Original Article

Obesity is a modifiable risk factor for incipient nephropathy in Type 2 diabetes mellitus

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Abstract

Objectives: Early screening of obese T2DM patients in the stage of incipient nephropathy and to find the association of microalbuminuria with other risk factors. **Methodology**: The study was conducted in the diabetic clinic of a tertiary care hospital in South India on 60 T2DM patients who were categorized into obese and non-obese groups for comparing microalbuminuria in them. As spot urine sample was taken, Albumin Creatinine Ratio (ACR) was used to compare the levels of microalbuminuria. **Result:** The mean albumin excretion was significantly higher in the obese group compared to the non-obese. ACR showed significant positive correlation with duration of diabetes, body mass index, fasting blood glucose and HbA1c. **Conclusion:** Obesity increases the risk for microalbuminuria in T2DM patients. Early intervention can prevent the development of nephropathy in such patients.

Keywords: Albumin creatinine ratio, Incipient nephropathy, Microalbuminuria, Obesity, Type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is an important metabolic disorder characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production.[1] There is a definite increase in the prevalence of diabetes mellitus from 366 million people in 2011, which is expected to increase to 522 million by 2030.[2] DM is associated with multi-organ damage; renal and cardiovascular involvement being highly critical. Type 2 diabetes mellitus (T2DM), which accounts for about 90-95 % of all diagnosed cases of diabetes, is an independent risk factor for microvascular and macrovascular complications.[3] Microvascular complications which include nephropathy, retinopathy and neuropathy are initiated by chronic hyperglycemia. Diabetic nephropathy (DN) is now the single most common cause of chronic kidney disease, which can lead to end stage renal disease (ESRD). The number of patients with ESRD caused by T2DM has progressively increased during the last few decades. The development of DN is characterized by a progressive increase in the excretion of protein in urine with albumin excretion rate > 300 mg/day, an early rise in systemic blood pressure and a late decline in Glomerular filtration rate, leading to ESRD.[4] The renal pathology and natural history of nephropathy in T2DM has been studied much less intensely than in T1DM. At the time of diagnosis of T2DM, about 30 % of patients will have abnormally high albumin levels; out of which about 75% will have microalbuminuria and about 25% will have overt DN.[5] When DN is diagnosed by the classical methods such as detection of proteinuria on urine analysis or decrease in creatinine clearance, usually it is too late and little can be done to prevent the progression to ESRD. Here lies the importance of an early predictor of DN. Microalbuminuria is the earliest and most sensitive predictor of DN. The normal rate of albumin excretion (normoalbuminuria) is <30 mg/day. Microalbuminuria represents an abnormally elevated urine albumin level that cannot be detected by the conventional methods. It is

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diagnosed when the urine albumin excretion rate in 24 hour urine or short time collected urine during day time is in the range of 30-300 mg/L. It is considered as a marker of generalized endothelial dysfunction that has been linked to increased transcapillary albumin leakage.[6] Protein excretion above 300 mg/day is considered to represent macroalbuminuria or overt proteinuria. The onset of clinical phase of DN is signaled by the presence of persistent proteinuria (>300 mg/day), usually accompanied by retinopathy, hypertension, declining GFR and plasma lipid abnormalities.[7] Microalbuminuria is a strong predictor and the first sign of nephropathy. So patients with persistent micoalbuminuria are referred to as having incipient nephropathy. Incipient nephropathy is also associated with increased risk of cardiovascular morbidity and mortality in T2DM patients. Endothelial dysfunction and chronic inflammation have been suggested to explain the association between microalbuminuria and cardiovascular disease. In diabetic kidney disease the first detectable alteration in renal function to occur after microalbuminuria is hyperfiltration which is indicated by a high glomerular filtration rate. Without intervention 20-40 % of T2DM patients with microalbuminuria progress to nephropathy.[8] The presence of microalbuminuria precedes the development of overt nephropathy by 10-14 years.[9] It is at this stage that we should interfere to reverse DN or prevent its progression. Obesity is a major potentially modifiable risk factor for T2DM and is associated with increased mean arterial pressure and therefore a generally increased workload for the kidneys. Existing evidence suggests that obesity and DM are states of low- grade inflammation and oxidative stress, both of which may lead to kidney damage. The increased prevalence of obesity is linked to the increased prevalence of T2DM, the presence of which multiplies the overall risk for chronic kidney disease.[10] Persistent elevations in blood sugar increase the risk of long-term vascular complications of diabetes. Assay of HbA1c gives valuable information about the glycemic status of the individual over the previous 2-3 months. Detecting the presence of earlier stages of diabetic kidney disease by screening for microalbuminuria in obese T2DM patients and finding its association with other risk factors will help in modifying the intervention strategies. This is the aim of the present study.

MATERIALS AND METHODS

This cross sectional study was conducted in the diabetic clinic of a tertiary care hospital in South India after getting approval from the Institutional ethics committee according to the provisions of Helsinki declaration. The study subjects were selected on a random basis and comprised of 60 adult patients of both genders in the age group 30-65 years with confirmed T2DM. They were categorized into obese (BMI > 25) and non-obese (BMI < 25) based on the WHO criteria of obesity in adult Asians.[11] Patients with urinary tract infection, hypertension, pregnancy, established renal disease and acute febrile illness were excluded from the study. A written informed consent was obtained from all the study subjects after which their demographic data were collected. Weight and height were measured using standard methods. Body mass index (BMI) is a measure of weight adjusted for height, calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Collection of Blood Sample

6 ml venous blood was collected after overnight fasting of 12 hours under strict aseptic precautions for measuring Fasting blood sugar, Blood urea, Serum creatinine and HbA1c. Blood for FBS was collected in bottles containing sodium fluoride, blood for Fasting blood sugar, urea and creatinine estimations in plain sample tubes and blood for HbA1c in EDTA bottles. FBS was estimated by Glucose oxidase method[12], Blood urea was estimated by Glutamate dehydrogenase- Urease method[13] and Serum creatinine was estimated by Jaffe's alkaline picrate method[14]. All estimations were done using reagents manufactured by Erba diagnostics in the fully automated clinical chemistry analyzer manufactured by Transasia Biomedicals. HbA1c was estimated by Ion exchange resin method[15] using reagent from Erba diagnostics in semi autoanalyzer manufactured by Transasia Biomedicals.

Collection of Urine Sample

Microalbuminuria can be diagnosed from a 24 hour urine collection or an overnight sample or more commonly from a spot sample. Here spot urine sample was preferred as it was easy to perform and was recommended by the American Diabetes Association guidelines. The patient was asked to take rest for some time.10 ml of midstream urine was collected in a sterile container. Samples were centrifuged and checked for albumin excretion. Quantitation of microalbumin was done by turbidimetric immunoassay[16] using the kit manufactured by Erba Mannheim in the fully automated clinical chemistry analyzer manufactured by Transasia Biomedicals. The antigen antibody reaction was measured by the end-point method. In the urine sample, albumin forms an insoluble complex with antibodies to human albumin. The turbidity caused by these complexes is measured at 340 nm. As values of albumin excretion can be distorted by the effects of urine concentration in a spot urine sample, the amount of albumin in the sample was compared with its creatinine concentration. This is termed Albumin creatinine ratio (ACR). Urine creatinine was estimated by

Jaffe's alkaline picrate method[14] in the fully automated clinical chemistry analyzer manufactured by Transasia Biomedicals. ACR was expressed as mg of albumin/gm of Creatinine. GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[17]

Statistical Analysis

Was done using SPSS version 22.0.Quantitative variables were expressed as mean and standard deviation. Quantitative data for the two groups were compared with unpaired 't' test. Categorical variables were expressed as proportion and compared by Chi-square test. Association between ACR and other parameters were assessed by Pearson correlation. *p* value less than 0.05 was considered as statisticaly significant.

RESULTS

The total sample size was 60 which comprised of 30 obese and 30 non-obese T2DM patients. Baseline and biochemical characteristics of the study population are given in Table 1.

Table 1: Baseline and Biochemical characteristics of the study population

Variable	Obese (N=30)	Non-obese (N=30)	t	*p*
Age (years)	52.3±8.1	56.0±8.0	-1.775	.081
Male-Sex Female -sex	3(10.0%) 27(90.0%)	11(36.7%) 19(63.3%)		.067
Duration of diabetes (years)	5.8±6.2	6.1±4.8	-.188	.852
FBS (mg/dl)	186.4±72.8	165.0±61.7	1.230	.224
HbA_1C(%)	6.4±1.5	6.5±1.2	. 490	.626
Blood Urea (mg/dl)	26.6±6.8	26.3±7.2	.147	.884
S.Creatinine (mg/dl)	0.8±0.1	0.8±0.2	.645	.522
eGFR	85.9±16.7	93.6±21.0	1.572	.121
ACR (mg/g)	118.6±81.8	81.1±55.1	2.082	.042

Quantitative variables expressed as mean ± sd, categorical variables expressed as N(%)

There was no significant difference in the mean age of the obese and non-obese groups ($p > 0.05$). both groups were comparable according to gender ($p > 0.05$). There was no significant difference in mean duration of diabetes between the two groups ($p > 0.05$). There was no significant difference in FBS, blood Urea, serum creatinine and eGFR between the two groups ($p > 0.05$).There was significant difference in mean HbA1c between the two groups ($p<0.05$) (Table 1).The obese had a higher HbA1c compared to the non-obese indicating poor control of blood sugar in them over the previous 2-3 months. Mean ACR of the obese group was significantly higher than that of the non-obese group ($p < 0.05$) (Table 1). Descriptive statistics and Box and Whiskers plot diagram of ACR in obese and non-obese T2DM patients is given in Table 2, Figure 1.

Table 2: Descriptive statistics of ACR in obese and non- obese T2DM patients

Descriptive statistics of ACR	Obese	Non-obese
N	30	30
Mean	118.6	81.1
Standard deviation	81.8	55.1
Minimum	31.5	13.4
Maximum	281.3	191.6
25^{th} percentile	51.0	31.7
Median	83.5	73.8
75^{th} percentile	170.8	143.3

Mean ACR among obese was 118.6 ± 81.8 and that of non-obese was 81.1 ± 55.1 median level of ACR with inter quartile range in obese and non-obese was 83.5 (51.0-170.8) and 73.8 (31.7 – 143.3) respectively.

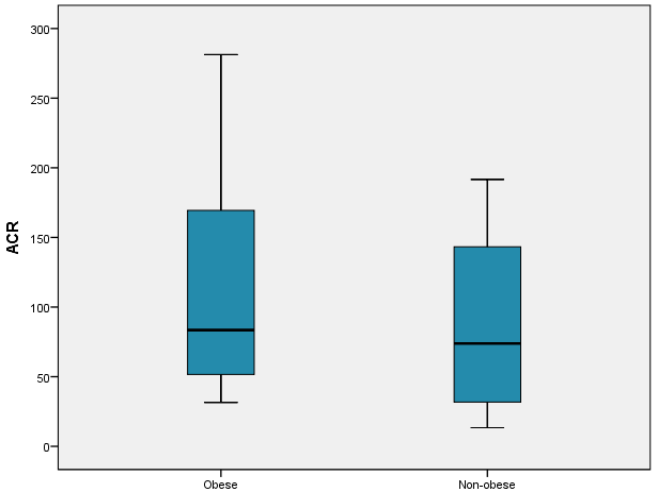

Figure 1*:* Box plot diagram describing ACR levels of obese and non obese

Lower and upper end of the whisker represents minimum and maximum ACR level. Lower border of the box represents 25^{th} percentile and upper border of the box represents 75^{th} percentile. The middle horizontal line represents the median ACR level in each group.

Table 3: Correlation of ACR with other study variables

Variable	Pearson correlation	
	r	p
Age	-.027	.839
Duration of Diabetes	.605	<0.001
BMI	.270	.037
FBS	.550	<0.001
HbA1c	.496	<0.001
Blood Urea	.019	.883
Serum Creatinine	-.077	.560
eGFR	.068	.607

Correlation of ACR with other study variables showed significant positive correlation of ACR with duration of diabetes, BMI, FBS and HbA1c (p<0.05) (Table 3). There was no correlation of ACR with age, blood urea, serum creatinine and eGFR.

DISCUSSION

The present study has demonstrated significantly higher ACR in obese T2DM patients compared to non-obese patients. This reflects a higher albumin excretion in the obese which shows that obesity increases the risk for microalbuminuria in patients with T2DM.This finding is similar to those reported by Klausen *et al*.[18] Increase in BMI was found to be associated with microalbuminuria in the present study as demonstrated by a significant correlation between ACR and BMI. Similar findings were seen in the study by Suma *et al*.[19] and Wiwanitkit.[20] Study byChowta *et al* could not demonstrate any correlation between ACR and BMI.[21] The present study did not show any correlation between ACR and age of the patients. This finding is in accordance with the findings of Afkhami *et al*.[22] Study by Sangeetha *et al*[23] has demonstrated significant correlation of ACR with age. There was significant positive correlation of ACR with duration of diabetes in the present study which was consistent with the findings of Kedam *et al*[24] indicating that albumin excretion increases with increase in duration of diabetes. FBS and HbA1c correlated significantly with ACR as demonstrated by previous studies by Varghese *et al*[25] thus indicating that a poor glycemic control is associated with albuminuria. These patients are more prone to develop diabetic nephropathy. Improving glycemic control improves microvascular outcomes as illustrated by randomized control trials like UKPDS and ACCORD.[26] Study by Tobe *et al*[27] has shown that reduction of HbA1c level by 1% from 7.5 to 6.5 significantly decreases albumin excretion. As BMI, duration of diabetes, FBS and HbA1c are found to correlate with urine albumin excretion, measures to reduce obesity and control blood sugar as early as possible can check the progression of microalbuminuria to chronic kidney disease and end stage renal disease. The period between the onset of microalbuminuria and CKD offers a substantial window for therapeutic intervention which can prevent the progression of microalbuminuria to macroalbuminuria. Even moderate reduction in weight has been shown to reduce the insulin resistance and improve the risk factors for microvascular disease in T2DM thus reducing urine protein excretion by 30%.[28] Annual screening for microalbuminuria is recommended by the American Diabetes association as a high proportion of patients with T2DM are found to have microalbuminuria or overt nephropathy shortly after diagnosis of diabetes. So intervention programs should be implemented early, at the stage of microalbuminuria. Prevention of the onset of microalbuminuria could be considered as the primary means of preventing DN. This primary prevention is possible with good glycemic control and weight reduction. Intensive treatment of diabetes in the Diabetes Control and Complications Trial (DCCT) reduced the incidence of microalbuminuria to 39%.[29] So treatment of hyperglycemia to reduce the HbA1c to <7% should be aimed to prevent the development of microalbuminuria. Early screening for microalbuminuria, adoption of intervention strategies targeting the major risk factors and appropriate use of therapeutic agents reduce the progression from normoalbuminuria to microalbuminuria and to end stage renal disease.

CONCLUSIONS

Diabetic nephropathy is a dreaded complication of type 2 diabetes mellitus which can be detected in the early stages from the presence of microalbuminuria.Obesity is a potential risk factor for T2DM and microalbuminuria. Microalbuminuria predicts the future risk for development of coronary artery disease, diabetic kidney disease and ESRD. Screening for early signs of nephropathy by measuring microalbuminuria is a cost effective intervention which together with life style modifications and therapeutic interventions can reduce the morbidity and mortality associated with obesity related diabetic kidney disease.

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