ORIGINAL ARTICLE

Effectiveness of Valsartan in Obese Versus Non-Obese Type 2 Diabetic patients presented with microalbuminuria

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ABSTRACT

Aim: To ascertain efficacy of Valsartan, an angiotensin receptor blocker (ARB) in reducing microalbuminuria in obese verses non obese patients.

Methods: This comparative study was done in Department of Nephrology Pakistan Institute of Medical Sciences Islamabad from July 1, 2018 to December 31, 1018. Patients fulfilling selection criteria were enrolled and categorized as two groups obese & non-obese; both groups were given valsartan. Urine ACR and serum creatinine was followed every month for 6 months.

Results: Average age of all cases as 52.06 ± 4.11 years while the mean age in obese and non-obese cases was 52.48 ± 4.25 years and 51.63 ± 3.95 years, respectively. The mean change in Urine ACR (from baseline to 6th months) in obese cases was 41.76 ± 25.81 and non-obese cases was 76.05 ± 7.63, p-value <0.001. In obese cases mean urine ACR at 1st and 2nd month was same from baseline, p-value > 0.05 while at 3rd, 4th month was statistically lower as compare to baseline urine ACR, p-value < 0.05. Moreover, in non-obese cases the mean urine ACR was statistically decreased at 1st, 2nd, 3rd, 4th, 5th and 6th month when compared with baseline, p-value < 0.001. At 4th month in obese cases none of the cases achieved ACR < 30 while in non-obese cases 4(7.4%) cases achieved ACR < 30 with significantly higher frequency in non-obese cases, p-value < 0.05. At 4th month in obese cases 12(22.2%) cases achieved ACR < 30 while in non-obese cases 31(57.4%) cases achieved ACR < 30 with significantly higher frequency in non-obese cases, p-value < 0.001. At 6th month in obese cases 20(37%) cases achieved ACR < 30 while in non-obese cases 41(75.9%) cases achieved ACR < 30 with significantly higher frequency in non-obese cases, p-value < 0.001.

Conclusion: Valsartan is more effective in reducing microalbuminuria in non-obese patients as compared to obese patients.

Keywords: Diabetes mellitus, obesity, microalbuminuria, Valsartan

INTRODUCTION

Diabetes is defined as metabolic disorders with hyperglycemia due to inability of body for proper secretion of insulin, action of insulin, or can involve both. The condition of chronic hyperglycemia associated with diabetes is related to damage that is long-term dysfunction, and organs failure, involving eyes, nerves, kidneys, blood vessels, heart.[1]

Because of the aging population and an increase in obesity and sedentary lifestyle, the prevalence of DM2 is growing, particularly in Asia. Economically, diabetes type 2 burden related to obesity is generally underestimated involving factors like literacy and socio-economic status. Asians have higher pre disposition for resistance to insulin at somewhat obesity of lesser degree and pronounces dysfunction in early insulin secretion[2,3,5]. According to strong evidence antihypertensive agents targeting RAS can slow down renal disease progression and give cardioprotection for Type 2 Diabetes patients and microalbuminuria[5]. Angiotensin II receptor blocker (ARB) can be used as an alternate of ACE inhibitor if one is not able to bear certain side effects of an ACE inhibitor, e.g., it can cause an irritating cough[6,7,8]. In ARB literature it is found that, Conversion of microalbuminuria to normoalbuminuria was 12.5-29%[9,10]. Microalbuminuria represents elevation of excretion of urinary albumin on subclinical level. It is associated with excretion rate for albumin as 30 to 300mg/day or ratio of albumin-creatinine (mg/gm) of 25-250 for males & 35-350 for females[4]. The presence of microalbuminuria leads to renal disease worsening and also diabetic nephropathy with CVD[5]. Almost 30% DM2 patients suffer urine albumin level as abnormally high; almost 75% among those patients suffer microalbuminuria & almost 25% suffer overt diabetic nephropathy[11].

Microalbuminuria is directly related to CVD diseases and renal failure. Patients suffering with DM2 and hypertension, reduction in serum albumin level is noted[5]

Rationale of this study is to study the outcome of ARB (Valsartan) in obese versus non-obese diabetic type 2 patients suffering with microalbuminuria. This study evaluated the role of valsartan in obese type 2 diabetic patient in reduction of microalbuminuria compared to non obese type 2 diabetic patients and thus its long term renoprotective effects.

MATERIAL AND METHODS

After approval from Institutional Ethical Review Board this comparative study was conducted at the Department of Nephrology PIMS Islamabad from July 1, 2018 to December 31, 1018. Patients were enrolled by following selection criteria;

Inclusion Criteria: Paitents of both gender with age $\geq$ 40 years having type 2 DM with microalbuminura and good blood pressure control of <140/90 mmHg (with or without use of drugs), CKD upto stage 3 with HbA1c upto 7% was included.

Exclusion Criteria: Patients having CKD stage 4, above, HbA1c > 7% were excluded. Microalbuminuria was defined as Urine ACR of 30-300mg/g, with at least 2 of 3 measurments over 2-3 months. Then patients were divided into two groups depending upon BMI; obese (BMI $\geq$30) and non-obese(BMI$\leq$29.9). Both groups were given valsartan. Urine Albumin creatinine ratio (ACR) and Serum creatinine was followed every month for 06 months.

The collected data was entered and analyzed through SPSS version 25. Quantitative variables like age, creatinine level was presented in form of mean ± S.D. Qualitative variables like gender, doubling of creatinine level, ESRD and mortality was presented in form of frequency and percentage. Independent sample t-test was applied to compare proteinuria between obese and non-obese patients. P-value≤0.05 was taken as significant.

RESULTS

The mean age of all cases was 52.06±4.11 years while the mean age in obese and non-obese cases was 52.48±4.25 years and 51.63±3.95 years respectively. In this study there was equal male to female ratio i.e. 50% male and female in either group.

eGFR in both groups: The mean eGFR at 0 day in obese cases was 81 ± 13.9 and in non-obese was 90±16.4, p-value 0.058. At 6th month the mean eGFR in obese cases was 67 ± 10.2 and in non-obese cases was 84±15.5, p-value <0.05. The mean eGFR in non-obese cases was statistically higher as compared to obese cases after treatment, p-value < 0.05. The mean Change (from baseline to 6th months) in eGFR in obese and non-obese cases, however, was 14±20.0 and 6±30 respectively, p-value = 0.07 which was not significant.

Urine ACR in both groups: At 0 day the mean urine ACR in obese cases was 113.54 ± 13.82 and in non-obese cases was 112.33 ± 12.40, p-value = 0.635. At 1st month of treatment, the mean urine ACR in obese cases was 112.97± 32.73 and in non-obese cases was 81.48 ± 16.75, p-value < 0.001. The mean urine ACR at 2nd month in obese cases was 105.13±33.59 and non-obese cases was 69.43±18.71, p-value <0.001. At 3rd month the mean urine ACR in obese cases was 96.34±35.45 and in non-obese cases was 57.70±19.10, p-value < 0.001. At 4th month the mean urine ACR in obese and non-obese cases was 87.56 ± 36.78 and 47.00 ± 18.74 respectively, p-value < 0.001. At 5th month of treatment, the mean urine ACR in obese cases was 78.04 ± 40.27 and in non-obese cases was 36.81 ± 18.28, p-value < 0.001. At 6th month the mean urine ACR in obese cases was 71.78 ± 39.63 and in non-obese cases 36.28 ± 20.03, p-value < 0.001. The mean urine ACR in non-obese cases was significantly lower as compare to obese cases at each follow ups, p-value < 0.05. The mean change in Urine ACR (from baseline to 6th months) in obese cases was 41.76 ± 25.81 and non-obese cases was 76.05 ± 7.63, p-value <0.001. Results are shown in Figure I and Table I.

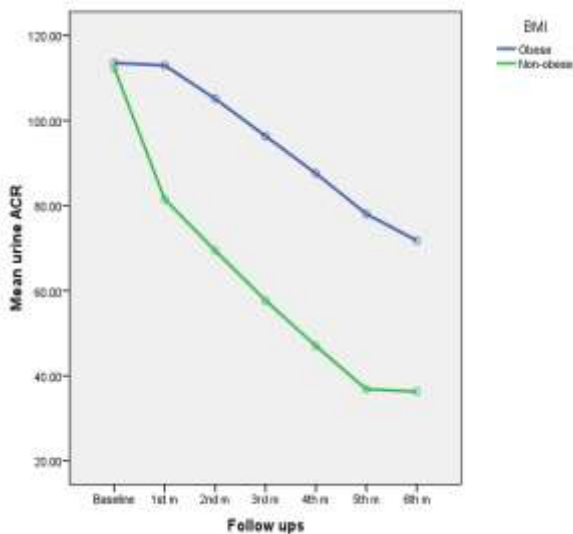Fig I: Comparison of urine ACR in both groups at each month of follow up

Table I: Comparison of ACR < 30 in both groups at 6th month

ACR < 30 at 6th months	BMI		Total
	Obese	Non-obese	
Yes	20	41	61
	37.0%	75.9%	56.5%
No	34	13	47
	63.0%	24.1%	43.5%

By the end of the study, 75.9% of the non-obese patients had achieved ACR<30 compared to only 37% of the obese patients.

DISCUSSION

High prevalence of obesity is increasing diabetes incidence; since both are interlinked for ESRD development, dissecting out individual chances of these is a difficult task. Considering pathophysiology of diabetic nephropathy and renal disease related to obesity are almost similar, both have raised initial glomerular filtration rate and intraglomerular capillary pressure, microalbuminuria and glomerular hypertrophy[12].

Obesity is a major clinical burden globally as its prevalence is at an elevated level at present time and reaches much near to the proportion of epidemic (BMI $\geq$ 30 kg/m^2)[13]. Many chronic disorders like type 2 diabetes, hypertension and cardiovascular diseases are main factors responsible for high obesity prevalence[14]. Obesity being closely linked to diabetes type 2, cardiovascular disease and hypertension, has worse health consequences like Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD), and any one of these factors leads to increased risk for progression of these diseases[15]. There is strong evidence in literature showing that obesity elevates risk for ESRD independent diabetes type 2 and also for hypertension[16]. Obesity may cause CKD and ESRD development independently or may be related to diabetes type 2 & hypertension contributes but the mechanisms related are not much understood. Major risk factors for ESRD are considered to be as diabetes type 2 & hypertension, constituting 70% of total patients suffering with ESRD[17].

A study reported that among diabetic cases there were 42.63% non-obese and 57.36% were obese with mean age was 55.9 years with 64.3% male and 35.7% female cases.[18] In current study the average age of all cases as 52.06 ±4.11 yrs that was almost similar to given study. We, by chance have both male and female cases with equal numbers.

The first choice of drugs for treatment of hypertension in diabetic patients are angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) due to the reduction in macrovascular and microvascular complications and their positive metabolic effects, which are independent of BP-lowering effects.[19] In people with type 2 diabetes, microalbuminuria is a strong, independent risk factor for diabetic nephropathy and cardiovascular morbidity and mortality. ACE inhibitor therapy decreased the risk of microalbuminuria in hypertensive subjects with type 2 diabetes and normoalbuminuria by about 40%. Available data suggest that angiotensin II receptor blockers (ARBs) might have a similar renoprotective effect and that this effect might be increased by combined ACE inhibitor therapy[20].

Recently, one study was done in order to see if any benefit could be taken from telmisartan for progression of microalbuminuria among normotensive individuals. more patients were reported to revert the levels to normoalbuminuria (UACR<30 mg/g creatinine) after using telmisartan as 15.5% in 40mg category, 19.6% in 80mg category, and 1.9% in placebo category. Moreover, no correlation was found in changes of blood pressure and UACR among the normotensive patients who were being given telmisartan. Also the side effects were similar in the two groups[21]. The findings are in agreement to findings in current study as we also found that the mean change in Urine ACR (from baseline to 6th months) in obese cases was 41.76 ± 25.81 and non-obese cases was 76.05±7.63, p-value < 0.001. In current study we extended the comparison over their obesity and found it more effective in non obese patients compared to obese patients.

Another randomized, placebo controlled, multicenter, double blind trial conducted in 2003 aimed to see the antiprotienuric effect of losartan in normotensive cases having

diabetes as well as microalbuminuria. Significantly high reduction of 25% was seen in rates of albumin excretion at week 5 after 50 mg dose of losartan and up to 34% was seen in coming 5 weeks at a dosage of 100mg[22]. Another study found higher percentage change in urea as found by Zandbergen et al., 2003 (cited above) as they reported UAER to be 56% after 24 weeks (95%CI, 49.6 - 63.0) with valsartan and 92% with amlodipine (95%CI, 81.7- 103.7), hence reporting a statistically significant between group effect (*P*<0.001), whereas, it was seen that valsartan had the same reduction in the levels of UAER among the two groups i.e. normotensive and hypertensive. Also normoalbuminuria became common after giving valsartan (29.9% vs. 14.5% and *P*=0.001)[23].

Another study concluded that for same reduction of BP and achieved levels of BP, among the patients of diabetes and microalbuminuria including normotensive patients, UAER was most effectively reduced by valsartan which lowered UAER more effectively than compared to amlodipine. Moreover, another study assessed the impact of angiotensin II receptor antagonist irbesartan among patients having hypertension as well as diabetes 2 with microalbuminuria. In their study, 10 among the 194 individuals in the 300mg category making 5.2% and 19 individuals among the 195 individuals from 150mg category making up 9.7% achieved primary end point, vs. 30 among 201 individuals from placebo category making up 14.9% (p-value< 0.001 and p-value=0.08for respective groups)[24].

CONCLUSION

Valsartan is more effective in reducing microalbuminuria in non-obese patients as compared to obese patients. However, it is useful even in obese diabetic type 2 patients suffering from microalbuminuria as well as non-obese type 2 diabetics.
Conflict of interests: None

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