Original research article

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CORRELATION BETWEEN SERUM LIPID PROFILE AND ALBUMINURIA IN NORMOTENSIVE DIABETIC SUBJECTS

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Abstract

Objective: This study is planned to study the relationship between dyslipidemia and albuminuria in normotensive diabetic subjects if any so that appropriate medical therapy may be initiated.

Material & Method: The present study was conducted on 50 diabetic subjects between age group of 45-70 years, out of which 31 were males and 19 were females. Out of 50 subjects, 25 were in control group i.e. diabetic patients with no micro/macro-albuminuria and 25 patients were having either micro or macroalbuminuric. The fasting serum lipid levels were estimated and all the parameters obtained were correlated with micro/macro-albuminuria.

Results: The longer duration of diabetes was significantly associated with higher level of albuminuria in test subjects ($P<0.05$).The male diabetic patients had significant higher level of micro/macroalbuminuria ($P<0.05$) in comparison to female diabetic patients. The BMI did not correlate significantly with albuminuria. The total cholesterol was significantly higher in diabetic patients with albuminuria ($P<0.05$). The triglyceride levels were significantly associated with macroalbuminuria in diabetic patients ($P<0.05$). The LDL-C and HDL-C did not correlate significantly with albuminuria in the study.

Conclusion: Male sex has been found to be a risk factor for development of albuminuria in diabetic patients. High levels of serum cholesterol and serum triglycerides have been found to be one of the risk factors for development of albuminuria in diabetic patients despite good blood pressure control and non-smoking.

Keywords: microalbuminuria, Diabetes mellitus, Hyperglycemia, dyslipidemia.

INTRODUCTION

"Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycaemia due to either a deficiency of insulin secretion or due to insulin resistance and increased insulin secretion to compensate or due to a combination of the two" **(1)**. In recent years diabetes mellitus has been found to be the most serious risk factor for cardiovascular disease identified at the

individual level **(2)**. In the new millennium diabetes will becoming a global epidemic proportion, and will emerge as one of the leading causes of morbidity and mortality; and will poses an enormous burden on health cost of virtually every society. Follow up studies of diabetic populations have indicated that patients with albuminuria are at particularly high risk of cardiovascular morbidity and mortality **(3)**.

According to a W.H.O. Report, diabetic population worldwide is expected to rise from 4% (135 million) in 1995 to 5.4% (300 million) in 2025, that is, an estimate 42% increase from 51 to 72 million in developed countries and 170% increase from 84 million to 228 million in developing countries **(4)**.

Individuals with diabetes mellitus may have several form of dyslipidemia. Some studies have shown that hyperlipidemia contributes to both macrovascular changes and to nephropathy. The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. This study is planned to study the relationship between dyslipidemia and albuminuria in normotensive diabetic subjects in the Mewar region of Rajasthan.

MATERIALS AND METHODS

This study was carried out in Diabetic patients (both type I and II), attending a Tertiary Care hospital, at Udaipur. A total of 25 patients of diabetes mellitus with micro/macroalbuminuria were assigned into the study group and 25 diabetic patients without micro/macro-albuminuria of similar profile were included in the control group. For diagnosing DM, the criteria laid down by ADA (American Diabetic Association, 2004) were followed. Besides this factor, age of onset, body weight, BMI, history of ketoacidosis, hypertension was taken into account.

Criteria for selection:

All patients admitted to the medical units or attending the medical outpatient department of Tertiary Care Hospital, Udaipur who satisfy the criteria laid down by the American Diabetic Association 2004 were selected.

Exclusion Criteria:

1. Patients on lipid lowering agents / weight reducing diet
2. Decompensated heart failure
3. Acute febrile illness
4. Urinary tract infection (identified by the presence of pus cells >3/HPF in urine)
5. Metabolic decompensation, specially diabetic ketoacidosis
6. High protein intake
7. Heavy exercise prior to 24 hrs of the test
8. Poorly controlled hypertension
9. Patients with deranged renal functions - serum creatinine > 1.5 mg/dl.

Patients with DM and satisfying the inclusion / exclusion criteria were enrolled into study are allotted into: **Group I:** Cases (25 patients). **Group II:** Controls (25 subjects).

Complete medical histories, family history with special emphasis on duration of illness, therapy, hypertension, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease were obtained. History of smoking, alcohol, dietary pattern, occupation and physical activity were recorded. A thorough physical examination was done including neurological examination prior to the entry into this study. The nature of the study, expected benefits and adverse effects were explained-to each patient. Anthropometric data

were obtained consisting of :Height, Weight, Body mass index - was calculated from the formula: BMI = (Weight in kg) / (Height in meter)^2 Blood pressure was measured in right upper limb in the sitting posture noting both systolic and diastolic pressure after a rest of 10 minutes with random zero sphygmomanometer. Fasting blood sample (defined as no calorie intake for at least 8 hours) for: Plasma glucose, Blood urea, Serum creatinine, Serum lipid profile (Total cholesterol, LDL cholesterol, HDL cholesterol, Triglyceride, Very low density lipoprotein, Urine examination routing - sugar, ketone bodies and microscopic examination for pus cells. Urine for microalbuminuria / macroalbuminuria by dipstick method.

Estimation of Blood Glucose:

Blood glucose was measured by glucometer Accutrend alpha, manufactured by Roche Diagnostics Manheim, Germany. This method works on the principles of glucose oxidase / peroxidase reaction.

Urine examination:

The first morning sample of urine was taken in a clean container. Testing was done within one hour after voiding. This was done with multiple reagent stripes for urine analysis (Bayer Diagnostic India Ltd.).

Collection of Blood Samples and Serum for Lipid Profile:

After overnight fast, 5 ml of blood was taken. The blood was then poured into a clean dry test tube. The test tube was kept in an incubator at 37°C for one hour, so, as to facilitate the coagulation of blood and separation of serum. The serum was then separated by centrifugation at 2500 revolution per minutes. The supernatant, clear serum was used for various investigations. Estimation of Serum lipid profile is done by calorimetric method on fully auto analyzer after proper calibration and controls.

Data Analysis: Statistical analysis was performed using SPSS version 9. Descriptive data were presented as mean $\pm$ s.d. Continues variables were compared using t test. P value < 0.05 was considered as significant.

RESULTS:

In this study total of 50 subjects were studied, of which 31 were male and 19 were female. Out of 19 patients with microalbuminuria 6 were female and out of 6 patients with macroalbuminuria, all were male. In the present study, the mean age of patients with microalbuminuria was 57.36 ± 4.08 years, patients with macroalbuminuria was 57.60 ± 4.21 years, while patients without albuminuria, mean age was 52.56 ± 3.89 years, the age was not found to be significantly associated with albuminuria.

The mean BMI was 24.31 ± 2.75 kg/m^2 and 23.70 ± 1.04 kg/m^2 in microalbuminuric and macroalbuminuric subjects respectively while mean BMI was 23.64 ± 2.66 kg/m^2 in nonalbuminuric subjects. There was no significant correlation found between BMI and albuminuria. The fasting blood sugar was 119.0 ± 12.24 mg% and 109 ± 10.35 mg% in microalbuminuric and macroalbuminuric subjects respectively while it was 114.0 ± 11.31 mg% in nonalbuminuric subjects. There was no significant correlation found between FBS and albuminuria.

Table – 1 Baseline characteristics of subjects

	Diabetic with micro-albuminuria (mean ± SD) n=19	Diabetic with macro-albuminuria (mean ± SD) n=6	Diabetic without albuminuria (mean ± SD) n=25	Range	P Value
Age (years)	57.36±4.08	57.66±4.21	52.56±3.89	45-70	0.439^{NS}
Duration (years)	9.37±3.85	11.50±3.21	5.92±3.09	3-17	0.001^{S}
BMI (kg/m^2)	24.31±2.75	23.70±1.04	23.64±2.66	17.71-28.76	0.685^{NS}
Males (%)	26% (13)	12% (6)	24% (12)		
FBS (mg %)	119.0±12.24	109.01±10.35	114.01±11.31	88-145	0.546^{NS}
T. Chol.(mg%)	208.29±147.79	268.50±152.06	189.13±134.29	135-306	0.001^{S}
TG (mg %)	139.39±154.25	190.02±146.39	127.28±156.20	46 -257	0.04^{S}
LDL-C (mg %)	126.92±140.02	136.10±180.36	116.32±135.49	50-219	0.539^{NS}
HDL-C (mg %)	43.08±19.75	42.35±10.79	45.94±10.53	22-69.2	0.520^{NS}
TCH-HDL	5.44±11.83	6.64±12.28	4.36±11.28	2.5-13.64	0.176^{NS}
S. creatinine (mg %)	0.97±0.25	1.14±0.27	1.03±0.27	0.57-1.5	0.41^{NS}

SD = Standard deviation, S = Significant, NS = Not significant

The mean serum creatinine level was 0.97 ± 0.25 mg% and 1.14 ± 0.27 mg% in micro and macroalbuminuric patients respectively and 1.03 ± 0.27 mg% in nonalbuminuric patients. It was not found be significantly associated with level of albuminuria.

In this study 50 patients of 45 to 70 years age group were included in both study and control group. Out of six patients with macroalbuminuria 5 patients were of age between 50-60 years and one patient was of age between 65-70 years. In patients with microalbumnuria; out of 19 patients, 10 patents were between ages of 50-60 years. In 25 patients, without albuminuria 14 patients were of age between 45-50 years. There were no significant correlation was found between age and albuminuria in this study. Out of 50 patients, 19 patients had microalbuminuria and the mean duration of diabetes was 9.37 ± 3.85 years. 6 patients had macroalbuminuria having diabetes from average 11.50 ± 3.21 years. 25 patients without albuminuria had diabetes duration of mean 5.92 ± 0.62 years. In this study the albuminuria was found to be significantly associated with longer duration of diabetes ($P<0.05$). In present study (Fig.4) the mean cholesterol level was 189.13 ± 34.29 mg% in non-albuminuria diabetic patients while it was 222.74 ± 54.46 mg% in albuminuric patients which was found to be significantly higher ($P<0.05$) than non-albuminuric patients.

TABLE-2 Correlation between duration of diabetes and micro/macroalbuminuria

	No. of patients (n)	Mean duration of diabetes in years	S.D.	SEm
Patient without albuminuria	25	5.92	3.09	0.62
Patient with macroalbuminuria	19	9.37	3.85	0.88
Patient with macroalbuminuria	6	11.50	3.21	1.31
Total	50	7.90	3.95	0.56
S.D. = Standard deviation SEm = Standard error of mean				

ANOVA

	Sum of Squares	d.f.	Mean square	F	P value
Between	216.739	2	108.369	9.299	< 0.05
Within	547.761	47	11.6564		
Total	764.500	49			

The mean triglyceride levels were 127.28 ± 11.24 and 151.54 ± 11.21 mg% in non-albuminuric and albuminuric patients respectively. Serum triglyceride levels were found significantly higher in macroalbuminuric than non-albuminuric patients. In present study serum LDL levels were 116.32 ± 7.09 mg% and 129.12 ± 10.12 mg% in non-albuminuric and albuminuric patients respectively which was statistically non-significant (P>0.05). The serum HDL-C level was 45.94 ± 2.10 mg% and 42.53 ± 2.07 mg% in non-albuminuric and albuminuric patients respectively. Though levels of HDL-C were lower in patients with albuminuria. It was statistically not significant (P>0.05). The mean fasting blood sugar level was 114.00 ± 12.01 mg% and 116.88 ± 28.71 mg% in non-albuminuric and albuminuric patients respectively which was not significantly associated with level of albuminuria. The mean serum creatinine level was 1.014 ± 0.26 mg% and 1.025 ± 0.26 mg% in non-albuminuric and albuminuric patients, respectively. There was no significant correlation found between serum creatinine levels and albuminuria in diabetic patients in present study.

DISCUSSION

Proteinuria in individuals with diabetes mellitus is associated with markedly reduced survival and increased risk of cardiovascular disease **(5)**. In addition to hypertension, glycemic control and genetic influence, diabetic dyslipidemia seems to play an important role in the pathogenesis and progression of vascular diseases in the diabetic patients and it is under discussion if it plays a role in the evolution of diabetic nephropathy.

Table-3 comparison of biochemical parameters in albumnuric and non-albuminuric Subjects

Parameters	Albuminuria	N	Mean	SD	SE
Total' cholesterol (mg %)	0	25	189.13	34.29	6.86
	1	25	222.74	54.46	10.89
	Total	50	205.94	48.14	6.81
Triglyceride (mg %)	0	25	127.28	56.20	11.24
	1	25	151.54	56.06	11.21
	Total	50	139.41	56.89	8.05
LDLC (mg %)	0	25	116.320	35.191	7.098
	1	25	129.128	50.627	10.125
	Total	50	122.724	43.751	6.187
HDL-C (mg %)	0	25	45.944	10.537	2.107
	1	25	42.532	10.360	2.072
	Total	50	44.238	10.484	1.483
FBS (mg %)	0	25	114.00	12.01	2.40
	1	25	116.88	28.71	5.74
	° Total	50	115.44	21.83	3.09
TCH : HDL	0	25	4.393	1.433	0.287
	1	25	5.821	3.448	0.689
	Total	50	5.107	2.711	0.383
S. creatinine (mg %)	0	25	1.034	0.276	5.51E-02
	1	25	1.017	0.264	5.27E-02
	Total	**50**	**1.025**	**0.267**	**3.78E-02**

0 - Patients without albuminuria, 1- Patients with albuminuria

In early and advanced stages of diabetic nephropathy lipid disorders may be present. In the present study patients with higher duration of diabetes had higher incidence of albuminuria. The duration of diabetes was significantly higher in patients with albuminuria ($P < 0.05$) than patients without it. The average duration was more in microalbuminuria and macro albuminria patients compare to patients without albuminuria (Table 2).

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type-1 DM but appears to be similar in type 2 DM. Glomerular hypertension and renal hypertrophy occur in the first years after the onset of DM and cause an increase of the glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy and mesangial volume expansion occur as the GFR returns to normal. After 5 to 10 years of type 1 DM, 40% of individuals begin to excrete small amount of albumin in the urine. The appearance of microalbuminuria (incipient

nephropathy) in type 1 DM is an important predictor of progression to overt proteinuria (> 300 mg/d) or overt nephropathy. Blood pressure may rise slightly at this point but usually remains in the normal range. Once overt proteinuria is present, there is a steady decline in GFR and 50% of individuals reach ESRD in 7 to 10 years. The early pathologic changes and albumin excretion abnormalities are reversible with normalization of plasma glucose. However, once overt nephropathy develops, the pathologic changes are usually irreversible **(5)**.

In this study, the occurrence of albuminuria was significantly higher in male patients than female (P<0.05) (Table 1). A study was conducted by De Cosmo S, Minenna A **(6)** to correlate sex specific association with increased urinary albumin excretion, and related cardiovascular risk factors in patients with type 2 diabetes. Urinary albumin excretion (UAE) was derived from the albumin to creatinine ratio (ACR). When two sexes were investigated separately a significant correlation between ACR and insulin resistance was found in men but not in women. Also ACR was significantly higher in men with two or more insulin resistance related cardiovascular risk factors (i.e. abdominal obesity, dyslipidemia and hypertension) than in men with fewer than two insulin resistance related cardiovascular risk factors (P = 0.005).

In this study serum cholesterol and triglyceride levels were found significantly higher in patients with albuminuria than without it, (P<0.05) showing that lipids may have a role in albuminuria in diabetic patients (Table 3).

Tseng CH *et al.* **(7)** showed lipid abnormalities associated with urinary albumin excretion rate (UAER) in Taiwanese type 2 diabetic patients. A total of 275 (122 men and 153 women; aged 60.6 ± 11.1 years) patients were selected with stringent criteria to prevent confounders. In their study total cholesterol triglycerides, Apo-B and non-HDL cholesterol were significantly (P<0.05) higher in patients with albuminuria. After adjusting for age, systolic BP and HbA1c correlation coefficient between the natural logarithm (In) ACR and lipid parameters, odds ratio for albuminuria, and standardized regression coefficient for In ACR, were significant for cholesterol, Apo-B and non-HDL-cholesterol in all subjects and in men, but only Apo-B was significant in women.

Thomas MC, Rosengard *et al.* **(8)**, showed that dyslipidemia contributes to the progression of microvascular disease in diabetes. However, different lipid variables may be important at different stages of nephropathy. A total of 152 patients with diabetes were recruited in order to represent various phases of nephropathy. Patients were followed for 8-9 years. In patients with normoalbuminuria (n=66), progression was associated with male sex (P < 0.05), and LDL free cholesterol (P = 0.02). In patients with microalbuminuria (n = 51), progression was independently associated with triglyceride content of LDL and IDL (P < 0.05). **(8)**

Cederholm J *et al.* **(9)** performed a prospective study of normoalbuminuric diabetic patients between 1997 and 2002 on 4097 type 1 and 6513 type 2 diabetic patients from the Swedish National Diabetes Register (NDR); mean study period was 4.6 years. The strongest independent baseline risk factor for the development of microalbuminuria (20-200 jag/min) was elevated HbA1c and duration in both type 1 and 2 diabetic patients. A subsequent larger cross-sectional study in 2002 showed that

established microalbuminuria was independently associated with HbA1c, diabetes duration, BMI, systolic blood pressure, smoking and triglycerides in type 1 and 2 diabetic patients, and also with HDL-cholesterol in type 2 patients .

Hadjadj S *et al* **(10)** showed that serum triglycerides are predictive factor for development and the progression of renal and retinal complications in diabetic patients. He prospectively followed 297 patients with type 1 diabetes without end stage renal disease for 7 years. Serum triglyceride levels were higher in patients who progressed to nephropathy than in those who did not (median 1.21 Vs 0.91 mmol/1; P = 0.0037). **(10)**

Vannini P *et al* **(11)** showed the relationship between serum lipid, lipoprotein, and apolipoprotein levels and abnormalities of renal function in 112 insulin-dependent (type I) diabetic patients. They were subdivided into three matched groups according to the amount of albuminuria: group A (albuminuria less than 20 micrograms/min), group B (albuminuria between 20 and 150 micrograms/min; Albustix negative), and group C (albuminuria greater than 150 micrograms/min; Albustix positive). Twenty-one nondiabetic subjects with albuminuria above 150 micrograms/min but without nephrotic syndrome and/or renal failure and 77 healthy subjects were also studied. When results were obtained Mean total and LDL cholesterol, triglycerides, and apo B were higher, while HDL cholesterol and HDL/LDL cholesterol ratio were lower in group C (albuminuria greater than 150 micrograms/min; Albustix positive) than in groups A and B; No correlation between lipid parameters and amount of albuminuria was observed. Significant differences in lipid concentrations were also found in diabetic patients when compared with nondiabetic subjects with albuminuria and with healthy subjects. The present study confirmed previous reports of lipid disorders in insulin-dependent (type I) diabetes; however, the most important observation was the finding of albuminuria-related differences in lipid parameters in diabetic patients without renal failure. They concluded that the greater lipid abnormalities observed in diabetic patients with larger amounts of albuminuria might be the consequence of impairment of glomerular permeability and of the diabetic state. **(11)**

CONCLUSION:

Male sex has been found to be a risk factor for development of albuminuria in diabetic patients. High levels of serum cholesterol and serum triglycerides have been found to be one of the risk factors for development of albuminuria in diabetic patients despite good blood pressure control and non-smoking. Serum LDL-C and HDL-C were not found to be significantly associated with development of albuminuria in diabetic patients. In view of their poor correlation with albuminuria in the present work, further larger study is warranted with' inclusion of more number of patients of various categories.

In conclusion, the main risk factors for development, progression and remission of microvascular disease in diabetic are much alike and closely interrelated. The improved kidney prognosis in diabetic patients reveals an urgent need for targeting early detection and treatment of cardiovascular diseases. To improve the prognosis and the quality of life in the diabetic patients even further, the treatment and care of

patients must deal with all aspects of the disease, and thus prevention and treatment of micro and macrovascular complications become vital. Whether the development of severe diabetic microangiopathy can be totally prevented or only postponed is not known at present time. However, early detection of high risk patients, even before development of microalbuminuria, is of substantial importance in order to target early intervention or even prevention of diabetic nephropathy.

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