipid metabolism and cholesterol transport genes are such important determinants of cardiometabolic risk.

ABCA1 gene is the ATP-binding cassettes transporter that is a major regulator of cholesterol homeostasis. ABCA1 gene, located on chromosome 9q2231, is the gene that encodes a protein that transfers cholesterol through the membrane to apolipoprotein A-I triggering the generation of HDL particles [14,15]. Availability of the correct functioning of ABCA1 is necessary to ensure the maintenance of lipid balance and avoidance of the intracellular accumulation of cholesterol. A defective ABCA1 activity has been associated with low levels of HDL and high vulnerability to atherosclerosis [16]. In addition, it has been demonstrated that conditions of diabetes may negatively influence the expression and activity of ABCA1 and thus contribute to the worsening of lipid abnormalities and cardiovascular risks [17].

ABCA1 gene has been extensively researched on genetic polymorphisms of the gene to associate with T2DM, CAD and lipid abnormalities. Several SNP modifications have been shown to have varied associations among populations such as rs2230806; rs1800977; rs4149313 and rs1800976 [18]. Although the inconsistent associations were observed between rs1800977 and T2DM and lipid profiles, there is emerging evidence suggesting that the promoter region variant, which is rs1800976, can be a more significant factor in the gene expression and cardiovascular risk [19]. Research in other populations has mentioned that the association between the risk of CAD, the modifications in the lipid parameters and the inflammatory reactions have been linked to the presence of the rs1800976 [20].

Although these results were obtained, a major gap in the research is the role of the ABCA1 polymorphisms in the comorbidity of the T2DM and CAD, especially in the Indian population. Prior research has investigated T2DM and CAD separately, and there have been few studies that investigate their co-occurring tendency and mutual genetic predisposition. Since the diseases have a high burden in India and the possibility of ethnic and environmental effects exist, population-specific research is needed.

Thus, the current research was aimed at examining how the association of ABCA1 gene polymorphism (rs1800977 and rs1800976) with T2DM and CAD, as well as with their co-occurrence (T2DM+CAD) was associated with a North Indian population in Haryana. Also, the paper seeks to determine the association between these genetic variations and both clinical and biochemical measures to gain further insight into their contribution to cardiometabolic risk.

2. Materials and methods

2.1 Study Design and Population

The study was planned as a case control study of an observational type to test the association between the polymorphisms in the ABCA1 gene and a predisposition to type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), and the two syndromes (T2DM+CAD). There were 600 respondents who were registered and divided into 4 categories which included healthy controls (n=150), T2DM (n=150), CAD (n=150), and T2DM+CAD (n=150).

The participants were recruited in various tertiary care hospitals in various geographical locations in Haryana, North India. Individuals aged ≥35 years were included. T2DM was diagnosed according to Indian Council of Medical Research (ICMR) criteria (fasting blood glucose ≥126 mg/dL and/or HbA1c ≥6.5%). CAD cases were angiographically established with 50 percent luminal constriction in one of the major coronary arteries.

The exclusion criteria were diabetes mellitus type 1, gestational diabetes, chronic kidney disease, malignancies, acute infections, and other severe systemic illnesses that may affect metabolic or biochemical values.

2.2 Sample Size and Power

The sample size was estimated by using the previous allele frequencies, the expected odds ratio of 2.0 -3.0, 95% confidence level and 80% statistical power. The group sizes needed 120 subjects, but more samples were needed to enhance strength and minimize sampling error, and this was 150 subjects per group. In that way, 600 subjects were researched. The post hoc power analysis established that the study had more than 80 percent of power to report significant genetic associations.

2.3 Ethical Approval

The protocol of the study was endorsed by the Institutional Ethics Committee, Kurukshetra University, Haryana, India (Approval No.: IHEC/23/20). Each process took place as per the "declaration of Helsinki". Informed consent was obtained by way of written sources of all the participants before the samples were collected.

2.4 Clinical and Biochemical Examination.

Age, gender, and medical history were among the demographic and clinical variables gathered by structured questionnaires. The body mass index (BMI) was calculated using the anthropometric measures of weight and height. Blood pressure was measured using the usual clinical protocols.

"Venous blood samples were sampled by overnight fasting. The biochemical parameters such as fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)" were analyzed with the help of standard enzyme methods on semi-automated analyser (ERBA Chem-7). The level of glycated haemoglobin HbA1c and fasting insulin was also determined through standard laboratory tests.

2.5 Genotyping of ABCA1 gene for SNPs rs1800977 and rs1800976

Genotyping of ABCA1 polymorphisms (rs1800977 and rs1800976) was performed using PCR-RFLP. PCR amplification was carried out in a 25µL reaction using specific primers under standard conditions. The products were digested with Alw26I and Bsp1286I and analyzed on 1.5–2% agarose gel. rs1800977 produced fragments of 345 bp (CC), 310/35 bp (TT), and 345/310/35 bp (CT) (Figure 1), while rs1800976 yielded 345 bp (CC), 308/37 bp (GG), and 345/308/37 bp (CG) (Figure 2).

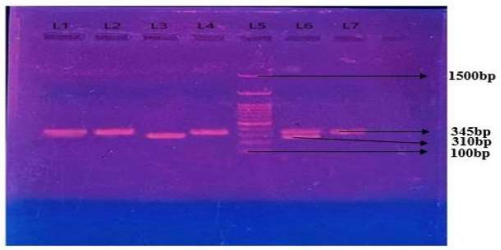

Figure 1: Restriction Digestion products of ABCA1 gene at SNP rs1800977. Lane 5 shows 100 bp ladder, Lanes 1,2,3,4,6,7 show restriction pattern by enzyme Alw26I.

Figure 2: Restriction Digestion products of ABCA1 gene at SNP rs1800976. Lane 26 shows 100 bp ladder, Lanes 1-25 show restriction pattern by enzyme Bsp1286I.

2.6 Statistical analysis

The statistical analysis was carried out using IBM SPSS software, specifically version 31.0. Frequencies and percentages were used to represent categorical variables, while standard deviation and mean were employed to represent continuous attributes. To compare the groups, independent sample t-tests were used.

"Pearson chi-square (χ^2) test was used to analyze genotype and allele frequencies. Polymorphisms were analysed using odds ratios (ORs) with 95% confidence intervals (CIs)" of association with disease risk. Genetic models such as additive, recessive, dominant and heterozygous were determined. There was Bonferroni correction ($p < 0.017$). The data was analyzed through SHEsis Plus software to analyse the haplotype.

3. Results

3.1 Clinical and Biochemical Characteristics

All the groups' biochemical and clinical data is included in Table 1. No statistically significant difference was found ($p > 0.05$) in the composition of the mean age of the various groups.

The systolic and diastolic blood pressure (SBP and DBP, respectively) were both found to be significantly increased in T2DM, CAD, and T2DM+CAD groups when compared to controls ($p < 0.05$). The levels of "fasting blood glucose (FBG), and HbA1c were significantly higher in T2DM and T2DM+CAD groups ($p < 0.05$) but the difference was not significant in the CAD group ($p > 0.05$)"

The lipid profile analysis revealed a strong "level of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) and a low level of high-density lipoprotein cholesterol (HDL-C) in all patient groups than controls ($p < 0.05$). These changes were the most evident in the T2DM+CAD group"

The levels of fasting insulin were considerably higher in the T2DM, and T2DM+CAD groups compared to the controls ($p < 0.05$), but the CAD group did not vary significantly from the controls ($p > 0.05$).

Table 1. Comparison of clinical parameters among different groups

Clinical	Contr	T2DM	CAD	T2DM+CAD	p-valu	p-v	p-value (T2D

Parameter	ol Mean ±SD	Mean ± SD	Mean ± SD	Mean ± SD	e (T2DM)	alue (CAD)	M+CAD)
AGE (Years)	54.85±12.35	55.55±13.08	54.85±12.34	57.23±11.64	0.634	0.086	0.378
DBP (mmHg)	81.17±4.65	84.86±8.06	83.25±4.75	83.17±6.19	<0.05	<0.05	<0.05
SBP (mmHg)	121.72±4.84	130.53±14.31	123.74±10.01	126±11.34	<0.05	<0.05	<0.05
FBG (mg/dl)	93.91±10.03	161.63±49.68	94.38±12.3	166.67±58.0	<0.05	0.72	<0.05
TC (mg/dl)	177.78±73.98	188.01±48.21	243.35±52.11	250.03±42.06	<0.05	<0.05	<0.05
TG (mg/dl)	105.61±54.46	170.71±34.02	154±59.64	191.76±72.02	<0.05	<0.05	<0.05
HDL-C (mg/dl)	46.44±12.4	40.16±11.30	42.77±11.81	31.62±14.01	<0.05	<0.05	<0.05
LDL-C (mg/dl)	104.22±78.75	123.11±44.27	171.51±46.55	177.73±54.17	<0.05	<0.05	<0.05
HbA1c (%)	4.74±0.96	7.72±1.94	4.71±0.83	7.46±1.82	<0.05	0.77	<0.05
Fasting Ins ulin (IU/ml	13.10±10.76	19.93±18.96	14.78±9.75	25.31±21.72	<0.05	0.158	<0.05

SD: Standard deviation. p value <0.05 is significant. T2DM: type 2 diabetes mellitus. CAD: coronary artery disease.

3.2 Genotype and Allele Distribution of ABCA1 Polymorphisms

rs1800977

Study groups' genotype and allele distributions for SNP rs1800977 are shown in Table 2. Genotype distributions for CC, CT, and TT were comparable between the two groups of people. When comparing T2DM, CAD, or T2DM+CAD genotypes and allele frequencies, no statistically significant differences were found ($p > 0.05$).

Additive, dominant, recessive, and heterozygous genetic model analysis did not also reveal any significant association with disease status following Bonferroni correction.

Table 2. Genotypic distribution and allele frequencies of SNP rs1800977 of ABCA1 gene

SNP rs1800977	Healthy subjects	T2DM Patients	Chi square χ^2 1	Odd Ratio (OR) (95% CI)	p-value	CAD patient	Chi square χ^2 2	Odd Ratio (OR) (95% CI)	p-value	CAD + T2DM patient	Chi square χ^2 3	Odd Ratio (OR) (95% CI)	p-value
CC	59 (39.3%)	73 (48.6%)	2.88		0.23	70 (46.6%)	2.6		0.26	69 (46%)	1.37		0.50

CT	68 (45.3%)	60 (40%)				65 (43.3%)				61(40.6%)			
TT	23 (15.3%)	17 (11.3%)				15 (10%)				20 (13.3%)			
Allelic													
C	186(62%)	206(68.6%)	0.109	0.947(0.685–1.309)	0.741	169(56.3%)	0.334	0.909(0.657–1.256)	0.563	172(57.3%)	0.109	0.947(0.685–1.309)	
T	114(38%)	94(31.3%)				131(43.6%)				128(42.6%)			
Additive													
CC	59 (39.3%)	73 (48.6%)				70 (46.6%)				69(46%)			
CT	68 (45.3%)	60 (40%)	1.84	0.713 (0.43-1.16)	0.174	65 (43.3%)	0.76	0.80 (0.49-1.3)	0.38	61(40.6%)	1.12	0.76 (0.47-1.25)	0.28
TT	23 (15.3%)	17 (11.3%)	2.01	0.55 (0.23-1.14)	0.156	15 (10%)	2.56	0.55 (0.26-1.14)	0.10	20(13.3%)	0.70	0.74 (0.37-1.48)	0.40
Dominant (CC vs CT+ TT)													
	59 (3	73 (4	2.	0.68	0.	70	1.6	0.74	0.	69(	1.3	0.76	0.
	9.3%)	8.6%)	65	(0.43-1.0)	10	(46.6%)	4	(0.46-1.17)	20	46%)	63	(0.48-1.20)	24
Recessive (TT vs CT+ CC)													
	23 (15.3%)	17 (11.3%)	1.03	0.70 (0.36-1.38)	0.30	15 (10%)	1.92	0.61 (0.30-1.22)	0.16	20 (13.3%)	0.24	0.84 (0.44-1.62)	0.62
Heterozygous (CT vs CC+ TT)													
	68 (45.3%)	60 (40%)	0.87	0.80 (0.50-1.27)	0.35	65 (43.3%)	0.12	0.92 (0.58-1.45)	0.72	61(40.6%)	0.66	0.82 (0.52-1.30)	0.41

*p-values are uncorrected. Bonferroni correction for multiple comparisons sets the significance threshold at $p < 0.017$.

rs1800976

Table 3 indicates that SNP rs1800976 did not show significant differences in genotype or allele frequencies in the T2DM group compared to controls. In contrast, the CAD group exhibited a higher frequency of the GG genotype and G allele, suggesting increased risk. The T2DM+CAD group also displayed significant variations. Genetic model analysis confirmed that the GG genotype is linked to a higher risk in both the CAD and T2DM+CAD groups.

Table 3. Genotypic distribution and allele frequencies of SNP rs1800976 of ABCA1 gene

SNP rs1800976 Genotype	Healthy subjects	T2DM Patients	Chi square χ^2_1	p-value	Odd Ratio (OR) (95% CI)	CAD patient	Chi square χ^2_2	p-value	Odd Ratio (OR) (95%	CAD + T2DM patient	Chi square χ^2_3	p-value	p-value

									CI)				
CC	58(38.7%)	50(33.3%)	1.34			16(10.6%)	44.59	<0.05		24(16%)	31.17	<0.05	
CG	72(48%)	82(54.7%)				73(48.7%)				70(46.7%)			
GG	20(13.3%)	18(12%)				61(40.7%)				56(37.3%)			
Allelic													
C	188(62.7%)	182(60.7%)	0.25	1.08(0.78-1.56)	105(35%)	44.95	<0.05	3.11(2.23-4.35)		118(39.3%)	32.68	<0.05	2.58(1.86-3.59)
G	112(37.3%)	118(39.3%)			195(65%)					182(60.7%)			
Additive													
	58(38.7%)	50(33.3%)	0.9600	1.32(0.81-2.16)	16(10.6%)	15.594	<0.05	3.68(1.93-6.9		24(16%)	7.629	<0.05	1.32(1.32-(
	72(48%)	82(54.7%		1.04(0.50-2.19)	73(4	2.46	<0.05			70(46.7%	3.38	<0.05	
	20(13.3%)	18(12%)	1.08	0.29	0.77	61(40.7%)	0.00	1.00	0.97	56(37.3%)	0.01	0.90	1.05
Dominant (CC vs. CG+GG)	58(38.7%)	50(33.3%)	0.71	0.40	0.79(0.49-1.27)	16(10.6%)	30.15	<0.05	5.28(2.86-9.75)	24(16%)	18.28	<0.05	(1.92-
Recessive (GG vs. CG+GG)	72(48%)	82(54.7%)	0.03	0.86	1.13()	73(48.7%)	27.06	<0.05	0.22	70(46.7%)	21.59	<0.05	0.26

zygous (CG vs. CC+GG)	)													

"*p-values are uncorrected. Bonferroni correction for multiple comparisons sets" the significance threshold at $p < 0.017$.

3.3 Association of rs1800977 Genotypes with Clinical Parameters

Table 4 reveals the relationship between the genotypes of the association (rs1800977) of genotype CC versus CT +TT and the clinical parameters. There were no notable differences between control and T2DM groups ($p > 0.05$).

CT + TT genotypes were significantly less in SBP ($p = 0.028$), DBP ($p = 0.001$), triglycerides ($p = 0.001$) and HDL-C ($p = 0.001$) and total cholesterol ($p = 0.021$) in the CAD group.

CT +TT genotypes in T2DM +CAD were related to reduced SBP ($p = 0.004$), DBP ($p < 0.001$), and total cholesterol ($p = 0.003$).

Table 4. Statistical analysis of association of biochemical parameters with genotypes of SNP rs1800977

Clinical Parameters	**Healthy CC (n=59)**	**Healthy CT+TT (n=91)**	**p-Value**	**T2DM CC (n=73)**	**T2DM CT+TT (n=77)**	**p-Value**	**CAD CC (n=70)**	**CAD CT+TT (n=80)**	**p-Value**	**CAD+T2DM CC (n=69)**	**CAD+T2DM CT+TT (n=81)**	**p-Value**
Age (years)	54.6 ± 12.50	55.0 ± 12.50	0.846	55.6 ± 11.90	55.50 ± 12.80	0.962	54.80 ± 13.00	54.90 ± 12.60	0.961	57.10 ± 11.60	57.30 ± 11.80	0.917
BMI (kg/m²)	24.7 ± 3.5	25.0 ± 3.8	0.621	26.1 ± 4.0	26.3 ± 4.2	0.766	26.2 ± 3.9	27.4 ± 4.3	0.075	27.0 ± 4.2	28.5 ± 4.5	**0.037**
SBP (mmHg)	121.90 ±	121.50 ±	0.630	130.80 ± 14.60	130.2 ± 14	0.798	125.80 ± 10.10	122.10 ± 10.30	**0.028**	128.90 ± 11.30	123.40 ± 11.50	**0.004**
DBP (mmHg)	81.50 ±	80.90 ±	0.441	85.10 ±	84.20 ±	0.498	86.30 ±	82.10 ±	**0.001**	88.00 ± 6.90	83.00 ± 7.40	**0.000**
FBG (mg/dL)	95.50 ±	92.80 ±	0.117	162.50 ± 49.00	160.80 ± 50.20	0.834	96.80 ± 12.30	92.90 ± 11.80	**0.050**	168.20 ± 55.00	160.30 ± 60.20	0.403
TG (mg/dL)	108.50 ±	103.40 ±	0.549	172.20 ± 34.50	169.50 ± 33.80	0.629	182.10 ± 60.20	147.30 ± 58.00	**0.000**	198.40 ± 72.00	182.00 ± 71.50	0.165

HDL-C (mg/dL)	45.80 ± 12.60	47.10 ± 12.10	0.532	39.60 ± 11.20	40.50 ± 11.50	0.628	36.50 ± 10.10	44.20 ± 12.00	**0.000**	32.80 ± 13.80	36.50 ± 12.00	0.085
LDL-C (mg/dL)	102.50 ± 17.60	106.80 ± 80.50	0.743	124.50 ± 43.90	121.20 ± 44.50	0.648	178.90 ± 46.00	165.20 ± 46.70	0.073	185.60 ± 54.00	171.90 ± 53.00	0.121
Total Cholesterol (mg/dL)	176.80 ± 74.60	178.50 ± 73.50	0.891	189.20 ± 48.00	186.60 ± 48.40	0.742	255.20 ± 550.00	235.10 ± 55.20	**0.021**	262.00 ± 42.00	240.50 ± 45.00	**0.003**
HbA1c (%)	4.78 ±	4.71 ±	0.664	7.74 ±	7.68 ±	0.776	4.75 ±	4.68 ±	0.609	7.62 ± 1.78	7.30 ± 1.86	0.284
Fasting	13.50 ±	12.80 ±	0.694	20.40 ±	19.60 ±	0.794	15.10 ±	14.60 ±	0.752	26.80 ± 21.50	24.00 ± 20.80	0.421

3.4 Association of clinical parameters and genotype distribution of SNP rs1800976

The correlation of the genotypes of rs1800976 (CC vs CG +GG) with the biochemical parameters is demonstrated in Table 5. There were no great differences found between control and T2DM groups ($p > 0.05$).

The genotypes CG+GG in the CAD group had a significant difference in the levels of triglycerides ($p = 0.021$) and HDL-C levels ($p = 0.013$).

CG+GG genotypes were found to have an increased level of triglycerides ($p = 0.004$), reduced HDL-C ($p = 0.036$), increased total cholesterol ($p = 0.020$) and raised DBP ($p = 0.007$) in T2DM+CAD.

Table 5: Comparison of Clinical and Biochemical Parameters Between Genotypes (CC vs CG+GG)

Parameter	**Control CC (n=58)**	**Control CG+GG (n=92)**	**p-value**	**T2DM CC (n=500)**	**T2DM CG+GG (n=1000)**	**p-value**	**CAD CC (n=16)**	**CAD CG+GG (n=134)**	**p-value**	**T2DM+CAD CC (n=24)**	**T2DM+CAD CG+GG (n=126)**	**p-value**
Age (years)	54.90 ± 12.00	55.10 ± 12.40	0.922	55.70 ± 12.80	55.40 ± 11.80	0.892	54.60 ± 12.80	54.90 ± 12.20	0.925	57.30 ± 11.50	57.00 ± 11.90	0.908
BMI (kg/m²)	24.86 ± 3.6	25.14 ± 3.9	0.630	26.62 ± 4.1	26.44 ± 4.0	0.763	26.0 ± 3.8	**27.3 ± 4.2**	**0.048**	27.1 ± 4.3	28.4 ± 4.6	0.076
SBP (mm	122.0 ±	121.7 ±	0.720	131.0	130.5 ±	0.839	124.0	127.5 ±	0.211	126.5 ± 1	130.5 ± 1	0.115

Hg)	4.9	5.1		±14.3	14.0		±10.2	10.5		1.0	1.6	
DBP (mmHg)	81.2±4.6	81.9±4.8	0.374	84.4±8.1	84.9±8.4	0.726	81.0±7.6	85.0±7.9	0.062	82.0±7.0	**86.5±7.5**	**0.007**
FBG (mg/dL)	94.2±10.1	95.8±10.2	0.348	162.0±500.0	160.5±548.5	0.861	95.5±12.0	94.0±11.5	0.641	167.0±556.0	161.2±558.0	0.647
HbA1c (%)	4.75±0.97	4.80±1.01	0.763	7.78±1.31	7.70±1.25	0.721	4.72±0.84	4.70±0.86	0.929	7.55±1.80	7.40±1.82	0.711
Triglycerides (mg/dL)	107.5±49.0	104.0±50.5	0.674	171.0±345.0	170.5±355.0	0.933	150.0±600.0	**190.0±588.0**	**0.021**	160.0±720.0	**210.0±700.0**	**0.004**
HDL-C (mg/dL)	46.5±12.	45.2±12.	0.527	40.2±11	40.5±11.	0.877	44.5±1	**36.0±10.**	**0.013**	42.0±13.5	**35.5±12.2**	**0.036**

dL)	0	6		1.0	5		1.8	**8**				
LDL-C (mg/dL)	103.0±78.0	105.5±79.0	0.849	122.0±44.0	123.5±44.5	0.845	160.0±46.0	180.0±46.5	0.117	168.0±54.0	185.0±52.5	0.165
Total Cholesterol (mg/dL)	175.5±73.0	178.0±74.0	0.839	188.0±48.0	187.0±47.5	0.904	235.0±50.0	255.0±52.0	0.149	242.0±42.0	**265.0±44.0**	**0.020**
Fasting Insulin (µIU/mL)	13.0±10.5	13.5±11.0	0.781	19.8±18.8	20.2±19.0	0.903	15.0±9.5	14.5±9.8	0.845	25.0±21.0	23.5±20.5	0.750

3.5 Haplotype analysis

The result of haplotype analysis is presented in Table 6. CG (OR = 2.20, p < 0.001) and TG (OR = 2.60, p < 0.001) haplotypes were also highly prevalent, and less prevalent in the CAD group, and CC (OR = 0.51, p = 0.0007) and TC (OR = 0.42, p < 0.001).

The same tendency was noted in the T2DM+CAD group with the increase of CG (OR = 1.95, p = 0.001) and TG (OR = 2.34, p = 0.003) haplotypes at the expense of the CC and TC ones.

There were no considerable differences in the T2DM group ($p > 0.05$).

Table 6. Haplotype association analysis

Haplotype	Control (freq)	T2DM (freq)	Chi² (T2DM)	p-Value (T2DM)	OR [95% CI] (T2DM)	CAD (freq)	Chi² (CAD)	p-value (CAD)	OR [95% CI] (CAD)	CAD+T2DM (freq)	Chi² (CAD+T2DM)	p-Value (CAD+T2DM)	OR [95% CI] (CAD+T2DM)
CC	94 (0.313)	109 (0.363)	1.675	0.227	1.25 [0.891–1.755]	57 (0.19)	12.115	0.000678	0.5144 [0.352–0.752]	60 (0.2)	10.098	0.0001	0.5447 [0.377–0.796]
CG	92 (0.306)	97 (0.323)	0.193	0.725	1.08 [0.765–1.524]	148 (0.493)	12.177	0.000042 6	2.201 [1.576–3.073]	139 (0.463)	15.549	0.000109	1.951 [1.397–2.726]
TC	94 (0.313)	73 (0.243	3.659	0.068	0.704 [0.49	48 (0.16)	19.521	0.000013 6	0.417 [0.28	58 (0.193)	11.419	0.0000098	0.5255 [0.36–
		)			2–1.009]				1–0.6188]				0.765]
TG	20 (0.066)	21 (0.07)	0.026	0.999	1.053 [0.558–1.987]	47 (0.156)	1.248	0.000658	2.6 [1.5–4.5088]	43 (0.143)	9.381	0.003	2.3422 [1.342–4.0877]

4. Discussion

The current research assessed the relation between ABCA1 gene polymorphisms (rs1800977 and rs1800976) and T2DM and CAD, as well as their presence in the case of their combination in a population in North India. The biochemical results showed that there was a significant change in lipid profile, glycemic and blood pressure levels especially in the T2DM+CAD group, which showed an increased cardiometabolic risk. These findings are in line with the earlier research that dyslipidemia and hyperglycemia are known to interact with acceleration of atherosclerosis and cardiovascular complications [21,22].

Genetic analysis showed that there is no significant correlation between the disease susceptibility and the rs1800977, which is consistent with previous findings that show it plays a limited and non-reliable role in different populations [23,24]. Conversely, rs1800976 was highly associated with CAD and T2DM+CAD where G and GG genotypes were associated with higher risk. This has been also reported in prior studies which have indicated that ABCA1 promoter variants influence cholesterol efflux and HDL metabolism and are thus contributory to atherosclerotic progression [25,26].

Moreover, the genotype-phenotype correlation showed that the variations of the genotype of the rs1800976 gene were linked to poor lipid profiles, such as high triglycerides and low levels of HDL-C, which is why it is believed that the genotype is functional in the process of lipid regulation. Haplotype analysis also found out that CG and TG haplots were related with higher disease risk, but CC and TC were found to be protective. These

results are consistent with the findings of studies indicating that joint genetic influences could be more significant on cardiometabolic vulnerability compared to SNPs alone [27].

5. Conclusion

In conclusion, this study demonstrates that genetic variants rs1800977 and rs1800976 significantly influenced biochemical profiles in CAD and CAD+T2DM patients but not in healthy or T2DM-only individuals in the population of Haryana state. Our findings support the role for ABCA1 variants in cardiovascular risk among diabetic patients. While rs1800977 showed limited associations, rs1800976 might be a significant predictor of CAD and combined T2DM+CAD, indicating its importance as a genetic marker for risk stratification. Larger multi-ethnic research and functional analyses are needed to validate these results and investigate therapeutic applications in precision medicine.

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