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Original Research Paper

Diabetology

TO STUDY THE RELATIONSHIP BETWEEN SPOT URINARY ALBUMIN TO CREATININE RATIO AND 24 HOUR URINARY PROTEIN IN TYPE 2 DIABETIC PATIENTS AND ASSOCIATION OF PROTEINURIA WITH DIABETIC RETINOPATHY, HYPERTENSION AND HYPERGLYCEMIA: A CROSS SECTIONAL STUDY

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ABSTRACT

"Spot Urinary Albumin to Creatinine Ratio to Measure Quantitative Proteinuria in Diabetics"

BACKGROUND AND OBJECTIVES: A cross sectional study to study the relationship between spot urinary albumin to creatinine ratio and 24 hour urinary protein in type 2 diabetic patients and association of proteinuria with diabetic retinopathy, hypertension and hyperglycemia.

METHODS: 75 type-2 diabetes mellitus patients admitted patients in medicine were included in the study.

RESULTS: The mean duration of diabetes was 7 years (7.23 ± 5.67). Mean 24 hour urine protein was 0.37 g/24hour (0.37 ± 0.33) and mean spot urine albumin:creatinine ratio was 0.3 mg/mg (0.3 ± 0.21). Mean serum creatinine was 0.97 mg%.

CONCLUSION: Measurement of albumin to creatinine ratio in random urine samples seems to be a good alternative to collecting 24hr urine sample.

KEYWORDS : Spot urine albumin:creatinine ratio; 24 hour urine protein

INTRODUCTION

Diabetes mellitus is a disorder of carbohydrate metabolism characterized by - *Impaired Insulin Secretion, Insulin Resistance & Excessive Hepatic Glucose Production.* Cardiovascular complications and renal disease are two complicated health problems linked with diabetes[24].

Renal disease affects 40% of diabetic patients. Diabetic nephropathy is the commonest kidney disease in diabetic patients requiring renal replacement therapy[8].

Around 30% patients with microalbuminuria progress to proteinuria while 40% can revert to normoalbumniria with the control of hyperglycemia and hypertension[18]. Persitent albumin excretion in the range of 30-300 mg/d is called "Microalbuminuria". Microalbuminuria is an independent predictor of cardiovascular disease ancause mortality in both diabetic[20] and nondiabetics[13]. Hence the study was undertaken, to investigate if the urine albumin levels normalized by urine creatinine levels give results comparable to the urinary albumin excretion rate (UAER) with timed (24 hour) urine for detecting microalbuminuria, easier and faster.

1. Aim of the study is to find out the relationship between spot urinary albumin to creatinine ratio and 24 hour urinary protein in type 2 diabetic patients.
2. Association of proteinuria with diabetic retinopathy, hypertension and level of hyperglycemia.

MATERIALS & METHODS:

Study Population: Type 2 Diabetes Mellitus patients who provided written informed consent were included in the study.

Study Design: Cross Sectional Study.

Sample Size: Considering the prevalence being 36.3% according to study by Varghese et al[24] sample size will be 174 by formula $4pq/E^2$ where p is prevalence, q is 100 – prevalence & E is allowable error which is 10% to 20% of prevalence[14]. However, cosidering the short time period to addresses the study, only 75 subjects are included in the study.

Inclusion Criteria:

- Type 2 diabetic patients (according to ADA 2011 criteria)
- Age > 18 years to < 75 years
- Pt. with Serum Creatinine < 1.4 mg/dl for both males and females & absence of any clinical or laboratory evidence of other kidney or renal tract disease.

Exclusion Criteria:

- Presence of hematuria & evidence of obstructive uropathy and of scarred kidneys.
- Presence of heart failure or acute coronary syndrome.
- Presence of fever.
- Presence of infection.
- Hypertensive patients.
- Excess physical activity on the day of and day prior to 24 hour urine collection.

METHODOLOGY:

Diabetes was diagnosed according to American Diabetes Association (ADA) revised criteria[2] or the current or past use of insulin or oral hypoglycemic drugs. Type 1 diabetes was differentiated from type 2 diabetes by age of onset, body habitus and evidence of ketoacidosis. Hypertension was defined as systolic blood pressure (SBP) of equal to or more than 140 mmHg and/or diastolic blood pressure (DBP) of equal to or more than 90 mmHg or when antihypertensive treatment was being taken earlier. Stages of hypertension were defined as per the JNC 7 report[19].

A detailed history including the duration of diabetes, hypertension and the medications used. Presence of other comorbid illness and diabetic Nephropathy and Retinopathy were enlisted.

Followed with detailed General & Systemic Physical Examination including Height (cm), Weight (kg), BMI [wt (kg)/ht (meter) ^{2}], and B.P. in supine position (average of 3 readings 5 minutes apart).

Patients were evaluated for the presence of vascular (micro and macrovascular) complications i.e. coronary artery disease, retinopathy and nephropathy by relevant investigations.

Retinopathy was diagnosed by fundus examination. Fundoscopy was also confirmed by ophthalmologist. Patients were classified. Nonproliferative retinopathy: microaneurysms, haemorrhages, exudates, and intra-retinal microvascular abnormalities. Proliferative retinopathy: new vessels, glial proliferation, preretinal or vitreous haemorrhages, or scars of photocoagulation.

Presence of cardiovascular disease was confirmed by positive history of cardiovascular disease, medical records or current symptoms, ECG and Echocardiography.

Laboratory Investigations done in patients:

- Urine routine and microscopic examination.
- Hemogram

- Fasting and Post prandial blood sugar level
- Blood Urea and Serum Creatinine
- Relevant investigations needed.

- Then the urine collected for quantification of albuminuria and albumin to creatinine ratio:
- Urinary Albumin detected
- Urinary Creatinine detected
- Albumin Creatinine Ratio= ---------- * 1000 (mg/g) Creatinine (mg/dl)

Instructions for patient:
- Early morning spot urine sample.
- Collect urine from 8 AM to next day 8 AM for 24 hour estimation.
- Avoid Excess physical activity on the day of and day prior to 24 hour urine collection as well spot collection.

Specifics for collection and panels:
- Specimen type: Urine
- Container: Plastic urine tube
- Collection method: 24-hour collection or spot urine specimen
- Specimen volume for spot sample: 5 mL
- No preservatives in 24-hour collection container
- Confirm positive findings with second specimen over two to three months of period.

The median values of the 24-h urine collections and albumin to creatinine ratio were calculated, and the patients were classified as having normoalbuminuria, microalbuminuria, or macroalbuminuria (overt nephropathy) accordingly. Microalbuminuria was defined 0.03-0.29 (g/24 hour) and macroalbuminuria (or overt nephropathy) as values > 0.3 g/24 h. For albumin-to-creatinine ratio, the definition of microalbuminuria was 0.03-0.29 mg/mg creatinine. Nephropathy was defined as values > 300 mg/mg creatinine.

Statastical Methods: Corelation tested using Pearson correlation coefficient & T- test applied. Values of p less than 0.05 were considered as significant.

RESULTS

The data was grouped into various categories.

1. Age and Sex Wise Distribution:

The total sample consisted of 49 (65.33%) males and 26 (34.67%) females. The male to female ratio was 1.88. The minimum age of the patients was 32, while the maximum age was 74. The average age of patients was 54 years (54.39 $\pm$ 10.68). The maximum number of patients (36%) was in the age group of 51-60 years (for both male and female).

2. Height, Weight and Body Mass Index (BMI):

The mean weight of patients was 63kg (63.32 $\pm$ 7.5), 65kg (65.2 $\pm$ 6.53) for men and 60kg (59.96 $\pm$ 8.17) for women. The weight ranged from 45kg to 80kg. The mean height was 164cm (164 + 6.28), 166cm (166.55 $\pm$ 5.24) for male and 159cm (159.19 $\pm$ 5.22) for female. The mean BMI was 23.5 (23.56 $\pm$ 2.61), 23 for both male and female. The BMI ranged from 17.30 to 28.76. The difference in the BMI between male and female was not statistically significant (p=0.793).

3. Distribution of Hypertension:

2/3rd of the patients had hypertension (BP more than 140/90). The maximum patients, 30 (40%), were in stage I hypertension, 20 (26.67%) had stage II hypertension while 23 (30.67%) were in the stage of pre-hypertension. The mean systolic and diastolic BP were 146 (146 $\pm$ 17) and 87 (87 $\pm$ 6.9) mm of Hg respectively.

4. Duration of Diabetes:

The duration of diabetes ranged from newly diagnosed cases upto 20 years. The mean duration of diabetes was 7 years (7.23$\pm$5.67). The maximum number of patients, 31 (43.06%) was between 5-10 years duration.

5. Distribution of proteinuria:

The mean 24 hour urine protein was 0.37 g/24 hour (0.37 $\pm$ 0.33) and ranged from 0.02 to 1.4 g/24 hour. The mean spot urine albumin creatinine ratio was 0.3 mg/mg (0.3$\pm$ 0.27) and ranged from 0.02 to 0.98 mg/mg. The mean serum creatinine was 0.97 mg% (0.97 $\pm$ 0.24) and ranged from 0.5 to 1.4.

6. Stage and Sex – wise Distribution of Albuminuria:

It shows that out of the 75 patients studied, 38 (50.67%) patients had microalbuminuria while 33 (44%) had macroalbuminuria or overt nephropathy. 4(5.33%) had normoalbuminuria. The prevalence of micro-albuminuria among male and female was 46.94% and 57.69% respectively.

Out of the 75 patients studied, 32 patients (42.67%) had microalbuminuria while 39 (52%) had macroalbuminuria and 4 patients (5.33%) had normoalbuminuria. The prevalence of microalbuminuria among male and female was 40.82% and 46.15% respectively. The above tables also show that although the sex-wise distribution of the population differed at each level of albuminuria, it was still comparable (p=0.251 and 0.08 for the two methods).

7. Correlation between Spot Urine Albumin Creatinine Ratio and 24 hour Urine Protein:

The correlation was also studied at the various ranges of proteinuria – normoalbuminuria (<0.03), microalbuminuria (0.03-0.29) and macroalbuminuria (>0.3) and accordingly the correlation coefficient (r) and p value were calculated for each of the ranges of albuminuria.Normoalbuminuria

The correlation between the amount of proteinuria by the two methods of 24 hour urine protein (24 UP) and spot urine albumin:creatinine ratio (SUACR) was studied, all the observations being in the range of normoalbuminuria (<0.03mg/mg).

The correlation in this range of proteinuria is not significant, r = 0.813, p=0.29, as there were only four observations (n=4) in this group.

a. Microalbuminuria

The correlation between the aount of proteinuria by the two methods of 24 hour urine protein (24 UP) and spot urine albumin:creatinine ratio (SUACR) was studied in the range of microalbuminuria (0.03-0.299 mg/mg).

The correlation between the two tests in this range of proteinuria – microalbuminuria – was significantly strong, r=0.693, p=0.018, n=33.

b. Macroalbuminuria

The correlation between the amount of proteinuria by the two methods of 24 hour urine protein (24 UP) and spot urine albumin:creatinine ratio (SUACR) was studied in the range of macroalbuminuria (> 0.3 mg/mg).

There is a strong correlation between the two tests and it is highly significant in this range of proteinuria – mcroalbuminuria, r = 0.69, p = 0.001, n = 38.

8. Prevalence of Diabetic Retinopathy :

The prevalence of diabetic retinopathy in the study population was 20% (15 out of 75 patients had diabetic retinopathy). Only 1 patient had a proliferative diabetic retinopathy while 14 (18.67%) patients had non-proliferative type of diabetic retinopathy.

9. Association between Systolic Hypertension and Albuminuria:

The maximum number of patients had stage I hypertension. Most patients with pre-hypertension (HT) and stage I HT, had microalbuminuria while most patients with stage II HT had macroalbuminuria.

10. Association between Diastolic Hypertension and Albuminuria

The maximum number of patients had stage I hypertension. Most was prevalent in the pre-HT and stage-I Hypertension (HT). Macroalbuminuria was common in stage II hypertension.

11. Association between Fasting Blood Sugar Level (F-BSL) and albuminuria

The maximum number of patients had a poorly controlled blood sugar level (BSL)> most of them had a BSL in the range of 126-200 and they had both microalbuminuria (30.7%) and macroalbuminuria (28%).

12. Association between HbA1c and Albuminuria:

Table 18: Frequency Distribution of HbA1c against Stages of Albuminuria

The maximum number of patients, 17 (42.5%) patients had poorly controlled long term blood sugar level (BSL) – HbA1c. Almost equal number of the remaining patients had good (6.5 – 7.5) to fair (7.5 – 8.5) control of BSL (given by the value of HbA1c).

13. Association between Retinopathy and Albuminuria

The 15 (20%) patients had an evidence of retinopathy (non-proliferative or proliferative). Out of those with presence of retinopathy, none had normoalbuminuria, while 3 (20%) microalbuminuria and 12 (80%) had macroalbuminuria.

14. Correlation between Spot Urine Albumin:Creatinine Ratio (SUACR) and various variables:

24 hours urine protein, duration of diabetic, systolic and diastolic blood pressure, fasting blood sugar, HbA1c levels, presence of retinopathy among the study population were studied according to the stages of albuminuria (measured by spot urine albumin:creatinine ratio – SUACR). There is a strong correlation between 24 hour urine protein and spot urine albumin:creatinine ratio. Coefficient of correlation (r) = 0.743 which was found to be highly significant (p = 0.001).

DISCUSSION

1. Age and Sex wise distribution:

In this study the male to female ratio was 1.88. The mean age of the population was 54.39 ± 10.68 years.

2. Weight, Height and BMI:

The weight and height in this study ranged from 148 to 178 cm and 46 to 80 kg. The BMI ranged from 17.3 to 28.76. Sabharwal et al[21] had a BMI of about 25.6 for male and 23.8 for female.

3. Distribution of Hypertension:

The mean systolic and diastolic blood pressure in our study was 146.24 ± 10.68 mm of Hg and 87.79 ± 6.92 mm of Hg, respectively.

4. Duration of Diabetes:

The mean duration of diabetes in this study was 7.23 ± 5.66 years. Distribution of Proteinuria:

Stage and Sex-wise Distribution of Albuminuria- The prevlance of microalbuminuria among males was (46.94%) while in females it was (57.69%) which was statistically insignificant (p = 0.251). The female had a higher prevalence of microalbuminuria. Creatinine is a metabolic byproduct of skeletal muscle creatinine and phosphocreatinine metabolism and is thus lower in subjects with lower muscle mass such as women or the elderly[39]. We found significantly higher levels of urine creatinine in men but no significant differences in urine albumin concentration.

Olivarius et al[17] found microalbuminuria using the albumin/creatinine ratio (ACR) of 33.6% among male and 28.8% among female newly diagnosed diabetics. The prevalence of microalbuminuria was not statistically different for the two sexes as in our study, which was similar to the findings reported by Mather et al[15] in European diabetic patients.

Correlation between untimed (spot) urinary albumin to creatinine ratio (SUACR) and 24 hour urinary protein (24 UP):

SUACR has been recommended as a screening test for early detection of nephropathy[2]. In this study also, there is statitstically significant correlation between 24 hour urine protein and spot urine albumin to creatinine ratio (r = 0.743 and p = 0.001). Also the prevention of Renal and Vascular End stage Disease (PREVEND)[24] study group in Europe and Jafar et al[11] in an Indo-Asian population assessed the validity of timed urinary albumin concentration (24 hour) and the albumin-to- creatinine ratio to detect individuals with microalbuminuria and found the diagnostic performance of albumin concentration and albumin-to-creatinine ratio to be similar and acceptable with coefficient of correlation (r), 0.92 for PREVEND study group and 0.88 for study by Jafar et al. Chaiken et al[3] found a correlation between the 24 UP and SUACR was 0.96 (p = 0.0001).

Correlation between 24 hour urine protein (24 UP) and spot urine albumin:creatinine ratio (SUACR) was studied over various ranges of proteinuria Thus the 24 hour urine protein (24 UP) and spot urine albumin:creatinine ratio (SUACR) correlate well with statistical significance at the stages of microalbuminuria and macroalbuminuria. The results obtained were compared with a study by Chaiken et al[3].

5. Prevalence of Diabetic Retinopathy:

Our study showed the prevalence rate of 20% which is in the same range.

Correlation between Age and Microalbuminuria

A statistically significant correlation (p = 0.006) was found between age and albuminuria in this study. Similar results were reported by Varghese et al[25] among 1425 type 2 diabetic patients. No statistically correlation was found by Allawi et al[1] and Yazd et al[27] between microalbuminuria and the age among 650 diabetic patients.

6. CorrelationbetweenSystolicandDiastolicHypertensionand Microalbuminuria in Diabetes:

No significant correlation of systolic (p = 0.081) or diastolic BP (p = 0.179) with albuminuria was found in this study, other investigators[17] found it to be correlating. Nishijo et al[16] in a study of 245 nondiabetic Japanese men concluded that urinary albumin was significantly related to systolic and diastolic blood pressure, independent of other factors such as BMI and plasma insulin.

A statistically significant correlation was found between the prevalence of microalbuminuria and the diastolic blood pressure by Verghese et al[25], Huraib et al[33] reported a good correlation between the prevalence of microalbuminuria and hypertension. Svensson et al[22] showed that high blood pressure increased the risk of developing signs of nephropathy (p = 0.003).

There are studies that document the reduction of serious morbidity or mortality by the use of angiotensin converting enzyme (ACE) inhibitor[9,23] in diabetics.

7. Duration of diabetes and microalbuminuria:

The duration of diabetes was shown in previous studies[15,26] to play an important role in the development of microalbuminira. Huraib et al[10] in Saudi Arabia, Varghese et al[25] in south India, Viberti et al[26] and Mather et al[15], all reported a significant correltion between microalbuminuria and the duration of diabetes.

8. Comparison between Hyperglycemia and albuminuria (fasting BSL and HbA1c)

No statistically significant correlation was found between fasting BSL (r = 0.185, p = 0.056) and albuminuria, HbA1c correlated with albuminuria (r = 0.541, p = 0.012). The value of HbA1c as a marker for long term BSL control correlated well with albuminuria in our study.

9. Correlation between Retinopathy and Albuminuria

No correlation was found between the presence of retinopathy and microalbuminuria (p = 0.681). Erasmus et al[6] showed that in 113

patients suffering from type 2 diabetes, the incidence rate of microalbuminuria was as high as 54% among males (46.94% in our study) and 59% among females (57.69% in our study). Diagnostic uncertainty exists in some patients with type 2 diabetes since the onset of diabetes is unknown and retinopathy is absent in a significant proportion (48%) of these patients. Biopsy studies have suggested that as much as 30% of proteinuric type 2 diabetic patients may not have typical diabetic lesions and that these atypical lesions are more frequent in proteinuric individuals with no sign of diabetic retinopathy as reported by Christensen et al[5]. Another article by Christensen et al[4] has demonstrated that the course of Kidney function and albuminuria in type 2 diabetic patients with persistent albuminuria and with nondiabetic glomerular patterns is less rapid than in the patients with diabetic nephropathy.

CONCLUSIONS

1. The mean BMI for the population was 25.6.
2. The mean systolic and diastolic BP were 146 (146$\pm$17) and 87 (87$\pm$6.9) mm of Hg respectively. The maximum number of patients had stage I hypertension.
3. The mean duration of diabetes was 7 years (7.23 $\pm$ 5.67). The maximum number of patients, 31 (43.06%), had the duration of diabetes between 5- 10 years duration.
4. Mean 24 hour urine protein was 0.37 g/24hour (0.37 $\pm$ 0.33) and mean spot urine albumin:creatinine ratio was 0.3 mg/mg (0.3 $\pm$ 0.21). The mean serum creatinine was 0.97 mg%.
5. 38 (50.67%) patients had microalbuminuria while 33 (44%) had macroalbuminuria and 4 (5.33%) patients had normoalbuminuria. The prevalence of micro-albuminuria among male and female was 46.94% and 57.69% respectively.
6. There was a strong (r = 0.743) and statistically significant (p = 0.001) correlation between 24 hour urine protein and spot urine albumin:creatinine ratio. The correlation was also true at microalbuminuria (r = 0.693), p = 0.018) and macroalbuminuria (r = 0.690, p = 0.001) level.
7. The factors which correlated well with the degree of albuminuria were the age of patients® = 0.288, p = 0.006), the duration of diabetes (r = 0.355, p = 0.001) and long term glycemic control (HbA1c) (r = 0.541, p = 0.012).
8. No significant correlation was found in this study between systolic (p = 0.081) or diastolic (p = 0.062) blood pressure, retinopathy or fasting blood sugar levels with the level of albuminuria.

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