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Association of Serum Lipids with High Blood Pressure and Hypertension among Diabetic Patients. Mathematical Regression Models to Predict Blood Pressure from Lipids. An Experience from 12-year Follow Up of more than 9000 Patients' Cohort

Kamran Mahmood Ahmed Aziz*

Consultant Diabetologist, Honorary Professor and Research Scientist (Endocrinology, Diabetes and Metabolism), Aseer Diabetes Center of Aseer Central Hospital, Ministry of Health, Saudi Arabia

***Corresponding author:** Aziz KMA, Diabetology Clinic, Aseer Diabetes Center, Aseer Central Hospital, Ministry of Health, P.O.Box 34, Abha, Saudi Arabia, Tel: 00966-568361040; E-mail: drkamran9999@yahoo.com

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Abstract

Dyslipidemia and hypertension alone predispose to the risk of coronary artery disease, especially if the patient is diabetic. This risk is increased and multiplied when both dyslipidemia and hypertension coexists. There is a lack of studies and significant data for the correlation or association of blood pressure with serum lipids. The studies conducted in the past showed the conflicting results with poor associations. Furthermore, these studies were not conducted on diabetic subjects and lack regression models or mathematical linear equations. Hence, we conducted a prospective, observational cohort study on 9340 diabetic subjects for the duration of 12 year (2005-2017), with the aim to find significant associations, correlations between serum lipids (total cholesterol, triglycerides, LDL-C, HDL-C and Non-HDL-C) and blood pressure (systolic and diastolic). Our data has demonstrated that total cholesterol, triglycerides, and LDL-C were significantly correlated with systolic and diastolic BP, and raised among hypertensive patients as compared to non-hypertensive ($p<0.001$ for all lipids). The highest correlations were found between Non-HDL-C with systolic and diastolic blood pressures ($r=0.414$ and $r=0.415$, respectively with $p<0.001$). However, HDL-C was inversely correlated with systolic and diastolic BP and was raised among non-hypertensive patients. Regression models and mathematical linear equations were developed to estimate increasing blood pressure by the given serum lipid levels. All regression models were significant ($p<0.0001$). We concluded and developed regression models, for the first time in medical research that high lipid levels contribute to the development of increase systolic and diastolic blood pressures. With triglycerides, total-cholesterol, and HDL-C, Non-DHL-C levels should also be calculated in diabetology clinics and general practice. Screening should be done for diabetic patients to detect high blood pressure (or HTN) and elevated serum lipids, and early initiation of management to prevent diabetes complications.

Keywords: Lipids; Blood pressure; Coronary artery disease; Diabetes

Introduction

Currently hypertension is defined as the blood pressure (BP) values of ≥ 140/90 mmHg. Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of morbidity and mortality among diabetic patients and also general population with high economic cost and burden [1-3]. Essential hypertension is the silent killer because it is usually asymptomatic and undetected. Uncontrolled hypertension can cause damage to all organs of body. Dyslipidaemia and hypertension are the commonest risk factors for coronary artery disease (CAD). Hypertension and hypercholesterolemia (or dyslipidemia) each predisposes to CAD and their combined effects are demonstrated to be multiplicative. There is also pronounced influence of blood pressure on the rate of atheroma formation in human subjects. Isolated systolic hypertension, commonly seen in elderly subjects, can be attributed to atherosclerosis induced stiffening of aorta and major arteries. Atherosclerosis is more extensive and severe in hypertensive patients than in normotensive; this was the conclusion after the autopsy studies conducted on human coronary arteries and aortas collected from various parts of the world [4-6].

Untreated hypertension has various adverse effects on the human body, including end organ damage. Both high blood pressure and elevated serum lipids are major risk factors for the development of ischemic heart disease (IHD) or CAD, and their progression is accelerated among diabetics. Furthermore, these metabolic abnormalities are also associated with macrovascular and microvascular complications of type 2 diabetes and risk factors for atherosclerosis in children and young adults [7-10].Current research literature has shown that diabetes mellitus is a cardio-vascular risk equivalent and has been further confirmed by Framingham study and other landmark studies [11,12]. Diabetic dyslipidemia is defined as elevated triglyceride, elevated low-density lipoprotein cholesterol (LDL-C) and low high density lipoprotein cholesterol (HDL-C) levels [13]. Furthermore, new guidelines have recommended targeting non-HDL cholesterol for reducing cardiovascular morbidity and mortality. Although in 1963 Albrink demonstrated that triglyceride was an important atherosclerotic risk in diabetes, however, recent trials have proved that by lowering triglyceride levels, primary end point of major coronary events was not reduced significantly. This evidence was further supported by Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Hence, it was demonstrated high density lipoprotein (HDL-C) is a strong inverse co-variate of triglyceride and

HDL-C with Non-HDL-C must also be considered while managing dyslipidemia [14,15].

In the past, some research trials were conducted and attempts were made to show a positive relation between serum total cholesterol and blood pressure [16-24]; however, their results were inconsistent and these trials concluded that these associations were insignificant. Some studies have shown positive correlations [25,26], but these studies were not conducted on diabetic subjects, and have not developed statistical regression models for serum lipids and blood pressure. Under this overview, the aim of the current study was to find associations and significant correlations between serum lipids (total cholesterol, LDL-C, HDL-C, Non-HDL-C and triglycerides) and to develop statistical regressions models and linear equations by which systolic and diastolic blood pressure elevations can be predicted or calculated by increasing serum lipids among diabetic patients.

Methods

This is a prospective, cross-sectional observational cohort study conducted at the diabetology clinic of Aseer Diabetes Center, Aseer Central Hospital. Total study duration was 12 years, from August 2005 until July 2017, with total number of patients 9340, who, were routinely followed up in the diabetes clinic. We selected all type-1 and type-2 diabetic subjects who, were in regular follow up in the diabetes center. However, Children (age<13 years), pregnant diabetic women, and patients on end stage renal disease (ESRD) or on dialysis and with active hepatic disease were excluded from the study. Detail history and physical examination was done. Blood pressure was measured by standardized methodology. Blood pressure of ≥ 140/90 was labelled as "hypertension". All blood samples were collected in fasting state of not less than 12 hours, early in the morning. Low-density lipoprotein cholesterol, LDL (mg/dl) was measured directly in plasma by Automated Low-Density Lipoprotein (ALDL) method for the Dimension® clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), *in vitro* diagnostic test intended for quantitative determination of LDL-C. HDL-C (mg/dl) was measured directly in plasma by Automated High Density Lipoprotein (AHDL) method by the Dimension® clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), *in vitro* diagnostic test intended for quantitative determination of HDL-C. Similarly, total cholesterol (T. cholesterol) was measured directly by CHOL method (based on enzymatic procedures), a quantitative determination by the Dimension® clinical chemistry system and analyzer. Non-HDL-C was calculated as total cholesterol – HDL-C. Serum triglyceride (mg/dl) was measured by an enzymatic procedure; the sample is incubated with lipoprotein lipase (LPL) enzyme reagent that converts triglycerides to free glycerol and fatty acids. These are further oxidized to dihyhroxyacetone phosphate and hydrogen peroxide (H_2O_2) which is again converted to quinoneimine, absorbance of which is directly proportional to the total amount of glycerol. Absorbance is measured by bichromatic (510,700 nm) endpoint technique. Collectively, patients with LDL ≥ 100 mg/dl, triglycerides ≥ 150 mg/dl and HDL ≤ 40 mg/dl were labeled as "dyslipidemia". All laboratory sample requests were entered in a computer software and results retrieved by Natcom Hospital Information System (NATCOM HIS; National Computer System Co. Ltd [27]. Patients' data were analyzed by IBM® SPSS® statistics, version 20, for Microsoft Windows. All statistical tests were applied according to the available standard medical statistical methods. Data were summarized as percentages with mean ± SD and 95%CI for the variables.

Normal distribution of variables was confirmed via SPSS by observing skewness and kurtosis values between -1 and +1 with no potential/influential outliers before further proceedings. Hence, this required no data transformations. For this purpose, normality tests were also performed with Q-Q plots, hence confirming their normal distribution. Independent t-test was performed to test the significant difference between groups of variables. Pearson's correlation analysis was used to test the correlation between variables.

Predictive regression models were used to develop relationship of serum lipids and blood pressures, and it was then estimated by mathematical linear equations to confirm that how serum lipids contribute to the development of high or increased blood pressure. This study was designed to have a statistical power of 90% to detect significant changes. All p-values were two-sided, and p-values less than 0.05 were considered statistically significant. This study was reviewed and approved by the research committee of Aseer Diabetes Center; consent was taken from the participating patients and all methodologies on subjects reported in current study were in accordance with Helsinki Declaration of 1975 (revised in 2008).

Results

Demographic data is presented in Table 1, while descriptive statistics is demonstrated in Table 2. It was found that 42% of patients were hypertensive and 61% demonstrated dyslipidemia.

Parameters	Description with N (%) ; Total=9340	
Gender	Male	Female
	59%	41%
Type of Diabetes	Type-1	Type-2
	16%	84%
Hypertension status	Hypertensive	Non-Hypertensive
	42%	58%
Dyslipidemia status	Abnormal Lipids	Normal Lipids
	61%	39%

Table 1: Demographic data of diabetic patients.

Serum lipid values with or without hypertension status (with Mean ± SD; 95% CI and p-values) is presented in Table 3. It was found that serum lipid values were higher among hypertensive patients (p-value<0.001 for all serum lipids). However, HDL-C was lower in hypertensives (p-value<0.001).

Tables 4 and 5, present the correlation between serum lipids and blood pressure (systolic and diastolic, respectively). It is evident from the tables that correlations and p-values were positively significant. However, HDL-C was found to be negatively significant with systolic and diastolic blood pressures. Regression models and linear equations for the serum lipids with systolic and diastolic blood pressures are presented in Tables 6 and 7, respectively. The linear mathematical equations are constructed in these tables by which systolic or diastolic BP can be calculated by the given lipid levels. All the models were found to be significant (p<0.0001).

Variables	Mean ± SD
Age	53 ± 15
Diabetes duration	16 ± 9.8
Triglycerides (mg/dl)	154 ± 97.9
Total cholesterol (mg/dl)	190 ± 48.8
LDL-C (mg/dl)	119 ± 49.5
HDL-C (mg/dl)	42 ± 18
Non-HDL-C (mg/dl)	151 ± 48
Systolic blood pressure (mmHg)	128.7 ± 16.3
Diastolic blood pressure (mmHg)	79.2 ± 9

Table 2: Variables with descriptive statistics (mean ± SD).

Serum lipids (in mg/dl)	Hypertension status with serum lipids		P-value
	Yes	No	
Total cholesterol	194 ± 50; 95% CI 190 to 197	185 ± 46 ; 95% CI 182 to189	<0.001
Triglycerides	162 ± 94 ; 95% CI 156 to 169	152 ± 89 ; 95% CI 146 to159	<0.001
LDL-C	123 ± 55; 95% CI 119 to 127	115 ± 43; 95% CI 95 to 105	<0.001
HDL-C	40 ± 13; 95% CI 41 to 39	43 ± 23; 95% CI 42 to 45	<0.001
Non-HDL-C	153 ± 49 ; 95% CI 148 to 155	147 ± 45 ; 95% CI 142 to149	<0.001

Table 3: Serum lipids levels with hypertension state (Mean ± SD; 95% CI).

Variables tested for correlations	Pearson's correlation coefficient	P-value
Systolic BP and triglycerides	0.391	< 0.0001
Systolic BP and total Cholesterol	0.385	< 0.001
Systolic BP and LDL-C	0.358	<0.01
Systolic BP and HDL-C	-0.36	<0.01
Systolic BP and Non-HDL-C	0.414	<0.0001

Table 4: Correlation of lipids and systolic BP.

Variables tested for correlations	Pearson's Correlation Coefficient	P-value
Diastolic BP and triglycerides	0.428	<0.0001
Diastolic BP and T cholesterol	0.383	<0.001
Diastolic BP and LDL-C	0.349	<0.01
Diastolic BP and HDL-C	-0.371	<0.01
Diastolic BP and Non-HDL-C	0.415	<0.0001

Table 5: Correlation of lipids and diastolic BP.

Variables	F-value	T-value	P-value	Regression/Linear equations y=a+bx
Serum Triglyceride and systolic BP	13.3	162.8	<0.0001	Sys BP = 126.3+(0.015 × triglycerides)
Serum cholesterol and systolic BP	11.65	74.95	<0.0001	Sys BP = 123.3+(0.029 × total cholesterol)
Serum LDL-C and systolic BP	4.9	112.2	<0.0001	Sys BP = 126+(0.019 × LDL)
Serum HDL-C and Systolic BP	5.36	126	<0.0001	Sys BP = 130.6+(-0.052 × HDL)
Serum Non-HDL-C and systolic BP	19.4	89.9	<0.0001	Sys BP = 105+(0.343 × Non-HDL-C)

Table 6: Regression models for systolic blood pressure and serum lipids.

Variables	F-Value	T-Value	P-Value	Regression/Linear Equations y=a+bx
Serum Triglyceride and diastolic BP	26.76	181.5	<0.0001	Dias BP = 77.27+(0.012 × triglycerides)
Serum cholesterol and diastolic BP	11.2	84.3	<0.0001	Dias BP = 76.2+(0.015 × total cholesterol)
Serum LDL-C and diastolic BP	3.5	126.6	<0.0001	Dias BP = 78+(0.009 × LDL)
Serum HDL-C and diastolic BP	7.4	141.3	<0.0001	Dias BP = 80.6+(-0.034 × HDL)
Serum Non-HDL-C and diastolic BP	19.6	101.1	<0.0001	Dias BP = 76+(0.21 × Non-HDL-C)

Table 7: Regression models for diastolic blood pressure and serum lipids.

Discussion

Management of dyslipidemia is an essential part of managing diabetes as a whole. In general clinical practice, physicians target LDL-C as a primary target. However, recently to target non-HDL-C is also recommended. Non-HDL-C can be derived simply by abstracting HDL-C from total cholesterol which will give a better index of overall bad or harmful total cholesterol, a risk for CAD. According to recent evidence and recommendations from National Cholesterol Education Program (NCEP), target of LDL-C is to be <100 mg/dl in patients with diabetes, followed by non-HDL-C cholesterol of <130 mg/dl as a secondary target if triglyceride level remains elevated (>200 mg/dl). American Diabetes Association (ADA) has recommended similar management guidelines. This evidence indicates the importance of non-HDL-C as a potential marker of dyslipidemia [28-32]. It is essential to screen diabetic patients for dyslipidemia at initial and follow up visits as serum lipids contribute to the elevation of the blood pressure and poses CAD risk. Current study has demonstrated prevalence of diabetic dyslipidemia and hypertension to be 61% and 42% respectively, which is alarming. Furthermore, the data has demonstrated that hypertension state was associated with elevated serum lipids ($p<0.001$).

Although there are studies which have shown that elevated serum lipids are associated with high blood pressure or hypertension [16-24,33], however, they demonstrated conflicting results and their exact correlations with regression models were not developed in the past to predict BP elevation contributed by elevated serum lipids. No study has found correlation between non-HDL-C and blood pressure or HTN. Furthermore, these previous studies were not conducted in diabetic patients. This was achieved for the first time in the medical research history in our study. Between lipids and blood pressure, the highest correlations were found between non-HDL-C with systolic and diastolic blood pressures ($r=0.414$ and $r=0.415$, respectively, with $p<0.001$ for both); after non-HDL, the correlations for triglycerides were significant with systolic and diastolic blood pressures ($r=0.391$ and $r=0.428$, respectively with $p<0.0001$ for both). HDL-C, a good cholesterol, was inversely related with systolic and diastolic blood pressures. Non-HDL-C (i.e., non-HDL-C=total cholesterol–HDL-C), gives the value for overall harmful cholesterol. Our data has demonstrated that correlations for non-HDL-C with blood pressures were the most significant, and this cholesterol or lipid is contributing most for the elevated BP or HTN. Although in general practice it is ignored, however, non-HDL-C must be considered in tertiary care diabetes centers to reduce cardio-metabolic risk among diabetics. The linear equations (y=a+bx) can be used to predict blood pressures by given lipid values. For example, if given triglyceride value is 200 mg/dl, the systolic and diastolic BP will be 129 mmHg and 80 mmHg, respectively. However, if serum triglyceride value is 300, for example, then according to the given linear equation, it can raise systolic BP up to 131 mmHg. Similarly, LDL-C levels of 180 mg/dl can lead to BP elevations up to approximately 129.5 mm Hg. Hence, by this technique physicians can know that chronic exposures of high serum lipids can lead to significant elevations in the near future. Additionally, and according to our statistical analysis, HDL-C levels should be raised as they are associated with reduced systolic and diastolic BP. Dylipidemia and high non-HDL-C cholesterol is also associated with hypothyroidism among diabetic patients, and requires screening with regular follow up. Additionally, it has been demonstrated in research trials that dyslipidemia is associated with the development of nephropathy and early detection of dyslipidemia with nephropathy is recommended in primary care clinics [34-36].

Hypertension or elevated blood pressure is associated with CAD, cerebrovascular disease (CVA) and other diabetes related complications as well. Diabetic patients are at risk of cardiovascular and atherosclerotic disease development and progression. Efforts should be made to reduce elevated blood pressure among diabetics with available medications, as tight blood pressure control have shown reductions in morbidity and mortality and diabetes related complications [37-53]. Additionally, diabetic patients should be screened for dyslipidemia as well, as this pathological state leads to CAD or IHD with high morbidity and mortality rates. Dylipidemia and high triglycerides are associated with insulin resistance. Free fatty acid-induced insulin resistance is associated with activation of protein kinase C-theta (C-ɵ) and alterations in the insulin signaling cascade. Aggressive treatment should be initiated if dyslipidemia is detected with statins [54-62]. Furthermore, during management of diabetes in diabetology clinics, diabetologist should consider options for the management of type-1 and type-2 diabetic patients. For type-1, basal bolus insulin is the best strategy. For type-2 diabetics, oral agents (sulfonylurea or oral hypoglycemic agents, Metformin, DPP-4 inhibitors, SGLT-2 inhibitors, thiazolidinediones) can be used alone or in combination with insulin; these treatments can be shifted to insulin with metformin if they remain uncontrolled on oral agents. Metformin should be prescribed to type-2 diabetic patients (if not contraindicated) because metformin has cardiovascular protective effects, reduces insulin resistance, increases insulin sensitivity, and decreases the serum lipids while elevates HDL-C as has been demonstrated by research studies [63-70]. It is recommended following best available guidelines for the management of diabetes and its complications [71,72].

Our research, for the first time in medical history has demonstrated significant correlations, associations and regression models/linear mathematical equations between serum lipids (including non-HDL-C)

and blood pressure (or HTN). Most significant elevations of BP were attributed due to raised non-HDL-C and then the triglycerides. Further research at multi-center level and randomized controlled trials are required to confirm the findings of the current study.

Conclusion and Recommendations

Diabetes mellitus is cardiovascular risk equivalent and cardiovascular atherosclerotic disease is accelerated in diabetics. These conditions are resulting due to the coexistence dyslipidemia and hypertension. While these two pathologies predispose to the cardiovascular risk, these may also cause development or progression of nephropathy. While managing diabetes, it is recommended to screen these patients for hypertension, dyslipidemia, and nephropathy and to initiate management at early stages to prevent diabetes related complications.

Conflict of Interest and Funding

Author declares no conflict of interest in this work. This study was not funded by any organization. For the current research project, corresponding author himself designed the study, reviewed the literature, collected and analyzed the data with paper and medical writing.

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