

# Association of Microalbuminuria with Ischemic Heart Disease, Dyslipidemia and Obesity among Diabetic Patients: Experience from 5 Year Follow up Study of 1415 Patients

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## Abstract

This paper presents a microalbuminuria, a novel marker incipient nephropathy, and its simultaneous association at cross sectional level with ischemic heart disease, dyslipidemia and obesity among diabetic patients which has not been studied together in the past. Variables BMI, HbA1c, creatinine, total cholesterol, triglycerides, LDL-C, HDL-C, microalbuminuria, systolic and diastolic blood pressure were measured and compared for the two groups with and without IHD, nephropathy, dyslipidemia and obesity. Statistically it was observed that microalbuminuria, nephropathy, hypertension, and dyslipidemia were significantly associated with the development of ischemic heart disease (p-value < 0.0001 for all). Furthermore, Hypertension was significantly associated with nephropathy as obesity was associated with development of hypertension (p-value < 0.0001 for both variables). Additionally, it was demonstrated that both BMI and HDL-C were inversely and significantly correlated (p-value < 0.05). Both systolic and diastolic blood pressure significantly correlated with the development of microalbuminuria in this diabetic population (p-value < 0.0001 for both). Current study recommends screening diabetic patients early for microalbuminuria at primary care level, to target high BMI and HbA1c, early diagnosis and treatment of hypertension and dyslipidemia to prevent further diabetic complications and economic burden.

**Keywords:** Diabetes; Dyslipidemia; ESRD; Hypertension; IHD; Microalbuminuria; Nephropathy; Obesity; Type-1 diabetes; Type-2 diabetes

## Introduction

Diabetes currently is imposing a global burden, and is the cause of morbidity and mortality with increasing prevalence worldwide. Furthermore, coronary artery disease (CAD) itself is leading cause of morbidity and mortality in most of the developed countries. The economic and social burden further intensifies in terms of cost when both diabetes and coronary heart disease coexist. Similarly it has been reported that 97 million adults in United States are overweight or obese and 75% of adult Americans have minimal physical activity or exercise. Both excessive fat and Obesity (body mass index or BMI  $\geq 30$  kg/m<sup>2</sup>), and physical inactivity predisposed to the risk of developing type-2 diabetes and other co morbid conditions such as cardiovascular complications. Diabetes mellitus is a major independent risk factor for cardiovascular disease (CVD). Increase prevalence of CVD in diabetes has been observed due to accelerated coronary atherosclerosis occurring at earlier age and advances more rapidly in diabetic population as compared to those without diabetes. Moreover, CAD is often diffuse with stenosis affecting multiple vessels; after revascularization with percutaneous transluminal coronary angioplasty (PTCA), these diabetic patients often demonstrate increased rate of restenosis. Hence it can be concluded that diabetes mellitus itself is a cardiovascular risk equivalent [1-11].

Excretion of albumin (and other proteins) in the urine is an early and progressive marker of renal dysfunction and damage in diabetes. Nephropathy still remains an important complication of diabetes, may

lead to end stage renal disease (ESRD) with high incidence (40-50%), high morbidity and mortality. Persistence albumin excretion in urine in the range 30-299 mg/24 h (also known as microalbuminuria) is the earliest indicator of incipient diabetic nephropathy in type-1 and type-2 diabetic subjects, and may also lead to ESRD. The term microalbuminuria was introduced and defined in 1985 and since then it is widely accepted as an early indicator of renal damage.

Traditionally, the term "diabetic nephropathy" was defined as chronic kidney disease (CKD) resulting due to diabetes. However, recently the Diabetes and Chronic Kidney Disease work group of the National Kidney Foundation (NKF) and Kidney Disease Outcomes Quality Initiative (KDOQI) suggested that a diagnosis of CKD presumed to be caused by diabetes should be referred to as "diabetic kidney disease (DKD)" and the term "diabetic nephropathy" should be reserved for kidney disease attributed to diabetes with histopathological injury demonstrated by renal biopsy. CVD risk is doubled in diabetic patients with microalbuminuria than those without microalbuminuria. Furthermore, there is inverse relation between microalbumin and GFR; as albumin excretion in urine increases, GFR decreases and also CVD risk increases progressively. Additionally, diabetic patients who progress from microalbuminuria stage to macroalbuminuria ( $\geq 300$  mg/24 h) are likely to progress ESRD [12-23].

Coronary artery disease (CAD) or ischemic heart disease (IHD) is common in diabetes. Moreover, myocardial ischemia is usually silent in diabetic patients and undiagnosed IHD undoubtedly worsens the prognosis, including diabetic cardiomyopathy associated with diabetic glomerulosclerosis. Type-2 diabetic subjects have underlying insulin resistance (IR) which is in turn a risk for CVD. Furthermore,

metabolic syndrome (or Syndrome-X) contributes to the development of insulin resistance. Patients with diabetic dyslipidemia also demonstrate underlying insulin resistance (IR). Hypertension is another well-established risk factor for CVD/IHD, to the development and progression of diabetic nephropathy (DKD) and has association with IR [24-46].

Research trials have shown a positive association between impaired glycemic control (HbA1c) (hyperglycemia) and the risk of CHD (coronary heart disease) (IHD/CAD). In the UKPDS (United Kingdom Prospective Diabetes Study) have showed significant relative risk reduction of fatal or nonfatal MI (myocardial infarction) of 39% ( $P=0.023$ ) with intensive control. Additionally, DM subjects have two to three fold higher mortality risk due to the "diabetic cardiomyopathy" that is not related to the atherosclerosis. The DIGAMI study has shown that mortality following MI can be reduced by insulin infusions in intensive care units. Meigs and Associates have shown a Longitudinal Association of Glycemia and Microalbuminuria. Similarly In the landmark Diabetes trial, DCCT, microalbuminuria was more prevalent (13 vs. 7%,  $P<0.01$ ) and HbA1c was higher (9.1 vs. 7.4%,  $P<0.01$ ) in the conventional treatment group as compared to the intensive insulin treatment group [47-52].

Under this background, purpose of the current study was to measure the novel screening patent, the micro-albuminuria, for cardiac and renal disease and its association with lipids (dyslipidemia) and obesity in diabetic patients simultaneously, which so far has not been studied in such population. Also it was the aim to analyze other associated variables (risk factors) for the development of albuminuria with significant statistical associations.

## Material and Methods

Current research is a retrospective cross sectional analytical study. For this study, data for 1415 patients were collected on initial and follow up visits at diabetology clinic of Aseer Diabetes Center of Aseer Central hospital, from January 2009 till January 2014. These patients were referred from primary health care centers to tertiary care diabetes center for annual evaluations. Known type-1 and type-2 diabetic subjects were included in the study. Pregnant subjects and children of less than 13 years of age, severe hepatic disease, and patients with ESRD or on dialysis were excluded from the study. Patients with a history of urinary tract infection, and known cases of kidney disease or nephrotic syndrome before the diagnosis of diabetes were also excluded from the study. Detailed history was taken so as to reveal past history of other co morbid conditions such as hypertension (HTN), IHD or CAD and those went for interventional cardiac procedures, PTCA and CABG (coronary artery bypass grafting). Patients with a documented history of IHD and on regular medications, PTCA, and CABG were labeled collectively as IHD and separately analyzed as "IHD profile" with other associated variables. All demographic data, including systolic and diastolic blood pressure with BMI ( $\text{kg}/\text{m}^2$ ), were recorded at first visit to the diabetology clinic by standardized methodology. Those with  $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$  were labeled obese and analyzed with selected variables in "obesity profile". All specimens of blood and urine were collected at first visit by standardized methodology and in fasting state of not less than 12 hours. All laboratory samples of blood and urine were sent to main laboratory. Subsequent data were then recorded on follow up visit and all samples request were retrieved by Natcom Hospital Information System (NATCOM HIS; National Computer System Co. Ltd), a server based HIS software [53].

LDL-C (mg/dl) was measured directly in plasma by Automated Low Density Lipoprotein (ALDL) method and HDL-C (mg/dl) was measured directly in plasma by Automated High Density Lipoprotein (AHDL) method by the Dimension<sup>®</sup> clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), an in vitro diagnostic test intended for quantitative determination of low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C). Similarly, total cholesterol and triglycerides were measured directly, by CHOL and TGL method respectively (based on enzymatic procedures), a quantitative determination by the Dimension<sup>®</sup> clinical chemistry system and analyzer. Patients demonstrating elevated lipid values ( $\text{LDL-C} \geq 100 \text{ mg}/\text{dl}$ ,  $\text{HDL} < 50 \text{ mg}/\text{dl}$ , or  $\text{Triglycerides} \geq 150 \text{ mg}/\text{dl}$ ) were labeled as dyslipidemia and analyzed as "dyslipidemia profile" with selected variables.

Serum creatinine (mg/dl) was measured by Flex reagent cartridge using the CREA method (an enzymatic biochemical reaction between creatinine and picrate in the presence of strong base NaOH) used on the Dimension<sup>®</sup> clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), an in vitro diagnostic test for the quantitative determination of creatinine in human serum and plasma.

For the detection of nephropathy and presence of albumin or protein in urine, fasting urine samples were analyzed for the presence of micro-albuminuria, macro-albuminuria or proteinuria. All urine samples were first analyzed for the presence of proteinuria by Quik Check<sup>™</sup> urinalysis reagent strips (ACON biotech, Co., Ltd) to rule out macro-albumin in urine. Samples demonstrating macro-albuminuria or gross proteinuria by the color change of the reagent strips were labeled as nephropathy. Samples with negative albumin or protein in urine were again screened for the presence of micro-albumin in urine by MALB method used on Dimension<sup>®</sup> clinical chemistry system, in vitro diagnostic test for quantitative measurement of albumin (mg/L) in human urine by particle-enhanced turbidimetric inhibition immunoassay (PETINIA) methodology (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A). Micro-albumin positive samples were again labeled as micro-albumin positive and nephropathy as well. Nephropathy status was analyzed separately as "nephropathy profile" with selected variables.

HbA1c was measured by A1c Flex<sup>®</sup> Reagent by the Dimension<sup>®</sup> clinical chemistry system, an in vitro diagnostic assay for the quantitative determination of both percent hemoglobin A1c and total hemoglobin, based on a turbidimetric inhibition immunoassay (TINIA) principle, and the measurement of total hemoglobin is based on a modification of the alkaline hematin reaction, an NGSP certified methodology (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A). The percentage of total hemoglobin that is glycosylated was calculated and reported as %HbA1c (in g/dL), and final result has been standardized to the results obtained in DCCT.

All data of the subjects were analyzed using statistical software, SPSS<sup>®</sup> version 12 for Windows (SPSS<sup>®</sup> Inc, USA). All statistical tests were performed by standardized methodology. For testing normality normal Q-Q plots were used as well to assure that variables are approximately normally distributed.  $\chi^2$  test was utilized for significant analysis between categorical variables. Student's t-test was utilized to test significant difference among different groups. While Pearson's Correlation test was used to test significant associations among continuous variable. Logistic regression was used to calculate magnitude and association of risk factors and odd ratio/adjusted odds

ratios. 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.

## Results

Demographic characteristics of diabetic patients are shown in Table 1.

Demographic Data of Diabetic Patients		
Parameters	Description with N (%) ; Totals = 1415	
Gender	Male	Female
	890 (62.9%)	525 (37.1%)
Type of Diabetes	Type-1	Type-2
	105 (7.4%)	1310 (92.6%)
Obesity	Obese	Non Obese
	619 (43.7%)	796 (56.3%)
Hypertension	Hypertensive	No hypertension
	635 (45%)	780 (55%)
Dyslipidemia Status	With dyslipidemia	Without Dyslipidemia
	806 (57%)	609 (43%)
PTCA Status	Post PTCA	Without PTCA
	105 (7.4%)	1310 (92.6%)
CABG (coronary artery bypass graft) Status	Post CABG	Without CABG
	35 (2.5%)	1380 (97.8%)
Ischemic Heart Disease Status (including post PTCA and CABG)	With IHD	Without IHD
	305 (21.6%)	1110 (78.4%)
Microalbumin in Urine	With Micro-albuminuria	Without Micro-albuminuria
	295 (20.8%)	1120 (79.2%)
Overall Nephropathy Status	With Nephropathy	Without Nephropathy
	435 (30.7%)	1037 (73.3%)

**Table 1:** Demographic data for diabetic patients

Descriptive statistics with mean and standard deviation ( $\pm$ SD) for the other interested variables, BMI, HbA1c, serum creatinine, serum lipids, urinary micro-albumin, systolic and diastolic blood pressure, are shown in Table 2.

Interested variables (diabetes duration, HbA1c, serum creatinine, HDL-C, and micr-oalbumin in urine) were statistically compared among the two groups of the patients, IHD and without IHD status, and results are summarized with Mean, SD with 95% CI in Table 3. It should be noted that total cholesterol, triglycerides and LDL-C were not tested in IHD profile as all patients with IHD were on statin therapy which significantly lowers these lipids.

Descriptive Statistics For Variables of Interest	
Variables	Mean $\pm$ SD
Age (years)	56.45 $\pm$ 14.77
Diabetes Duration (years)	14.7 $\pm$ 9.06
BMI (kg/m <sup>2</sup> )	29.59 $\pm$ 5.91
HbA1c % (g/dL)	9.66 $\pm$ 2.18
Serum Creatinine (mg/dl)	1.021 $\pm$ 0.73
Triglyceride (mg/dl)	156.46 $\pm$ 96.26
Total Cholesterol (mg/dl)	190.84 $\pm$ 48.757
HDL-Cholesterol (mg/dl)	41.63 $\pm$ 13.54
LDL-Cholesterol (mg/dl)	117.78 $\pm$ 41.49
Microalbumin in Urine (mg/L) / Urine Albumin Excretion (UAE)	79.67 $\pm$ 109.94
Systolic BP (mmHg)	126.81 $\pm$ 17.14
Diastolic BP (mmHg)	78.66 $\pm$ 9.2

**Table 2:** Variables with Mean  $\pm$  SD

Ischemic Heart Disease Profile Analysis			
Variables and Indicators	Patients Variable Values With or Without IHD		
	Mean $\pm$ SD (95%CI)		P-value
	With IHD	Without IHD	
Diabetes Duration	17.82 $\pm$ 8.21	14.30 $\pm$ 9.09	<0.0001
	(95% CI 16.22 to 19.43)	(95% CI 13.68 to 14.93)	
HbA1c % (g/dL)	9.84 $\pm$ 2.08	9.641 $\pm$ 2.1936	0.043
	(95% CI 9.43 to 10.2)	(95% CI 9.4 to 9.791)	
Serum Creatinine (mg/dl)	1.149 $\pm$ 0.66	1.004 $\pm$ 0.73	0.007
	(95% CI 1.02 to 1.28)	(95% CI 0.95 to 1.05)	
HDL-C (mg/dl)	38.7 $\pm$ 13.39	42 $\pm$ 13.52	<0.0001
	(95% CI 36.02 to 41.39)	(95% CI 41.05 to 42.95)	
Systolic BP (mmHg)	129.27 $\pm$ 16.82	126.50 $\pm$ 17.16	0.11
	(95% CI 125.98 to 132.56)	(95% CI 125.33 to 127.67)	
Microalbumin in Urine (mg/L)	98.9708 $\pm$ 114.37	76.2411 $\pm$ 108.93	<0.0001
	(95% CI 70.62 to 127.31)	(95% CI 65.02 to 87.45)	

**Table 3:** Grouped variables with and without IHD

It was found that those with IHD had mean duration of diabetes 17.82 years as compared to those without IHD, with the mean 14.3 years ( $p < 0.0001$ ). HbA1c, Serum creatinine, and urine micro-albumin levels were also found to be higher with the IHD as compared to those without IHD, while HDL-C levels were on lower side with IHD.

The selected interested variables (duration of diabetes, HbA1c, serum creatinine, systolic BP, BMI and all lipids) were compared among the two groups of patients, with nephropathy and without nephropathy and the results with the mean  $\pm$  SD and 95% CI are presented in Table 4. Duration of diabetes was found to be more in the group with nephropathy. Subjects with nephropathy demonstrated a higher BMI, systolic BP, HbA1c, serum creatinine, and all serum lipid values except for HDL-C which was observed to be non-significantly lower in the group with nephropathy.

Nephropathy Profile Analysis			
Variables and Indicators	Patients Variable Values With or Without Nephropathy Mean $\pm$ SD (95%CI)		
	With Nephropathy	Without Nephropathy	P-value
Diabetes Duration	17.4833 $\pm$ 9.24 (95% CI 16.22 to 18.53)	13.3674 $\pm$ 8.67 (95% CI 12.68 to 14.04)	<0.0001
HbA1c % (g/dL)	9.978 $\pm$ 2.15 (95% CI 9.73 to 10.22)	9.513 $\pm$ 2.17 (95% CI 9.34 to 9.68)	<0.0001
Serum Creatinine (mg/dl)	1.287 $\pm$ 1.06 (95% CI 1.166 to 1.4)	0.891 $\pm$ 0.43 (95% CI 0.85 to 0.92)	<0.0001
HDL-C (mg/dl)	41.03 $\pm$ 11.76 (95% CI 39.67 to 42.39)	41.93 $\pm$ 14.33 (95% CI 40.77 to 43.08)	0.142
Total-Cholesterol (mg/dl)	198.17 $\pm$ 51.80 (95% CI 192.23 to 204.11)	187.25 $\pm$ 46.82 (95% CI 183.51 to 191.00)	0.032
LDL-C (mg/dl)	123.80 $\pm$ 44.305 (95% CI 118.64 to 128.95)	114.86 $\pm$ 39.779 (95% CI 111.65 to 118.08)	0.014
Triglycerides (mg/dl)	170.20 $\pm$ 110.98 (95%CI 157.49 to 182.92)	149.74 $\pm$ 87.48 (95%CI 142.74 to 156.74)	0.005
Systolic BP (mmHg)	136.76 $\pm$ 18.43 (95% CI 134.67 to 138.86)	122.04 $\pm$ 14.20 (95% CI 120.92 to 123.15)	< 0.0001
BMI (kg/m <sup>2</sup> )	29.829 $\pm$ 5.76 (95% CI 29.17 to 30.48)	29.486 $\pm$ 5.98 (95% CI 29.016 to 29.95)	0.831

**Table 4:** Grouped variables with and without nephropathy

Variables (BMI, HbA1c, serum creatinine, micro-albuminuria, and systolic BP) were compared among the two groups, with and without dyslipidemia. Statistical results with mean, SD and 95% CI are presented in the Table 5. It was observed that dyslipidemia group

exhibited higher BMI, systolic BP, HbA1c, serum creatinine, and micro-albumin in urine.

Dyslipidemia Profile Analysis			
Variables and Indicators	Patients Variable Values With or Without Dyslipidemia Mean $\pm$ SD (95%CI)		
	With Dyslipidemia	Without Dyslipidemia	P-Value
BMI (kg/m <sup>2</sup> )	29.841 $\pm$ 5.84 (95%CI 29.39 to 30.28)	29.004 $\pm$ 6.05 (95%CI 28.27 to 29.73)	0.037
HbA1c % (g/dL)	9.777 $\pm$ 2.18 (95% CI 9.60 to 9.94)	9.388 $\pm$ 2.15 (95%CI 9.12 to 9.64)	0.51
serum creatinine (mg/dl)	1.027 $\pm$ 0.77 (95% CI 0.96 to 1.08)	1.004 $\pm$ 0.62 (95%CI 0.92 to 1.07)	0.043
Microalbumin in urine (mg/L)	83.17 $\pm$ 114.75 (95% CI 70.24 to 96.10)	71.14 $\pm$ 97.09 (95% CI 53.95 to 88.33)	0.02
Systolic BP (mmHg)	127.28 $\pm$ 16.84 (95%CI 126 to 128.57)	125.67 $\pm$ 17.82 (95% CI 123.53 to 127.80)	0.015

**Table 5:** Grouped variables with and without dyslipidemia

Obesity Profile Analysis			
Variables and Indicators	Patients Variable Values With or Without Obesity Mean $\pm$ SD (95 %CI)		
	Patients without Obesity (BMI < 30 kg/m <sup>2</sup> )	Patients with Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )	P-value
Triglycerides (mg/dl)	163.96 $\pm$ 104.74 (95 %CI 147.96 to 179.96) SEM $\pm$ 8.105	151.56 $\pm$ 78.54 (95%CI 141.59 to 161.52) SEM $\pm$ 5.059	0.002
Total-Cholesterol (mg/dl)	197.51 $\pm$ 56.81 (95%CI 188.83 to 206.19)	187.84 $\pm$ 46.85 (95%CI 181.90 to 193.79)	0.04
HDL Cholesterol (mg/dl)	41.68 $\pm$ 13.29 (95% CI 39.65 to 43.71)	43.17 $\pm$ 14.09 (95 % CI 41.38 to 44.95)	0.03
LDL Cholesterol (mg/dl)	122.41 $\pm$ 45.65 (95% CI 115.44 to 129.39)	114.58 $\pm$ 41.26 (95% CI 109.34 to 119.81)	0.037
Systolic BP (mmHg)	131.13 $\pm$ 17.09 (95% CI 128.52 to 133.74)	124.90 $\pm$ 16.59 (95% CI 122.79 to 127)	<0.0001
Urinary Albumin Excretion (mg/L)	89.6569 $\pm$ 112.73 (95% CI 72.43 to 106.88)	71.3959 $\pm$ 108.21 (95% CI 57.66 to 85.12)	0.02

**Table 6:** Grouped variables with and without Obesity

Regarding the obesity profile analysis, variables (triglycerides, total cholesterol, HDL-C, LDL-C, systolic BP, and micro-albuminuria) were compared with and without obesity status. All significant statistical results are presented in Table 6. Systolic BP, micro-albuminuria levels (UAE or urinary albumin excretion) and lipids were observed to be higher in obese diabetic population except for HDL-C which was observed to be on lower levels with obesity.

The categorical data (status or profiles) of IHD, nephropathy, and obesity with HTN and micro-albuminuria were tested for significant statistical associations with Pearson's chi-square test and are presented in Table 7 with their explanations. All results were significant with higher odds ratios except for the dyslipidemia with IHD.

Data for BMI, HDL, micro-albuminuria, systolic and diastolic BP were tested for the significant bivariate correlations and are presented in Table 8.

## Discussion

Current study is confirmatory for the past studies. However, no research study could be found among diabetic patients who have enrolled patients to monitor multiple risk factors and their significant association at cross sectional level. Hence, our study is of first kind to find such associations simultaneously.

According to the observed results of the current study, it was found that most of the diabetic patients under the study were obese (43.7%). Prevalence of dyslipidemia was also found to be much higher (70.8%). Similarly nephropathy status was again significantly high (30.7%). These observations are alarming and matching with the world wide data. High body mass index (BMI) and sedentary lifestyle is a risk factor for the IHD or CAD and as well as development of microalbuminuria [54]. Furthermore, Glycemic control should be near the defined targets to prevent diabetes complications. The benefits of intensive diabetes management to prevent cardiovascular

complications has been demonstrated and documented in research literature [50,55,56]. For monitoring diabetes, HbA1c is now a standard methodology in diabetology clinics, which measures patient's glycemic control for the past 2-3 months [57].

Significant Statistical Associations Between Categorical Variables :					
IHD, Nephropathy, Dyslipidemia and Obesity Status					
Variables Tested Together for Significant Associations	Pearson Chi Square	Likelihood Ratio	Fisher's Exact Test	Linear-by-Linear Association	Logistic Regression and
	p-value	p-value	p-value	p-value	Odds Ratio
					(95% CI)
IHD with Nephropathy	<0.0001	<0.0001	<0.0001	<0.0001	2.16 (1.43 to 3.271)
HTN with IHD	<0.0001	<0.0001	<0.0001	<0.0001	6.53 (3.9 to 10.96)
Microalbuminuria with IHD	<0.0001	<0.0001	<0.0001	<0.0001	3.53 (2.27 to 5.5)
HTN with Nephropathy	<0.0001	<0.0001	<0.0001	<0.0001	3.97 (2.96 to 5.31)
Obesity with HTN	<0.0001	<0.0001	<0.0001	<0.0001	1.63 (1.25 to 2.12)
Dyslipidemia with IHD	<0.0001	<0.0001	<0.0001	<0.0001	0.37 (0.24 to 0.56)

**Table 7:** Significant Associations among variables IHD, nephropathy, dyslipidemia, microalbuminuria, obesity and hypertension with their explanations

Significant Statistical Associations of Continuous Data								
Variables	Pearson Correlation (r)	p-value for correlation	Regression Analysis / Model					
			R <sup>2</sup>	F	ANOVA model P-value	t	P-value	Regression model or equation
BMI and HDL-C	r = - 0.074	< 0.05	.005	4.8	0.029	20 / -2.1	< 0.0001	HDL = 46.6 + (-0.169 × BMI)
systolic BP and Microalbu-minuria	r = 0.366	<0.0001	0.134	66.2	< 0.0001	-5.9 / 8.1	<0.0001	Microalbuminuria = -218.6 + (2.34 × systolic BP)
diastolic BP and Microalbu-minuria	r = 0.274	<0.0001	0.075	34.6	< 0.0001	-3.9 / 5.8	< 0.0001	Microalbuminuria = -166 + (3.1 × systolic BP)

**Table 8:** Significant Pearson's correlation and associations among variables

In the current study, when IHD profile was analyzed, it was found that HbA1c levels were higher for the patients with a history of IHD as compared to those without history of IHD (P<0.0001). Serum creatinine was higher in IHD group compared to those without (P=0.007) indicating a link between IHD or CAD and renal impairment or diabetic kidney disease (DKD) [58-60]. This was further supported by the evidence that urine microalbumin levels were

higher among IHD group (P<0.0001). Additionally systolic BP was again non-significantly higher in IHD group (p=0.11). However, association between HTN and IHD was highly significant ( $\chi^2$  p-value < 0.0001). Hence it can be concluded that hypertension and hyperglycemia precedes the development of incipient nephropathy [61,62]. As evident by results (Table 7), association between the two variables, IHD and development of microalbuminuria, was highly

significant ( $\chi^2$  p-value < 0.0001), concluding that microalbuminuria is a predictor of future developments of IHD/CAD. HDL cholesterol levels were observed to be reduced in IHD group (P<0.0001). HDL-C is good cholesterol and elevated HDL-C levels are protective against CAD/IHD development [63,64]. HDL-C levels can effectively be raised by regular exercise/activity or daily regular walk [65]. Furthermore, in the current study association between dyslipidemia and development of IHD was again significant ( $\chi^2$  p-value < 0.0001), indicating the role of lipid management in diabetes to prevent cardiac disease [63,64]. However, the odds ratio was 0.37 (95% CI 0.24 to 0.56). This was due to the fact that most of the subjects with IHD were on statins therapy.

Regarding nephropathy profile analysis, most of the patients (30.7%) that developed nephropathy, had duration of diabetes more than 17 years, nearly matching with IHD profile. This might indicate development of the two diseases soon after the other or simultaneously. For the glycemic status, HbA1c levels were higher in nephropathy group (P<0.0001). In other words, reducing blood sugars and HbA1c to the targets will prevent nephropathy and better prognosis in nephropathy and ESRD as well [66-69]. Serum creatinine, lipids was observed to be higher in nephropathy group (P<0.0001). Creatinine is an indicator of renal function and should be monitored periodically in diabetic patients. It has been documented that dyslipidemia contributes to the progression of DKD and nephropathy. Furthermore, IHD and nephropathy demonstrated significant association ( $\chi^2$  p-value<0.0001). These all observations indicate the importance of dyslipidemia management in diabetic patients with albuminuria/ DKD and IHD [70]. Systolic BP was higher among nephropathy group (p <0.0001). Association between HTN and development of nephropathy was statistically significant ( $\chi^2$  p-value< 0.0001) and it was observed that bivariate correlation and regression analysis for microalbuminuria with systolic blood pressure and diastolic blood pressure was highly significant (p-value < 0.0001; r=0.366 and p-value < 0.0001; r=0.274 respectively). In type-1 and type-2 diabetic patients, natural history of DKD usually demonstrates initially elevated blood pressure or HTN, albuminuria and then finally decreased GFR [71]. It has been demonstrated by randomized controlled trials that HTN is a risk factor for progression of nephropathy or DKD while antihypertensive therapy with ACE (angiotensin converting enzyme) inhibitors, calcium channel blocker, and ARBs (angiotensin receptor blockers) reduces this risk [16,72-80]. Also it is recommended that diabetic hypertensive patients should be treated with ACE inhibitors or ARBs, usually in combination with a diuretic. Target blood pressure for diabetics and those with DKD/CKD stages 1-4 should be < 130/80 mmHg [16]. Statistical results also have shown that in the current study BMI was non-significantly higher among nephropathy group (29.829 ± 5.76 versus 29.486 ± 5.9844; p-value 0.831). This was an incidental non-significant finding. Hence obesity may be associated with proteinuria and could be a risk factor for ESRD [81,82].

It was found that subject labeled with dyslipidemia showed a higher mean BMI. It is well known that subjects with a more abdominal type of fat distribution are at increased of developing type-2 diabetes [83,84]. Thus treatment of obesity and dyslipidemia is essential. Higher HbA1c levels with the dyslipidemia group was another finding of this study, although non-significant (p=0.5). In fact, it has been found that defects in insulin action or diabetes state can lead to changes in plasma lipoproteins and lipid abnormalities exclusive of hyperglycemia [85,86]. As indicated by results, serum creatinine was significantly higher among dyslipidemia group, indicating association of dyslipidemia with renal impairment. It has been stated in research

literature that lipids contribute to the development and progression of nephropathy [87-90]. Furthermore, it was observed that mean microalbumin levels were higher among dyslipidemia group (83.17 ± 114.75 versus 71.14 ± 97; p=0.02). This explains effects of dyslipidemia among diabetic patients in the development of incipient nephropathy. Similarly, systolic BP values were higher in nephropathy group (127.28 ± 16.84 versus 125.67 ± 17.82; p=0.015). All these pathologies, dyslipidemia, hyperglycemia, and HTN significantly trigger the development of microalbuminuria/DKD. Microalbuminuria, if not treated early, may further leads to nephropathy, DKD, and later on ESRD over the next few years both in type-1 and type-2 patients [91-97].

Regarding the results of obesity profile analysis, total cholesterol, triglyceride, and LDL-C levels were observed high in obesity group, while HDL-C levels were found to be on lower side (Table 6). One of the statistically significant finding observed in this diabetic population was bivariate correlation of BMI with HDL-C while both variable were negatively associated (r=-0.074; p-value < 0.05), a fact indicating an inverse relation, i.e., high BMI and low HDL, and vice versa. Existence of both obesity and dyslipidemia together is well known [98-101]. Similarly, weight reduction programs and strategies for obesity / visceral obesity have shown to reduce the cardiovascular risk and better outcomes [102-105]. In the current study, obesity status was also associated with high systolic BP comparative to its non-obese counterpart (p<0.0001). Association of weight and high BMI with blood pressure in young adults and children has been demonstrated in research trials [106-113]. Obesity is also associated with cardiovascular risk as well [114,115]. Our data has indicated that obesity is associated with development of high systolic BP and HTN. Additionally, mean urinary albumin excretion rate was significantly higher among obese subjects (89.65 ± 112.73 versus 71.39 ± 108.21; p=0.02), explaining the fact of association of incipient nephropathy with obesity [116,117].

Limitations of the current study included non-randomization, and there was no control group. Further Randomized controlled, multicenter studies are required to confirm simultaneous positive findings and observations of the current study. Further studies are required to investigate these relationships in depth.

## Conclusion and Recommendations

Diabetes mellitus is cardiovascular risk equivalent. Microalbuminuria predicts the future risk for the development of ischemic heart events (IHD/CAD) and diabetic kidney disease and ESRD.

Therefore it is recommended that all diabetic patients should be screened at primary care level soon after the diagnosis or at first presentation for co-morbid conditions and risk factors. Diabetes education is an integral part of diabetes management and all diabetic patients should be educated for diabetes management and prevention of complications [118,119]. All diabetic patients should be referred to tertiary care diabetes center for follow up, monitoring, and adjustment of diabetes related therapy, to prevent diabetes complication and better prognosis. To manage diabetes and its associated disorders, it is advisable to follow best available guidelines [120,121].

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