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CORRELATION OF SPOT URINE PROTEIN/CREAT RATIO AND 24-HOUR URINARY PROTEIN FOR PROTEINURIA ESTIMATION IN DIABETIC NEPHROPATHY

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ABSTRACT

Background: The first step in the screening and diagnosis of diabetic nephropathy is to look for proteinuria. Quantitative measurement of protein in a 24-hour urine collection remains the gold standard, since protein excretion may vary with the circadian rhythm. However, the 24 hour urine collection is cumbersome, inconvenient especially in female patients, is often incomplete and difficult to administer in outpatients and it is reported that 24 hour urine collection is unreliable in up to one third of the patients due to incomplete collection. An alternative method for quantitative evaluation of proteinuria is the measurement of urine protein to creatinine ratio. This study aims to evaluate the diagnostic value of P:C ratio in single voided urine sample for detection of proteinuria compared to that of a 24-hr sample in patients with diabetic nephropathy. **Methods:** The present study was carried in the department of General Medicine at Civil hospital affiliated with a government medical college, Gujarat after the approval from Institutional Ethical Committee (IEC).This was a cross sectional study in which 50 patients with diabetic nephropathy were taken.50 patients were taken who met the inclusion and the exclusion criteria. 24 hour urine sample was collected by instructing the participants to begin collection immediately after completion of first voiding in morning and to collect all urine into the same container having 5ml of 10% thymol in iso-propanol as a preservative for 24 hours. This was thoroughly mixed and a sample of 10 ml was taken for the estimation of proteins. On the next day, early morning second sample was collected. Approx 10 ml of mid stream urine was collected. This sample was used to test spot protein creat ratio. Urine creatinine was measured by modified Jaffe's method and urine protein was measured by pyrogallol red modified fujita method. **Results:** In our study, the mean expected 24 hours urinary protein was 2.972 grams and standard deviation was 0.832. Estimated 24 hour urinary protein was 3.065 and standard deviation was 0.569. The correlation coefficient ratio was 0.851 with a p value of 0.03. In our study, in patients with minimal proteinuria, the correlation coefficient was 0.881 with a p value of 0.03 when estimated 24 hour urine protein was compared with expected 24 hour urine protein. In patients with moderate proteinuria, the correlation coefficient was 0.851 with a p value of 0.02. In patients with heavy proteinuria, the correlation coefficient ratio was 0.755 with a p value of 0.05. This shows that as the protein loss increases in urine, the correlation coefficient reduces showing that the correlation between expected 24 hour urinary protein measured from spot protein creat ratio and estimated 24 hour urinary protein decreases. **Conclusion:** There is no significant difference between expected and estimated 24 hours urine protein from both samples. The correlation is best in patients with mild and moderate degree of proteinuria and the correlation reduces when there is heavy proteinuria. Urine Protein Creatinine ratio is easy to perform, inexpensive,less time consuming and a very accurate method for measuring of proteinuria when compared to estimated 24 hours urinary protein.

INTRODUCTION

The worldwide prevalence of Diabetes Mellitus (DM) has risen dramatically over the past two decades from an estimated 30 million cases in 1985 to 415 million in 2020. Based on the current trends, it is projected that 642 million individuals will have diabetes by the year 2040. The prevalence of type 2 DM is increasing more rapidly as compared to type 1 DM because of increase in obesity, reduced activity levels as countries become more industrialized and the aging of the population. The prevalence of Diabetes Mellitus in India is 9.6%.[1]

Diabetic nephropathy is the leading cause of chronic kidney disease in India.[2] It is estimated that 5.9% of diabetic patients in India suffer from diabetic nephropathy.[1] Diabetic nephropathy is classically defined as persistent albuminuria >300mg/24 hours in at least 2 out of 3.[3] In the early 1980s, studies from Europe revealed that small amounts of albumin in the urine, not usually detected by conventional methods, were predictive of the later development of proteinuria in type 1 and type 2 diabetic patients. This stage of renal involvement was termed microalbuminuria or incipient nephropathy. Diabetic nephropathy is viewed as a descending path from normoalbuminuria to ESRD which is marked by intermediate stage microalbuminuria and overt proteinuria.

The cut off values adopted by the American Diabetes Association for the diagnosis of micro- and macroalbuminuria in 24-h, and spot urine collection respectively are

Microalbuminuria: 30 - 300 mg albumin in 24 hr urine
30- 300 mcg albumin / mg of creatinine

Macroalbuminuria: > 300 mg albumin in 24 hr urine
> 300 mcg albumin / mg creatinine

The first step in the screening and diagnosis of diabetic nephropathy is to look for proteinuria. Screening should not be performed in the presence of conditions that increase urine albumin excretion, such as urinary tract infection, hematuria, acute febrile illness, vigorous exercise, short-term pronounced hyperglycaemia, uncontrolled hypertension, and heart failure.

Quantitative measurement of protein in a 24-hour urine collection remains the gold standard, since protein excretion may vary with the circadian rhythm. However, the 24 hour urine collection is cumbersome, inconvenient especially in female patients, is often incomplete and difficult to administer in outpatients and it is reported that 24 hour urine collection is unreliable in up to one third of the patients due to incomplete collection.

An alternative method for quantitative evaluation of proteinuria is the measurement of urine protein to creatinine ratio. The protein creatinine ratio takes into account the fact that creatinine excretion remains fairly constant in presence of a stable GFR. The protein excretion would also be fairly stable. Therefore, the ratio of the two in a single voided sample would reflect the cumulative protein excretion over the day, as the two stable rates would cancel out the time factor. Measurement of total protein to creatinine ratio on random (spot) urine sample correlates well with 24 hours total protein excretion.

Several studies have compared Urine protein creatinine ratio (PCR) to 24 hr urine estimation and found to have a positive correlation between the two in the screening and evaluation of diabetic nephropathy. The correlation between urine PCR and 24 hr urine protein was found to be good for all renal function levels, but demonstrated more marked differences as urinary protein excretion increased.

There remains the need for a reliable quantitative measurement of urinary protein excretion that will be quick, easy to administer and correlate well with 24-hr urine protein excretion. The use of the urinary protein to creatinine ratio has been extensively demonstrated to possess the potential to fill this vacuum. But no consensus for specific Protein-creatinine (P:C) cutoff value has been obtained. These uncertainties have added to the resistance of substituting it for timed collections when evaluating diabetic nephropathy.

This study aims to evaluate the diagnostic value of P:C ratio in single voided urine sample for detection of proteinuria compared to that of a 24-hr sample in patients with diabetic nephropathy.

METHODS

The present study was carried in the department of General Medicine at Civil hospital affiliated with a government medical college, Gujarat after the approval from Institutional Ethical Committee (IEC).This was a cross sectional study in which 50 patients with diabetic nephropathy were taken.

Inclusion Criteria: Diabetes Mellitus type I and type II patients with age between 18 years and 80 years (diagnosed based on The National Diabetes Data Group and WHO criteria) with a duration of more than 5 years and Chronic Kidney Disease based on KDIGO criteria as shown below (any of the criteria shown below for >3 months)

1. Decreased GFR <60ml/min/1.73m^2
2. Albuminuria ≥30mg/24hr
3. Urine sediment abnormalities
4. Electrolytes and other abnormalities due to tubular disorder
5. Abnormalities detected by histology
6. Structural abnormalities detected by imaging
7. History of kidney transplantation

Exclusion Criteria: Patients with

1. Acute febrile illness
2. Patients with active UTI or Cystitis or Pyelonephritis
3. Glomerulonephritis due to systemic conditions
4. Malignancies, collagen vascular disorders or any other systemic condition causing proteinuria
5. Hypertension preceding Nephropathy (Hypertensive Nephropathy)
6. Autosomal Dominant Polycystic Kidney Disease
7. Patients on long term Nephrotoxic medications
8. Age < 18 yrs
9. Pregnant women or women during menstruation period

The indoor patients in the department of Medicine were enrolled in the study. Informed consent was taken from patients. Their history and relevant clinical and biochemical data were noted in a preformed questionnaire. A detailed medical history including the chief complaints such as complaints of decreased urine output, pedal edema, abdominal distension, breathlessness on exertion/rest and any history of major illness in the past was taken. Clinical parameters like age, duration of diabetes, insulin requirement, presence of diabetic retinopathy as well as micro and macro vascular complications of diabetes were evaluated. A detailed history of drugs, addictions was noted. The patients were observed for the outcomes during the hospital stay.

The clinical status examination at admission including vital signs, examination of respiratory system, cardiovascular system, central nervous system and abdomen was done. Complete blood count, routine urine examination, peripheral smear, blood glucose,HbA1c,fasting blood sugar, post prandial 2hr blood sugar, lipid profile, blood urea and serum creatinine, serum electrolytes, SGPT, SGOT, serum bilirubin, Alkaline Phosphatase, serum albumin, total protein, Arterial blood gas analysis were done. The results were registered into a computerized data sheet.

No specific recommendations were advised to the patients about fluid intake, physical exercise or dietary protein intake. 24 hour urine sample was collected by instructing the participants to begin collection immediately after completion of first voiding in morning and to collect all urine into the same container having 5ml of 10% thymol in iso-propanol as a preservative for 24 hours. This was thoroughly mixed and a sample of 10 ml was taken for the estimation of proteins. On the next day, early morning second sample was collected. Approx 10 ml of mid stream urine was collected. This sample was used to test spot protein creat ratio. Urine creatinine was measured by modified Jaffe's method and urine protein was measured by pyrogallol red modified fujita method.

Expected 24 hour urinary protein was calculated from Protein Creatinine ratio by using the following formula.[4]

$$\text{Expected 24 hours Urinary Protein (male)} = \frac{[140-\text{Age (yrs)}] \times \text{wt (kg)}}{5000} \times \text{P/C Ratio}$$

$$\text{Expected 24 hours Urinary Protein (female)} = \frac{[140-\text{Age (yrs)}] \times \text{wt (kg)}}{5000} \times \text{P/C Ratio} \times 0.85$$

Glomerular filtration rate (GFR) was calculated from age and plasma creatinine by Modified Diet in Renal Disease (MDRD) Formula.[5]

GFR (mL/min/1.73 m^2) = 186 x $(Pcr)^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if

Female) x (1.210 if African - American) The GFR is expressed in mL/min/1.73m^2

The data was further systematically arranged in a Microsoft Excel sheet -master chart, so that analysis can be done and inferences drawn.

RESULTS

The baseline characteristics of the study population are shown in the table below:

Table 1: Baseline Characteristics of the Study Population.

Age	**56 years**	
Gender	62% males	38% females
Mean Duration of Diabetes	24 years	
Mean GFR	37 mL/min/1.73 m^2	
Mean Protein Creat Ratio	2.897	
Mean 24 hr urine protein	3.065 ± 0.569 grams	

The baseline characteristics of the study population is shown in the table 1. The mean age of the study population was 56 years. There were 62% males and 38% females. Mean duration of Diabetes Mellitus was 24 years. Mean GFR was 37 ml/min/1.73m^2. Mean protein creat ratio was 2.897. Mean 24 hour urine protein was 3.065 ± 0.569 grams.

Table 2: Distribution of The Patients Based on The Degree of Proteinuria.

Degree of Proteinuria	Protein excretion/day	No of patients	Percentage
Minimal	0.15-0.50 grams	19	38%
Moderate(Sub nephritic range proteinuria)	0.5 to 3.5 grams	22	44%
Heavy(Nephrotic range proteinuria)	More than 3.5 grams	9	18%

Out of the 50 patients, 9 patients (18%) of the patients had minimal proteinuria (0.15-0.5 grams proteinuria per day). 11(22%) patients had moderate proteinuria (0.5-3.5 grams/day) and 30 patients (60%) of the patients had heavy proteinuria (more than 3.5 grams/day).

Table 3: Distribution of the Patients Based on the Stages of Nephropathy.

Stages of Nephropathy	No of patients	Mean urine Protein Creat Ratio(mg/mg)	Mean 24 hour urine protein(mg/day)	Mean duration of Diabetes(yrs)
Stage 1 (eGFR >90)	3(6%)	0.44	560	2
Stage 2 (eGFR 60-89)	10(20%)	0.56	670	2.6
Stage 3a (eGFR 45-59)	13(26%)	1.67	2015	6.12
Stage 3b (eGFR 30-44)	09(18%)	2.98	2677	6.98
Stage 4 (eGFR 15-29)	07(14%)	3.47	3948	8.857
Stage 5 (eGFR <15)	08(16%)	4.12	5100	8.625

The patients were divided into various stages of CKD based on the KDIGO criteria. 3 patients(6%) had eGFR >90. 10 patients(20%) had Stage 2 CKD(eGFR 60-89). 13 patients (26%) had Stage 3a CKD (eGFR 45-59). 9 patients (18%) had Stage 3b CKD(eGFR 30-44). 7 patients (14%) had Stage 4 CKD(eGFR 15-29). 8 patients (16%) had stage 5 CKD(eGFR <15).

Mean urine protein creat ratio in stage 1 CKD was 0.44 (mg/mg) and mean 24 hour urinary protein was 560(mg/day). Mean urine protein creat ratio in stage 2 CKD was 0.56 (mg/mg) and mean 24 hour urinary protein was 670(mg/day). Mean urine protein creat ratio in stage 3a CKD was 1.67 (mg/mg) and mean 24 hour urinary protein was 2015(mg/day). Mean urine protein creat ratio in stage 3b CKD was 2.98 (mg/mg) and mean 24 hour urinary protein was 2677(mg/day). Mean urine protein creat ratio in stage 4 CKD was 3.47 (mg/mg) and mean 24 hour urinary protein was 3948(mg/day). Mean urine protein creat ratio in stage 5 CKD was 4.12 (mg/mg) and mean 24 hour urinary protein was 5100(mg/day). These results show that as the stage of nephropathy increases, there is an increase in the protein loss through kidneys and there is an increase in protein creat ratio.

Table 4: Overall Correlation Between Expected 24 Hours Urinary Protein From 7am Sample And Estimated 24 Hours Urinary Protein.

	MEAN	STD DEVIATION
Expected 24 hours urinary protein (calculated from PCR)	2.972 gram	0.832
Estimated 24 hour urinary protein (actually measured from lab)	3.065 gram	0.569

In our study, the mean expected 24 hours urinary protein was 2.972 grams and standard deviation was 0.832. Estimated 24 hour urinary protein was 3.065 and standard deviation was 0.569. The correlation coefficient ratio was 0.851 with a p value of 0.03.

Table 5: Correlation Between Expected 24 Hour Urine Protein And Estimated 24 Hour Urine Protein In Patients With Varying Degrees Of Proteinuria.

Degree of Proteinuria	Protein excretion	No of patients	Correlation coefficient(r)	P value
Minimal	0.15-0.50 grams	19(38%)	0.881	0.03
Moderate(Sub nephritic range proteinuria)	0.5 to 3.5 grams	22(44%)	0.851	0.02
Heavy(Nephrotic range proteinuria)	More than 3.5 grams	9(18%)	0.755	0.04

In our study, in patients with minimal proteinuria, the correlation coefficient was 0.881 with a p value of 0.03 when estimated 24 hour urine protein was compared with expected 24 hour urine protein. In patients with moderate proteinuria, the correlation coefficient was 0.851 with a p value of 0.02. In patients with heavy proteinuria, the correlation coefficient ratio was 0.755 with a p value of 0.05. This shows that as the protein loss increases in urine, the correlation coefficient reduces showing that the correlation between expected 24 hour urinary protein measured from spot protein creat ratio and estimated 24 hour urinary protein decreases.

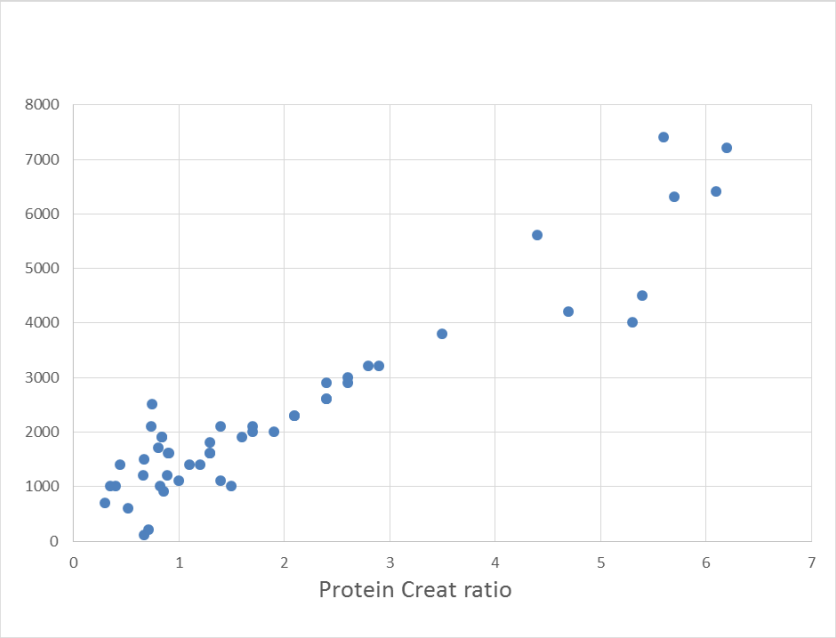

Figure 1: Scatter Plot Showing The Correlation Between Spot Protein Creat Ratio And 24 Hour Urinary Protein.

The above chart shows the comparison between urine protein creat ratio with 24 hour urine protein and it shows that as the degree of proteinuria increases, the correlation changes. When the proteinuria increases from minimal to moderate, the correlation coefficient decreases from 0.881 to 0.851 and when the proteinuria increases to heavy range proteinuria, the correlation coefficient reduces to 0.755.

Table 6: Correlation Between Expected 24 Hour Urine Protein And Estimated 24 Hours Urinary Protein In Patients With Various Stages Of Ckd.

Stages of Nephropathy	No of patients	Correlation coefficient (r)	P value
Stage 1	3(6%)	0.939	0.04
Stage 2	10(20%)	0.837	0.04
Stage 3	22(44%)	0.764	0.03
Stage 4	07(14%)	0.744	<0.01
Stage 5	08(16%)	0.732	0.01

In our study, when patients were divided based on the stages of CKD, the correlation coefficient was 0.939 (p value 0.04) in patients with stage 1 of CKD. In stage 2 CKD patients, the correlation coefficient was 0.837 (p value 0.04). In stage 3 CKD patients, the correlation coefficient was 0.764 (p value 0.03). In stage 4 CKD patients, the correlation coefficient was 0.744 (p value <0.01). In stage 5 CKD patients, the correlation coefficient was 0.732 (p value 0.01). These results show that as the eGFR reduces and the severity of CKD increases by increasing in the stage, the correlation coefficient reduces showing that there is a reduced correlation between spot protein creat ratio and estimated 24 hour urine protein as the disease progresses.

DISCUSSION

Diabetic nephropathy is one of the major microvascular complications of Diabetes Mellitus. Diabetic nephropathy is a serious complication as there is a subtle progression in the disease when blood sugar levels are not under proper control. It is estimated that there is a 8-10ml/min/1.73m^2 fall in GFR per year once patients develops diabetic nephropathy.

In this study, a total of 50 patients were taken who met the inclusion and the exclusion criteria**.** Protein creatinine ratio was estimated from an early morning sample. A quantitative estimation of proteinuria was done from samples using Protein Creatinine Ratio values and analyzed which correlated best with 24 hours urinary

protein value. The mean age in our study was 56 years. In our study, there were 31(62%) males and 19(38%) females. In our study, there were 15(30%) of patients with type 1 Diabetes Mellitus and 35(70%) of patients with type 2 Diabetes. The mean duration of diabetes in our study is 20.96 years. In our study, hypertension was present in 22(44%) of the patients. In our study, the incidence of CV stroke was 5(10%). The incidence of peripheral vascular disease 1(2%) in our study. IHD was present in 21(42%) of the patients in our study.

In our study, minimal proteinuria was present in 19(38%) patients. Moderate proteinuria was present in 22(44%) of the patients and heavy proteinuria was present in 9(18%) of the patients. Our findings are in contrast to the findings by Mohan et al,[6] study and Abubacker et al,[7] study as all the patients in our study had developed nephropathy while in the study by Mohan et al only 21% of the study population had developed nephropathy. In the study by Abubacker et al, the patients had a different distribution of the stages of CKD when compared to the patients of our study. In our study, mean expected 24 hours urinary protein was 2.972 ± 0.832 and estimated 24 hour urinary protein was 3.065 ± 0.569. The mean expected 24 hours urinary protein was 3.36 ± 2.46 and estimated 24 hour urinary protein was 3.25 ± 1.96 in the study by Abubacker.

However, Indira Agarwal[8] et al study found excellent correlation between spot Protein Creatinine ratio and 24 hours proteinuria in all degrees of proteinuria. Sharma et al,[9] also observed a good positive correlation even in patients with advanced renal failure. Correlation co efficient (r) values were 0.889, 0.788, 0.375 in patients with serum Creatinine < 1.5 mg/dl, 1.5-4 mg/dl, > 4 mg/dl respectively.

Correlation coefficient of comparison of expected 24 hours urinary protein and estimated 24 hours urinary protein was 0.939,0.837,0.764,0.744 and 0.732 in stage 1, stage 2, stage 3, stage 4 and stage 5 CKD respectively. This is comparable to the study by Abubacker et al in which the correlation coefficient reduces as the stages of CKD progresses.

The possible explanation is the erratic and decreased excretion of creatinine in patients with advanced renal failure as observed in numerous studies like Carrie BJ et al,[10] Perrone RD et al,[11] Levey AS et al.[12]

CONCLUSION

Detection of albumin in urine is the hallmark for the diagnosis of diabetic nephropathy and it is of utmost importance to detect albuminuria and proteinuria early in patients with Diabetes. 24 hour urinary protein estimation and urine protein creatinine ratio are commonly used for quantitative estimation of protein loss in urine. Protein Creatinine ratio in the random urine sample is found to be a useful index for quantification of proteinuria in patients with varying degree of proteinuria and renal dysfunction in diabetes patients. There is no significant difference between expected and estimated 24 hours urine protein from both samples. The correlation is best in patients with mild and moderate degree of proteinuria and the correlation reduces when there is heavy proteinuria. Urine Protein Creatinine ratio is easy to perform, inexpensive, less time consuming and a very accurate method for measuring of proteinuria when compared to estimated 24 hours urinary protein. It can thus be used in the outpatient setting for screening and quantification of proteinuria in patients with diabetic nephropathy.

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