



MICROALBUMINURIA – AN INCREASINGLY RECOGNIZED CARDIOVASCULAR RISK FACTOR

Dr. S. Aruna, M.d.*

Assistant Professor, Department Of Biochemistry, Karur Govt. Medical College, Karur *Corresponding Author

Dr. J. Sowndharya, M.d.

Tutor, Department Of Biochemistry, Karur Govt. Medical College, Karur

Dr. R. S. Monish Anand, M.b.b.s.

ABSTRACT

AIM: The Aim of the study is to determine the prevalence of Microalbuminuria in newly diagnosed patients with Type 2 Diabetes Mellitus and to compare the effectiveness of Microalbuminuria with the fasting Lipid profile in detecting Cardiovascular risk in these patients in terms of Atherogenic Index. **Material & Methods:** The study group includes 100 patients with Type 2 Diabetes Mellitus. Patients with urinary tract infection, Macro albuminuria, Renal failure and Heart failure are excluded from the study. Fasting and post-prandial blood sugar, Fasting Lipid profile, Atherogenic Index, Creatinine and Urine Albumin are measured in all the patients. The patients were divided in to two groups: Group A without Microalbuminuria and Group B with Microalbuminuria.

RESULTS: BMI, FBS, PPBS, Total Cholesterol, TGL, Atherogenic Index, Creatinine and Urine Albumin are found to be higher in Group B compared to Group A patients and Serum HDL is found to be lower in Group B compared to Group A patients. Pearson correlation coefficient of Atherogenic Indices with Urine Albumin excretion of Group B patients shows that there is a significant positive correlation ($r = 0.5981$).

CONCLUSION: Microalbuminuria can be used as an independent marker for early prediction of Cardiovascular complications and can be used as a screening procedure in all patients diagnosed with type 2 Diabetes mellitus.

KEYWORDS : Microalbuminuria, Atherogenic Index, Cardiovascular Diseases, Diabetesmellitus.

INTRODUCTION:

Diabetes mellitus is the most common metabolic disorder.¹The incidence of cardiovascular diseases in patients with Type 2 Diabetes Mellitus is increasing nowadays. Assessment of cardiovascular risk in patients with Type 2 Diabetes Mellitus is the primary concern in managing these patients.

Microalbuminuria is a known important risk factor for Kidney disease. Recent studies have highlighted Micro albuminuria as an independent marker for endothelial dysfunction and cardiovascular diseases.² Microalbuminuria is a consequence of vascular diseases. Albumin leakage into urine is a reflection of widespread vascular damage.³ Microalbuminuria is defined as the excretion of 30-300 μg of albumin per mg Creatinine excreted in a spot urine sample or 30-300mg of Albumin excreted per day in a 24 hours urine sample.⁴Microalbuminuria is highly prevalent in patients with Diabetes Mellitus, its prevalence ranging from 10 to 40 %⁴. In India, the prevalence of Microalbuminuria varies from 19.7 to 28.5 % in patients with Type 2 Diabetes Mellitus.¹

A duration of more than 6 years may have existed before the patients are diagnosed with Type 2 Diabetes mellitus, due to its insidious onset. As a result, patients often present with Microalbuminuria at the time of diagnosis.⁵ Microalbuminuria leads to increased risk of Cardiovascular diseases and Death.⁶

Studies have reported that the risk factors for Cardiovascular disease such as the fasting Lipid profile varied significantly between type 2 Diabetes Mellitus patients with and without Microalbuminuria. This study is to evaluate the prevalence of Microalbuminuria in recently diagnosed cases of Type 2 Diabetes Mellitus and to study the correlation of the parameters of fasting Lipid profile and Microalbumin excretion in these patients, so that Microalbuminuria can be used as an independent marker for early prediction of Cardiovascular complications and can be used as a screening procedure in all patients diagnosed with type 2

Diabetes mellitus.

REVIEW OF LITERATURE:

Microalbuminuria is defined as excretion of low levels of albumin in urine about 30 to 300 mg/dl. The prevalence of Microalbuminuria varies from 10 to 40%^{7,8,9, 10,11}. It is urinary excretion of albumin that is persistently increased above normal levels, but below the sensitivity of conventional semi-quantitative test strips¹².

Microalbuminuria has been proposed as a strong and independent indicator of increased cardiovascular risk in subjects with and without diabetes. Endothelial dysfunction and chronic low-grade, subclinical inflammation has been implicated as a common pathophysiologic process in the association between microalbuminuria and cardiovascular disease^{13,14,15,16,17,18}

Physiologically, the glomerular filter forms a barrier to prevent macromolecules from reaching the urinary space. The proximal tubule has an effective albumin reabsorption system that metabolizes albumin, so that urine contains no or only small quantities of albumin. Increase in albumin excretion reflects the loss of filtration power of glomerulus due to damage of Glomerular endothelial cells (podocytes)^{4,10,19}.

The incidence of subclinical atherosclerosis is increased in type 2 diabetic patients with microalbuminuria, Insulin resistance and hyperglycemia^{20,21,22}.

The pathophysiological process of atherosclerosis is mainly due to endothelial dysfunction. Impaired endothelium leads to increased susceptibility to thrombus formation, increased adhesion of platelets and increased transmigration of leukocytes. The normal blood flow maintenance is by prostacyclin and nitric oxide which inhibits platelet activation. People with DM have reduced prostacyclin and NO, due to a chronic impairment of endothelial NO synthase activity. This also has been proposed as a mechanism of Atheroma

formation in patients with type 2 Diabetes mellitus²².

The endothelial function in type 2 Diabetes mellitus patients has a negative correlation with microalbuminuria²³. The leakage of albumin through Glomerulus reflects a widespread atherosclerosis-mediated capillary vasculopathy²⁴. Angiographic studies proved that the extent of endothelial dysfunction correlates with the degree of albumin excretion¹⁰. Microalbuminuria is an index of vascular damage^{25,26}.

Urinary excretion of large amounts of proteins may lead to increased serum levels of total cholesterol and LDL-cholesterol²⁷. The number of patients attending Cardiology outpatient setting is increasing, indicating that cardiovascular high risk is common and possibly underestimated²³. Microalbuminuria can be used as a prognostic factor for morbidity and mortality due to Cardiovascular diseases in Type 2 Diabetes patients^{25,28,29}. There is evidence that reduction of albuminuria leads to improvement in the risk profiles of patients with type 2 Diabetes Mellitus¹¹.

Lipid profile and Atherogenic index have been shown to be significant predictors for metabolic disturbances^{30,31}.

Atherogenic index was calculated by the formula = log (TG/HDL-C).

Friedewald formula is used for calculating LDL and VLDL.

$$VLDL = TG/5, LDL = Total\ Cholesterol - (VLDL + HDL)^{30,31}$$

Atherogenic Index has been found to be an independent determinant of chronic subclinical inflammation in patients with type 2 diabetes mellitus³². The Atherogenic index of plasma has been positively correlated with cholesterol, TG, LDL, VLDL and negatively correlated with HDL and the correlation is found to be statistically significant³³. Compared to conventional Lipid levels, ratios such as TG/HDL-C have a better statistical link with the prevalence and severity of Coronary Artery disease³⁴.

AIMS & OBJECTIVES:

1. To determine the prevalence of Microalbuminuria in newly diagnosed patients with Type 2 Diabetes Mellitus.
2. To compare the effectiveness of Microalbuminuria with the fasting Lipid profile in detecting Cardiovascular risk in these patients in terms of Atherogenic Index.

MATERIALS & METHODS:

The current study is a cross-sectional study and carried out for a period of two months. The study group includes 100 patients with Type 2 Diabetes Mellitus. The patients are selected from those attending Diabetic Out Patient Department. Informed written consent was obtained from all the 100 participants.

INCLUSION CRITERIA:

Patients with recently diagnosed Type 2 Diabetes Mellitus

TABLE 1:

S.No.	BMI	FBS	PPBS	T.CHOL	TGL	HDL
Group A	27.2±1.74	100.9±16.52	234±104.61	183.8±36.49	97.4±16.91	38.6±2.35
Group B	27.6±1.39	115.7±16.85	288.5±104.8	200.3±28.21	140.5±27.63	35.6±4.93
p value	<0.5 Significant	<0.001 Significant	<0.005 Significant	<0.05 Significant	<0.001 Significant	<0.001 Significant

S.No.	CREAT	A.I.	M.ALB.
Group A	27.2±1.74	100.9±16.52	234±104.61
Group B	27.6±1.39	115.7±16.85	288.5±104.8
P value	<0.001 Significant	<0.001 Significant	<0.001 Significant

TABLE 2:

S.No.	Pearson Correlation Coefficient
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(within 2 years of diagnosis) and age less than 40 years.

EXCLUSION CRITERIA:

Patients presenting with

1. Urinary tract infection
2. Macroalbuminuria
3. Renal failure
4. Heart failure of any stage.

METHODOLOGY:

BMI (Body Mass Index) is calculated and it is expressed as Kg/m²(35).

Fasting and postprandial blood samples and early morning urine samples are collected from the selected patients.

In the fasting blood sample, plasma Glucose, serum Lipid profile and serum Creatinine are measured. In the post prandial blood sample, plasma glucose is measured. In the early morning collected urine sample, Microalbumin is measured. The parameters are determined using semi-auto analyzer.

Plasma glucose is measured by Glucose oxidase - Peroxidase Enzymatic method, Serum Creatinine by Alkaline Picrate method, serum Total Cholesterol by Cholesterol Oxidase-Peroxidase method, serum Triglycerides by Enzymatic Colorimetric method, serum HDL - cholesterol by Phosphotungstate/magnesium precipitation method and urine Microalbumin by Turbidimetric Immunoassay method. LDL is calculated by the Friedewald formula. VLDL is calculated by the formula TGL/5⁽³⁰⁾.

OBSERVATION & RESULTS:

The patients were divided into two groups: **Group A**, without Microalbuminuria and **Group B**, with Microalbuminuria. Atherogenic Indices were calculated by using the following equation log (Triglycerides /HDL cholesterol)^{35,30,31}.

STATISTICAL ANALYSIS:

All values are presented as Mean ± Standard Deviation. The results were statistically analyzed by using student's 't' test and by Pearson's correlation coefficient using Microsoft Excel Worksheet. 'p' Value <0.05 is considered as significant.

The study consisted of 100 patients out of which 54 patients had no Microalbuminuria and 46 patients had Microalbuminuria. The Prevalence of Microalbuminuria is 46% in newly diagnosed cases of diabetes Mellitus.

TABLE-1: Shows the Biochemical Characteristics of the study - Mean, Standard deviation and unpaired T test correlation between Group A and Group B. TABLE-2: Shows the Pearson correlation of Atherogenic Indices with Urine Albumin excretion of Group B patients.

1.	0.5981 (Significant positive correlation)
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DISCUSSION:

The results show that BMI, FBS, PPBS, Total Cholesterol, TGL, Atherogenic Index, Creatinine and Urine Albumin to be higher in Group B compared to Group A patients and Serum HDL is found to be lower in Group B compared to Group A patients.

Pearson correlation coefficient of Atherogenic Indices with Urine Albumin excretion of Group B patients shows that there is a significant positive correlation ($r = 0.5981$).

So, from the results obtained it is clear that the Lipid profile is deranged in a significant manner in type 2 Diabetes Mellitus patients with Microalbuminuria (Group B) compared to those with Type 2 Diabetes Mellitus without Microalbuminuria (Group A). And from the Pearson Correlation, it is clear that there is a significant positive correlation between Atherogenic Index and Microalbuminuria as found in Group B patients.

Endothelial dysfunction in the vascular wall has been proposed to play a pivotal role in the development and progression of subclinical atherosclerosis. The excretion of albumin into the urine is also due to a disturbance in the barrier function of endothelial glomerular cells (Podocytes). So, the pathogenesis is systemic endothelial dysfunction and is common for both Atherosclerosis and Albumin excretion in urine. So the two parameters can be related. Hence, Microalbuminuria can be used as an independent biochemical marker for early prediction of Cardiovascular risk factors and for primary prevention from Cardiovascular diseases.

Albuminuria being a modifiable risk marker and studies of secondary prevention have shown that blood pressure-lowering drugs effectively reduce the albumin excretion rate, ACE inhibitors seem to be particularly effective. The current observation may lead to new therapeutic strategies in the prevention of CV disease. Albumin excretion levels may represent the primary marker for success of such therapies.

CONCLUSION:

Microalbuminuria can be used as an independent marker for early prediction of Cardiovascular complications and can be used as a screening procedure in all patients diagnosed with type 2 Diabetes mellitus. Periodic screening for microalbuminuria could allow early identification of vascular disease and help stratify overall cardiovascular risk, especially in patients with risk factors such as Diabetes. A positive test for urinary albumin excretion could signify the need for an intensive multifactorial intervention strategy, including behavior modification and targeted pharmacotherapy, aimed at preventing further renal deterioration and improving the overall CVD risk factor profile.

In our study, the measurement of urinary albumin excretion is based on a single early morning urine sample. The urine albumin values of first void sample are close to the 24 hours urine protein values than spot urine as found in previous other studies. But, a 24 hour urine sample would have been preferable²⁵. This study is cross-sectional, and without control participants. So, new studies are needed in this topic rectifying these limitations.

SUGGESTIONS:

The American Diabetes Association recommends that patients with type 2 diabetes be tested for albuminuria at the time of initial diagnosis of Diabetes Mellitus and every year thereafter^{25,11}. Physicians should measure urinary albumin excretion in patients with type 2 Diabetes and Hypertension routinely and be aggressive in treating this modifiable risk factor.

REFERENCES:

1. Dr. Kedam. Durga Prasad, Dr. Perumalla Rajaseker (2012) Study Of Microalbuminuria As A Cardiovascular Risk Factor In Type 2 Diabetes Mellitus, Asian J Pharm Clin Res, 2012, Vol 5, Issue 2, 42-43.
2. Coen D.A. Stehouwer, Yvo M. Smulders, 2006, Microalbuminuria And Risk For Cardiovascular Disease: Analysis Of Potential Mechanisms, 2006, J Am Socnephrol 17: 2106-2111.
3. Matthew R. Weir, 2007, Microalbuminuria And Cardiovascular Disease, 2007, Clin J Am Socnephrol 2: 581-590.

4. Dick De Zeeuw, Hans-Henrikparving, And Robert H. Henning, 2006, Microalbuminuria As An Early Marker For Cardiovascular Disease, 2006, J Am Socnephrol 17: 2100-2105.
5. James T. Lane, 2004, Microalbuminuria As A Marker Of Cardiovascular And Renal Risk In Type 2 Diabetes Mellitus: A Temporal Perspective, 2004, Am J Physiol Renal Physiol 286: F442-F450.
6. Hisashi Adachi, 2014, Microalbuminuria Is An Independent Prognostic Information For Cardiovascular Disease, 2014, Atherosclerosis 237, 106-107.
7. Jan Skov Jensen, Bo Feldt-Rasmussen, Svendstrandgaard, Marianne Schroll, Knut Borch-Johnsen, Arterial Hypertension, Microalbuminuria, And Risk Of Ischemic Heart Disease, Hypertension. 2000;35:898-903.
8. Vito M. Campese, Stefano Bianchi And Roberto Bigazzib, Is Microalbuminuria A Predictor Of Cardiovascular And Renal Disease In Patients With Essential Hypertension?, Current Opinion In Nephrology And Hypertension 2000, 9:143-147.
9. Roberto Pedrinelli, Giulia Dell'omoa, Giuseppe Pennob And Mario Mariani, Non-Diabetic Microalbuminuria, Endothelial Dysfunction And Cardiovascular Disease, Vascular Medicine 2001; 6: 257-26.
10. R Habbal, Ar Sekhri, M Volpe, Prevalence Of Microalbuminuria In Hypertensive Patients And Its Associated Cardiovascular Risk In Clinical Cardiology: Moroccan Results Of The Global I-Search Survey - A Sub-Analysis Of A Survey With 21 050 Patients In 26 Countries Worldwide, Cardiovasc J Afr 2010; 21: 200-205.
11. Seema Basi, Md, Msci, Piere Fesler, Md, Albert Mimran, Md, Julia B. Lewis, Md, Microalbuminuria In Type 2 Diabetes And Hypertension A Marker, Treatmenttarget, Orinnocent bystander? Diabetes Care, Volume 31, Supplement 2, February 2008, S194-S201.
12. P H Winocour, Microalbuminuria - Worth Screening for In Early Morning Urine Samples In Diabetic, Hypertensive, And Elderly patients, Bmj Volume 304, 9 May 1992, 1196-1197.
13. Aida Jimenez Corona, David Rivera Martinez, Mauricio Hernandez Avila, Steven Haffner, Ken Williams, Ma. Elena Gonz' Alez Villalpando, Jesus Simon, Michael Stern, And Clicerio Gonzalez-Villalpando, Microalbuminuria As A Predictor Of Myocardial Infarction In A Mexican Population: The Mexico City Diabetes Study, Kidney International, Vol. 68, Supplement 97 (2005), Pp. S34-S39.
14. Chien-Yu Lin, Ming-Fong Chen, Lian-Yu Lin, Chia-Suungliu, Yuan-Teh Lee And Ta-Chen Su, Insulin Resistance Is The Major Determinant For Microalbuminuria In Severe Hypertriglyceridemia: Implication For High-Risk Stratification, Inter Med (2008)47: 1091-1097.
15. Roberto Bigazzi, Stefano Bianchi, Duccio Baldari, Gianpaolosgheri, Giorgio Baldari, Vito M. Campese, Microalbuminuria In Salt-Sensitive Patients A Marker For Renal And Cardiovascular Risk Factors, Hypertension Vol 23, No 2 February 1994, 195-199.
16. A Varghese, R Deepa, M Rema, V Mohan, Prevalence Of Microalbuminuria In Type 2 Diabetes Mellitus At A Diabetes Centre In Southern India, Postgrad Med J 2001;77:399-402.
17. Coen D.A. Stehouwer, Mari-Anne Gall, Jos W.R. Twisk, Elisabeth Knudsen, Jef J. Emeis, And Hans-Henrikparving, Increased Urinary Albumin Excretion, Endothelial Dysfunction, And Chronic Low-Grade Inflammation In Type 2 Diabetes- Progressive, Interrelated, And Independently associated With risk of death, Diabetes 51:1157-1165, 2002.
18. Knut Borch-Johnsen, Bo Feldt-Rasmussen, Svendstrandgaard, Marianne Schroll, Jan Skov Jensen, Urinary Albumin Excretion An Independent Predictor Of Ischemic Heart Disease, Arteriosclerthrombvasc Biol. 1999;19:1992-1997.
19. Ulrichtebbe, Peter Bramlage, Martinthoenes, D.W. Dieter Paar, Nicolas Danchin, Massimovolpe, Jochen Schrader, Georg Noll, Michael Burnier, Michael Böhm, Prevalence of microalbuminuria and its associated cardiovascular risk: German and Swiss results of the recent global I-Search Survey, Swiss Med Wkly 2009;139(33-34):473-480.
20. Andreas Festa, Ralph D'agostino, Jr., George Howard, Leena Mykka - Nen, Russell P Tracy, And Steven M. Haffner, Inflammation And Microalbuminuria In Nondiabetic And Type 2 Diabetic Subjects: The Insulin Resistance Atherosclerosis Study, Kidney International, Vol. 58 (2000), Pp. 1703-1710.
21. Hiroki Yokoyama, Tomomi Aoki, Masumi Imahori, And Masae Kuramitsu, Subclinical Atherosclerosis Is Increased In Type 2 Diabetic Patients With Microalbuminuria Evaluated By Intima-Media Thickness And Pulse Wave Velocity, Kidney International, Vol. 66 (2004), Pp. 448-454.
22. Christos Kalofoutis Bsc, Christina Piperi Phd, Anastasios Kalofoutis Md, Fred Harris Phd, David Phoenix Phd, Jaipal Singh Phd, Type II Diabetes Mellitus And Cardiovascular Risk Factors: Current Therapeutic Approaches, Exp Clin Cardiol 2007;12(1):17-28.
23. G. Dogra, L. Rich, K. Stanton, G.F. Watts, Endothelium-Dependent And Independent Vasodilation Studied At Normoglycemia In Type I Diabetes Mellitus With And Without Microalbuminuria, Diabetologia (2001) 44:593-601.
24. Hans L. Hillege, Md; Vaclav Fidler, Phd; Gilles F.H. Diercks, Md; Wiek H. Van Gilst, Phd; Dick De Zeeuw, Md; Dirk J. Van Veldhuisen, Md; Rijk O.B. Gans, Md; Wilbert M.T. Janssen, Md; Diederick E. Grobbee, Md; Paul E. De Jong, Md, Urinary Albumin Excretion Predicts Cardiovascular And Noncardiovascular Mortality In General Population, Circulation- 2002;106:1777-1782.
25. Janakakaralliedde And Giancarlo Viberti, Microalbuminuria And Cardiovascular Risk, American Journal Of Hypertension, 2004, 17: 986-993.
26. C. Lydakis And G.Y.H. Lip, Microalbuminuria And Cardiovascular Risk, Q J Med 1998; 91:381-391.
27. Js Jensen, B Feldt-Rasmussen, K Borch-Johnsen, P Clausen, M Appleyard And G Jensen, Microalbuminuria And Its Relation To Cardiovascular Disease And Risk Factors. A Population-Based Study Of 1254 Hypertensive Individual, Journal Of Human Hypertension (1997) 11, 727-732.
28. Roberto Pedrinelli, Vitantonio Di Bello, Giosuè Catapano, Luigi Talarico, Franco Materazzi, Gino Santoro, Costantino Giusti, Franco Mosca, Eliomellilo, And Mauro Ferrari, Microalbuminuria Is A Marker Of Left Ventricular Hypertrophy But Not Hyperinsulinemia In Nondiabetic Atherosclerotic Patient, Arteriosclerosis And Thrombosis 1993;13:900-906.
29. M. Murussi, N. Campagnolo, M. O. Beck, J. L. Gross And S. P. Silveiro, Micro- And Macroalbuminuria And Mortality M. Murussi Et Al., High-Normal Levels

- Of Albuminuria Predict The Development Of Micro- And Macroalbuminuria And Increased Mortality In Brazilian Type 2 Diabetic Patients: An 8-Year Follow-Up Study, *Diabet. Med.* 2007, 24, 1136-1142.
30. Pallavi S. Kanthe , Bheemshetty S. Patil , Shrilaxmibagali , Anita Deshpande , Gouharbanushaikh , Manjunathacaiihala, Atherogenic Index As A Predictor Of Cardiovascular Risk Among Women With Different Grades Of Obesity, *International Journal Of Collaborative Research On Internal Medicine & Public Health*, 2012, Vol. 4 No. 10, 1767-1774.
 31. Miladadobiášová, Jiri Frohlich, Michaela Šedová, Marian C. Cheung, And B. Greg Brown, Cholesterol Esterification And Atherogenic Index Of Plasma Correlate With Lipoprotein Size And findings On Coronary Angiography, *J. Lipid Res.* 2011. 52: 566-571.
 32. Muhammad Saiedullah, Mdmahfuzurrahmanand Mohammad Abdul Haisiddique, Atherogenic Index And Female Gender Are Independent Determents Of Chronic Subclinical Inflammation In Subjects With Type 2 Diabetes Mellitus, *Diabetes Case Rep, Volume 1, Issue 3, 2016*, 1-4.
 33. Vandanasaini, Kamna Singh, Meghakataria, Amitayadav And Ritu Singh, Atherogenic Index Of Plasma And Oxidised Ldl In Overt Hypothyroidism In North Indian Female Population, *Biochem Anal Biochem* 2: 141, Issue 4, 2013, 1-3.
 34. Akifacay, Memnunesenaulu, Ahmetahsen, Gulayozkececi, Kasimdemir, Ufukozuguz, Serefyuksel, Gurselacarturk, Atherogenic Index As A Predictor Of Atherosclerosis In Subjects With Familial Mediterranean Fever, *Medicina* 50 (2014) 329-333.
 35. S. Bhardwaj, J. Bhattacharjee, M.K Bhatnagar, S. Tyagi, Atherogenic Index Of Plasma, Castelli Risk Index And Atherogenic Coefficient- New Parameters In Assessing Cardiovascular Risk, *Ijpbs |Volume 3| Issue 3 |Jul-Sep|2013|359-364*.
 36. Subinaydatta, Mrinal Pal, Comparison Between Different Methods Of Urine Collection For Estimation Of Albumin-Creatinine Ratio In Patients With Type-2 Diabetes Mellitus, *Advances In Biological Chemistry*, 2013, 3, 403-407.