

# Comparison of Urinary Protein Creatinine Index (uPCI) and Dipsticks for the Prediction of Renal Dysfunction in Chronic Cigarette Smokers

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## ABSTRACT

**Background:** Proteinuria is recognized as one of the earliest sign of renal function deterioration in chronic smokers. Proteinuria occurs due to alteration in glomerular permeability and later due to failure of reabsorption of filtered protein by the tubular cells. Normally, most healthy adults excrete 20 – 150 mg of protein in urine over 24 hours. However, it is difficult to collect 24 hrs urine samples. **Objectives:** To advocate the use of PCI (protein creatinine index) in assessment of proteinuria and to compare dipstick result with PCI in the assessment of proteinuria in chronic cigarette smokers. **Material & Methods:** A total of 30 cigarette smokers and 40 age and sex matched controls were included for the study. A random specimen of urine collected from each cigarette smoker and non-smoker was tested quantitatively by manual sulfosalicylic acid colorimetric method for the estimation of protein concentration. Creatinine concentration in each specimen was measured by modified Jaffe's method and the urinary PCI was calculated. **Results:** Normal range of PCI which has been established in this study is 50 to 259. Significantly higher amounts of protein were found to be excreted in urine in chronic smokers ( $9.313 \pm 4.003$  mg/dl) as compared to healthy non smokers ( $7.738 \pm 2.05$  mg/dl). On comparison of PCI between healthy non smoker and chronic smoker subjects, PCI has been found to be significantly elevated in chronic smokers (healthy non smoker-  $118.32 \pm 56.86$ , chronic smoker-  $180.1 \pm 88.23$ ) ( $p=0.001$ ). **Conclusion:** PCI of random urine sample can provide a very useful, simple and convenient method for the quantitative assessment of proteinuria to confirm the advent of kidney damage, avoiding the drawbacks of 24 hrs urine collection.

**Keywords:** Proteinuria, PCI (Protein Creatinine Index) and dipstick

## INTRODUCTION

Cigarette smoking is increasingly being considered as a leading cause of morbidity and mortality worldwide. In recent years, smoking is known to have a negative impact on renal function as well. Nephropathy can be accelerated by nicotine present in tobacco smoke heralded by an increased incidence of microalbuminuria progressing to proteinuria.<sup>1</sup> Early detection of proteinuria can prevent serious renal complications in such individuals. Nicotine increases synthesis of fibronectin, which is a critical matrix component involved in the progression of chronic renal diseases.<sup>2</sup> Smoking induces a transient decrease in renal plasma flow and glomerular filtration rate.<sup>3</sup> These

small repeated episodes of transient renal hypoperfusion may damage some glomeruli which may result in hyperfiltration, together with capillary albumin leakage.<sup>4</sup>

Also, nicotine increases sympathetic activity (influencing blood pressure & renal hemodynamic) & chronic effects, particularly endothelial cell dysfunction. Nicotine directly stimulates catecholamine release from peripheral sympathetic nerve endings and adrenal medulla.<sup>5</sup> Increased sympathetic activity may also accelerate progression of glomerular dysfunction with an increase in incidence of microalbuminuria progressing to proteinuria.

Deterioration of renal function in smokers is preventable by the diagnosis of proteinuria at early stage.

In recent years, dipsticks have been developed for the detection of proteinuria which are claimed to be more convenient and sensitive as compared to the qualitative tests.<sup>6</sup> Urine dipsticks yield semi – quantitative results. It has been found by many researchers that dipstick tests are too insensitive to quantitate microalbuminuria. In

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Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530/ami.2015.1.16	

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these situations, the quantitative assessment of urine protein becomes necessary.<sup>7</sup>

The most accurate method considered for detection of microproteinuria is the measurement of protein content in 24 hours urine. An excretion of more than 150 mg/24 hours is considered as abnormal.<sup>8</sup>

Urinary protein creatinine index (PCI) has been devised as a simple alternative to 24 hrs urine collection in which the concentration of protein and creatinine in a random urine specimen are determined.<sup>9</sup> Urinary PCI can detect even minor increase in protein excretion in a random urine specimen.<sup>7</sup>

## MATERIAL & METHODS

### Selection of Controls & Cigarette Smoker

In the present study, 30 cigarette smokers aged 20 to 30 years were selected, who were confirmed by taking their history; selection criteria for cigarette smoker was a history of smoking for at least one year regularly & consuming minimum of 10 cigarettes per day. The cigarette smokers were selected from the general population of Teerthanker Mahaveer Medical College and Research Centre, Moradabad. 40 normal healthy subjects' age and sex matched with the cigarette smokers were selected as controls.

The individuals with any history of diabetes mellitus, hypertension, cardiovascular disease, pulmonary disease and any other concomitant diseases that may alter urinary protein excretion were excluded from this study. Also, individuals with any abstinence from smoking even for a brief intermittent period were ruled out.

Qualitative test for urinary protein detection was done by Heller's nitric acid test,<sup>10</sup> heat coagulation test<sup>10</sup> and sulfosalicylic acid test. Spectrophotometric estimation of urinary creatinine was done by modified Jaffe's method,<sup>11</sup> estimation of urinary protein by urinary dipstick method and estimation of urinary protein by spectrophotometric sulfosalicylic method.<sup>11</sup>

### Calculation of Protein Creatinine Index<sup>11</sup>

Urinary PCI was calculated by the following equation as proposed by Shaw et al.

$$\text{Urinary PCI} = \frac{\text{urinary protein (mg/L)}}{\text{urinary creatinine (mmol/L)}} \times 10$$

### Statistical Analysis

Normal range of urinary PCI was calculated from the data obtained from urine sample from normal healthy subjects. Since the distribution was non- Gaussian, a non- parametric

method was used to determine the normal range. The 95% range (2.5<sup>th</sup> to 97.5<sup>th</sup> percentile) was taken as the reference range. Student's t- test was used to compare urinary protein, urinary creatinine and PCI of normal healthy controls and chronic smokers.

## RESULTS

### Calibration Plot for Creatinine and Protein

Figure 1 shows the calibration plot for creatinine. Creatinine concentration ranged from 0.442 to 3.54 mmol/dl and the graph was found to be linear.

Figure 2 shows the calibration plot for protein. Protein concentration ranged from 6.5 mg/dl to 32.5 mg/dl and the graph was found to be linear.

The mean level of urinary protein ( $9.313 \pm 4.003$  mg/dl) and urinary creatinine ( $0.611 \pm 0.264$  mmol/dl) of chronic smokers show significant difference from that of healthy non smokers.

Frequency distribution curve for urinary PCI of normal individuals showed a non – Gaussian distribution of observations. The PCI established in this population was 50 to 259 (Figure 3).

Higher values of PCI were recorded for chronic smokers as compared to healthy non smokers. These high value of PCI in chronic smokers were found to be statistically significant ( $p = 0.001$ ).

Seven out of 30 (23.33%) chronic smokers were found to have urinary PCI value greater than the established normal range.

## DISCUSSION

Smoking is one of the most important modifiable renal risk factors. Early detection of proteinuria in chronic smokers may help in preventing reversible renal damage in chronic

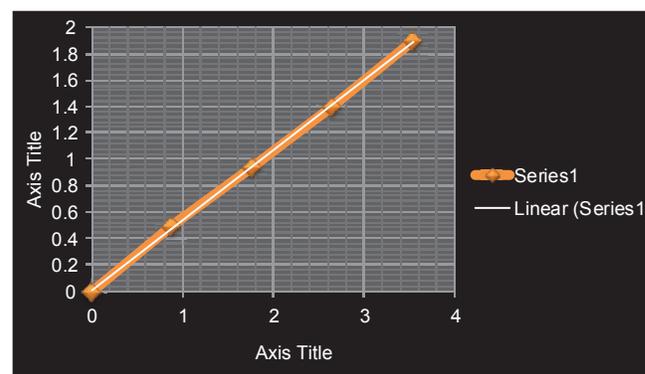


Figure 1: Calibration curve for creatinine

smokers. Well documented tests for the diagnosis of proteinuria have been the timed collection of urine over 24 hours.<sup>12</sup> However, collection of 24 hour urine sample is inconvenient as it is subjected to errors, if the patient's compliance is poor.<sup>13</sup> In an attempt to fulfill the need for a reliable and quick measurement of urinary protein various researchers have proposed the calculation of urinary protein/urinary creatinine, urinary albumin/urinary creatinine and PCI on spot urine samples.<sup>14</sup> Measurements of these ratios are based on the fact that creatinine excretion remains fairly constant in an individual with a stable GFR, thus eliminating the variation in urinary protein concentration during the day. The results of proteinuria obtained from these parameters shows strong correlation of that calculated from 24 hours urine sample. But, no universally acceptable reference interval for PCI has been obtained.<sup>15</sup> Hence, an attempt has been made in this study to validate PCI as an important tool to assess the extent of proteinuria.

The outcomes from the study are as follows.

### Urinary Protein Excretion

The mean urinary protein concentration found in the chronic smokers group was  $9.313 \pm 4.003$  mg/dl in the healthy non smokers groups was  $7.738 \pm 2.05$  mg/dl (Table 1). The protein excretion in random urine sample in chronic smokers group

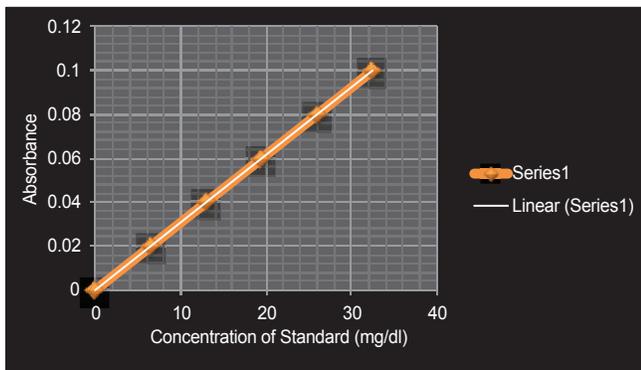


Figure 2: Calibration curve for protein

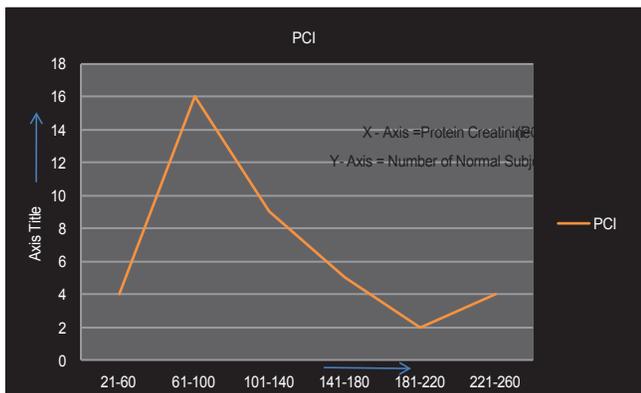


Figure 3: Frequency distribution curve for urinary protein – creatinine index (PCI) in healthy non smoker subjects

was found to be significantly higher in comparison to the healthy non smokers group with  $p=0.036$ . These findings are consistent with the results obtained by Shan Trushna et al (2013) as they have indicated that 99.9% of chronic smokers have higher microalbuminuria in comparison to that of non smokers.

Smokers are known to have small repeated episodes of transient renal hypoperfusion which may damage some glomeruli and may result in hyperfiltration together with capillary albumin leakage. Also, nicotine increases sympathetic activity (influencing blood pressure & renal haemodynamics) which causes glomerular dysfunction with increase in the incidence of microalbuminuria progressing to proteinuria. Some studies have reported that cigarette smoke contains glycotoxins, which increases vascular permeability leading to albuminuria.<sup>16</sup> Also, cigarette smoke contains carbon monoxide, which forms carboxy-hemoglobin, ultimately leading to ischemia in renal glomeruli and basement membrane causing microproteinuria.<sup>17</sup>

On the other hand, oxidative stress may be another cause of smoking induced renal injury. Increased release of glutathione via activation of HMP shunt is maintained in reduced state induced by the free radicals generated by the tobacco smoke.<sup>18</sup> The activity of glutathione peroxidase and superoxide dismutase also decreases which may ultimately culminate into renal insufficiency.<sup>19</sup>

### Urinary Creatinine Excretion

The amount of creatinine excreted in urine in chronic smokers ( $0.611 \pm 0.264$  mmol/dl) was comparable to that in the healthy non smokers ( $0.802 \pm 0.4117$  mmol/dl) (Table 2). The lower value of creatinine found in this study group as compared to other may be responsible for comparatively higher normal range (50 - 259) for PCI which has been established in the study.

### Normal Range of Urinary PCI in healthy non smokers

In this study normal range of urinary protein- creatinine index (PCI) in healthy non smokers (40) has been established by non – parametric method because of non- Gaussian distribution of data. In non – Gaussian distribution curve 95<sup>th</sup> (2.5<sup>th</sup> to 97.5<sup>th</sup> percentile) percentile was taken and the range of PCI was found to be 50 – 259.

### Urinary PCI

Significantly higher values of PCI were recorded for chronic smokers ( $180.1 \pm 88.33$ ) as compared to healthy non smokers ( $118.32 \pm 56.86$ ) with  $p < 0.001$  (Table 3). This indicated that spot urine protein: creatinine index can be used as baseline predictor of progression of renal dysfunction in chronic smokers. The significant change of PCI, may be due to

**Table 1: Comparison of urinary protein between chronic smokers and healthy non smokers by student's t- test**

Parameters	Healthy non smokers (n=40)	Chronic smokers (n=30)	p- value
Urinary protein (mg/dl)	7.738±2.05	9.313±4.003	0.36

**Table 2: Comparison of urinary creatinine between chronic smokers and healthy non smokers by student's t- test**

Parameters	Healthy non smokers (n=40)	Chronic smokers (n=30)	p-value
Urinary creatinine (mg/dl)	0.802±0.417	0.611±0.264	0.031

**Table 3: Comparison of urinary PCI between chronic smokers and healthy non smokers by student's t- test**

Parameters	Healthy non smokers (n=40)	Chronic smokers (n=30)	p-value
Urinary PCI	118.32±56.86	180.1±88.23	0.001

alteration in renal plasma flow (RPF) leading to deranged glomerular filtration in chronic smokers. Consequently, greater quantities of albumin and other solutes pass through the glomerular basement membrane. The advantages of calculating PCI is that errors due to improper collection of urine sample or due to inaccuracy in the timing of collection do not affect the index. In the present study it was seen that seven out of 30 chronic smokers (23.33%) had PCI > 259, thus indicating significant proteinuria in chronic smokers.

### Comparison of Dipsticks Result with PCI

The analysis of proteinuria by dipsticks showed moderate correlation with the calculated PCI. Dipsticks analysis for urinary protein shows false negative result of proteinuria in five cases out of seven cases of proteinuria with increased PCI. So, it is suggested that dipstick test be used only as a screening test and not for the assessment of severity of proteinuria, where as PCI can be used for both, for screening test as well as for the assessment of severity of proteinuria.

### CONCLUSION

The present study suggests that random urinary PCI can be used as a predictor of significant proteinuria in renal dysfunction in chronic smokers. It is therefore, recommended that PCI may especially be used for the assessment of microproteinuria in chronic smokers when usually a negative result is obtained by semi - quantitative dipstick test. PCI is thus, a simple, accurate and a low cost diagnostic tool for the detection of incipient nephropathy. But, since the creatinine excretion is different in different racial populations; it becomes essential to establish normal reference range in local population to predict the level of significant proteinuria.

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**How to cite:** Kapoor S, Mehta DK, Yadav S, Verma A, Mathur S. Comparison of urinary protein creatinine index (uPCI) and dipsticks for the prediction of renal dysfunction in chronic cigarette smokers. *Acta Medica International*. 2015;2(1):96-99.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

**Handling Editor:** Rohin Garg