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Research Article

CORRELATION BETWEEN APOB100/APOA1 RATIO AND INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: Various lipid abnormalities are associated with Type 2 diabetes, thereby increasing the risk of cardiovascular disease and metabolic syndrome. The objective of the study is to correlate apolipoprotein ratio with insulin resistance (IR) to understand its role in Type 2 diabetes mellitus.

Methods: The study population included 416 subjects of which 197 were non-diabetic and remaining 219 were non-diabetic and served as control subjects. Body mass index was calculated. Fasting plasma glucose, insulin, glycated hemoglobin levels, total cholesterol, triglyceride and high-density lipoprotein, ApoA-1, and ApoB-100 were measured using commercially available kits. Statistical analysis was performed with SPSS for Windows 16.0. Significance was defined as $p<0.05$.

Results: Apolipoprotein A-1 levels were lower in the diabetic group whereas apolipoprotein B-100 levels, apolipoprotein ratios were higher in the diabetic group. ApoB100 and apolipoportein ratio showed a positive correlation with IR.

Conclusions: The study results indicate that apolipoprotein B100/ApoA-1 ratio can act as a strong biomarker for IR.

Keywords: Apolipoproteins, Insulin resistance, Diabetes, Dyslipidemia.

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INTRODUCTION

Prevalence of diabetes is increasing in a alarming rate worldwide. A total of 72.1 million diabetic cases have been identified in 2013 of which 65.1 million were in India [1]. Epidemiologic studies suggest that the risk of developing dyslipidemia during lifetime is said to be increased with diabetes mellitus.

It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease [2,3]. At present, India faces an uncertain future in relation to the potential burden that diabetes may impose on the country [4]. Many factor influences affect and prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges. Genetic factors coupled with environmental influences such as obesity-associated with rising living standards, steady urban migration, and lifestyle changes contribute to the multifactorial etiology of diabetes in India [5-7].

Dyslipidemia is one of the common disorders which are seen in most of the diabetes patients. Insulin resistance (IR) is a metabolic disorder independently associated with cardiovascular (CV) disease [8-10]. IR is associated with aging and a cluster of important cardiometabolic risk factors (dyslipidemia, arterial hypertension, hyperglycemia, and obesity) and is believed to be the common shared pathophysiological disturbance [11-14]. Thus, accurate and early prediction and detection of IR are very important in clinical practice so as to identify patients at high risk for CV disorders.

ApoB and ApoA-I are the two major apolipoproteins involved in lipid transport and in the processes causing atherosclerosis and its complications [15]. ApoB100 is the main structural apolipoprotein of low-density lipoproteins (LDL) and there is only one molecule of ApoB100 per LDL particle [16]. ApoA-I reflects the antiatherogenic potential in high-density lipoprotein (HDL) particles; the higher the value, the better the protection against CV risk [17]. Therefore, in this study, we analyzed the apolipoprotein A1 and apolipoprotein B in diabetic and non-diabetic individuals and assessed the association between IR and apolipoprotein B/apolipoprotein A-I ratio in diabetic and non-diabetic individuals.

METHODS

Study population

The study population included 416 subjects individuals of which 197 were confirmed cases of Type 2 diabetes mellitus (T2DM) and remaining 219 were non-diabetic and served as control subjects under the age group of 30–60 years. Subjects were excluded if they have orthopedic limitations, weight loss/gain over the previous 6 months, or any diagnosis of vascular disease, Type 1 diabetes mellitus, cancer (clinically or by anamnesis), renal disease, liver disease, thyroid disease, and acute or chronic inflammatory diseases. Subjects consuming any medications (antihypertensive, antidyslipidemic, and antithrombotic drugs).

This study was reviewed and approved for human subjects by the Central Ethics Committee of Nitte University, Ref INST.EC/EC/47/2016-17.

Clinical measurements

Body weight and height were measured. Body mass index (BMI) was calculated as body weight in kilograms divided by height in square meters (kg/m^2). Venous blood samples were drawn after a minimum of 8 h of fasting. Plasma insulin level was measured commercially available enzyme-linked immunosorbent assay kits. IR was calculated with the homeostasis model assessment of IR (HOMA-IR) as described by Matthews *et al.* [17] (fasting serum insulin [μU/ml]×fasting serum glucose [mmol/l]/22.5). Fasting plasma glucose was measured by glucose oxidase method (LyphoCHEK™AGAPPE). Glycated hemoglobin (HbA1c) was measured using ion exchange resin method

on spectrophotometer (NycoCard READER). Total cholesterol (TC), triglyceride (TG), and HDL were measured using commercially available kits (LiquiCHEK™ AGAPPE).

LDL cholesterol (LDL-C) was estimated indirectly using the Friedewald formula. ApoB and ApoA-I levels were measured using commercially available kits (Agappe).

Statistical analysis

Statistical analysis was performed with SPSS for Windows 16.0. Parametric data are presented as mean±standard deviation. For categorical values, frequency counts, and percentages were applied. For group comparisons of means, t-test was applied and significance was defined as a $p<0.05$.

RESULTS

The results of the study cover a total of 416 subjects of which, 197 (47.3%) were diabetic and 219 (52.6%) were non-diabetic. Of which non-diabetic group includes 23% male and 29% female, and the diabetic group includes of 28.21% male and 20% female.

Age, BMI, fasting blood sugar (FBS), HbA1c, insulin, and HOMA-IR

Table 1 represents the mean age, height, weight, BMI, FBS, HbA1c, plasma insulin, and HOMA-IR values of both non-diabetic and diabetic group FBS, HbA1c, insulin, and HOMA-IR showed a statistically significant difference between non-diabetic and diabetic individuals ($p<0.05$) (Tables 1-3).

Correlation between apolipoproteins, lipid ratios, and HOMA-IR in non-diabetic and diabetic group

In non-diabetic subjects, LDL/HDL ratio showed a positive correlation with HOMA-IR and negative correlation with ApoB100, whereas a negative correlation was observed between ApoA1/HDL, ApoB/LDL, and HOMA-IR. ApoB100/ApoA1 ratio also showed a positive correlation with HOMA-IR. ApoB100 showed a positive correlation with HOMA IR (Table 4).

Table 1: Represents the mean age, height, weight, body mass index in diabetic, and non-diabetic group

Variables	Non-diabetic group	Diabetic group	p-value
	Mean±standard deviation	Mean±standard deviation	
Age (year)	48.61±10.94	53.14±10.40	<0.05
Height (cm)	156.51±10.54	157.66±10.06	NS
Weight (kg)	60.05±12.06	62.33±12.76	NS
Body mass index (kg/m^2)	24.34±3.66	24.83±5.04	NS

p=0.05 or less was be considered statistically significant

Table 2: Serum fasting blood glucose, insulin, and HOMA-IR in diabetic and non-diabetic group

Variables	Non-diabetic group	Diabetic group	p-value
	Mean±standard deviation	Mean±standard deviation	
FBS (mg/dl)	103.32±24.65	182.62±83.17	<0.05
HbA1c (%)	4.55 ±0.81	6.90±2.20	<0.05
Insulin (pmol/ml)	27.26±4.22	40.26±4.22	<0.05
HOMA-IR	0.87±0.75	2.51±1.48	<0.05

p=0.05 or less was be considered statistically significant. FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance

In diabetic subjects, ApoB100/ApoA1 ratio also showed a positive correlation with HOMA-IR. ApoB100 showed a positive correlation with HOMA IR (Table 5).

Distribution of dyslipidemia based on patient characteristics

Total recruited diabetic (197) subjects with and without dyslipidemia have been characterized based on age, sex, control of diabetes, and obesity (Tables 6 and 7).

Dyslipidemia, apolipoproteins, and HOMA-IR in diabetic group

Individual apolipoprotein levels (ApoA-1 and Apo-B100) and apolipoprotein ratios were compared in the diabetic group between dyslipidemic and non-dyslipidemic subjects. Statistically significant difference was found between dyslipidemic and non-dyslipidemic subjects with regard to ApoB100 and ApoB100/ApoA1 ratio. HOMA-IR did not show a statistically significant difference (Table 8).

DISCUSSION

In diabetic cases with metabolic abnormality, disturbances in the production and clearance of plasma lipoproteins are commonly found [18]. Diabetic dyslipidemia generally comprises postprandial lipidemia, high TG, reduced HDL-C, and low or relatively normal LDL-C [19,18], and the development of dyslipidemia may, therefore, be a signal of future diabetes onset. Debate still exists on the nature and extent of the association between conventional lipid measures and incident Type 2 diabetes [20].

This study is a representative of dyslipidemia and apolipoprotein ratios in diabetic and non-diabetic individuals. In the present study, we found that cholesterol, TG, LDL, HDL, and very LDL (VLDL) elevated in the diabetic group compared to the non-diabetic group.

Increased levels of TC in diabetic group compared to a non-diabetic group, maybe due to an increase in the plasma concentration of VLDL and LDL, which may be due to an increase in the hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation.

On studying the deranged individual lipid parameters among Type 2 diabetic subjects with dyslipidemia, the most prevalent lipid abnormality was high LDL (68%) followed by high TG (63%). An increase in the LDL in diabetic patients may be attributed to insulin. Insulin increases the number of LDL receptor, so chronic insulin deficiency might be associated with a diminished level of LDL receptor [20]. This causes an increase in LDL particles and results in the increase in LDL-C value in diabetes mellitus. Higher levels of TG may

Table 3: Lipid profile and apolipoproteins of study subjects in diabetic and non-diabetic group

Variables (mg/dl)	Non-diabetic group	Diabetic group	p-value
	Mean±standard deviation	Mean±standard deviation	
TC	180.59±64.64	206.59±66.26	<0.05
TG	175.02±91.20	206.40±134.78	<0.05
HDL	42.77±15.93	43.50±13.64	NS
LDL	102.85±64.94	121.38±60.39	<0.05
VLDL	35.00±18.24	41.28±26.96	<0.05
ApoA1	129.38±6.22	125.40±5.08	<0.05
ApoB100	76.53±1.98	86.20±6.23	<0.05
ApoB100/A-1	0.59±0.03	0.69±0.06	<0.05
ApoA1/HDLC	2.11±1.05	2.01±0.73	NS
ApoB100/LDLC	2.17±7.46	3.95±0.62	<0.05
LDLC/HDLC	2.93±2.42	3.16±2.07	NS

p=0.05 or less was be considered statistically significant. TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, LDLC: Low-density lipoprotein cholesterol, HDLC: High-density lipoprotein cholesterol

Table 4: Correlation between apolipoproteins, lipid ratios, and HOMA-IR in non-diabetic group

Status			ApoA-1/HDL	ApoB/LDL	ApoB100 /ApoA-1	ApoA-1	ApoB100	HOMA-IR
Non-diabetic	LDL/HDL	Pearson correlation	**−0.227****	**0.656****	−0.066	−0.013	**−0.168****	**0.004****
		Sig. (2-tailed)	**0.000**	**0.000**	0.258	0.826	**0.004**	**0.047**
	ApoA1/HDL	Pearson correlation		−0.079	0.065	−0.012	**0.129***	**−0.052****
		Sig. (2-tailed)		0.175	0.268	0.844	**0.027**	**0.037**
	ApoB/LDL	Pearson correlation			0.006	−0.030	−0.052	−0.017
		Sig. (2-tailed)			0.913	0.604	0.374	0.767
	Apo B100/ApoA1	Pearson correlation				**−0.896****	**0.479****	**0.019****
		Sig. (2-tailed)				**0.000**	**0.000**	**0.040**
	ApoA1	Pearson correlation					**−0.045****	0.007
		Sig. (2-tailed)					**0.040**	0.906
	ApoB100	Pearson correlation						**0.036****
		Sig. (2-tailed)						**0.034**

p=0.05 or less was be considered statistically significant. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 5: Correlation between apolipoprotein and lipid ratio in diabetic group

Status			ApoA1/HDL	ApoB/LDL	ApoB100 /ApoA1	ApoA1	ApoB100	HOMA-IR
Diabetic	LDL/HDL	Pearson correlation	**−0.651****	**0.713****	−0.028	−0.103	−0.109	0.116
		Sig. (2-tailed)	**0.000**	**0.000**	0.735	0.216	0.193	0.165
	ApoA1/HDL	Pearson correlation		**−0.247****	**0.251****	0.009	**0.317****	−0.041
		Sig. (2-tailed)		**0.003**	**0.002**	0.913	**0.000**	0.626
	ApoB/LDL	Pearson correlation			−0.043	0.017	−0.044	0.126
		Sig. (2-tailed)			**0.604	0.838	0.595	0.131
	Apo B100/ApoA1	Pearson correlation				**−0.605****	**0.814****	**0.312****
		Sig. (2-tailed)				**0.000**	**0.000**	**0.000**
	ApoA1	Pearson correlation					−0.032	0.009
		Sig. (2-tailed)					0.700	0.912
	ApoB100	Pearson correlation						**0.005***
		Sig. (2-tailed)						**0.022**

p=0.05 or less was be considered statistically significant. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 6: Patient characteristics and prevalence of dyslipidemia in diabetic group

Characteristic	No. of patients (n=197)	%	Patients with dyslipidemia (n=129)	%
Age				
30–45	57	28.93	23	17.82
45–60	140	71.06	106	82.17
Sex				
Male	107	54.31	77	59.68
Female	90	45.68	52	40.31
Control of DM				
Controlled	79	40.10	35	27.03
Uncontrolled	117	59.39	94	72.97
Obesity				
Obesity (BMI>23)	120	60.91	97	75.19
Non obese (BMI <23)	76	38.57	32	24.80

Percentage in each group is from total patient in that group. BMI: Body mass index

Table 7: Pattern of dyslipidemia in diabetic group

Variables	Diabetic subjects with dyslipidemia n (%)
Mixed dyslipidemia	
High TG, high LDL-C, and low HDL-C	57 (44.2)
Combined dyslipidemia	
High TG and low HDL-C	12 (9.2)
High TG and high LDL-C	15 (10.8)
High LDL-C and low HDL-C	10 (7.8)
Isolated single parameter dyslipidemia	
High TG	11 (8.74)
High LDL	15 (12.16)
Low HDL	18 (14.3)

TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

also be due to insulin deficiency in hyperglycemia and mobilization of fatty acids from adipose tissue.

The current study is not in accordance with few previous studies, which showed lower levels of HDL in diabetic patients. The study done by Bodhe *et al*. [18], on Indians showed that HDL-C levels varied with glycemic control. As in our study, all patients with diabetes showed higher HDL level when compared to non-diabetic individuals but were statistically insignificant. The reason for insignificant result as also suggested by Garg *et al*., 2016 [1], appears that average HDL concentration in all Asian subgroups, whether residing in India or elsewhere, is lower than Caucasians [20]. Mixed dyslipidemia was the most common dyslipidemia pattern observed in our study.

The ApoB number indicates the total number of atherogenic particles; the higher the number, the higher the CV risk [21]. According to Barkas *et al*. [22], Apo-B represents an ideal marker for the management of dyslipidemia in individuals with diabetes.

High level of total blood cholesterol, particularly in the form of LDL-C, has been recognized for over three decades as a major risk factor for developing coronary heart disease [23]. However, recent research has shown that LDL-C is not the only lipoprotein species involved in atherogenesis. Elevated levels of intermediate-density lipoprotein and

Table 8: Comparison of dyslipidemia, apolipoprotein ratio, and HOMA-IR in diabetic group

Variables	Dyslipidemia	Mean	Standard deviation	Standard error	95% confidence interval for mean		p-value
					Lower bound	Upper bound	
ApoA1	Absent	127.28	5.83	0.29	126.70	127.87	0.240
	Present	126.23	5.09	0.75	124.72	127.740	
ApoB100	Absent	81.56	6.49	0.33	80.91	82.21	0.012**
	Present	84.09	5.57	0.82	82.43	85.74	
Apo B100/ApoA1	Absent	0.643	0.07	0.003	0.64	0.65	0.017**
	Present	0.66	0.06	0.009	0.65	0.69	
HOMA-IR	Absent	2.76	0.99	0.12	116.90	117.17	0.108
	Present	3.14	1.19	0.21	146.70	127.87	

Correlation is significant at the 0.05 level (2-tailed). HOMA-IR: Homeostasis model assessment of insulin resistance

VLDL are also associated with increased CV risk. All these potentially atherogenic lipoproteins contain one ApoB molecule and therefore, the total ApoB value indicates the total number of potentially atherogenic lipoproteins [24,25]. The association of ApoB with incident Type 2 diabetes has been proven with improved risk prediction compared to LDL-C or HDL-C [24]. Thus, ApoB has been found to be a better predictor of risk than LDL-C, VLDL, and chylomicrons.

ApoA-I reflects the antiatherogenic potential in HDL particles; the higher the value, the better the protection against CV risk [26], but the ApoA1 was lower in diabetic group, this was not in accordance to the previous studies by Onat *et al*., 2010 [26] who reported that high ApoA1 levels independently predicted incident Type 2 diabetes among a sample of Turkish participants.

In diabetic subjects, ApoB100/ApoA1 ratio also showed a positive correlation with HOMA-IR, suggesting that as apolipoprotein ratio increases, IR also increases. ApoB100 also showed a positive correlation with HOMA IR.

The ApoB/ApoA-I ratio indicates the balance between atherogenic and antiatherogenic particles; the higher the value, the higher the CV risk, the ApoB/ApoA1 ratio is strongly associated with IR [25]. However, only a few studies have shown the associations between apolipoprotein levels and the risk of diabetes. Hwang *et al*. [27] indicated that the ApoB/ApoA-I ratio is an effective predictor of T2DM in the Korean population. The ApoB/LDL-C ratio has been associated with T2DM in a population-based study of Turkish adults14 and ApoB in the Aboriginal Canadian population [28].

CONCLUSIONS

Based on our study results, it is clear that aggressive dyslipidemia management is the need of the hour in diabetic individuals. In diabetic individuals, the overall control rate of dyslipidemia is low. The pattern of lipid profile of the study may, therefore, be a significant risk factor for the increased rate of CV problem in diabetics than normal individuals. ApoA1/ApoB-100 was highly associated with IR in both non-diabetic and diabetic groups. Further study is needed to determine the role of ApoA1/HDL-C in the development of diabetes, as susceptible individuals are increasingly considered as candidates for appropriate interventions.

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AUTHORS' CONTRIBUTIONS

Both authors have contributed equally to planning, execution, data analysis, preparation, and editing of the manuscript.

CONFLICTS OF INTEREST

We declare that there are no conflicts of interest.

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