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Clinical Correlation between ApoB/ApoA1 Ratio in Type 2 Diabetic Nephropathy-A Tertiary Centre Experience

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***Abstract*- Background-** The aim of this study was to evaluate the lipid abnormalities associated with different stages of albuminuria and also examine role of ApoB lipoprotein as a predictor of early diabetic nephropathy in type 2 diabetic patients.

Methods and Results- A total 100 diabetic patients (58 men and 42 women) with mean age group 59.15±10.4 years were studied. Normoalbuminurea (n=36), microalbuminurea (n=42) and macroalbuminurea (n=22) were defined as <30, 30-299 and >300 mg/day respectively. Lipid parameters included, total cholesterol, triglyceride (TG), high and low density lipoprotein cholesterol, apolipoproteins A1, and Apo B. Result showed that Apo B differed significantly ($P<0.05$) between normoalbuminurea and micro and macroalbuminurea. Triglyceride increases progressively with increasing albuminurea. In multivariate logistic regression analysis, with 24 hours urinary albumin levels was dependent on triglyceride, total cholesterol, HDL, LDL, VLDL, Apo-B, Apo-A1 , Apo-B/Apo-A1 and for triglyceride, none of the other variables were significantly associated with the outcome. The model had an excellent explanatory power ($r^2=0.674$).

Conclusion-. In conclusion during the development of diabetic nephropathy atherogenic lipoproteins may play significant role. Apo B was associated with the early development of microalbuminuria and remained elevated throughout the course of abnormal albuminuria. Apo-B/Apo-A1ratio may be early indicator of diabetic nephropathy.

***Index Terms*-** Type 2 diabetes, Nephropathy, Apo A1, Apo B, Apo-B/Apo-A1

I. BACKGROUND AND OBJECTIVES

Diabetes mellitus (DM) is a metabolic disorder, of which the number of patients is rapidly increasing worldwide due to several conditions such as aging, westernization, and increasing prevalence of obesity and physical inactivity every year. Particularly, it is one of the major treatment-requiring diseases nowadays. The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions .[1,2] It is estimated that there are currently 285 million people with diabetes worldwide and this number is set to increase to 438 million by the year 2030.[3]

According to world diabetes Atlas, India is projected to have around 51 million people of diabetes.[4] The prevalence diabetes is traditionally known as "silent disease" exhibiting no symptoms until it progresses to severe target organ damage.[5] Diabetes related life threatening complications were worldwide approximately 6% of total global mortality, accounting for 3.8 million deaths in 2007[6]. Diabetic population is predisposed to an increased risk of both micro and macrovascular complications and some 50% of people with diabetes die of cardiovascular disease.[7] Age adjusted mortality rates among diabetics is 1.5 to 2.5 times higher than general population.[8]

Diabetic patients are also known to be at increased risk of dyslipidemia which can contribute to the higher morbidity and mortality.[9] Dyslipidemia in diabetes is characterized by elevated triglycerides, low high density lipoprotein (HDL) cholesterol levels, and increased low density lipoprotein (LDL).[10] There are four major groups of lipoproteins that are known, namely chylomicrons, very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL).The protein moiety of a lipoprotein is known as apolipoprotein which can be of different types with different functions . Apo B is the major protein component of VLDL and LDL in serum, forms an important part of their structure, while Apo A1 is a major protein component of HDL .[11]

Microalbuminuria, an early marker of diabetic nephropathy, is an independent risk factor for cardiovascular disease. Microalbuminuria is excretion of albumin 30 to 300 mg/day in a 24 hour urine collection or 30 to 300 µgram/mg creatinine in a spot collection. Diabetic nephropathy is characterised by progressive increase of urinary albumin excretion rate (UAER). The increased levels of urinary albumin excretion may represent a more generalised vascular injury alone. During the past decade, the incidence of end stage renal disease has risen dramatically, primarily due to an increase in the incidence of diabetes.

The presence of microalbumin in the urine of persons with type 2 diabetes is perhaps the most important early signal heralding the onset of systemic vasculopathy and associated with target organ damage (Brain, heart and kidney).[12] Microalbuminuria also identifies patients who need more rigorous cardiovascular risk management, especially more intensive blood pressure control, strict attention to glycemic control and lipid level. Interestingly it has been suggested that hyperglycemia, hypertension, and dyslipidemia cause disorders of albumin excretion rate by damaging the podocyte and slit diaphragm protein scaffold with overproduction of and extracellular release of oxygen radical species at the glomerular level.[13]

Diabetic nephropathy is the leading cause of diabetes related morbidity& mortality.Microalbuminuria is considered to be

earliest marker of nephropathy.[14] There are evidences which link microalbuminuria to atherogenesis.[15] Diabetes is also associated with alteration in the amounts of several classes of lipoproteins and apolipoproteins, the specific action of which can affect the development of vascular disease and nephropathy in patients with diabetes. Apolipoprotein B (ApoB), the main surface protein on LDL particles, and LDL-C and Apolipoprotein A_1(Apo A1), the main surface protein on HDL particles are respectively, positive and negative risk factors for coronary heart disease and atherogenesis.[16] There is paucity of literature on this context. So this study was planned to observe correlation of Apo B /ApoA1 ratio in context of diabetic nephropathy patients.

II. MATERIAL AND METHOD

The present study was a cross sectional study done over a period of one year in the Department of Medicine, King George Medical University, Lucknow India from August 2009 to July 2010. Patient having type 2 diabetes mellitus, attending diabetic clinic and admitted in medical ward of Gandhi Memorial & Associated Hospital and fulfilling the inclusion criteria were enrolled in the study. After written informed consent 100 patients were studied. The study was approved by the Institutional ethic committee of, King George Medical University Lucknow to use human subject in the research study.

Patient with duration of diabetes for 5 years or more with GFR more than 60 ml/min were included in the study. Subject not fulfilling the above mentioned criteria, proteinuria due to other causes like urinary tract infection, congestive heart failure, pregnancy and patients on Angiotensin Converting Enzyme Inhibitor (ACEI) / Angiotensin Receptor Blocker (ARB), lipid lowering drugs were excluded from the study. After detailed history and thorough physical examination, relevant investigations were done.

A 24 hour urine sample was collected in a five litre clean plastic container. All the subjects were provided with a labelled container containing 5 ml toluene as preservative and a bag in which to carry the container. The patients were instructed to refrain from exercise at least 24 hours before urine collection which was started in the morning at 8:00 Am. After discarding the first voided urine sample, then all the urine of day and overnight was added to the specimen container till the next morning at 8:00 Am was subjected for measurement of microalbuminuria. Microalbuminuria was measured by Nephalometry method. On the basis of 24 hours urinary albumin, patients were divided into three groups. Normoalbuminuria, albumin excretion less than 30 mg/24 hour, microalbuminuria having albumin levels between 30-300 mg/24 hour, and macroalbuminuria were above 300 mg/24 hour. Creatinine clearance rate (Ccr, ml/min) was calculated from the Cockcroft – Gault formula as: [(140-age in years)×body weight in kg/ 72 × serum creatinine in mg/dl)]. For women, the values were multiplied by 0.85.

About 5 ml of venous blood were drawn under aseptic precautions, in a sterile bulb from selected subject after a period of overnight fasting; serum was separated by centrifugation and used for analysis. Serum lipid profile which includes triglycerides (TG), total cholesterol (TC), high density cholesterol (HDL-C) were measured by enzymatic method and serum low density cholesterol (LDL-C) and very low density cholesterol (VLDL-C) were calculated by using Friedwald formula (LDL-C=TC (HDL-C + TG/2.2).[24] Lipid profile was analyzed by using ERBA kits in microlab semi analyzer of MERK Company, all the reagents used in the estimation were of analytical grade. Serum apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) were measured by Nephelometry method from random blood samples of the patients. This method is based upon a comparison of the intensity of light scattered by the sample under certain defined conditions with the intensity of light scattered by a standard reference suspension. The higher the intensity of scattered light, higher the turbidity. A standard suspension of Formazin is used for calibration.

Age, sex, body mass index (BMI), duration of diabetes, history of hypertension, smoking, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood urea , serum creatinine , fasting plasma glucose (FPG), glycosylated haemoglobin (HbA_{1c}), were treated as potential confounder.

Blood pressure was measured in the right arm after 20 minute rest on a sitting position with a standard mercury sphygmomanometer. Body height in centimetres and body weight in kilograms (kg) were measured with light clothes and bare feet , and BMI in kg/m^2 was calculated. Blood urea, serum creatinine and plasma glucose levels were measured on an automatic biochemistry analyzer (Transasia GM360 India). All the reagents used in the estimation were of analytical grade. HbA_{1c} was measured by means of boronate affinity chromatography.

III. STATISTICAL ANALYSIS

The data were entered in MS-Excel program and descriptive statistics were given in the form of mean±SD along with median, if indicated for quantitative variables and proportion for qualitative variables. Wherever needed, the quantitative variables were categorized and categorical description were given. The significance of the association between two categorical variables was tested by χ^2 statistics. The magnitude of the risk of the exposure variables for nephropathy VS control was expressed as Odds ratio (95%CI). Fisher's exact test was used for risk association calculation and corresponding exact OR and p values were reported. The comparison of means for the normally distributed data between two groups was done by using two-sample t-test and correction for unequal variance was applied, if required. If data were not normally distributed Mann-Whitney test was applied to test the difference between two central measures. The comparison of means for the normally distributed data among three groups was done by using oneway analysis of variance (ANOVA). If data were not normally distributed or the variance was not homogenous across groups Kruskal Wallis test was applied to test the difference among central measures. Normalcy of data distribution was tested prior to carrying out any statistical tests. Data were analysed using statistical software package, STATA 11.1 and the difference was considered to be significant if 'p' value was found to be <0.05.

IV. RESULTS

A total of 100 type 2 diabetic patients were studied. Table 1 shows base line characteristics. In type-2 diabetes mellitus patients included in the study mean age was 59.15±10.4 years. Patients of macroalbuminuria group (n=22) belonged to higher age 63.45±8.99 years as compared to those in normoalbuminuria, (n=36)58.14±10.32 years and microalbuminuria group (n=42) 57.76±10.87 years.

The duration of diabetes mellitus was highest in macroalbuminuria group 11.93±4.14 years followed by microalbuminuria group 8.69±5.78 years and least in normoalbuminuria group 6.25±1.53 years. (p<0.001)

Glomerular filteration rate (GFR) in study subject was between 60 to 123.9 ml/min. Mean value was 83.61± 18.1 ml/min. In normoalbuminuria group mean GFR was 83.47± 17.68 ml/min, in microalbuminuria group it was 83.24±19.66 ml/min and in macroalbuminuria group it was 84.54 ± 16.3) ml/min.

The 24 hours urinary albumin value among the patients included in the study was 17.08±5.77 mg/24 hours in normoalbuminuria group, 139.85±77.21 mg/24 hours in microalbuminuria group, 405.76±153.86 mg/24 hours in macroalbuminuria group. (p<0.001)

Mean waist circumference among was 86.50±10.75 in normogroup, 99.05±12.16 in microgroup and 96.55±10.72 in macrogroup. (p<0.001)

Mean hip circumference was 91.21±5.56 in normogroup, 95.82±8.16 in microgroup, 91.18±6.05 in macrogroup respectively. (p=0.005)

Mean waist hip ratio was 0.94±0.11 in normogroup, 1.03±0.12, in microgroup, 1.05±0.09 in macrogroup respectively. (p<0.001)

Mean Apo-B/Apo-A1 level was 1.27. Out of hundred patients fifty eight (58%) have raised Apo-B/Apo-A1 ratio, as shown in Table 3, in normoalbuminuria group 8.4% (3 out of 36), in microalbuminuria group 85.72% (36 out of 42), and in macroalbuminuria group 86.4% (19 out of 22). These differences were statistically significant (p <0.001).

Demographic, Clinical and Laboratory Data of patients in three subgroups of albuminuria are shown in Table 1. In addition to age, BMI, waist hip ratio,GFR were selected as potential confounder for adjustment in the logistic regression analysis. Blood urea and serum creatinine were not selected because they were highly associated with creatinine clearance, and history of hypertension was not selected because of its association with systolic blood pressure.

Table 1: Demographic, Clinical and Laboratory Data of patients in three groups

SN	Variable	Normo (n=36)	Micro (n=42)	Macro (n=22)	Significance of difference
1.	Mean Age±SD (Range) in years	58.14±10.32 (40-84)	57.76±10.87 (40-83)	63.45±8.99 (45-80)	F=2.482; p=0.089
2.	Female:Male	8 (22.2%): 28 (77.8%)	23 (54.8%): 19 (45.2%)	11 (50.0%): 11 (50.0%)	χ^2=9.167; p=0.010
3.	Mean Duration of DM ±SD (Range) in years	6.25±1.53 (5-14)	8.69±5.78 (5-40)	11.93±4.14 (7-20)	F=11.853; p<0.001
5.	Positive family history	5 (13.9%)	17 (40.5%)	18 (81.8%)	χ^2=26.621; p<0.001
6.	Hypertension	7 (19.4%)	27 (64.3%)	19 (86.4%)	χ^2=28.251; p<0.001
7.	Smoking				
	CM	0 (0%)	0 (0%)	2 (9.1%)	χ^2=14.131; p=0.028
	CS	4 (11.1%)	11 (26.2%)	4 (18.2%)	
	FS	3 (8.3%)	4 (9.5%)	5 (22.7%)	
	NS	29 (80.6%)	27 (64.3%)	11 (50.0%)	
9.	Alcohol use	5 (13.9%)	8 (19.0%)	3 (13.6%)	χ^2=0.511; p=0.778
10.	Daily intake of vegetables/ fruits	28 (77.8%)	24 (57.1%)	5 (22.7%)	χ^2=16.885; p<0.001
11.	Non-vegetarian diet	11 (30.6%)	25 (59.5%)	16 (72.7%)	χ^2=11.372; p=0.003
12.	Regular physical activity	29 (80.6%)	13 (31.0%)	5 (22.7%)	χ^2=25.819; p<0.001
14.	Mean BMI±SD	23.78±2.13	28.45±4.22	30.15±3.44	F=28.833; p<0.001
15.	Mean waist circumference±SD	86.50±10.75	99.05±12.16	96.55±10.72	F=12.543; p<0.001

16.	Mean hip circumference±SD	91.21±5.56	95.82±8.16	91.18±6.05	F=5.507; p=0.005
17.	Mean WHR±SD	0.94±0.11	1.03±0.12	1.05±0.09	F=8.968; p<0.001
18.	Mean FBS±SD	114.63±35.79	154.40±57.91	145.82±36.47	F=7.291; p=0.001
19.	Mean HbA_{1c}±SD	6.77±0.59	8.55±1.36	9.16±1.60	F=32.863; p<0.001

Data are expressed as mean ±SD or %, p value for one way ANOVA p<0.005

A positive correlation between 24 hour urinary albumin excretion and Apo-B/Apo-A1 ratio was observed . Apo-B/Apo-A1 ratio gradually increases with increasing proportion of urinary albumin excretion (r = 0.788, p <0.001). TG differed significantly among the three subgroup of albuminuria but statistically significant (p <0.001) .(Table 2 and 3)

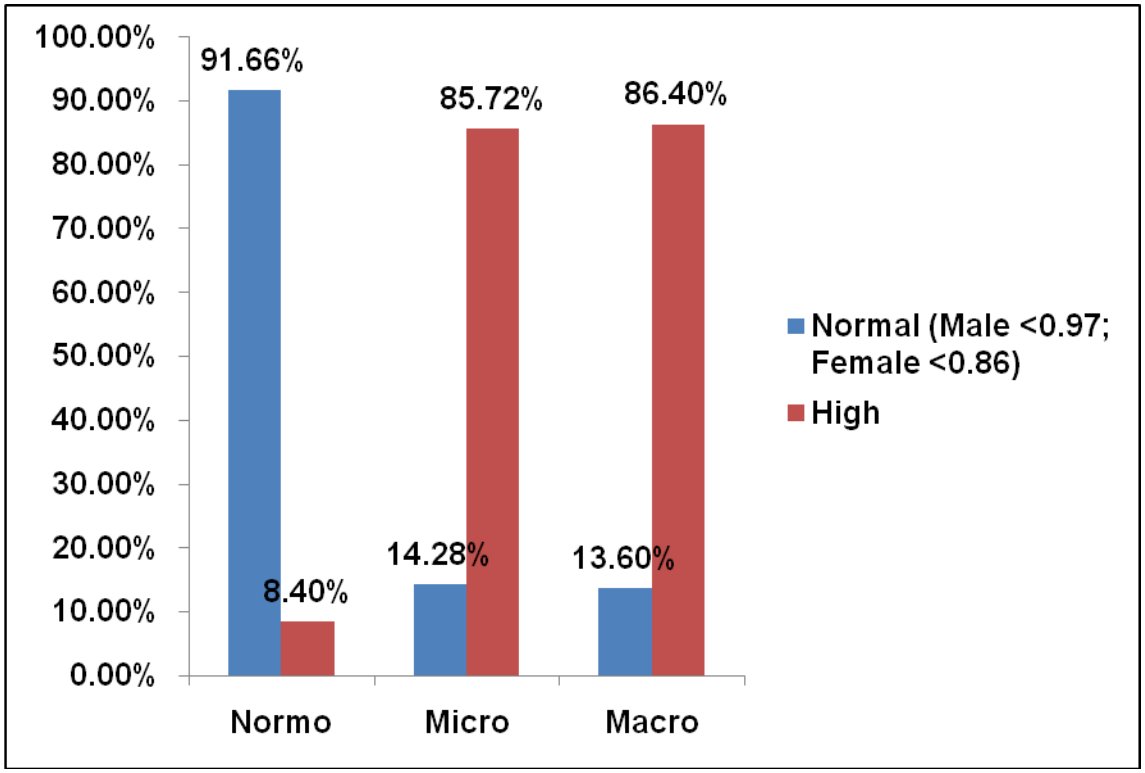
Table- 2 Lipid Profiles of Three Groups

SN	Variable	Normo (n=36)	Micro (n=42)	Macro (n=22)	Significance of difference
1	Mean TG±SD	132.98±43.92	203.47±87.29	185.50±47.00	F=11.394; p<0.001
2.	Mean TC±SD	129.57±29.50	165.90±36.41	194.47±30.56	F=28.249; p<0.001
3.	Mean HDL±SD	34.86±9.19	30.33±7.84	29.60±8.05	F=3.802; p=0.026
4.	Mean LDL±SD	75.22±27.61	109.61±40.04	139.44±32.51	F=24.863; p<0.001
5.	Mean VLDL±SD	20.48±11.11	26.23±16.90	29.94±21.58	F=2.507; p=0.087
6.	Mean GFR±SD	83.47±17.68	83.24±19.66	84.54±16.26	F=0.038; p=0.963
7.	Mean Apo-B±SD	1.01±0.30	1.19±0.50	1.46±0.66	F=5.926; p=0.004
8.	Mean Apo-A1±SD	1.55±0.65	1.00±0.37	0.89±0.43	F=16.270; p<0.001
9.	Mean Apo-B/Apo-A1±SD	0.82±0.64	1.26±0.60	2.03±1.29	F=15.138; p<0.001
10.	24 hrs Urinary Alb±SD	17.08±5.77	139.85±77.21	405.76±153.86	F=134.43; p<0.001

Data are expressed as mean ±SD or %, p value for one way ANOVA p<0.005

Table 3:- Apo-B/Apo-A1 Ratio Among Three Groups

Apo-B/Apo-A1	Normo	Micro	Macro	Total (%)
Normal (Male <0.97; Female <0.86)	33(91.66%) p<0.001	6(14.28%) p<0.001	3(13.6%) p<0.001	42
High	3(8.4%) p<0.001	36(85.72%) p<0.001	19(86.4%) p<0.001	58
Total	36	42	22	100



r=0.788; p<0.001 (Overall)

24 hrs of urinary albumin excretion (x axis)with Apo-B/Apo-A1 ratio(y axis) in all subjects.

On multiple logistic regression analysis with 24 hours urinary albumin levels as dependent on Total Cholesterol, HDL, LDL, VLDL, Apo-B, Apo-A1,Apo-B/Apo-A1and for Triglyceride none of the other variables were significantly associated with the outcome. This model had an excellent explanatory power (r^2=0.674). (Table 4)

Table 4: Multiple Logistic Regression of different variables on microalbumin levels

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-267.675	174.130		-1.537	0.128
	AGE	-.240	1.224	-.015	-.196	0.845
	BMI	5.643	3.469	.143	1.627	0.108
	Waist hip ratio	-11.501	122.990	-.008	-.094	0.926
	GFR	-.408	.768	-.044	-.531	0.597
	FBS	.155	.270	.045	.574	0.568
	HBA1C	16.989	9.357	.158	1.816	0.073
	Triglyceride	-.431	.202	-.189	-2.132	**0.036**
	Total Chl	-4.631	1.250	-1.127	-3.706	**<0.001**
	HDL Chl	3.958	1.889	.198	2.095	**0.039**
	LDL Chl	6.475	1.215	1.597	5.328	**<0.001**
	VLDL Chl	7.009	1.113	.700	6.299	**<0.001**
	Apo-B	6.039	31.496	-.018	-.192	**<0.001**
	Apo-A1	-18.133	33.776	-.061	-.537	**<0.001**
	Apo-B/Apo-A1	19.239	20.055	-.106	-.959	**<0.001**

a Dependent Variable: 24hrs Urinary Alb
r^2=0.674

V. DISCUSSION

Chronic diabetic complications constitute a group of diseases responsible for substantial morbidity and mortality, and prevention of such complications is a key issue in the management of the diabetes epidemic.[17,18,19] Therapeutic modalities for diabetes have evolved a great deal in the management of the diabetes. However, most people with this disorder go on to develop complications leading to damage to various body tissues, out of them diabetic nephropathy is the leading cause of chronic kidney disease in India.[20,21]

It has been predicted that world wide the prevalence of diabetes in adults would increase to 5.4% by the year 2025 from the prevalence rate of 4.0% in 1995. The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions .[14] It is estimated that there are currently 285 million people with diabetes worldwide and this number is set to increase to 438 million by the year 2030.[3]The major proportion of this increase will occur in developing countries of the world where disorder predominantly affects younger adults in the economically productive age group[4]. There also consensus that the South Asia region will include 3 of top ten countries in the world (India, Pakistan and Bangaladesh) in terms of the estimated absolute numbers of people with diabetes.[3]

According to world diabetes Atlas, India is projected to have around 51 million people of diabetes. However these datas are based on small sporadic studies done in some parts of the country. Even a few multicentere studies that have been done, have several limitations. Also marked heterogenicity between states limits be generalizability of results. The prevalent diabetes is traditionally known as "silent disease" exhibiting no symptoms until it progresses to severe target organ damage.[22] Diabetes related life threatening complications were worldwide approximately 6% of total global mortality, accounting for 3.8 million deaths in 2007. According to International Diabetes Federation (IFD) , datas shows that world diabetes and pre diabetes prevalence in 2007 was 5.7% and 7.5% respectively. In India diabetes prevalence range from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas.[8] Diabetes causes long term dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels. Diabetic population is predisposed to an increased risk of both micro and macrovascular complications and some 50% of people with diabetes die of cardiovascular disease. Age adjusted mortality rates among diabetics is 1.5 to 2.5 times higher than general population.[8]

Consequently the number of adults with diabetes in the world would rise from 135 million in 1995 to 300 million in the year 2025.[23] It is expected that much of this increase in prevalence rate will occur in developing countries. While a 42% increase is expected in developed countries, a 170% increase is expected in the developing countries. In the latter, most of the diabetic patients are in the age range of 45–64 years, while in developed countries most of them are ≥65 years. Therefore diabetic patients in developing countries are even more vulnerable to develop the micro- vascular complications of diabetes including diabetic nephropathy.

TG differed significantly among the three subgroups of albuminuria (Table 2) and was correlated with AER for all ranges of albuminuria (Table 4). Furthermore, TG was independently associated with microalbuminuria and macroalbuminuria after adjustment for selected confounders multiple logistic regression analysis (Tables 4). The association between TG and albuminuria could possibly reflect an association between the atherogenic small dense LDL particles

and albuminuria, because TG level was inversely correlated with LDL size (r^2=0.67401, p<0.0) [24] and a TG level >1.5 mM (or 134 mg/dL) is significantly associated with small dense LDL .[25] However, further investigations are required to confirm this speculation.

There are evidences which link microalbuminuria with diabetic dyslipidemia.[2] Atherosclerosis which may began early in presence of diabetes, lipid and lipoprotein abnormalities can be a cause of chronic complications in such patients. Current study reveals significant correlation between urinary albumin excretion and ApoB/ApoA1ratio in type 2 diabetic patients. Microalbuminuria is regarded as a measure of generalized endothelial damage, it reflects transvascular albumin leakage and has been proposed to indicate increased endothelial permeability. Theoretically, such a leakiness may allow for an increased lipid insudation into the large vessel wall, thereby linking microalbuminuria to atherogenesis.[15] High level of ApoB and low level of ApoA1 lead to atherogenesis and may contribute in development of nephropathy. There is paucity of data available in this regard. **Mulec *et al***[26] demonstrated Apo B as a significant predictors of subsequent nephropathy**. Jerkins and Lyons *et al*** [27]also related higher Apo-B level and low ApoA1 with urinary albumin excretion. In a cross-sectional study **Attman *et al*** [28] also demonstrated higher Apo B levels in subjects with type 1diabetes with nephropathy in comparison to type 1 diabetic subjects without nephropathy. Result of our study is accordance with study done by **Tamsma *et al*** [29] showed higher value of interstitial ApoB/ApoA1 ratio in diabetic nephropathy patients. Recently a study published by **Z.C.Sun in 2009**[30] in China showed that Apo-B/Apo-A1ratio is associated with diabetic nephropathy both in men and women with type 2 diabetes mellitus. When Apo-B/Apo-A1ratio is ≥0.9, the incidence of diabetic nephropathy was markedly higher.

VI. Conclusion

In conclusion during the development of diabetic nephropathy, atherogenic lipoproteins may play significant role in different stages. TG may increase throughout the three stages of albuminuria. Apo B was associated with the early development of microalbuminuria and remained elevated throughout the course of abnormal albuminuria. Apo-B/Apo-A1ratio may be early indicator of diabetic nephropathy. In our study sample size is small so needs further large scale study.

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