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STUDY OF MICROALBUMINURIA AND SERUM CREATININE IN HYPERTENSIVE PATIENTS AS EARLY INDICATOR FOR RENAL DISEASES

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ABSTRACT

Introduction: Renal damage occurs in maximum case of hypertension. It may be 100% prevalent when duration is more than 10 yrs and gets accelerated when there is simultaneous presence of other metabolic syndromes like DM-2, insulin resistance and obesity. If Kidney damage is detected in early stage with progression to end stage of renal disease drug treatment can be decided. **Methodology:** The Blood and Urine sample of 50 hypertensive patients with HTN were collected from OPD, Dawadmi Hospital and Health Centers, Dawadmi KSA for determination of serum creatinine and ACR respectively. **Result:** Hypertensive patients as having more than normal serum creatinine level have high value of UACR thus we can say that increment in serum creatinine level is advance stage of renal damage. **Conclusion:** The study concludes that hypertensive patients are more prone to renal damage which can be efficiently diagnosed by microalbuminuria than serum creatinine assessment which is extensively used in other countries and can be used frequently for the better management of the Renal diseases.

KEYWORDS: Microalbuminuria, Creatinine, hypertensive and renal diseases**.**

1. INTRODUCTION

Hypertension (HTN) also known as high blood pressure, is a long term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure may increase the risk of heart, kidney and eye disorders.[1,2] HTN is a major public health problem in the worldwide. The incidence of hypertension in Saudi Arabia is 5-15% in adult population against 10-12% in European countries.[3,4] Renal dysfunction occurs in most of hypertensive cases.[4,5] It may be 100% prevalent when duration is more than 10 yrs and gets accelerated when there is simultaneous presence of other metabolic syndromes like Type 2 DM, Insulin resistance and obesity.[6, 7]. Detection of kidney damage in early stage can prevent the progression to end stage of renal disease and helpful to choice of treatment.[8] Renal failure is a condition where kidney looses their normal functioning and is characterized by the reduction in the excretory and regulatory functions of kidneys.[9] Renal damage may be assessed by imaging techniques, substance accumulation, clearance techniques, urine analysis, and microalbumin quantification. Among these substance accumulation and microalbumin quantification are the easy and feasible markers of early renal damage which indicates the presence of proteinuria.[8, 9] An abnormally high amount of albumin excretion in urine is an important risk factor for identifying kidney disease.[10] Microalbuminuria is prevalent in 25-100% patients with hypertension.[1, 11, 12, 13] Creatinine has also found to be fairly reliable indicator of kidney function, any impairment in kidney function will result in rise of blood creatinine level due to poor clearance by the kidneys.[14] In present scenario substance accumulation is used as a routine procedure while microalbuminuria is an independent predictor of mortality in patients with essential Hypertension.[15, 16, 17] This is strongly correlated with severity and duration of Hypertension.[18] Screening of microalbuminuria requires either collection of 24 hrs urine or determination of albumin/creatinine ratio in spot urine sample. It is found that albumin/creatinine ratio didn't provide any advantage compared with microalbumin measurement alone.[19] The measurement of blood creatinine, and proteinuria are relatively insensitive and show abnormalities when the disease process is advanced. Very few studies previously reported on hypertension in KSA. The most recent estimates date back to 2005 and provided a prevalence of 11.5% of reportedly diagnosed hypertension, among individuals aged 15–64 years, a much higher prevalence than 5.6% from our study. Data from 1995–2000 for Saudis aged 30 years or older showed a hypertension prevalence of 26.1%. In comparison, we found that 27.2% of those aged 30 or older had hypertension. There are several factors that could explain these differences. First, our study is national and applied standardized methodology for data collection. Second, we used weighted analyses to generalize our findings. However, the 2005 STEPS survey and our study should be comparable and possibly indicate a leveling of the hypertension prevalence in KSA.[63] The aim of present study is assessing the

relative importance of microalbuminuria and substance accumulation to understand whether it should be used as a routine procedure in evaluation of renal damage in hypertension in Saudi Arabian Population.

2. MATERIAL AND METHODS

The present study is a case control study conducted in Dawadmi, College of Medicine, Dawadmi KSA. The study comprises of 50 hypertensive subjects as study cases and age sex matched healthy controls. The Blood and Urine sample of 50 hypertensive patients with HTN were collected from OPD, Dawadmi Hospital and Health Centres, Dawadmi KSA for determination of serum creatinine and ACR respectively.

COLLECTION OF SAMPLE

2 ml of blood sample was collected in sterile vials and centrifuge for separating serum.

PRESERVATION OF SAMPLE

Separated serum was preserved in refrigerator at 2-8^{o}C until analysis.

PARAMETERS ESTIMATED

Serum Creatinine.
Urine Creatinine
Urine Microalbumin.
UACR

ESTIMATION OF SERUM CREATININE

Serum creatinine was estimated by alkanine picrate method of Jaffee (1977).

PRINCIPLE

Protein free solution of creatinine was obtained by precipitating step reacts with picric acid in alkaline medium to form an orange coloured complex, The Intensity of which is proportional to the amount of creatinine present in the sample and it is measured colorimetrically at 520 nm or with green filter.

REACTION

Creatinine (Protein free) + Picric acid $\xrightarrow{NaOH}$ Orange Coloured Complex

MATERIALS PROVIDED

Reagent 1- Picric acid
Reagent 2- 0.75 NaOH
Reagent 3- Stock Creatinine (150 mg/ dl)
To prepare working standard 0.1 ml reagent 3 was diluted with 10 ml of distilled water.

PROCEDURE

For De-Proteinisation.

Serum	1.0ml
Distilled water	1.0ml
Reagent 1	6.0ml

Mix well, keep in boiling water bath for 60 sec, cool under running tap water, centrifuge and filter.

FOR ESTIMATION

	Blank	**Test**	**Standard**
Filterate/ Supernatant	-	4.0ml	-
Working Standard	-	-	1.0ml
Distilled Water	1.0ml	-	-
Reagent 1	3.0ml	-	3.0ml
Reagent 2	1.0ml	1.0ml	1.0ml

Mix well and allow standing at room temperature for 20 min. Measure the absorbance of Blank, Test, Standard against distilled water, at 520 nm or green filter.

CALCULATION

$$\text{Serum Creatinine in mg \%} = \frac{\text{AT-AB X 3.0}}{\text{AS-AB}}$$

ESTIMATION OF URINE CREATININE

Urine Creatinine was estimated by alkanine picrate method of Jaffee (1977).

PRINCIPLE

Protein free solution of creatinine obtained by precipitating step reacts with picric acid in alkaline medium to form an orange coloured complex, The Intensity of which is proportional to the amount of creatinine present in the sample and it is measured colorimetrically at 520nm or with green filter.

REACTION

Creatinine (Protein free) + picric acid $\xrightarrow{NaOH}$ Orange Coloured Complex

MATERIALS PROVIDED

Reagent 1- Picric acid
Reagent 2- 0.75 NaOH
Reagent 3- Stock creatinine (150mg/dl)
To prepare working standard 0.1 ml reagent 3 was diluted with 10 ml of distilled water.

PEOCEDURE

For De-Proteinisation-

Diluted urine	1.0ml
Distilled water	1.0ml
Reagent 1	6.0ml

Mix well, keep in boiling water bath for 60 sec, cool under running tap water and centrifuge/filter.

FOR ESTIMATION

	Blank	Test	Standard
Filterate/ Supernatant	-	4.0ml	-
Working standard	-	-	1.0ml
Distilled water	1.0ml	-	-
Reagent 1	3.0ml	-	3.0ml
Reagent 2	1.0ml	1.0ml	1.0ml

Mix well and allow standing at room temperature for 20 min. measure the absorbance of Blank, Test, Standard against distilled water, at 520 nm or green filter.

CALCULATION

$$\text{Urine creatinine in mg/litre} = \frac{\text{AT-AB X 0.75}}{\text{AS-AB}}$$

ESTIMATION OF URINE MICROALBUMIN

It was estimated by Turbidimetric immunoassay based on agglutination reaction (1976).

PRINCIPLE

It is a turbidimetric assay for the detection of albumin in urine and is based on principle of agglutination reaction. The test specimen is mixed with the Activation Buffer (R1) and Anti Human Ab Solution (R2) and is allowed to react. Presence of albumin in the test specimen forms a turbidity, which is measured at wavelength 546 nm. The resulting turbidity corresponds to the concentration of albumin in the test specimen.

MATERIALS PROVIDED

R1- Activation Buffer
R2-v Anti Human Albumin
R3- Calibrator (100mg/dl)

PROCEDURE

Wavelength-546nm
Reaction temperature-37^{0}C.

Cuvette- 1 cm path length

	For Calibration	For Sam µL ple
R1	450µL	450 µL
R2	50 µL	50 µL

Mix well and incubate for 5 min

R3	10 µL	-
Sa µL mple	-	10 µL

Mix well and read absorbance at 10 sec (A1) and at 2 min(A2).

CALCULATIONS

$$\text{Concentration of Microalbumin in g/ l} = \frac{\triangle A \text{ Sample}}{A} \text{ X Conc. of Calibrator}$$

$$\triangle A = A2\text{-}A1$$

$$\text{UACR in mg/g} = \frac{\text{Urine Albumin (mg/dl)}}{\text{Urine Creatinine (g/dl)}}$$

3. OBSERVATIONS

Table- 1: Distribution of Hypertensive Patients According to Duration of Htn And Age.

DISTRIBUTION OF HYPERTENSIVE PATIENTS					
ACCORDING TO DURATION OF HTN			**ACCORDING TO AGE**		
Duration of HTN	**Number**	**Percentage**	Age	**Number**	**Percentage**
<4	23	46	**<30**	4	08
4-8	17	34	**30-40**	4	08
8-12	6	12	**40-50**	14	28
12-16	2	04	**50-60**	9	18
>16	2	04	**60-70**	13	26
-	-	-	**>70**	6	12

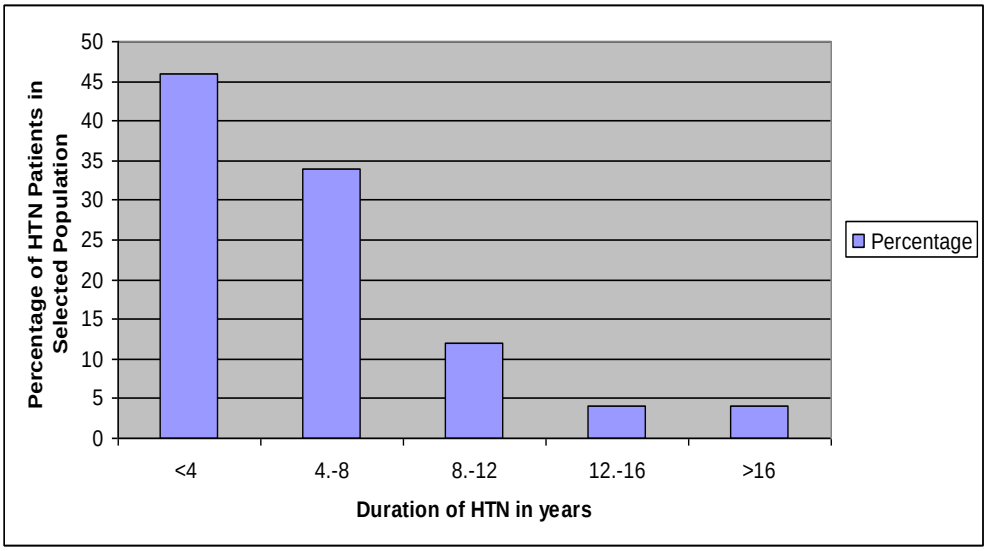

Figure-1: Maximum frequency of Hypertension patient fund with duration of less then 4 years.

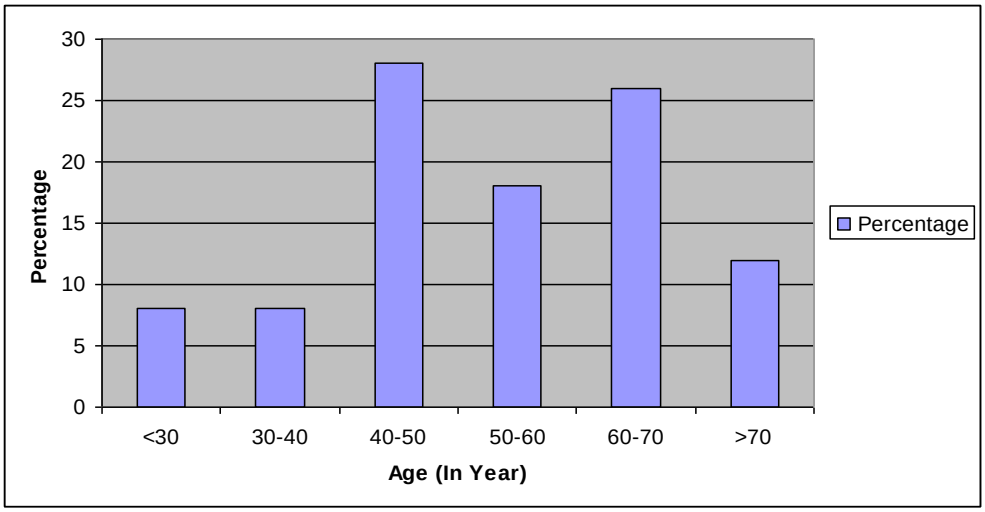

Figure-2: Maximum hypertensive patients belongs to age group 40-50 yrs.

Table-2: Distribution of Hypertensive Patients According to Serum Creatinine, Urine Creatinine and Urine Albumin.

Distribution Of Hypertensive Patients								
According To Serum Creatinine			**According To Urine Creatinine**			**According To Urine Albumin**		
Serum Creatinine	**Number**	**Percentage**	**Urine creatinine**	**Number**	**Percentage**	**Urine albumin**		
<.40	2	04	**<.30**	3	06	**<40**	40	80
0.40-0.80	14	28	**.30-.60**	12	24	**40-80**	3	06
0.80-1.20	24	48	**.60-.90**	28	56	**80-120**	5	10
>1.20	10	20	**.90-1.20**	6	12	**120-160**	1	02
-	-	-	**>1.20**	1	02	**>160**	1	02

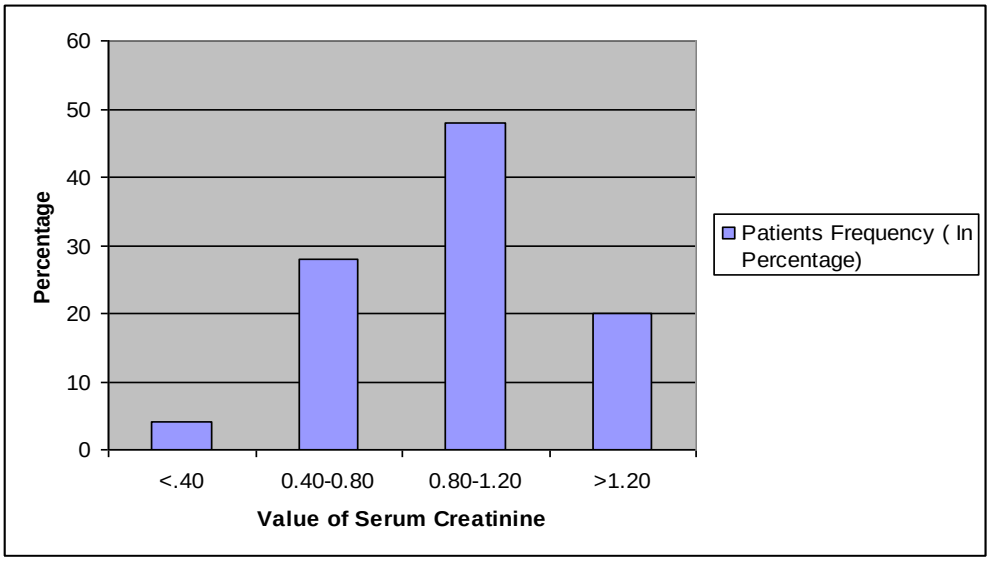

Figure-3: Maximum hypertensive patients have serum creatinine value 0.80-1.20 mg/dl.

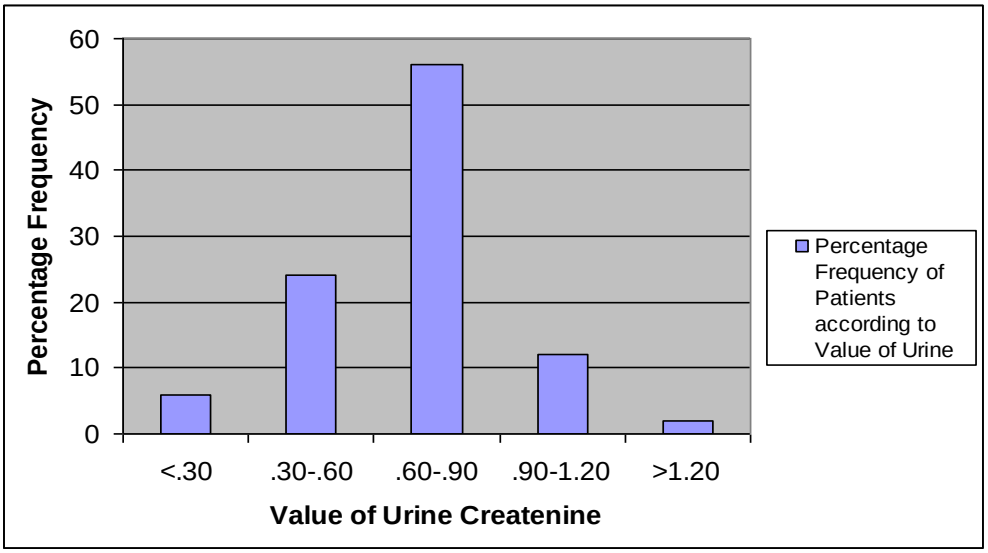

Figure-4: Maximum hypertensive patients have urine creatinine value in the range 0.60-0.90 g/ dl.

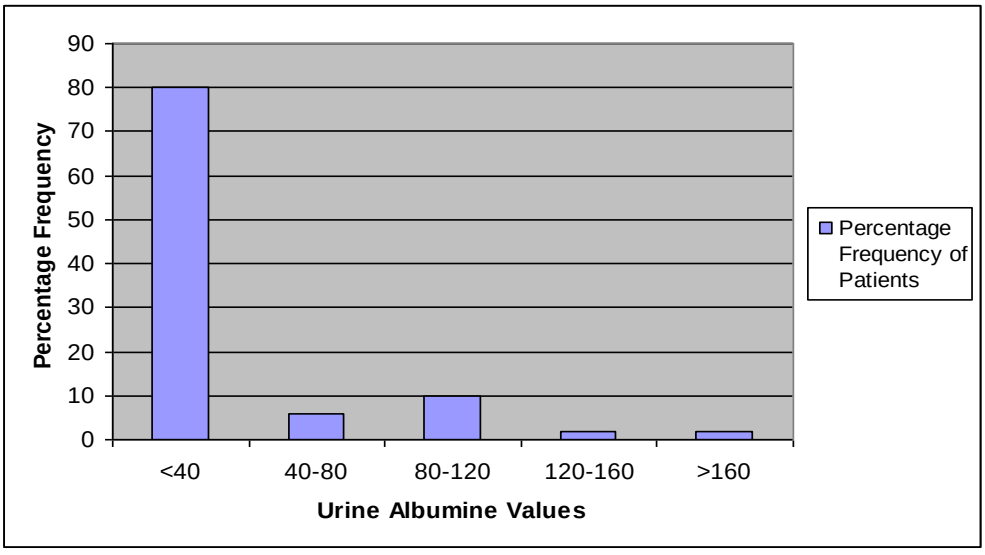

Figure-5: Maximum hypertensive patients have urine albumin <40 mg/ dl.

Table -3: Distribution Of Hypertensive Patients According To Type Of Hypertension

Stage of HTN	Hypertensive Patients		
	Male (In %)	Female In (%)	Total(%)
I	54	46	50
II	46	54	50

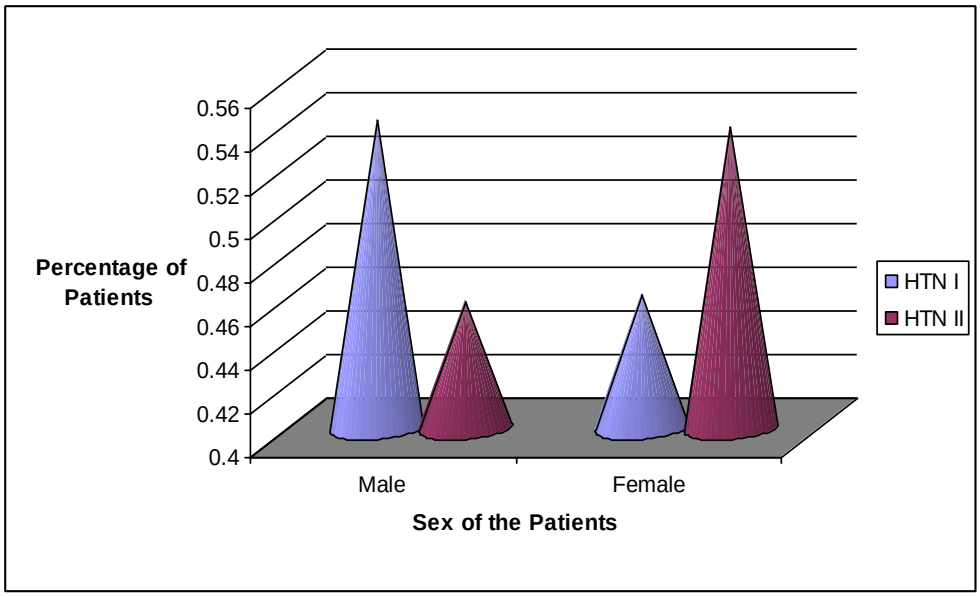

Figure-6: Type I and type II hypertension is equally prevalent among hypertensive patients, with proportion to 54:46 in male and 46:54 in female.

Table – 4: Correlation of Serum Creatinine, Urine Albumin and Uacr with Age, Duration of Htn and Type of Hypertension.

CORRELATION OF SERUM CREATININE, URINE ALBUMIN AND UACR WITH AGE			
Age	Mean Serum Creatinine	Mean Urine Alb	Mean UACR
<30	0.9425	22.7775	28.225
30-40	0.76	52.8	72.1075
40-50	0.9836	14.4864	23.10286
50-60	0.9478	39.871111	58.34556
60-70	0.8931	36.166	55.18294
>70	0.9567	43.84833	65.97833
CORRELATION OF SERUM CREATININE, URINE ALBUMIN AND UACR WITH DURATION OF HTN			
Duration of HTN	Mean Serum Creatinine	Mean Urine Alb.	Mean UACR
<4	0.8158	20.57	30.02654
4.-8	0.9379	15.416	22.79
8.-12	1.1714	60.13833	83.22167
12.-16	1.245	95	115.1
>16	1.345	147.865	230.4
CORRELATION OF SERUM CREATININE, URINE ALBUMIN AND UACR WITH TYPE OF HYPERTENSION			
Stage of HTN	Mean Serum Creatinine	Mean Urine Alb.	Mean ACR
I	1.018	36.66	53.568
II	0.8456	27.228	38.039

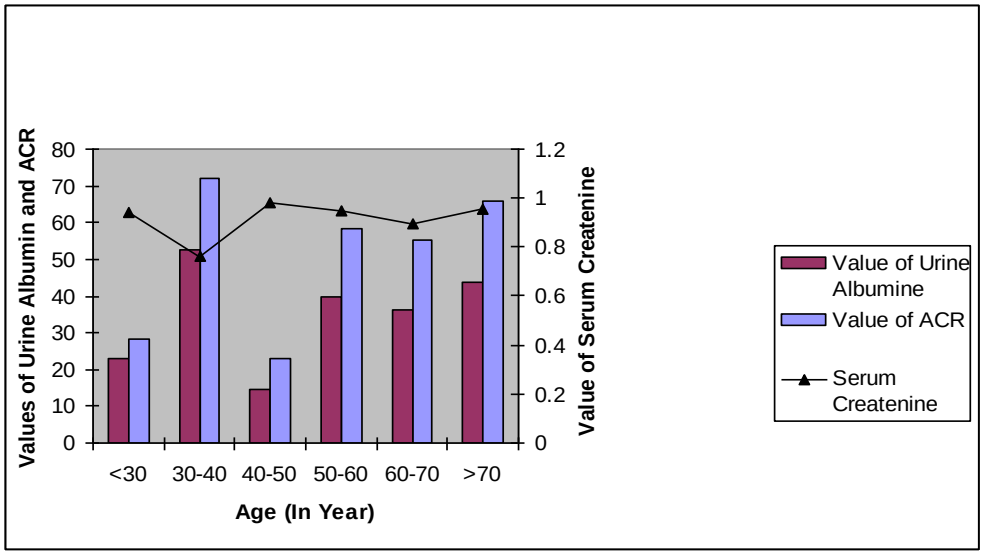

Figure-7: Serum creatinine urine albumin and UACR shows no correlation with age.

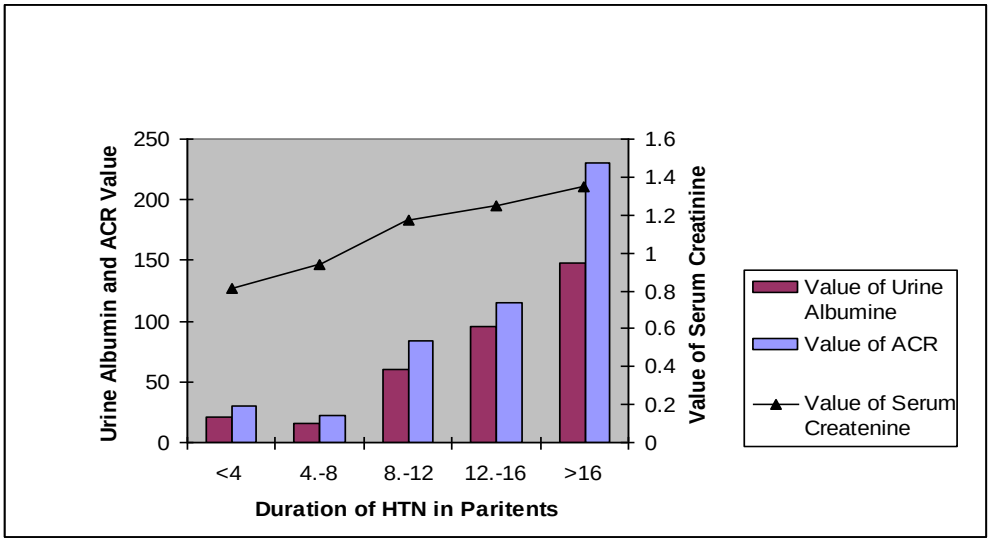

Figure-8: Serum Creatinine, Urine Albumin and UACR is increasing with Duration of HTN shows positive correlation with duration of HTN.

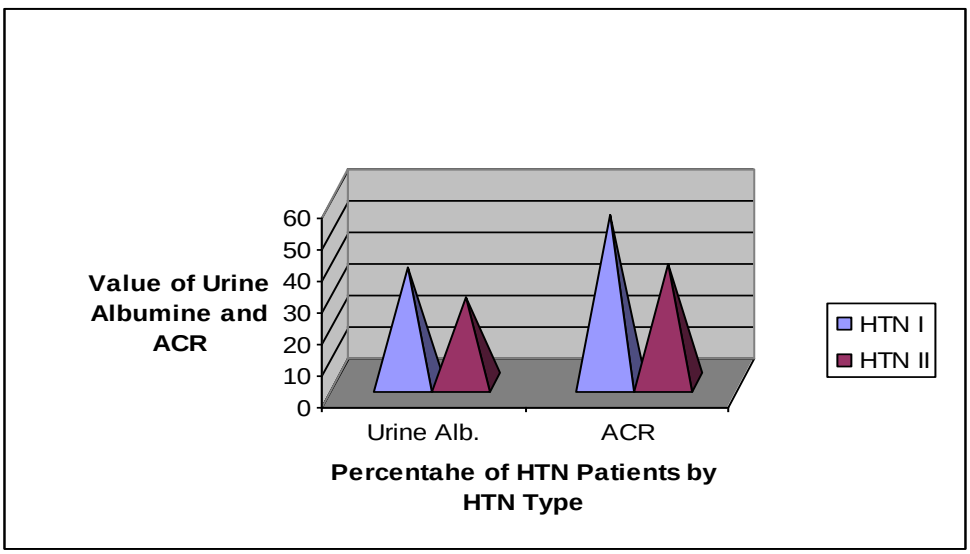

Figure-9: Serum Creatinine, urine albumin and UACR is found to be high in type I than in type II HTN.

Table – 5: Prevalence of Microalbuminuria In Hypertensive Patients, Duration of Htn, Age And Sex Ratio.

PREVALENCE OF MICROALBUMINURIA IN HYPERTENSIVE PATIENTS		
UACR	**Frequency**	**Percentage**
<30	36	72
30-300	14	28
PREVALENT DURATOIN OF HYPERTENSION IN HYPERTENSIVE PATIENTS MANIFESTED WITH MICROALBUMINURIA		
UACR	**DURATION OF HTN**	
<30	3.0416	
30-300	10.0178	
PREVALENT AGE IN HYPERTENSIVE PATIENTS MANIFESTED WITH MICROALBUMINURIA		
UACR	**Age**	
<30	53.916	
30-300	56.285	
SEX RATIO OF HYPERTENSIVE PATIENTS MANIFESTED MICROALBUMINURIA		
UACR	**Male**	**Female**
<30	44.44	55.56
30-300	57.14	42.86

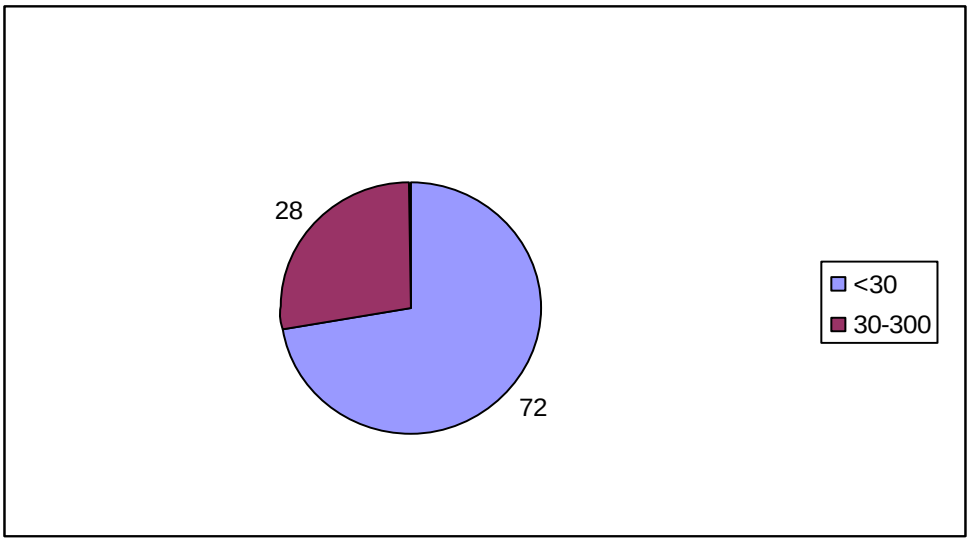

Figure-10: Microalbuminuria is 28% prevalent among hypertensive patients.

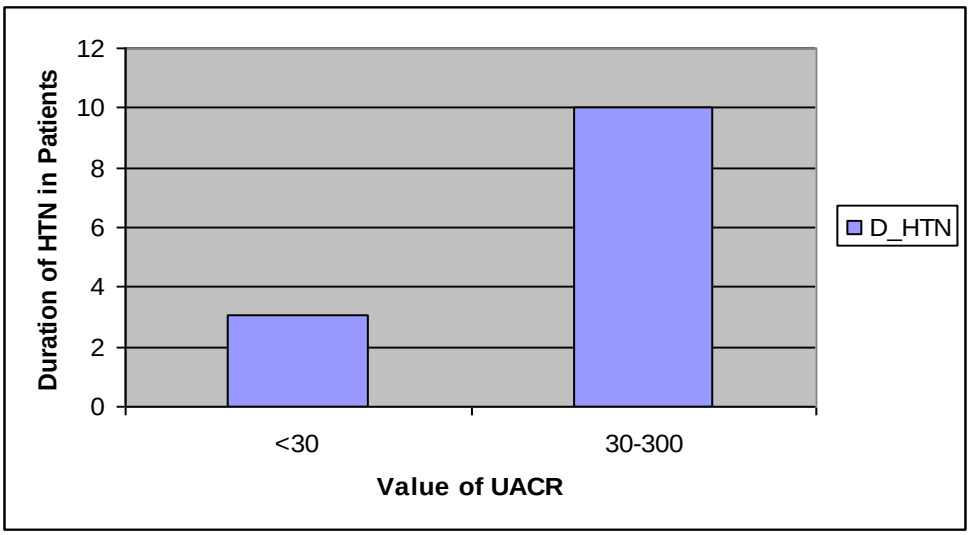

Figure-11: Hypertensive patients having duration of HTN more than 10 years are at increased risk of renal disease.

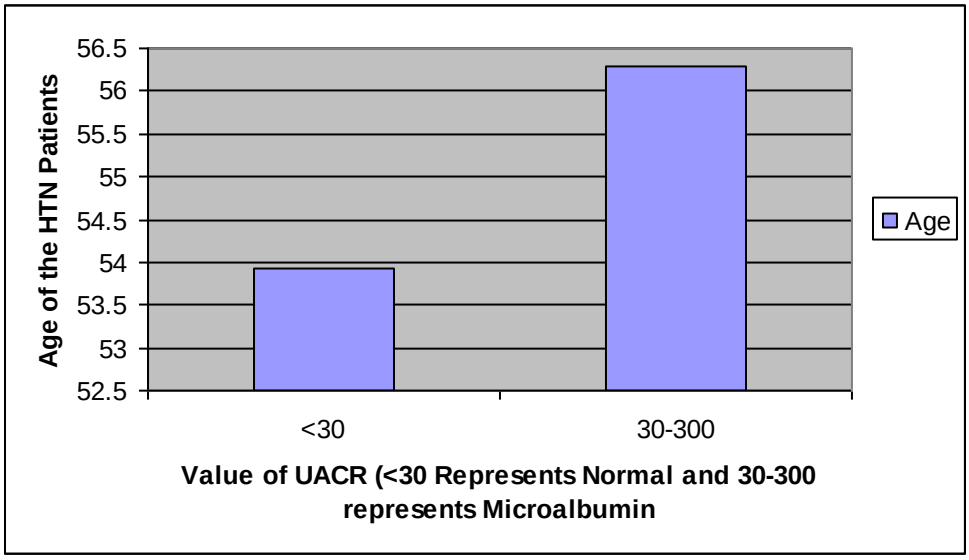

Figure-12: Mean age of hypertensive patients manifesting MAU is 56.295 yrs.

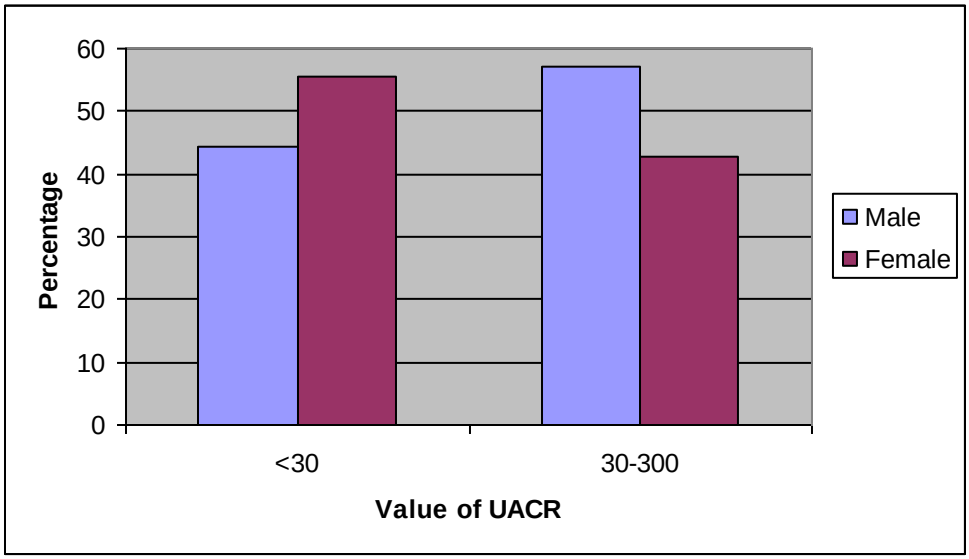

Figure-12: Percentage of microalbuminuric hypertensive males is high than females.

4. RESULTS

The present study is a case study conducted in Dawadmi, College of Medicine. Dawadmi KSA. The study comprises of 50 hypertensive subjects as study group, in which Serum Creatinine and Urinary Albumin Creatinine Ratio were estimated.

The study includes the patients with mean and standard deviation.

Variable	Male	Female
Age	59±13.48	51±13.73
Average BMI	22.56±3.26	26.95±4.42
Duration of HTN	5.61±5.08 yr	4.4±6.23 yr
Ser. Creat.	1.03±0.23	0.83±0.28
Urine Creat.	0.69±0.20	0.68±0.27
Urine Alb.	37.36±43.81	26.94±36.61
UACR	51.29±56.72	40.73±55.84

Maximum hypertensive patients belong to
Duration of HTN- less than 4 years
Age-40-50 years
BMI-20-26 Kg/m^2
Mean serum creatinine-0.80-1.20mg/dl
Mean UACR-<30mg/g
Mean urine creatinine-0.60-0.90g/di
Mean urine albumin-<40mg/dl

The following observations were noted

1. Correlation of Serum Creatinine, Urinary Albumin & UACR with Duration of Hypertension

Subjects were divided according to duration they are suffering from hypertension and their UACR was correlated with duration of hypertension. The study done by VK Sharma *et al*. Bhopal found a positive correlation of UACR with duration of hypertension. Our results supported the study we also found a positive correlation of UACR with duration of hypertension. Similarly serum creatinine and urine albumin were positively correlated with duration of the Hypertension.

2. Correlation of Serum Cretinine, Urine Albumin and UACR with stage of HTN

Higher value of serum creatinine, urinary.albumin and UACR was found in HTN-I than HTN-II.

3. Prevalence of MAU in hypertensive patients

We observed UACR 30-300 mg/ gm in 28 % patients that is in the present study prevalence of MAU among hypertensives is 28%.

Prevalence's observed by different authors.

Roberto Bigazzi *et al*. (1988)	40%
Robesto Pontremoli *et al* (1997)	6.7%
S. Jalal *et al* (2007)	37.5%
Steven J Chadban(2003)	2.4%
T Konta *et al* (2006)	17.8%

4. Prevalence of serum creatinine among hypertensive patients:

Serum creatinine exceeding 1.4 mg/dl was found in 10% hypertensive patients that are if it is taken as a measure for renal disease then only 10% hypertensive patients are showing renal dysfunctions. These 10% patients show higher values of ACR that means increase in serum creatinine is advanced stage of microalbuminuria.

Percentage of Microalbuminuric Hypertensive patients when assessed by spot UACR and Urinary Albumin alone

In our study we found that prevalence of MAU when assessed by spot UACR and urinary albumin is 28% and 22% respectively. The frequency of Urine Albumin and UACR is 78.57 % correlated.

Thus it is a better measure for routine diagnosis of renal dysfunctions. It will provide convenience and decreases; about the measuring urine creatinine values. Ulla Derhaschnig *et al*. (1985) also justify the use of albumin screening alone in place of ACR.

5. DISCUSSION

HYPERTENSION AND THE KIDNEYS

The kidney can be considered as both culprit and victim in hypertension process,[62] The kidney responds rapidly to changes in blood pressure by alteration of renal hemodynamics and sodium excretion. These functions of the kidney are reset in established HTN.[63] Deranged renal function contributes to the development of arterial HTN and of secondary vascular damage at the glomerulus and arteriolar level and accounts for the development of progressive nephrosclerosis. The most common alteration of renal function observed in humans from the early stages of essential HTN is the presence of renal vasoconstriction.[62]

MAU is commonly thought of as an important risk factor for identifying kidney disease. A number of studies strongly verifies the prevalence of MAU in HTN. MAU is associated with an increased risk for renal morbidity and mortality in patients with HTN.[64, 65, 66, 67, 68] Roberto bigazzi et al, 1988 (5) studies UAE in group of 123 patients with essential HTN and 40% of patients manifested a UAE exceeding 30 mg/24 hrs. Damsgaard et al, 1990 reported a higher prevalence of MAU in a group of 216 elderly hypertensive patients.[70]

Agewell et al (1993) reported an 23% prevalence of MAU in a population of hypertensive patients who were selected at high risk for cardiovascular disease.[71] Summerson et al, 1995 studies 190 patients with essential HTN and prevalence of MAU was found 32% in blacks and 14% in whites[69] Robesto pontrimoli et al, 1997 studies prevalence of MAU in HTN and it's clinical correlates. Out of 1787 patients prevalence of MAU was 6.7%. (2). S. Jalal et al (2001) studied 288 patients with HTN among which 37.5 manifested MAU. Steven J Chadban et al, 2003 found proteinuria in 2.4% cases which was increasing with age.[8] 25-44 years 0.8%, 65 years 6.6%.

Hens Henrick Parving(2004) found 22% prevalence of MAU in hypertensive patients with DM-II. (72). T Konta et al (2006) examined the prevalence of MAU and it's associated risk factors in Japan. A total of 2321 subjects were examined, the prevalence of MAU was 17.8%.[73]

V.K. Sharma et al studied 50 patients with essential HTN and found 24% prevalence of MAU. The prevalence was increasing as the duration of HTN increases.[18]

DIAGONOSIS OF RENAL DAMAGE IN HTN

Routine blood and urine analysis is done commonly to detect renal damage. The National Kidney Foundation recommends, three simple tests to screen for kidney disease.[20,9] A blood pressure measurement. A spot check for protein or albumin in urine.

Calculation of GFR based on a serum creatinine measurement. Blood urea nitrogen provides additional information.

6. SUMMARY

The present study entitled "Renal Damage Assessment With Reference To Microalbuminuria In Hypertensive Patients" is done to assess prevalence of microalbuminuria among hypertension subjects and it's

utility over serum creatinine assessment. Serum creatinine. Prevalence of microalbminuria was compared with more than normal serum creatinine levels among hypertensive patents.

The study group comprises of 50 hypertensive patents. The pointwise conclusion of result is as follows.

1. Microalbuminuria is 28% prevalent among hypertensive patients.
2. Hypertensive patients as having more than normal serum creatinine level have high value of UACR thus we can say that increment in serum creatinine level is advance stage of renal damage.
3. Out of 14 patients which are considered microalbuminuric on the basis of UACR value, 11 have high urine albumin also thus it can be diagnosed for microalbuminuria.
4. Hypertensive males are more prone to microalbuminuria than hypertensive females.
5. Maximum hypertensive patients belongs to duration less than 4 years Serum creatinine is increasing with Age while urine albumin and UACR shows no correlation with duration of HTN
6. Maximum hypertensive patients belong to age group 40-50 yrs then in age of 60-70 yrs.
7. Serum creatinine urine albumin and UACR shows no correlation with age.
8. Serum creatinine is decreasing with increment in non-vegetarian diet while UACR and Urine Albumin can not be correlated
9. Type I and type II hypertension is equally prevalent among hypertensive patients
10. Serum creatinine, urine albumin and UACR is found to be high in type I than in type II HTN.
11. Serum creatinine is decreasing with increment in non-vegetarian diet while UACR and Urine Albumin can not be correlated.
12. Serum creatinine, urine albumin and UACR is found to be high in male than in female hypertensive patients.
13. Maximum hypertensive patients have serum creatinine value 0.80-1.20 mg/dl
14. Maximum hypertensive patients have normoalbuminuria
15. Maximum hypertensive patients have urine creatinine value in the range 0.60-0.90 g/dl
16. Maximum hypertensive patients have urine albumin <40 mg/dl
17. Patients having high serum creatinine value have high value of UACR also.

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