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Association of Albumin to Creatinine Ratio with Cardiovascular Risk Markers and Determination of Their Cut off Points in Type 2 Diabetic Nephropathy Patients

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Abstract : *Urine albumin to creatinine ratio (ACR) is found to be the most promising indicator for confirmation of nephropathy in type 2 diabetes mellitus patients. It is also known that the increased excretion of urine microalbumin is associated with high risk of cardiovascular diseases. The present study was aimed to attain the association of BMI, FBG, HbA1c, cardiovascular markers, urine creatinine & urine microalbumin, and also to find out the cut off points of these markers for the prediction of cardiovascular disease in type 2 diabetic nephropathy patients. We included 110 type 2 diabetic nephropathy patients and 110 healthy age and gender matched healthy controls. The value of BMI, and levels of FBG, triglycerides, VLDL cholesterol, urine creatinine and urine microalbumin were found to be positively associated and HDL cholesterol was negatively associated with ACR in type 2 diabetic nephropathy patients. Further, ROC curve analysis of BMI, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol and VLDL cholesterol gave the cut off values of >24.3, >187.2, >143.1, ≤42.7, >119.9 and >37.2, respectively with significant area under the ROC curve, highest sensitivity and highest specificity. From these results we conclude that the ACR apart from its function as an indicator of nephropathy can also serve as an indicator of cardiovascular risk in type 2 diabetic patients. These cut off values can be used for prediction of cardiovascular disease risk in type 2 diabetic nephropathy patients.*

Keywords: *Albumin to creatinine ratio, cardiovascular disease, triglycerides (TGs), type 2 diabetic nephropathy*

I. Introduction

The incidence of diabetes mellitus is increasing globally, with its potential complications like heart disease, stroke, and kidney damage. [1] Diabetes is characterized by hyperglycemia, in most cases of diabetes; occurrence of hypertension is seen sooner or later, which is an established causal factor for diabetic nephropathy (DN). [2] DN is one of the most common clinical conditions leading to end stage renal disease (ESRD). [3] It is a life threatening complication resulting in a poor prognosis for patients as well as high medical costs. [4] The pathophysiological mechanisms of DN are attributed primarily to metabolic and hemodynamic derangements including hyperglycemia induced production of advanced glycation end products (AGEs), activation of polyol pathway, protein kinase C and rennin angiotensin system. [5, 6] The earliest demonstrable abnormalities include intrarenal hypertension, increased glomerular filtration rate, and microalbuminuria. [7] The characteristic increased albumin excretion of nephropathy, even microalbuminuria, is known to increase the risk of cardiovascular disease in diabetic as well as non-diabetic patients. The mechanism of this may be linked to the increased levels of atherogenic lipoproteins promoted by endothelial dysfunction. [8, 9] Albuminuria (>300mg/24 hours) or microalbuminuria (≥30 mg/24 hours to 300mg/24 hours), or albumin/creatinine ratio (≥30 mg/g), is used as a marker of renal damage and is used to define chronic kidney disease along with low estimated glomerular filtration rate (eGFR). [10]

Both cardiovascular disease and diabetes mellitus share many risk factors in common (the "common soil" hypothesis), [11] also lipid metabolism has been extensively investigated in diabetes; little information is available whether urine ACR is associated with lipids and lipoproteins. Therefore, we hypothesized that the cardiovascular markers are associated with ACR, cut off values of lipids and lipoproteins can be calculated for the prediction of cardiovascular disease.

II. Material And Methods

The present study consisted of, 110 T2DM patients with nephropathy within the age limit of 35-60 years. Patients visiting Medicine Department, BVDU Medical College and Hospital, Pune were included in the study. T2DM nephropathy patients, having cardiovascular, pulmonary diseases, with diabetic complications other than nephropathy, pregnant and lactating women and those on insulin therapy were excluded from the

study. In addition to T2DM nephropathy patients, age and gender matched 110 healthy non-diabetic individuals were also included in the study. The healthy individuals had no history of cardiovascular disorders or any major illness. The research protocol was accepted by Institutional Ethical Committee of BVDU Medical College, Pune (BVDU/MC/55/2013-2014) and informed written consent was obtained from every individual before any study related activity.

The blood samples were collected by venipuncture after fasting of 12 hours. Plasma from the blood collected in fluoride vacutainer was used for estimation of fasting blood glucose (FBG) using commercially available kit (ERBA Diagnostics, Mannheim, Germany), and glycated hemoglobin (HbA1c) was estimated from samples collected in EDTA vacutainer by HPLC technique (D10, Bio-Rad). The serum was separated from plain vacutainer after centrifugation, and used for estimation of total cholesterol (TC), TGs and high density lipoprotein cholesterol (HDL cholesterol). Low Density Lipoprotein cholesterol (LDL cholesterol) and Very Low Density Lipoprotein cholesterol (VLDL cholesterol) were calculated by Friedwald's formula. Urine samples collected were used for estimation of urine creatinine and microalbumin level, and from these values the ratio of ACR was calculated. All biochemical parameters were estimated by standard, commercially available kits (ERBA Diagnostics, Mannheim, Germany).

The correlation between ACR and cardiovascular markers was tested by Pearson's correlation coefficient. Further, the cut off values of cardiovascular markers were calculated at highest sensitivity and specificity with corresponding area under the curve by Receiver Operating Characteristics (ROC) curve analysis. The P values ≤0.05 were considered significant.

III. Results

The ACR was calculated from urine albumin and urine creatinine values, then the correlation of ACR with BMI, FBG, HbA1c, cardiovascular markers, urine albumin and creatinine was evaluated. The relevant details of association of ACR with BMI, FBG, HbA1c, cardiovascular markers, urine microalbumin, and urine creatinine are represented in table 1 and figure 1a to 1g shows respective scatter diagram. 'r' denotes correlation coefficient with 95% confidence interval and respective 'p' values..

Table 1: Association of ACR with biochemical parameters in type 2 diabetic nephropathy patients

	r	95% CI	P
BMI	0.5030	0.3486 to 0.6309	<0.0001*
FBG	0.2525	0.06845 to 0.4199	0.0078*
HbA1c	0.1040	-0.08492 to 0.2857	0.2797
Total Cholesterol	0.1005	-0.08843 to 0.2824	0.2963
Triglycerides	0.2859	0.1043 to 0.4491	0.0025*
HDL-C	-0.3213	-0.4797 to -0.1426	0.0006*
LDL-C	0.07630	-0.1126 to 0.2598	0.4282
VLDL-C	0.2861	0.1044 to 0.4493	0.0024*
Urine creatinine	0.2990	0.1184 to 0.4605	0.0015*
Urine microalbumin	0.6986	0.5884 to 0.7834	<0.0001*

*** Statistically significant, r:** Correlation coefficient; **BMI:** Body mass index; **FBG**: Fasting blood glucose; **HDL-C**: High density lipoprotein cholesterol; **LDL-C**: Low density lipoprotein cholesterol; **VLDL-C**: Very low density lipoprotein cholesterol; **CI:** Confidence Interval

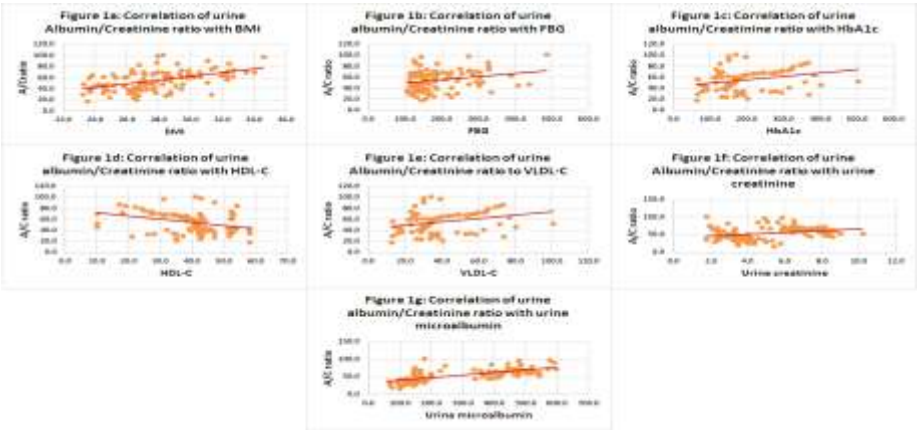

Figure 1: The scatter diagrams of biochemical parameters in patients with type 2 diabetic nephropathy

It was observed that BMI (p<0.0001), FBG (p=0.0078), TG (p=0.0025), VLDL-C (p=0.0024), urine creatinine (p=0.0015) and urine microalbumin (p<0.0001) were positively associated while HDL-C (p=0.0006) was negatively associated with ACR.

Table 2: The area under the ROC curves with 95% confidence interval of BMI and cardiovascular markers for type 2 diabetic nephropathy patients

Parameters	AUC ± SE	95% CI	p value
BMI	0.825 ± 0.0275	0.768 to 0.873	<0.0001*
Total cholesterol	0.724 ± 0.0342	0.660 to 0.782	<0.0001*
Triglycerides	0.725 ± 0.0341	0.661 to 0.783	<0.0001*
HDL-C	0.823 ± 0.0322	0.766 to 0.871	<0.0001*
LDL-C	0.730 ± 0.0338	0.667 to 0.788	<0.0001*
VLDL-C	0.725 ± 0.0341	0.661 to 0.783	<0.0001*

*** Statistically significant, AUC: Area** under the ROC curve; **HDL-C**: High density lipoprotein cholesterol; **LDL-C**: Low density lipoprotein cholesterol; **VLDL-C**: Very low density lipoprotein cholesterol; **SE:** Standard Error; **CI:** Confidence Interval

Table 3: The cut off points for BMI and cardiovascular markers with corresponding highest %sensitivity and %specificity

	Cut off value	Specificity (%)	95% CI	Sensitivity (%)	95% CI
BMI	>24.3	90.91	83.9 - 95.6	54.55	44.8 - 64.1
Total Cholesterol	>187.2	60.00	50.2 - 69.2	74.55	65.4 - 82.4
Triglycerides	>143.1	71.82	62.4 - 80.0	58.18	48.4 - 67.5
HDL-C	≤42.7	71.82	62.4 - 80.0	93.64	87.3 - 97.4
LDL-C	>119.9	70.91	57.1 - 82.4	86.36	78.5 - 92.2
VLDL-C	>37.2	58.18	44.1 - 71.3	94.55	88.5 - 98.0

BMI: Body mass index; **HDL-C**: High density lipoprotein cholesterol; **LDL-C**: Low density lipoprotein cholesterol; VLDL-**C**: Very low density lipoprotein cholesterol; **CI:** Confidence Interval

We further plotted the ROC curves for BMI, TC, TGs, HDL cholesterol, LDL cholesterol and VLDL cholesterol in T2DM patients with nephropathy. The significant (p<0.0001) area under the ROC curve was found for BMI (AUC=0.825), TC (AUC=0.724), TGs (AUC=0.725), HDL cholesterol (AUC=0.823), LDL cholesterol (AUC=0.730) and VLDL cholesterol (AUC=0.725) with corresponding cut off values of >24.3, >187.2, >143.1, ≤42.7, >119.9 and >37.2, respectively with the highest sensitivity and specificity. The values of area under the ROC curve with 95% confidence interval and respective p values are depicted in table 2. Table 3 indicates the cut off values for these parameters at highest specificity and sensitivity with respective 95% confidence intervals for T2DM patients with nephropathy and figure 2a to 2f indicates the ROC curves including 95% confidence boundaries, plotted against 100-specificity.

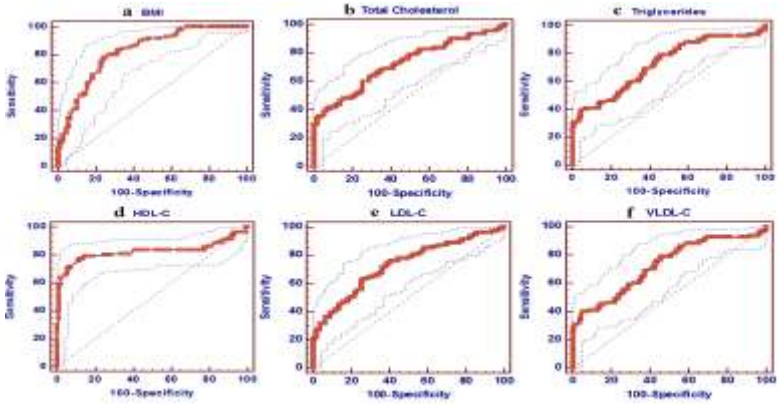

Figure 2- a to f: The ROC curves for BMI and cardiovascular markers in patients with type 2 diabetic nephropathy

IV. Discussion

Diabetes with its characteristic hyperglycemia shows long term complications on various organs, therefore regular monitoring of organ functions for early preventive interventions of these complications is

necessary. [12] Renal impairment is one of such common complications of diabetes mellitus. [13] Kidney damage is already present in some type 2 diabetic patients at the time of diagnosis of diabetes. [14] About one third of the diabetic patients develop microalbuminuria, nearly after few years of onset of diabetes. The overt nephropathy is developed in 50% of microalbuminuric patients with simultaneous increase in risk of cardiovascular disease. [13] The process starts from the early stages of diabetic nephropathy to ESRD, cardiovascular diseases also progressively develop in these patients and cardiovascular diseases (CVDs) are the most important reason of the mortality in DN patients. [15]

Use of the ACR in urine samples is recommended as the preferred screening strategy for albuminuria in diagnosis of diabetic nephropathy in diabetic patients. [15, 16] Relation of increased urine ACR with Apo B containing lipoproteins has also been proved previously. [8] The present study attempted to find out the association of ACR with biochemical and cardiovascular markers in diabetic nephropathy patients. The positive association of ACR was found with BMI, FBG, TGs, VLDL cholesterol, Urine creatinine & Urine microalbumin, while it is negatively associated with HDL cholesterol. Further, we calculated the cut-off values of BMI and lipid markers for the prediction of cardiovascular disease risk in diabetic nephropathy patients by means of ROC curve analysis. With significant area under the ROC curve, we found the cut off values of >24.3, >187.2, >143.1, ≤42.7, >119.9 and >37.2 for BMI, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol and VLDL cholesterol, respectively.

In accordance with our results, a significant positive correlation of urine ACR was observed with plasma creatinine, and urine microalbumin in a study of Karar et al. [12] In a study population, Zhang et al. [17], found positive association of ACR with LDL cholesterol and log of LDL cholesterol/HDL cholesterol ratio in men, in females none of the lipids and lipid related ratios were associated with ACR. Sun et al. [18] reported association of ACR with the levels of TGs, HDL cholesterol, Non-HDL cholesterol/HDL cholesterol ratio, TGs/HDL cholesterol ratio, and compared to other lipids and their ratios. TGs/HDL cholesterol ratio was reported by the authors to show highest rise with increased level of ACR and odds of chronic kidney disease.

There is also a report contrasting to the results observed in the present study. Study by Bose et al. [9] found association of microalbuminuria and macroalbuminuria with HbA1c levels, and no association was found for other measured lipids. Increase in HDL cholesterol was noted with decreased incidence of microalbuminuria, while no significant association of lipid markers was found with urinary ACR.

V. Conclusion

The ACR, calculated simply from urine albumin and urine creatinine excretion, can be utilized as an indicator of cardiovascular disease risk in type 2 diabetic nephropathy patients. The normal ranges for lipid profile of general population cannot be used to assess the risk of CVDs in type 2 diabetic nephropathy patients. Therefore, we defined the cut off points for lipid markers; these values can be used to predict the future risk of CVDs in type 2 diabetic patients with nephropathy.

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