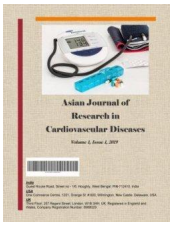

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An Age-dependent Association between Diabetic Hyperglycemia and Dyslipidemia in Patients with Ischemic Heart Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Author MAS designed the study. Author HN performed the statistical analysis. Author SA managed the literature searches, performed the experimental work, wrote the protocol and wrote the first draft of the manuscript. Authors SA, FA and MI managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Dyslipidaemia and diabetes mellitus (DM) are major causes of cardiovascular diseases. Both of these two have varying effects on individuals of different age and gender. An age-dependent association between blood glucose level and lipid profile of patients with DM and ischemic heart disease (IHD) were investigated.
Design of Study: The Age-dependent association between the selected variables was determined by the linear, exponential, and polynomial regression models.
Place and Duration of Study: The present study was conducted at the outdoor patient department of Chaudhary Pervez Elahi Institute of Cardiology, Multan, Pakistan during June 2014-August 2018.
Methodology: The study includeda total of 756 individuals (Age range = 21-80 years) divided into male (n = 420) and female (n = 336) gender groups each subdivided into four groups i) Non-diabetic

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without IHD, ii) Non-diabetic with IHD, iii) Diabetic without IHD, and iv) Diabetic with IHD. Each of the four groups was further divided into six age groups. The blood samples were analyzed for fasting blood glucose (FBG) and lipid profile using standard methods.

Results: The diabetic patients with and without IHD of both genders showed significant elevation in FBS and components of lipid profile except high-density lipoprotein. Regression analysis showed an age-dependent significant increase ($p < 0.05$) in the studied parameters of cardiac patients with and without IHD. The components of the lipid profile of diabetic patients with IHD showed positive linear, exponential, and polynomial correlations with FBG of the respective group.

Conclusion: The age-dependent elevation in FBG, TG, CH, LDL and VLDL, and positive correlations between lipid profile and FBG of diabetic patients with IHD provides a piece of evidence for a strong association between diabetic hyperglycemia, dyslipidemia, and ischemia. The study would be a significant contribution in the literature and useful information for physicians regarding the interrelationship of the three clinical disorders.

Keywords: Diabetes mellitus; dyslipidemia; fasting blood glucose; hyperglycemia; ischemic heart disease; lipid profile.

1. INTRODUCTION

The prevalence of Type-II Diabetes mellitus (DM), a metabolic disorder known to be associated with hyperglycemia, is continuously increasing and creating medical, social and economic problems in modern societies. DM is a well-known risk factor for cardiovascular diseases (CVD) such as coronary heart disease (CHD), ischemic heart disease (IHD), peripheral vascular disease, myocardial infarction (MI), congestive heart failure, atherosclerosis, stroke, and anginas [1]. Patients with type-II diabetes mellitus have been reported to be at 2 to 4 folds higher risk of CVD than individuals without DM. The long-term survival rate of patients with DM and coronary artery disease (CAD)is lower than that of individuals without DM but with coronary artery disease [2]. DM has been also found to cause vascular inflammation by promoting the accumulation of foam cells in the sub endothelial space by increasing the production of leukocyte adhesion molecules and pro-inflammatory mediators [3]. The studies have shown that DM contributes to develop diabetic cardiomyopathy due to myocardial damage after ischemic strokes [4,5].

Dyslipidaemia, a pathological condition with abnormal lipid profile, is another major risk factor associated with DM, CHD, and IHD [6,7]. It is common in Egyptian, Sudanese, European and American populations [8]. IHD has ever been found to be directly correlated with triglyceride (TG), cholesterol CH and low-density lipoprotein (LDL) and inversely correlated with high-density lipoproteins (HDL) [9,10]. Studies have shown a strong association between dyslipidemia and Type-II DM [11,12]. A significant increase in TG, CH and LDL and a decrease in HDL level of the patient with Type-II DM has been observed [13,14]. Dyslipidemia is a risk factor and a significant contributor to the development of Type-II DM at a younger age [15]. High glycemic diets have been reported to influence not only the lipid and metabolic biomarkers but also the biomarkers of inflammation, coagulation and vascular function [16]. Despite DM and dyslipidemia, the male gender has been also considered as a risk factor of CVD. The prevalence of IHD is high in males as compared to females [17,18]. According to the National Cholesterol Education Program (NCEP), male sex is considered a risk factor due to 3-4 times higher prevalence of IHD in men than in women. Release of estrogen in women is known to reduce the incidence of IHD and cardiovascular mortality [19].

IHD is generally characterized by the reduced blood supply to heart muscles due to the narrowing of coronary arteries by plaque formation also known as atherosclerosis. There are several factors such as excessive alcohol consumption, diabetes mellitus, hypertension and cigarette smoking involved in the onset of atherosclerosis [20,21]. The most important factor causing atherosclerosis is a high blood plasma concentration of CH in the form of LDL cholesterol. A high level of LDL cholesterol is an important risk factor for CAD [22]. Cholesterol is transported by LDL particles into arterial wall attracts macrophages which engulf LDL particles and plaque formation occurs. In diabetic patients glycation of Apo-B increases which contributes to the development of atherosclerosis [23]. The reduction in hypercholesterolemia is associated with a decrease in atherosclerosis [24]. The other

components of lipid profile, acting as markers of CVD, include HDL and triglycerides (TG). Low HDL and high TG levels have been reported in patients of cardiovascular accidents [25,26]. HDL exerts its atheroprotective effects by facilitating the reverse transport of cholesterol *via* its anti-inflammatory properties [27].

In Pakistan, the majority of people frequently use fat and carbohydrate-rich meals in their nutrition. The increasing trends in the use of fast foods and lipid-rich fried products may be the major cause of diabetes, dyslipidemia, and cardiovascular abnormalities in well to do families of Pakistan. However, little data has been found regarding the prevalence of DM, dyslipidemia, and CVD in the population residing in Southern Punjab, Pakistan. The present study was, therefore, planned to investigate the age-dependent variation in fasting blood glucose and lipid profile of the Pakistani population with and without DM and IHD. The study would provide useful information for physicians about the association of DM with lipid profile and IHD.

2. MATERIALS AND METHODS

2.1 Study Design

The present study was conducted at the outdoor patient department of Chaudhary Pervez Elahi Institute of Cardiology, Multan, Pakistan. The study was performed on a total of 756 individuals including 420 males and 336 females. All the participants of each group were subjected to clinical screening for diabetes and renal and hepatic problems by a physician based on the clinical history and symptomatic observations. The individuals within the age of 21-80 years with no clinical history or symptoms of any disease were selected as control. The individuals with a history of DM and CVD in the similar range of age were selected as the diabetic or IHD groups. However, the individuals suffering from or having a clinical history of renal and hepatic diseases, regular smokers (smoking at least 1-5 cigarettes/day in routine) and the individuals of an age below 21 year and above 80 years were excluded from the study.

Based on their clinical history of DM and screening for CVD, each of the male and female groups was subdivided into four groups i) Non-diabetic without IHD, ii) Non-diabetic with IHD, iii) Diabetic without IHD, and iv) Diabetic with IHD. Each subgroup was further divided into six age groups like 21-30, 31-40, 41-50, 51-60, 61-70 and 71-80 years. The non-diabetic individuals without IHD were used as the normal control while the diabetic patients without IHD were considered as the diabetic control. Age-dependent significant variations in fasting blood glucose (FBG) and lipid profile of each group were studied by regression analysis. The distribution of individuals is in each group is given in Table 1. The social characteristics of the participants are presented in Table 2.

2.2 Analysis of Blood Samples

All the volunteers were directed to remain fasting for 12 h before collection of blood samples. Blood samples (5 ml from each individual) were collected using a disposable syringe and a portion of blood (2 mL) was subjected to immediate determination of fasting blood glucose level. The sera were obtained from the rest of the blood by centrifugation at 3000 rpm for 20 min at room temperature. The sera were stored in Eppendorf tubes at -4°C and subjected to an analysis of the lipid profile.

The previously reported glucose oxidase enzymatic method was used to determine the serum glucose level using commercially available kits on an automated biochemistry analyzer (Micro-lab 300) [28]. The lipid profile including CH, TG, and HDL was determined by standard UV methods using kits by Human, Germany Cat. No.10017, 10724 and 10018 respectively on Micro-lab 300 [29–31]. The LDL and very-low-density lipoprotein (VLDL) were determined by using Fried Wald's formula [30].

$$LDL(mg/dL) = Totalcholesterol - (Triglycerides/5) - HDL \quad (1)$$

$$VLDL(mg/dL) = Triglycerides/5 \quad (2)$$

2.3 Statistical Analysis

The results were expressed as the means ± SD of at least five subjects in each of the study groups. The means were compared by one-way analysis of variance (ANOVA) and the significant differences among various study groups regarding the levels of studied parameters were analyzed by applying Tukey's multiple range tests at confidence level $p \leq 0.05$ using statistical software SPSS 19. The trends of significant age-dependent variation and the statistical correlation between FBG level and the parameters of lipid profile in the studied parameters of the control and the study groups were explained by regression analysis of the experimental data using Microsoft Excel (Version 2010).

Table 1. Distribution of individuals in various groups on the basis of gender, age and clinical condition

Age	Male				Female				Total
	Non-diabetic without IHD	Non-diabetic with IHD	Diabetic without IHD	Diabetic with IHD	Non-diabetic without IHD	Non-diabetic with IHD	Diabetic without IHD	Diabetic with IHD	
21-30	5	28	5	29	5	27	5	19	208
31-40	5	27	5	29	5	27	5	18	194
41-50	5	28	5	29	5	25	5	17	200
51-60	5	29	5	29	5	25	5	21	200
61-70	5	29	5	29	5	25	5	21	226
71-80	5	29	5	45	5	27	5	24	247
Total	30	170	30	190	30	156	30	120	756*

**Male 420, Female = 336*

IHD: Ischemic heart disease

Table 2. Some social characteristics of the participants

Variable	Total	Male	Female	p-value
Total participants No. (%)	756	420 (55.56)	336 (44.44)	0.00
Education				
Uneducated	141	54 (12.86)	87 (25.89)	0.00
High school	319	186 (44.29)	133 (39.58)	0.02
College degree	179	105 (25)	74 (22.02)	0.03
University degree	117	75 (17.86)	42 (12.5)	0.01
Marital status				
Unmarried	72	46 (10.95)	26 (7.73)	0.01
Married	620	347 (82.62)	273 (81.25)	0.63
Divorced/Widow	64	27 (6.42)	37 (11.02)	0.00

3. RESULTS

The social characteristics of the participants are presented in Table 2. Overall 756 participants were included in the study out of which 420 were males and 336 females. Among both of the male and female participants some of the participants (12.86 and 25.89% respectively) were uneducated. The rest of the participants were educated up to high school level (39.58-44.29%), college level (22-25%) and university level (12-17%). Majority of the participants were married (81.25-82.62%) while the number of unmarried (7.73-10.95%) and divorced/widows (6.42-11.02%) were comparatively low.

In the present study, FBG of male and female individuals of different study groups ranged from 86±10 to 233±52 and 86±12 to 319±56 mg/dL respectively. The levels of the components of the lipid profile of male and female individuals of the study groups ranged from TG: 157±24 to 196±60 and 159±26 to 263±53 mg/dL, CH: 180±34 to 211±41 and 170±33 to 274±32 mg/dL, HDL: 57±9 to 102±13 and 56±11 to89±10 mg/dL, LDL: 115±15 to 157±34 and 110±18 to 185±23 mg/d Land VLDL: 37±9 to 66±9 and 40±12 to 65±8 mg/dL respectively (Table 3).

One way analysis of variance (ANOVA) of the experimental results showed that the FBG level of both the male and female patients of different study groups was significantly different ($p < 0.05$) from those of the individuals of the respective control group. The levels of the studied components of the lipid profile of the patients of both genders in the study groups were also found to be statistically different from those of their respective controls (Table 2). The diabetic patients of both genders without IHD showed comparatively higher levels of FBS, TG and LDL levels among the study groups. The CH level was found to be comparatively high in male diabetic patients with IHD and the female diabetic patients without IHD. The HDL and VLDL levels were found to be comparatively high in both the male and female diabetic patients with IHD. However, the levels of the studied parameters of the control group (non-diabetic without IHD) of both genders were in the normal ranges [32,33].

4. DISCUSSION

Diabetes is a prime risk factor for cardiovascular disorders including peripheral vascular disease, ischemic stroke, and coronary artery disease. The studies have shown that hyperglycemia, pre-diabetes and presence of the metabolic syndrome contribute to ischemic strokes followed by myocardial damage [5,34,35]. Glycemic control is highly influenced by lipid abnormalities, known as dyslipidemia, in patients with DM. Insulin resistance and metabolic syndrome are the main causes of dyslipidemia in type 2 DM [36]. Both of the DM and dyslipidemia further contribute to IHD and other cardiovascular abnormalities.

In the present study, the elevated levels of FBG and the components of lipid profile in diabetic patients with and without IHD provide a piece of evidence for a strong association among hyperglycemia, dyslipidemia, and ischemia. The regression analysis of data generated the following generalized linear, exponential, and second-order polynomial regression equations (Eq. 3, 4, 5 respectively) to explain the trends of age-dependent variation in the studied parameters.

$$y = Slope \times x \pm Intercept \quad (3)$$

$$y = Intercept \times e^{slope \times x} \quad (4)$$

$$y = Slope \times x^2 \pm Slope \times x \pm Intercept \quad (5)$$

where y is the particular parameter and x is a particular level of age.

Table 3. Experimental values of the fasting blood glucose (FBG) and components of lipid profile of different study groups

Parameter (mg/dL)	Male				Female				p-value
	Non-diabetic without IHD N = 30	Non-diabetic with IHD N = 170	Diabetic without IHD N = 30	Diabetic with IHD N = 190	Non-diabetic without IHD N = 30	Non-diabetic with IHD N = 156	Diabetic without IHD N = 30	Diabetic with IHD N = 120	
FBS	95±10^{c*}	86±10^{c**}	233±52^{ab}	198±38^{b}	96±10^{c}	86±12^{c}	319±56^{a}	189±36^{b}	0.001
TG	157±24^{b}	184±54^{ab}	196±40^{ab}	185±64^{ab}	159±26^{b}	179±46^{ab}	263±53^{a}	174±26^{b}	0.026
CH	188±18^{b}	180±34^{b}	201±39^{b}	211±41^{ab}	193±25^{b}	170±33^{b}	274±32^{a}	182±41^{b}	0.032
HDL	62±9^{bc}	77±9^{b}	57±9^{c}	102±13^{a}	56±11^{c}	77±10^{b}	49±8^{c}	89±10^{ab}	0.004
LDL	145±10^{b}	115±15^{c}	157±34^{ab}	131±27^{bc}	147±12^{b}	110±18^{c}	185±23^{a}	127±26^{bc}	0.002
VLDL	38±8^{c}	44±8^{bc}	37±9^{c}	66±9^{a}	41±8^{bc}	40±12^{bc}	45±10^{b}	65±8^{a}	o.006

**Values expressed as mean ± standard deviation of the N number of replicates.*

***The means labelled with the different alphabets in the same row are significantly different at 95% confidence level using Tukey's multiple range tests.*

IHD: Ischemic heart disease, TG: Triglycerides, CH: Cholesterol, HDL: High-density lipoprotein, LDL: low-density lipoprotein, VLDL: Very low-density

Table 4. Statistical value obtained from one-way analysis of variance, regression analysis, and statistical correlations of the experimental data

Study group	Parameter	Male			Female		
		p-value	Regression equation	R^2	p-value	Regression equation	R^2
Trends of age-dependent variations in FBG and components of lipid profile							
Non-diabetic without IHD	HDL	0.0315	y = 1.5661x2 - 13.66x + 81.59	0.9434			
Non-diabetic with IHD	TG	0.039	y = 7.1362x2 - 31.293x + 259.69	0.9041	0.033	y = 4.6786x2 - 16.786x + 179	0.9521
	CH	0.026	y = 20.992x + 194.86	0.7735			
	HDL	0.014	y = 8.018x2 - 38.849x + 325.81	0.9163			
	LDL				0.017	y = 6.38x2 - 27.763x + 126.23	0.9189
	VLDL				0.033	y = 24.236e0.1609x	0.877
Diabetic without IHD	FBG	0.003	y = 172.71e0.1195x	0.9409	0.001	y = 11.76x + 186.91	0.9084
	TG	0.002	y = 31.946x + 117.31	0.9741	0.018	y = 29.369x + 125.96	0.9654
	CH	0.022	y = 161.85e0.1016x	0.9154	0.001	y = 26.937x + 139.22	0.9368
	HDL	0.029	$y = 1.2411x^2 - 11.805x + 75.41$	0.9681	0.001	$y = 1.0161x^2 - 11.51x + 78.39$	0.9668
	LDL	0.00	y = 117.13e0.1149x	0.8523	0.000	$y = 116.81e^{0.1167x}$	0.8677
Diabetic with IHD	FBG	0.024	y = 26.873x + 98.445	0.9049	0.003	y = 30.605x + 83.216	0.953
	TG	0.002	y = 172.41e0.1207x	0.9011	0.038	$y = 136.91e^{0.099x}$	0.9572
	LDL	0.033	y = 7.2987x2 - 31.755x + 253.48	0.9668	0.038	y = 90.12e0.1248x	0.8924
	VLDL	0.003	y = 2.2479x2 - 9.7516x + 36.848	0.9935	0.001	$y = 29.052e^{0.1591x}$	0.8964

Study group	Parameter	Male			Female		
		p-value	Regression equation	R^2	p-value	Regression equation	R^2
Correlation between FBG and the components of lipid profile							
Non-diabetic without IHD	TG		$y = 0.032x^2 - 6.250x^{**} + 447.7$	0.034		$y = {}^{***}-0.071x2 + 12.82x - 409.0$	0.125
	CH		$y = 0.035x^2 - 6.051x + 439.3$	0.050		$y = -0.044x^2 + 9.386x - 294.5$	0.267
	HDL		$y = -0.032x^2 + 6.096x - 220.4$	0.158		$y = 0.031x^2 - 6.107x + 346.5$	0.199
	LDL		$y = 0.013x^2 - 2.127x + 227$	0.041		$y = 0.016x^2 - 3.243x + 300.1$	0.014
	VLDL		$y = -0.005x^2 + 1.549x - 59.61$	0.459		$y = -0.023x^2 + 4.651x - 190.2$	0.316
Non-diabetic with IHD	TG		$y = 156.3e^{0.001x}$	0.000		$y = 0.031x^2 - 5.320x + 402.8$	0.017
	CH		$y = 0.042x^2 - 6.559x + 429.3$	0.021		$y = -0.009x^2 + 1.723x + 95.98$	0.001
	HDL		$y = 0.087x^2 - 14.73x + 728.8$	0.035		$y = -0.311x + 103.3$	0.004
	LDL		$y = 0.049x^2 - 9.090x + 487.0$	0.028		$y = 85.16e^{0.001x}$	0.003
	VLDL		$y = 0.006x^2 - 1.109x + 93.67$	0.002		$y = 0.018x^2 - 2.967x + 154.0$	0.052
Diabetic without IHD	TG		$y = -0.008x^2 + 3.673x - 199.6$	0.105		$y = -0.003x^2 + 2.515x - 113.1$	0.353
	CH		$y = 0.000x^2 - 0.928x + 363.2$	0.377		$y = 0.001x^2 - 0.877x + 339.9$	0.373
	HDL		$y = 0.001x^2 - 0.531x + 113.5$	0.148		$y = 2E^{-05}x^2 - 0.042x + 58.30$	0.151
	LDL		$y = -0.001x^2 + 0.374x + 134.4$	0.182		$y = -0.001x^2 + 0.617x + 97.96$	0.152
	VLDL		$y = -0.000x^2 + 0.262x + 3.011$	0.043		$y = -0.000x^2 + 0.124x + 18.32$	0.132
Diabetic with IHD	TG		$y = 184.0e^{0.000x}$	0.004		$y = 118.8e^{0.001x}$	0.088
	CH		$y = 139.3e^{0.001x}$	0.108		$y = 119.3e^{0.002x}$	0.219
	HDL		$y = 23.47e^{0.005x}$	0.296		$y = 30.05e^{0.004x}$	0.194
	LDL		$y = 64.95e^{0.002x}$	0.173		$y = 52.33e^{0.003x}$	0.219
	VLDL		$y = 0.213x + 23.67$	0.099		$y = 0.480x - 26.11$	0.272

**y: The respective parameter and*

***x: Value of the respective parameter at a particular level of age, R^2: regression/correlation coefficient, IHD: Ischemic heart disease, ***The – sign in the regression equations indicates a negative correlation.*

FBG: Fasting blood glucose, TG: Triglycerides, CH: Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein'

The statistical parameters including the probability values, regression equations, and regression and correlation coefficients obtained from one-way analysis of variance, and regression analysis are given in Table 4.

The age-dependent significant ($p < 0.05$) variation in FBG levels of the control and study groups of both genders are presented in Fig. 1a, b. The regression analysis of data showed an age-dependent linear increase (R^2 = 0.9049-0.953) in FBG level of diabetic patients with IHD of both genders and female diabetic patients without IHD. The male diabetic patients without IHD showed an age-dependent exponential increase in FBG (R^2 = 0.9409). The age-dependent variation in FBG of the rest of non-diabetic individuals with and without IHD was found to be non-significant.

The age-dependent significant variation in TG and CH levels of the control and study groups of both genders are presented in Fig. 2a-d. An age-dependent second-order polynomial (R^2 = 0.9041, 0.9521), linear (R^2 = 0.9741, 0.9654), and exponential (R^2 = 0.9011, 0.9572) increase in TG levels of male and female patients was observed in non-diabetic with IHD, diabetic without IHD and diabetic with IHD study groups respectively. The CH level of male patients of the non-diabetic with IHD, diabetic without IHD and diabetic with IHD study groups was found to be increased in an age-dependent linear (R^2 = 0.7735), exponential (R^2 = 0.9154), and second-order polynomial (R^2 = 0.9163) fashion respectively. The CH level of female patients was found to be increased linearly (R^2 = 0.9368) only in diabetic patients without IHD.

Fig. 3a-f displays the age-dependent variation in lipoprotein levels of the control and study groups of both genders. The level of HDL was found to be decreased in a second-order polynomial trend in response to increases in the age of the male individuals of the control group (R^2 = 0.9434) and diabetic without the IHD study group (R^2 = 0.9681). The HDL level of female patients was decreased only in diabetic patients without IHD in a polynomial fashion (R^2 = 0.9681) in response to an increase in age. An exponential increase (R^2 = 0. 8523) in the LDL level of male diabetic patients without IHD and a polynomial increase (R^2 = 0.9668) in the level of the same parameter of diabetic patients with IHD was observed in response to an increase in the age. The LDL level of female patients was increased in a polynomial trend in non-diabetic patients with IHD and exponential trend in diabetic patients with and without IHD as a function of age (R^2 = 0.8677-9189). An age-dependent polynomial increase (R^2 = 0.9935) in the VLDL level of male patients was observed only in diabetic patients with IHD while in female patients it was increased exponentially as a function of age in non-diabetic and diabetic patients with IHD (R^2 = 0.877, 0.8964).

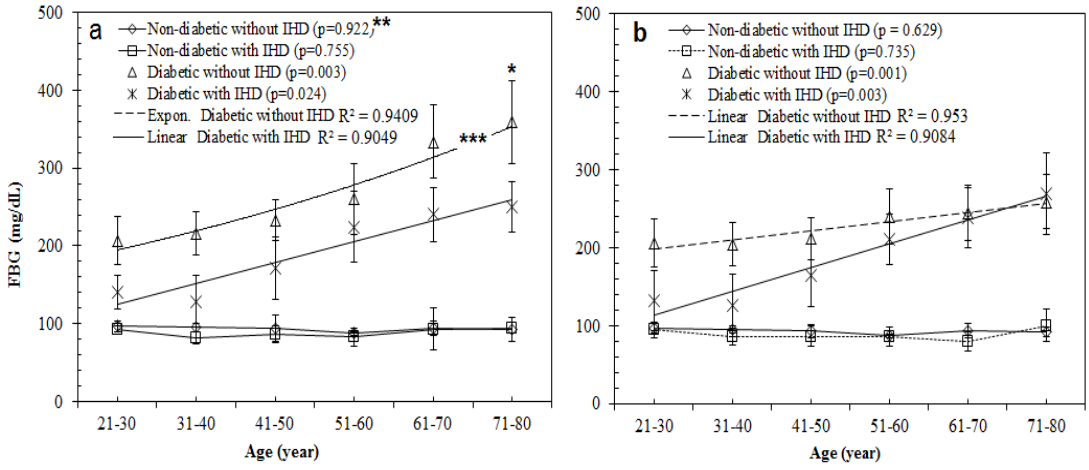

Fig. 1. Age-dependent variation in fasting blood glucose (FBG) level of various study groups

*a) Male, b) Female; *Error bar represents the standard deviation*

***p-value indicates the significance of variation among different age groups at a 95% confidence level ($p < 0.05$) using Tukey's multiple range tests.*

****The regression analysis was performed only on the data showing significant age-dependent variation in the response.*

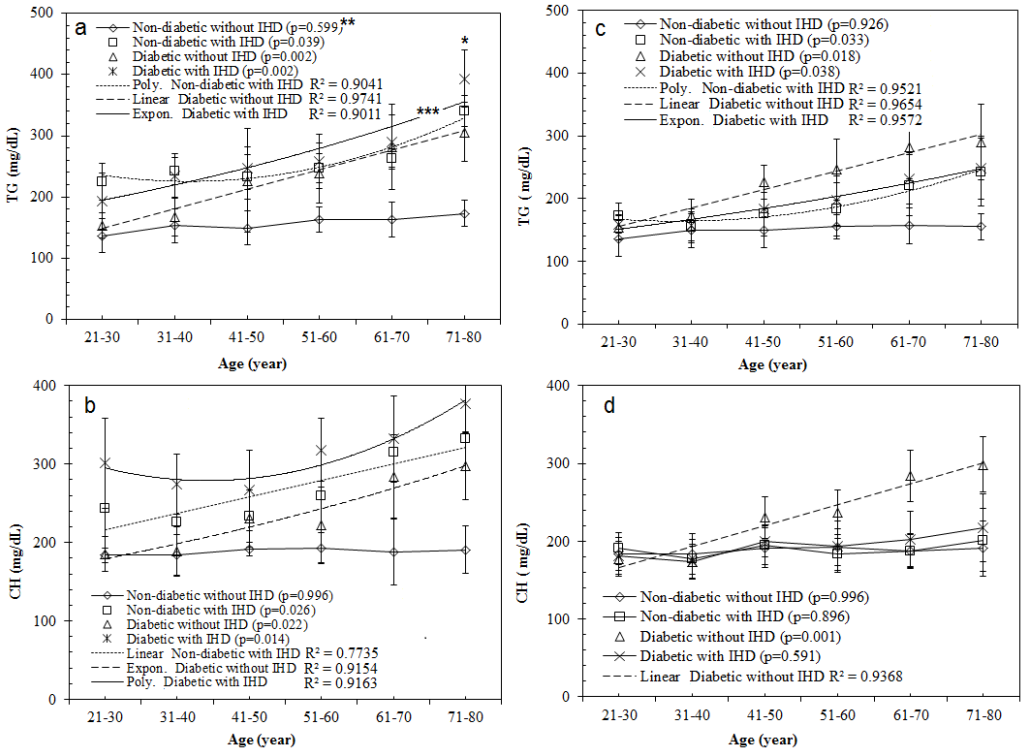

Fig. 2. Age-dependent variation in triglycerides (TG) and cholesterol (CH) levels of various study groups

a, b) Male, c, d) Female

**Error bar represents the standard deviation*

***p-value indicates the significance of variation among different age groups at a 95% confidence level ($p < 0.05$) using Tukey's multiple range tests.*

****The regression analysis was performed only on the data showing significant age-dependent variation in the response*

The correlations between lipid profile and FBG levels of male individuals of each study group are presented in Fig. 4a-d and those of female individuals are given in Fig. 4e-h. A polynomial correlation was observed between the FBG and components of lipid profile including TG, CH, LDL, and VLDL of the control individuals and non-diabetic patients with IHD of both genders. All of the studied components of the lipid profile of non-diabetic patients with IHD and TG, CH, and LDL of the control group showed a positive while HDL and VLDL showed a negative correlation with FBG. The TG, CH, and LDL of female control and CH, HDL, and VLDL of the female non-diabetic with the IHD group also showed a negative correlation with FBG. The CH and HDL of the diabetic patients without IHD of both genders showed a positive, while the rest of the parameters showed a negative polynomial correlation with the FBG. All of the components of the lipid profile of diabetic patients with IHD of both genders showed a positive exponential correlation with FBG except VLDL that showed a linear positive correlation with FBG.

The age-dependent significant elevation in FBG level of diabetic patients with IHD suggests a strong association between DM and IHD. An age-dependent elevation in CH, TG, LDL, and VLDL and a decrease in HDL levels of the diabetic and non-diabetic patients with IHD showed an association between dyslipidemia and IHD. The results are in agreement with those reported earlier [37,38]. Comparatively higher FBG, TG, CH and LDL and lower LDL levels in male diabetic and non-diabetic patients with IHD and above 50 years old were observed than those of female individuals of the respective study group. The elevation in lipid profile in diabetic patients without IHD may be attributed to the evidence that diabetic or pre-diabetic individuals have comparatively higher CH and

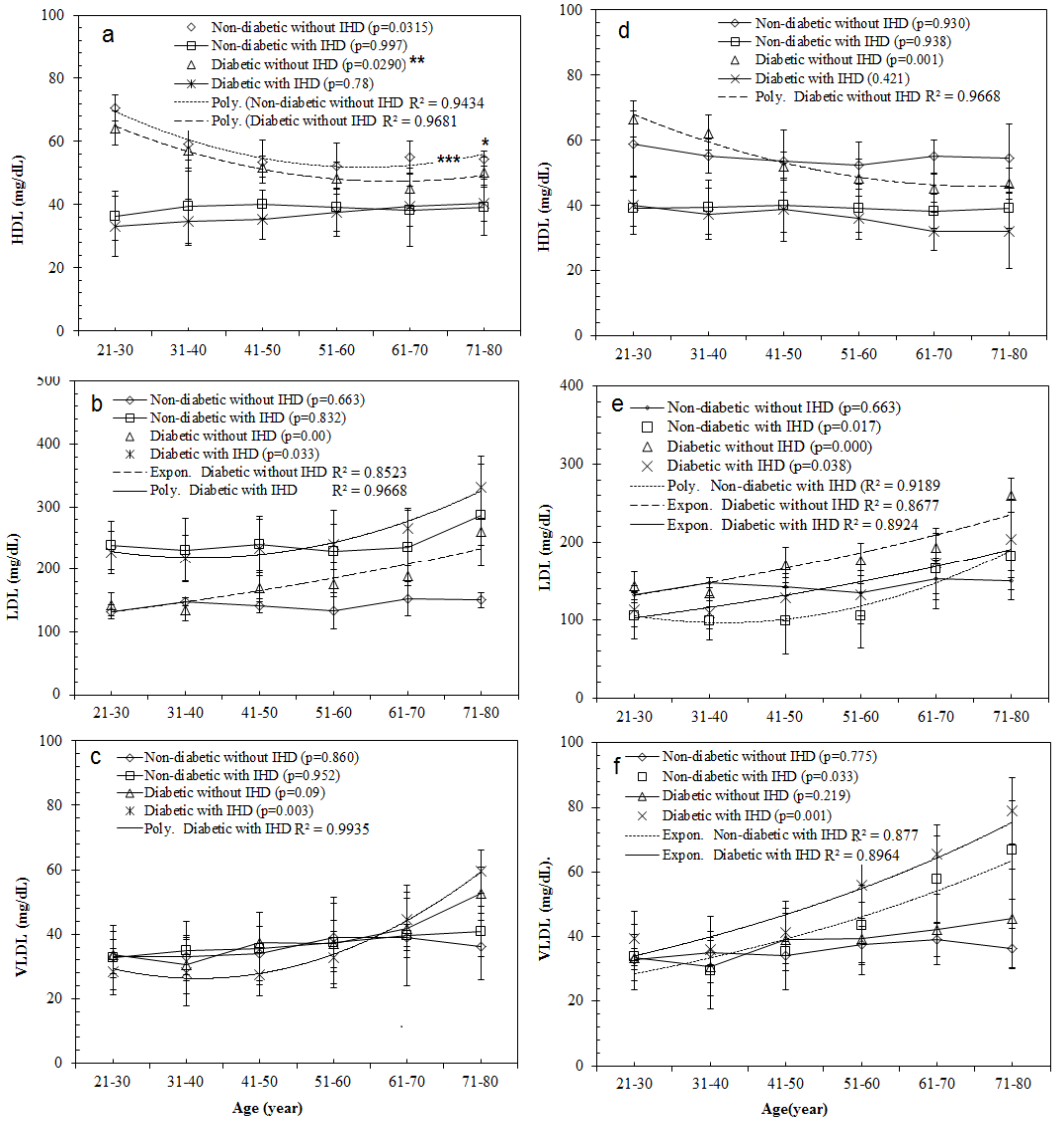

Fig. 3. Age-dependent variation in lipoprotein level of various study groups

a-c) Male, d-e) Female

HDL: High-density lipoprotein, LDL: low-density lipoprotein, VLDL: Very low-density lipoprotein

**Error bar represents the standard deviation*

***p-value indicates the significance of variation among different age groups at a 95% confidence level ($p < 0.05$) using Tukey's multiple range tests*

****The regression analysis was performed only on the data showing significant age-dependent variation in the response*

LDL levels which causes deterioration of β-cells of the pancreas resulting in the inhibition of glucose-stimulated insulin secretion [39,40]. High CH level also inhibits glycosidase activity as well as leads to deficient ATP binding cassette transporter AI activity which promotes cholesterol efflux in the extracellular space [41,42]. The positive exponential and linear correlations of lipid profile with FBG of diabetic patients with IHD suggest a strong association between hyperglycemia, dyslipidemia, and ischemia. Both the DM and dyslipidemia may accelerate the rate of IHD in the male and female populations. The results support the previous investigations regarding the mutual relationship among the said diseases [43–45].

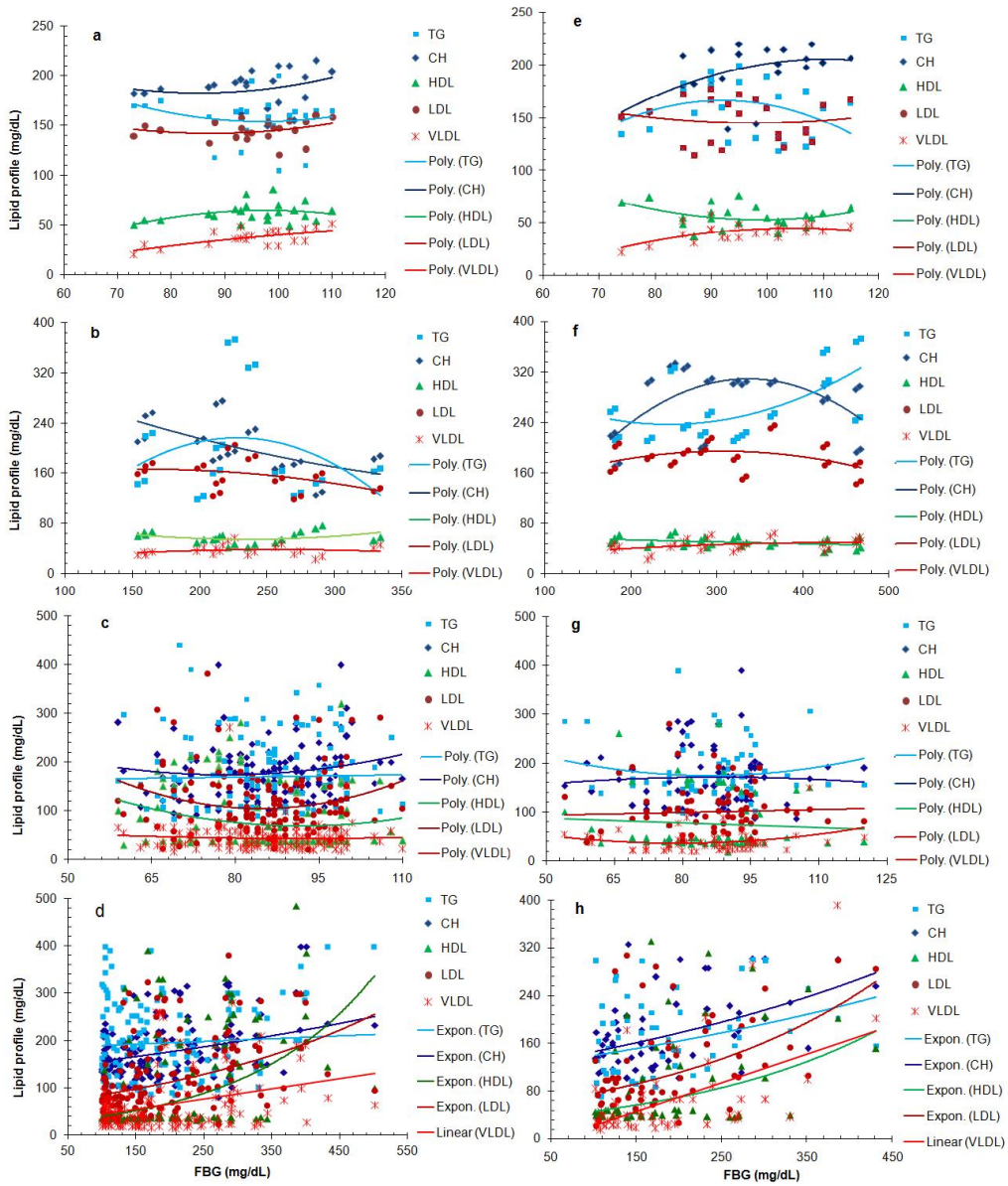

Fig. 4. Statistical correlation between the components of lipid profile and fasting blood glucose (FBG) levels of the different study groups

a-d) Male, e-h) Female

TG: Triglycerides, CH: Cholesterol, HDL: High-density lipoprotein, LDL: low-density lipoprotein, VLDL: Very low-density

4. CONCLUSION

The male and female diabetic patients with and without IHD showed elevated levels of FBG and lipid profile indicating an association among hyperglycemia, dyslipidemia, and ischemia. Both the male and female diabetic patients with and without IHD above 50 years of age experienced significantly elevated levels of FBG and lipid profile and found to be at more risk of cardiovascular diseases. The positive exponential and linear correlations of lipid profile with FBG of diabetic patients with a history of IHD also provide a piece of evidence for a strong association between diabetic hyperglycemia, dyslipidemia, and ischemia. A significant age-dependent increase in FBG, TG, CH, LDL, and VLDL was observed among the control and the

study groups consisting of diabetic patients with and without IHD. The study would be asignificant contribution to the literature regarding the interrelationship among three important clinical abnormalities including hyperglycemia, dyslipidemia, and ischemia in the individuals of different gender and age.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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