



Prevalence of micro albuminuria and diagnostic accuracy of urine dipstick for the screening of diabetic nephropathy in type 2 diabetes patients



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ABSTRACT

Diabetic nephropathy can be early diagnosed by the detection of micro albuminuria in spot urine sample. Microalbuminuria can strongly predict the progression of renal diseases such as diabetic nephropathy among high risk population. Hypertension is a major factor which doubles the risk of renal failures. Urine dipstick method is a frequently used way for screening and evaluation of microalbuminuria so as to detect the early symptoms of diabetic nephropathy.

In this background, a case control study of total 200 subjects were studied. The patient reports were diagnosed with HbA1c levels, systolic and diastolic BP, blood sugar level and other renal parameters were recorded and compared with micro albuminuria levels. Diagnostic performance of the dip stick was expressed in terms of sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value). The statistical analysis was carried out using logistic regression analysis. The prevalence rate of microalbuminuria was higher in females when compared with males. There is no association of sex, HbA1c, diastolic bp, FBS with microalbuminuria in type 2 diabetes mellitus male subjects. The area under ROC curve for UACR (urine albumin/creatinine ratio) was 0.92 in microalbuminuria ($p < 0.001$).

Urine dipstick method can be used for the detection of diabetic nephropathy at an early stage. It has a good diagnostic accuracy when compared with the other expensive instruments. The prevalence rate of micro albuminuria was found to be 75% for the overall population, wherein the rate was significantly higher in the case of females (41.5%) when compared to males (33.5%).

1. Introduction

Micro albuminuria refers to the excretion of a protein called albumin through urine which ranges from 30 to 300 mg over a period of 24 h. The albumin, otherwise called as the urinary protein have been predicted as the initial indication of vascular destruction of kidney and heart. The kidney disease extremely related to heart disease as well as presence of micro albuminuria acts as a predictor for worse consequences of heart and kidney patients (Koroshi, 2007). The significance of micro albuminuria as a resourceful predictor of advanced renal disease and cardiovascular events was then recognized by several potential studies mainly among diabetic patients (Gerstein et al., 2001) and hypertensive patients (Wachtell et al., 2003). The relationship between micro albuminuria, cardiovascular disease and advanced renal disease has been well recognized in subjects suffering from systemic diseases comprising diabetes mellitus (Strippoli et al., 2004). Micro albuminuria seems to be

present at a very initial phase of diabetes mellitus (DM), a time when the glomerular filtration rate (GFR) might be normal and there will be no indication of any irregularity in the filtration by the glomerulus. Therefore micro albuminuria has been emerged as a candidate marker in the early stage of DM in order to identify the consequent advancement in the levels of proteinuria leading to diabetic nephropathy (DN) (Buch et al., 2012).

Diabetic nephropathy is known to be an apparent cause of chronic kidney disease (CKD) (American Diabetes Association, 2004) that devoid of an early intervention can result in end stage renal disease (Gokulnath et al., 2013). Micro albuminuria is the clinical evidence of diabetic nephropathy which has also become a powerful predictor for cardiovascular death even among healthy populations (Borch et al., 1999). In order to prevent the progression of DN among the primary health centers the screening of micro albuminuria is required (Silveiro et al., 1993; Pinho et al., 1996; Suraniti et al., 1992; Ohkudo et al.,

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1995). Based on various studies, it is essential to quantify micro albuminuria because of the evidence that the progression of DN can be reduced by the strict control of blood glucose level as well as blood pressure control (Lee et al., 1994; Parving et al., 1987; DCCT Research Group, 1993; UK Prospective Diabetes Study Group, 1998a; UK Prospective Diabetes Study Group Study 33, 1998b). The screening micro albuminuria is an easy method which is inexpensive too when compared to other laboratory procedures and also a prognostic procedure for DN. Further it guides as an applicable intervention by reducing the advancement of the disease. Dipstick is a cost effective procedure which is affordable by common people (Volpe, 2008). The routine check-up of micro albuminuria levels in diabetic patients will thereby alert the specialists to modify the ongoing preventive approaches in the health policies (Gokulnath et al., 2013).

The renal failure has been linked with the early change in the glomerular filtration rate, initial urinary albumin excretion rate (UAE), age and hyperglycaemia (Preneuf, 2011; Ninomiya et al., 2009). UAE was proved to be firmly associated with hyperglycaemia which was investigated by means of a cross-sectional study about type 2 diabetes mellitus (Ninomiya et al., 2009). Hyperglycaemia as well as high blood pressure studied among type 2 diabetes patients showed association in renal failure (Opie and Parving, 2002). A prospective study by Ohkudo et al. exhibited a reduced risk of diabetic nephropathy among type 2 diabetic mellitus patients who were under severe insulin treatment (Ohkudo et al., 1995; Anavekar and Pfeffer, 2004). A study conducted in 2011 revealed the prevalence of type 1 diabetes people as 63.9% whereas type 2 people had a prevalence rate of 25.3% while type 1 diabetes dominated in young children, type 2 disease was significant in Southern and Eastern India. 15.4% prevalence (11.1% of type 1 diabetes; 26.4% type 2 diabetes) previously had one chronic complication of diabetes like nephropathy, retinopathy, neuropathy and coronary disease (<http://www.icmr.nic.in/sites/default/files/reports/Executive%20summary>).

The techniques used for the measurement of micro albuminuria are both qualitative (semi quantitative) as well as quantitative. Qualitative (semi-quantitative) test for micro albuminuria screening can be confirmed if >95% of patients shows positive result in the screening test (Salah et al., 2002). The dip stick test for micro albuminuria is considered to be an easy, prompt, effective, efficient and consistent method for the screening in diabetic patients (Gokulnath et al., 2013). The method of testing by dipstick are inexpensive when compared with the laboratory procedures and can be more beneficial in the clinic and primary care centers due to the fact that results would be rapidly given to the patients rather to keep them wait for the laboratory reports. For this reason dipstick method are found to be accurate then it can also be considered as a useful indicator for micro albuminuria (Berry, 2003).

Sensitivity and specificity are the two important measures of accuracy which is used as a gold standard for most of the diagnostic tests. Most of the screening test aim to be 100% sensitive and specific. Though the diagnostic screening tests will be often accurate because of the occurrence of false positives and false negatives (Greenhalgh, 1997). Several studies have reported that type 2 diabetic patients of the South Asian population are more susceptible towards diabetic nephropathy and renal failures when compared with European population (Dixon et al., 2006). Hence, the current investigation intent to assess the diagnostic performance of the dipstick method in the screening of micro albuminuria and also to evaluate the probable relationship between micro albuminuria as well as hypertension among the south Indian population.

2. Materials and method

2.1. Patient information

The patient information were gathered from type 2 diabetes mellitus patients with a diabetic history of both less and more than 5 years. The

subjects for the study were recruited from the outpatient department of general medicine, Chettinad Hospital and Research Institute, Chennai. Ethical Committee approval was also carried out for the study (IHEC Proposal No366/IHEC/10-17). The written informed consent was attained from almost all the subjects who were enrolled for the study. The age group of both the male and female patients who were selected for the study was 28-70 years. The sample from the patients were collected and evaluated for a period of January 2017-January 2018. Overall 200 participants were counted in for the prospective study. The 200 participants were distributed into 3 different groups: Group A [Uncontrolled DM with a duration of more than 10 years (n = 90)], Group B [Controlled DM (n = 60)], Group C [Healthy participants (n = 50)]. The information of the participants included for the study were obtained by a standardized questionnaire which covered questions such as age, sex, hospital id, duration of diabetes, fasting blood sugar (FBS), systolic and diastolic blood pressure, serum creatinine, serum blood urea nitrogen (BUN) as well as haemoglobin A1c levels. Besides this for the ACR (albumin: creatinine ratio) test, 5 ml of blood specimen were also collected from the patients. By using creatinine and albumin measurements the ACR was calculated. The patients with complications such as urinary tract infection, heart disease and also with incomplete records were excluded from the study.

2.2. Method

The patients were instructed to collect the early morning urine sample also called as spot sample. Samples were tested by urine dipstick method for the detection of micro albuminuria as this study was done by DIRUI H12-800 MA (Changchun, Jilin 130012 P.R. China) test strips in random urine sample. The test strips can test albumin with micro content and reach a high sensitivity of 0.08 g/L-0.15 g/L, or 2 mg/dL hence behaving as an immunoturbidimetry. The urine test strips were dipped in the urine sample and was taken out quickly. The strips were stained with a blotting paper in order to remove the excess urine and later it was compared with colours displayed on the colour scale on the strip vial within 60 s. DIRUI H12-MA test strips is specifically used because it can determine the level of albumin in urine sample using a semi-quantitative method.

The test for micro albuminuria was considered to be positive if the colour of the reaction strip corresponded to 0.15 mg/l of micro albuminuria as shown in the colour chart on the product reference chart. The urine samples which showed positive results for micro albumin were tested consecutively for several days in order to confirm the result. A false positive or false negative results can appear due to the intake of a low or high fluid intake. The false negative results can be formed because of the residual quantities of strong oxidizing agents present in the urine collection container also if the strip is dipped in urine for a long time.

The confirmatory tests and the laboratory methods and values conducted as gold standards were standardized based on the manufacturer's instructions and other standard methods (Bradley and Saunders, 2001). The dipstick method accuracy for the detection protein, glucose, nitrite as well as red blood cells were also compared with the confirmatory tests and with the gold standards.

2.3. Statistical analysis

The statistical data were analysed by using SPSS. The sensitivity, specificity, positive as well as negative predictive values of the urine dipstick tests were calculated based on standard methods and cross tabulation tables used for pairs of dipstick positive test on trace (1+) as well as reference standard of ACR values for 30 mg/g or > 300 mg/g. The results were expressed in the form of means \pm standard deviation (SD). Moreover the qualitative parameters were expressed as percentages. *t*-test were used for the comparison between the three groups. By using micro albuminuria as a dependant variable and the other

parameters like duration of diabetes, age, fasting blood sugar (FBS), Blood pressure, serum creatinine, serum blood urea nitrogen (BUN) and haemoglobin A1c levels as independent variables a logistic regression analysis was done. The significance test were two tailed and a p-value less than 0.05 were taken as statistically significant.

3. Results

A total of 200 subjects studied involved 104 females and 96 males. Among the overall population 150 cases had type 2 diabetes mellitus studied under group A and group B, and had a prevalence rate of 75%. The clinical characteristics of all the participants involved in the study and subjects with controlled and uncontrolled DM are being summarized in Table 1. The prevalence rate of micro albuminuria was greater in the case of females (41.5% vs 33.5%) when compared with males. The group 3 patients who had uncontrolled DM was detected with micro-albuminuria by dip stick method. These patients have shown a significant increase in the systolic and diastolic blood pressure when correlated with the group 2 and group 1 patients ($p < 0.05$). Whereas the mean BMI in group 1 was 24.1 ± 3.1 , group 2 was 24.3 ± 3.4 and group 3 was 24.5 ± 2.6 . Results didn't show any significance among the three groups. The cholesterol values was also not statistically significant. Other clinical parameters such as fasting plasma glucose, concentration of HbA1c also indicated higher significance when compared with other two groups.

The diagnostic accuracy test of dipstick method was calculated using sensitivity and specificity test result. For the detection of micro albuminuria the sensitivity of standard dipstick test was compared with albumin/creatinine ratio. When hypertension was present the sensitivity was 95.33% and the specificity was 60.53%. The diagnostic accuracy of dipstick trace result for the detection of albuminuria, $ACR \geq 300$ mg/g) has been illustrated in Table 2. The ROC curve was obtained by plot at different cut-off point of urinary albumin to creatinine ratio in the random urine samples for the screening test of micro albuminuria is being illustrated in Fig. 1. The AUC value was 0.929 and has a $p < 0.001$ which is statistically significant. Most of the calculated specificity for the clinical testing strategies was between 90-100%, except the, number of men and women population. For all the tests the negative predictive value was reliably high.

Table 3 illustrates the logistic regression analysis results to evaluate the contribution of the clinical covariates in the presence of micro albuminuria in the male and female population. In both the cases Age, systolic and diastolic Bp, duration of diabetes, fasting blood glucose (FBS), glycated haemoglobin (HbA1c) was taken as independent variables and micro albuminuria was taken as dependent variable. The other risk factors except Age ($p = 0.25$), HbA1c ($p = 0.46$), Diastolic blood pressure ($p = 0.07$) and Fasting blood sugar ($p = 0.08$) among the male

Table 1
Demographic and clinical characteristics of control and patients.

Characteristics	Group A	Group B	Group C
N	50	60	90
Male/Female	24/26	25/35	42/48
Age in years	52.9 ± 5.3	53.6 ± 7.9	55.5 ± 6.0
Duration of diabetes	–	6.0 ± 4.2	10 ± 5.1
BMI(kg/m ²)	24.1 ± 3.1	24.3 ± 3.4	24.5 ± 2.6
FBS (mg/dl)	87.9 ± 8.9	161 ± 21.8	188 ± 25.1
Serum Creatinine	0.8 ± 0.15	0.9 ± 0.24	2.8 ± 2.7
HDL	45 ± 5.9	52.9 ± 5.7	52.4 ± 6.1
LDL	99.3 ± 18.0	120.1 ± 23.1	128.6 ± 27.5
HbA1c (%)	5.6 ± 0.3	7.2 ± 0.8	11.2 ± 1.3
ACR (mg/g)	20.5 ± 0.2	35.0 ± 5.1	73.1 ± 10.1
Systolic Bp (mm Hg)	123 ± 12	130 ± 11	150 ± 5.2
Diastolic Bp (mm Hg)	70 ± 3.5	75 ± 4.2	92 ± 3.0

All the values are expressed as mean \pm SD; BMI: Body mass index, FBS: fasting blood glucose, HDL: high-density lipoproteins, LDL: low-density lipoproteins, HbA1c: glycated haemoglobin, ACR: albumin: creatinine ratio.

Table 2

Accuracy of dipstick urinalysis test result for the detection of $ACR > 300$ mg/g.

	Sensitivity	Specificity	PPV	NPV
Overall	97.67	39	89.0	90.0
Population	(87.7–99.9)	(24.0–56.6)	(82.1–93.4)	(83.2–94.2)
No: of Women	79.07	97.37	62.5	97.6
	(64.0–90.0)	(82.3–99.4)	(30.0–86.6)	(95.8–98.7)
No: of Men	74.42	97.37	75.9	97.2
	(58.8–86.5)	(86.2–99.9)	(31.1–95.6)	(95.4–98.3)
Incidence of hypertension	95.35	60.53	26.3	98.9
	(84.2–99.4)	(43.4–76.00)	(17.7–37.2)	(96.8–99.6)
Absence of hypertension	81.40	92.11	53.4	97.8
	(66.6–91.6)	(78.6–98.3)	(27.7–77.4)	(95.9–98.8)
Incidence of Micro albuminuria	95.3	60.53	21.2	99.2
	(84.2–99.4)	(43.4–76.00)	(15.3–28.6)	(96.7–99.8)
Absence of Micro albuminuria	88.3	89.4	48.3	98.6
	(74.9–96.1)	(75.2–97.1)	(26.8–70.3)	(96.8–99.4)

PPV: positive predictive value, NPV: negative predictive value.

population showed a significant association with microalbuminuria. The systolic blood pressure both in male and female showed statistically significant results whereas diastolic blood pressure was not statistically significant in males but females showed significant results which means the hypertension is related with the presence of micro albuminuria in the female diabetes patients ($p < 0.05$) when compared to male diabetes patients.

4. Discussion

In the recent years there have been a substantial increase of diabetes mellitus all over the world (<http://www.idf.org/diabetesatlas>). The indicated problem have currently become a global endemic which is linked with other diseases such as cardiovascular disease, renal disease and hypertension (Amo et al., 1997). Early detection of patients with arterial hypertension among a larger population is vital in order to avoid the organ damage (who show an increased risk of cardiovascular morbidity and mortality) (Zeller et al., 2005). The large prevalence rate of the microvascular complications of diabetes for instance diabetic nephropathy means the subjects with end stage renal disease by the cause of diabetes too will intensely increase (Ritz et al., 1999). Therefore diabetes specifically type 2 diabetes has become the main cause for the patients to switch to renal replacement therapy (Ritz and Orth, 1999; Parving, 2001).

The incidence of microalbuminuria among the South Asian men and women was amplified by 1.2 and 1.7 fold which is reliable with the earlier reports from a comparatively small group of south Asian patients in the UK. The glycaemic control was known to be considerably worse in South Asians when compared with Europeans providing a probable justification for their greater prevalence of microalbuminuria. It has been anticipated that microalbuminuria is a constituent of the insulin resistance syndrome and it has been established that South Asian people reveal classical features of this entity, such as glucose intolerance, hyperinsulinaemia and lipid instabilities. Given the significance of microalbuminuria as a predictive marker for morbidity and mortality additional work is vital in order to know the causes for high risks of renal diseases in this population so that the inevitable advancement of end stage renal disease can be avoided. The scrutiny of these risks should thereby comprise of an evaluation of genetic markers, which may contribute in an understanding of diabetic nephropathy in all ethnic groups (Mather et al., 1998). The distinct ethnic differences can also be a reason for the higher prevalence in females when compared to males. The difference in the prevalence rate can also happen because of the selection of samples or because of certain differences in the population.

A study by United Kingdom prospective diabetes study (UKPDS) on diabetes mellitus revealed the existence of hypertension as a risk factor

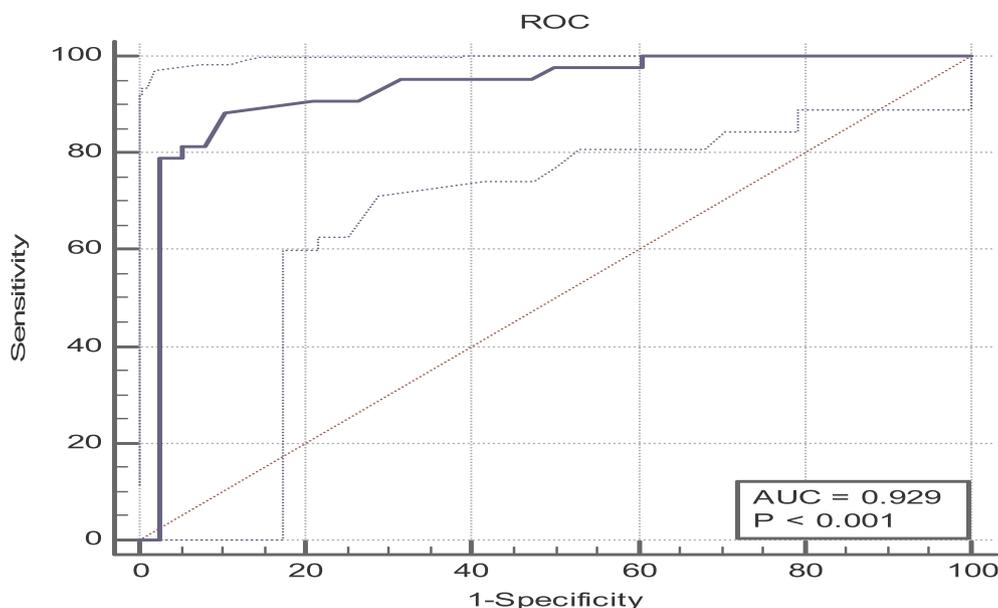


Fig. 1. ROC curve showing the cut-off point of urinary albumin to creatinine ratio of urine samples for the screening of micro albuminuria.

Table 3

Logistic regression analysis of independent variables with micro albuminuria.

Variables	Odds ratio	95% CI	P value
Subjects			
Female (N = 104)			
Age	0.88	0.79–0.99	0.03
Duration of diabetes (years)	1.3	1.10–1.56	0.002
Systolic blood pressure (mm Hg)	1.07	1.01–1.13	0.01
Diastolic blood pressure (mm Hg)	1.04	1.00–1.07	0.02
FBS(mg/dl)	1.05	1.00–1.10	0.03
HbA1C (%)	2.99	1.32–6.79	0.008
Males (N = 96)			
Age	0.94	0.86–1.03	0.25
Duration of diabetes (years)	1.32	1.11–1.58	0.001
Systolic blood pressure (mm Hg)	1.06	1.00–1.12	0.02
Diastolic blood pressure (mm Hg)	1.03	0.99–1.06	0.07
FBS(mg/dl)	1.03	0.99–1.08	0.08
HbA1C (%)	1.23	0.69–2.20	0.46

FBS: fasting blood glucose, HbA1c: glycated haemoglobin, OR: Odds ratio, CI: Confidence interval.

of micro albuminuria and retinopathy thereby decreasing the occurrence of persistent complications was linked with the high amplitude of decreased systolic blood pressure (Alder et al., 2000). A poor glycaemic control and blood pressure was found to be associated with micro albuminuria. Now even a very small amount of albumin present in the urine can indicate severe future events, like elevated systemic blood pressure, cardiovascular disease and advancement of renal dysfunction (Hillege et al., 2002; Ruggenti and Remuzzi, 2006). Micro albuminuria is a marker which can indicate the damage of kidney caused as a result of prolonged diabetes mellitus (Verhave et al., 2004).

A previous study have proposed that there is an inconsistent reverse correlation concerning the glucose and urinary albumin-to-creatinine ratio (UACR) in women with early diabetes or hypertension, who were not on medications, and whose blood glucose as well as blood glucose levels were seen to be slightly elevated. The indicated paradoxical reverse correlation between UACR glucose and was not detected in men. Hence, it can be assumed that in women diagnosed with early diabetes or hypertension or a certain remunerative mechanism in the renal proximal tubule which is known to play a role in adjusting the plasma glucose levels and such a compensatory mechanism may take place only

in women because of estrogen. Animal studies have proposed that estrogen play a part in the destruction of renal function in the chronic kidney disease and in the protection contrary to renal aging in cases of oxidative damage (Jang et al., 2015, AlFehaid, 2017).

The screening tests have proved to have high detection rates for abnormal samples. It is sufficient due to high sensitivity and high positive predictive value. A range of potential clinical testing approaches by means of laboratory ACR or urine dipstick measurements, subsequent and preliminary positive dipstick test had related or lower sensitivity linked to the sensitivity of a single dipstick test, and remained commonly linked with more number of repeat tests compared with the reference testing strategy. Urine dipstick is an easy as well as accurate technique used for the detection of micro albuminuria which can compared with the albumin creatinine ratio in a spot urine sample. The screening of micro albuminuria with DIRUI H12-MA test strips is comparatively fast, cheap and is proved to have an adequate and accurate sensitivity and specificity. These strips have been developed with a new chemical method to test the micro albumin in urine. These strips can test the albumin with a micro content and reach high sensitivity of 0.08 g/L–0.15 g/L or 2 mg/dL behaving as an immunoturbidimetry.

The semi-quantitative urine protein-to –creatinine (P/C) ratio is clinically relevant and is based on its enhanced sensitivity and screening capability for substantial proteinuria than other laboratory techniques. The common laboratory test for proteinuria detection is urine dipstick. Nevertheless the detection outcomes of urine protein could be undervalued for the variation in urine samples. The concentration or dilution due to extreme liquid consumption similar to the water ingestion former to the test is one main factor which affect the variation of urine samples. In order to resolve this problem the urinary creatinine level was measured and the urine protein-to –creatinine ratio was considered to be correct for the difference in urine samples. The protein-to –creatinine was revealed to have adequate sensitivity and specificity comparing with the 24 h urine protein testing. It was also established that the urine P/C ratio assessed by the semi-quantitative method could be feasible and reliable in the health screening for chronic kidney disease (Chang et al., 2016).

The present study it was observed that patients having uncontrolled DM and micro albuminuria had a significantly higher hypertension when compared to controlled patents and control subjects. Results of our study are mostly similar to other studies which found the sensitivity and specificity values between 80–90% when relating with the results

obtained from the micral –test and results of the current study are alike to those attained by laboratory techniques.

5. Conclusion

In conclusion, micro albuminuria in diabetic condition represents an early phase in the progression of diabetic nephropathy which is also associated with many potential modifiable risk factors. Hence micro albuminuria can be considered to be a potential marker indicating early renal damage in uncontrolled female diabetic mellitus patients. Dipstick method can also be considered as a cheap and accurate method to detect presence of micro albuminuria at an early stage of renal complications.

Conflicts of interest

All the authors declare that there is no conflict of interest.

Ethical approval

This study protocol was approved by the ethics committee of the Chettinad Hospital and Research Institute and the IHEC Proposal No was 366/IHEC/10–17. The informed Consent was obtained from all the patients for the study.

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