Use of Protein: creatinine ratio in a random spot urine sample for predicting significant proteinuria in diabetes mellitus

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ABSTRACT

Present study was undertaken during a period of 6 months (September 2008-February 2009) to see an correlation of 24 hours urine protein estimation with random spot protein-creatinine (P:C) ratio among a diabetic patients. The study comprised of 144 patients aged 30-70 years, recruited from Kantipur hospital, Kathmandu. The 24-hr urine sample was collected, followed by spot random urine sample. Both samples were analyzed for protein and creatinine excretion. An informed consent was taken from all participants. Sixteen inadequately collected urine samples as defined by (predicted creatinine - measured creatinine)/predicted creatinine >0.2 were excluded from analysis. The Spearman's rank correlation between the spot urine P:C ratio and 24-hr total protein were performed by the Statistical Package for Social Service. At the P:C ratio cutoff of 0.15 and reference method (24-hr urine protein) cutoff of 150 mg/day, the correlation coefficient was found to be 0.892 ($p<0.001$). The area under ROC curve at different cutoffs was 0.88 at 95.0% CI. The sensitivity and specificity of the P:C ratio to detect significant proteinuria at the cutoff of 0.15 are 96.6% and 74.4%. So the P:C ratio can predict significant proteinuria in diabetic subjects, avoiding the inconvenient 24-hr urine collection but the cutoff should be carefully selected for different patients group under different laboratory procedures and settings.

Keywords: 24-hr urinary protein, Protein: creatinine ratio, Proteinuria, ROC curve.

INTRODUCTION

Nephropathy is the major health problem in patients with diabetes mellitus (DM).The natural history of diabetic nephropathy has generally viewed as a descending path from normoalbuminuria to end stage renal disease (ESRD) through a intermediate stage marked by microalbuminuria and overt proteinuria.[1,2] Appearance of proteinuria heralds the onset of nephropathy and plays a critical role in the development of ESRD.[3] So, quantifying urine protein accurately and precisely, is vital in the monitoring disease activity in patients with DM. The measurement of protein in 24-hr urine collection has been regarded as the gold standard.[4] The use of 24-hr collection is necessitated by the variation in protein excretion throughout day which negates the use of concentration measurement in random urine collection.[5, 6] However, the 24-h urine collection is cumbersome, inconvenient especially in female patients, is often incomplete and difficult to administer in outpatients. A delay of 24-hr before definitive diagnosis further adds to the cost of the patients.[7-11] Some authors have even reported that 24-hr urine collection test is unreliable in up to one-third of cases due to incomplete urine collection.[12,13] Unfortunately the other most widely used screening test for proteinuria-the dipstick test, has also been found to be fraught with error and correlates poorly with 24-h urine protein excretion.[14-17]

There remains therefore 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 samples for detection of proteinuria compared to those of a 24-hr samples in patients with diabetic nephropathy and also to determine the optimal cutoff for P:C ratio with best sensitivity and specificity for prediction of significant proteinuria.

MATERIALS AND METHODS

One hundred forty four patients aged 30-70, attending a Kantipur hospital who were diagnosed as diabetic were recruited in this study. The diabetic status was defined as per the American Diabetes Association (ADA).[18] The study was undertaken for six months, from September 2008 to February 2009. The demographic data of patients including age, sex, body weight and height were obtained. 24-hr urine was collected from all participants. Participants were also instructed to collect un-timed spot

urine on the next day after the 24-hr urine collection. Informed consent was taken from all participants. Urine samples were collected at room temperatures without adding any preservatives. No specific recommendations were made about fluid intake, physical exercise or dietary protein intake. Women during menstruation period were not recruited for this study.

The adequacy of the 24-hr urine collection was assessed by comparing the total urinary creatinine in the sample with the predicted creatinine.

The predicted creatinine (mg/day) was calculated by- [28 - (0.2 × age in years)] × weight in kg for men and [23.8 - (0.17 × age in years)] × weight in kg for women. If the (predicted creatinine - measured creatinine)/predicted creatinine is >0.2, the sample was considered as incomplete collection and was excluded from analysis.[19]

The 24-hr urine was stirred to ensure homogeneity and volume was measured in graduated cylinder and 1 ml aliquot sample was obtained. Urine creatinine was measured by modified Jaffe's method[20] [accurex, biomedical]. Urine protein was measured by pyrogallol red modified fujita method[21] [chronolab sys S.L.]. All assays were performed, strictly adhering to standard operating procedures. The spot urine protein to creatinine ratio was obtained by dividing the urinary protein concentration by the urine creatinine concentration both expressed in mg/dl.

Statistical analysis: Statistical Package for Social Service (SPSS for window version; SPSS, 11.5, Inc., Chicago, IL) was used for statistical analysis. Spearman's rank correlation coefficient was used to show correlation between the spot urine p:c ratio and 24-hr urine total protein. Sensitivity, specificity and predictive values of the random urine P:C ratios at various cutoffs for prediction of significant proteinuria were estimated using the results from the 24-hr urine protein as the gold standard. A Receiver operating characteristics (ROC) curve was plotted and area under the curve was calculated.

Table-1: Sensitivity and Specificity of the P:C ratio at various cutoffs

Cutoff	Sensitivity	Specificity	PV + *	PV - **
(mg/mg)	(%)	(%)	(%)	(%)
0.12	95.6	45.4	42.3	96.1
0.13	95.6	58.2	48.9	96.8
0.14	95.6	69.1	56.4	97.4
0.15	95.6	74.5	61.1	97.6
0.17	91.3	74.5	60.0	95.3
0.19	86.9	74.5	58.8	93.2
0.02	82.6	74.5	57.6	91.1
0.22	82.6	76.4	59.4	91.3

*Predictive value of positive test, **Predictive value of negative test

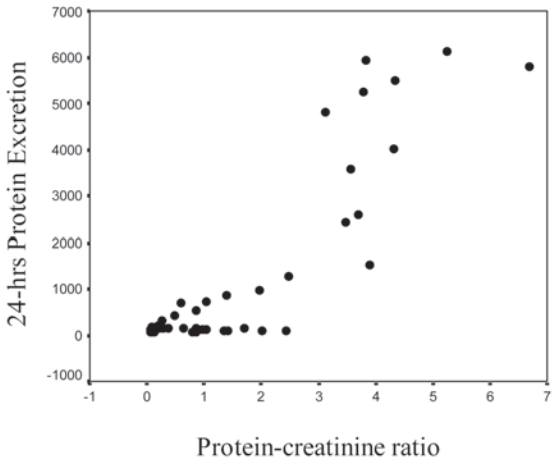

Fig.1. Scatter plot between 24 hrs urinary protein excretion and Spot urine protein creatinine ratio (r=0.892)

RESULTS

Among 144 subjects, 16 (11.5%) of urine samples were considered to be inadequately collected so excluded for analysis. In remaining 128 diabetic subjects (103 male and 25 female), 38 (29.0%) were found to have significant proteinuria by the gold standard, 24-hr urine protein estimation. A very good correlation was seen between the 24-hr urine protein and spot P:C ratio, with the Spearman's correlation (r) of 0.892 (Fig. 1).

The area under the ROC curve for random urine P;C ratio at various cutoffs is 0.88 (95.0% CI; 0.80-0.98 $p < 0.001$) (Fig. 2). Sensitivity and specificity of P:C ratio to detect proteinuria at various cutoffs is shown in Table-1. An excellent sensitivity of 95.6% and specificity of 74.5% were achieved to detect proteinuria at the P:C ratio cutoff greater than 0.15. With this cutoff, the positive predictive value was 61.1% and negative predictive value was 97.6%. At a cutoff 2.43, the specificity was 100.0% however the sensitivity drops to 52.2%, whereas at cutoff 0.07 the sensitivity became 100.0% limiting specificity only to 5.4%.

DISCUSSION

This study was conducted to evaluate the correlation between 24-hr urine protein and random urinary P:C ratio and to find the appropriate P:C cutoff for the prediction of significant proteinuria in diabetic subjects. Although some investigators advocate the use of albumin as an alternative to the total protein measurement[22-24] and others have suggested that the profile of protein

Table-2: Correlation of protein: creatinine ratio with 24-hr urine protein excretion shown in previous studies.

Author, year (Ref)	Correlation coefficient (r)
Ginsberg *et a*l, 1983 [10]	0.97
Houser *et al*, 1984 [27]	0.98
	0.97(ambulatory patient)
Schwab *et al*, 1987 [28]	0.98(hospitalized patient)
Lemann and Doumas, 1987 [29]	0.97
Boler *et al*, 1987 [9]	0.85(Normal pregnancy)
	0.95(Twin pregnancy)
	0.96(hypertensive pregnancy)
Ralston *et al*, 1988 [30]	0.92
Jachevatsky *et al*, 1990 [31]	0.92
Abitbol *et al*, 1990 [32]	0.95
Combs *et al*, 1991 [33]	0.98
Dyson *et al*, 1992 [34]	0.77
Mitchell *et al*, 1993 [35]	0.98
Quadri *et al*, 1994 [36]	0.92
Steinhauslin *et al*, 1995 [37]	0.93
Young *et al*, 1996 [38]	0.8
Robert *et al*, 1997 [39]	0.94
Sudan *et al*, 1997 [17]	0.93
Ramos *et al*, 1998 [40]	0.94
Evans *et al*, 2000 [41]	0.95
Rodriguez Thompson *et al*, 2001 [42]	0.8
Chitalia *et al*, 2001 [43]	0.97
Torng *et al*, 2001 [44]	0.79
Yamasit *et al*, 2004 [45]	0.95
Leung YY *et al*, 2006 [46]	0.91
Alfredo *et al*, 2007 [47]	0.98
Wahbeh *et al*, 2009 [48]	0.83

excreted has differential diagnostic and prognostic Value, [25] the National kidney foundation has recommended that an increased in protein excretion be used as a screening tools in patients at risk of developing renal disease.[26] Since a rapid and accurate test avoid the inconvenience of patients as well as delay in diagnosis, a spot P: C ratio was taken as a rapid tool in our study to correlate it with 24-hr protein.

A good correlation was seen (r =0.892) in our study like in many other previous studies as shown in Table-2.

The excretion of creatinine and protein is reasonably constant throughout the day when the glomerular

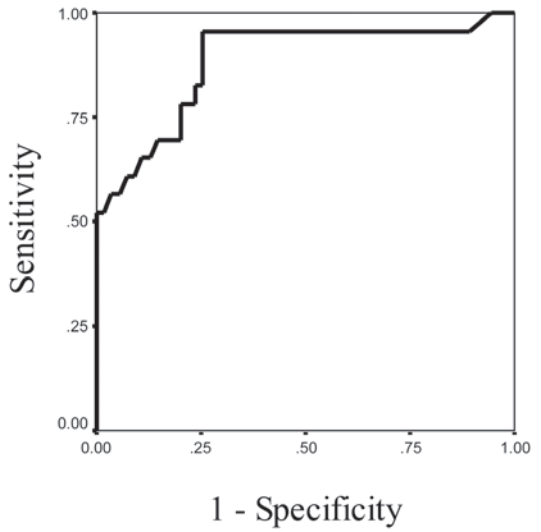

Fig.2. ROC curve at various cutoffs for the spot random urinary protein-creatinine ratio (The area under the curve was 0.88 (95% confidence interval 0.80–0.98; P<0.001)

filtration rate is stable.[10] The urine P:C ratio corrects for variations in urinary protein concentration due to hydration and is not affected by a decrease in urine output in patients with renal insufficiency. So, the numerical outcome of the urine P:C ratio in mg/mg is roughly equal to the 24-hr protein excretion in g/day/1.73 m^2 body surface area.

Though our results agree with most of the authors, but still there are some well known conflicting results. Some authors have reported only a medium correlation as shown in Table-3. These discrepancies are probably due to an increase in tubular secretion of creatinine in various rates in patients with established renal disease[53] and the interference of ketone bodies and some drugs in different creatinine assay method[54] adopted by various authors. We have taken the P: C cutoff value of 0.15 to find out the correlation. Similar cutoff was taken in the study of Young *et al*[38] and Mitchell *et al*[35]. The reference method cut off in **(**the study of Mitchell *et al* was taken as 150 mg/day whereas in the study of Young *et al* the reference method cutoff was taken as 300 mg/day.

We have taken the reference method cutoff as 150 mg/day. Because of the variability in laboratory methods for measuring proteinuria in different reported studies,

Table-3: Medium correlation shown between spot urine P:C ratio and 24-hr urinary protein excretion in previous studies

Author, year (Ref)	Correlation coefficient (r)
Lindow and Davey, 1992 [49]	0.53
Al *et al*, 2004 [50]	0.56
Durnwald and Mercer, 2003 [51]	0.64
Aggarwal N *et al*, 2008 [52]	0.596

Table 4: Various P:C ratio cutoff and reference method cutoff taken in previous studies.

Author, year (Ref)	Patient group	Reference method cutoff	P:C ratio cutoff
		(mg/day)	(mg/mg)
Ginsberg *et al*, 1983 [10]	Renal clinic	200	0.2
Ralston *et al*, 1988 [30]	Rheumatology clinic	300	0.35
Dyson *et al*, 1992 [34]	Renal transplant clinic	500	0.35
Mitchell *et al*, 1993 [35]	Elderly patient clinic	150	0.15
Quadri *et al*, 1994 [36]	Pregnant patient	300	0.3
Young *et al*, 1996 [38]	Pregnant patient	300	0.15
Robert *et al*, 1997 [39]	Pregnant patient	300	0.17
Sudan *et al*, 1997 [17]	Pregnant patient	300	0.26
Ramos *et al*, 1998 [40]	Pregnant patient	300	0.5
Evans *et al*, 2000 [41]	Pregnant patient	300	0.3
Rodriguez *et al*, 2001 [42]	Pregnant patient	300	0.19
Chitalia *et al*, 2001 [43]	Renal clinic	250	0.26
Torng *et al*, 2001 [44]	Renal transplant clinic	500	0.35
Durnwald and Mercer, 2003 [51]	Pregnant patient	300	0.3
Yamasit *et al*, 2004 [45]	Pregnant patient	300	0.19
Al *et al*, 2004 [50]	Pregnant patient	300	0.19

several cutoff points and different units for the urinary P:C ratio have been reported thereby precluding valid comparisons among such studies. The discrepancies shown above in the value of correlation coefficient also might be due to this heterogeneity of cutoff value adopted in different studies. reported studies, several cutoff points and different units for the urinary P:C ratio have been reported thereby precluding valid comparisons among such studies. The discrepancies shown above in the value of correlation coefficient also might be due to this heterogeneity of cutoff value adopted in different studies.

Not only the P:C ratio cutoff variation is seen in various studies but also the variations in reference method cutoff have been noted (Table-4).

In our study the ROC curve analysis showed an area under the curve of 0.88 indicating that the urinary P:C ratio is sufficiently accurate to predict significant proteinuria. At the optimal cutoff point of 0.15, the diagnostic performance was high with sensitivity and specificity of 96.65 and 74.4% respectively. The higher value found for sensitivity compared with specificity would suggest that the ratio test might be more valuable as a rule out test. Similarly the higher negative predictive value of 97.6% in comparison to positive predictive value of only 61.1% supports this tentative conclusion.

In conclusion, random P:C ratio is a good predictor of significant proteinuria in diabetic nephropathy. Since various studies have given their own reference method and P:C ratio cutoff , it is necessary to find out different cutoff (having optimal sensitivity and specificity) for different group of patients in our own laboratory settings to replace the gold standard method.

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