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Study of Comparative Evaluation of Atorvastatin and Salicinol (*Salacia roxburghii*) on Glomerular Filtration Rate and Carotid Intima Media Thickness in Diabetic and Non-Diabetic Chronic Kidney Disease Patients with Hypertension

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ABSTRACT

Background: Most of the newer concepts in nephrology developed in the 19th and 20th centuries. Progression of renal failure is an area of nephrology where our understanding has improved appreciably in the last century, but still, our knowledge is like a drop in the ocean. We have ample evidence that the progression of renal failure can be slowed down, but we still need more definite information on whether established renal failure can be reversed. This pilot clinical study was planned to explore the therapeutic potential of salicinol in retardation of chronic kidney disease progression and anti-atherosclerotic property by looking for if a reduction in carotid intima-media thickness test (CIMT) is possible. **Objectives:** To study of comparative evaluation of atorvastatin and salicinol (*Salacia roxburghii*) on Glomerular filtration rate (GFR) and CIMT in diabetic and non-diabetic Chronic kidney disease (CKD) patients with hypertension. **Methods:** The present study was conducted in the Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Eighty patients of mild to moderate stable chronic renal failure with hypertension attending nephrology OPD or admitted in the nephrology ward from May 2014 to June 2015 were included in the study. Patient with acute Myocardial Infarction (MI), congestive heart failure, unstable angina, and myopathy. Subsequently, patients were allocated to one of the two groups, the first group consisted of diabetic patient treated with atorvastatin salicinol, and second group was of non-diabetic treated patients. **Results:** Among total patients included in study, 35 were non-diabetic, and 45 were diabetic. Mean serum creatinine at baseline study in the diabetic and non-diabetic group were 4.3 ± 2.0 and 5.0 ± 1.6, and changes were statistically significant intragroup. Mean CIMT in diabetic and non-diabetic at baseline were 0.92 ± 0.07 and 0.90 ± 0.07, and when comparing both changes were statistically significant at three months and 6 months suggesting CIMT regression more in diabetic groups compared to non-diabetics. Mean GFR in a diabetic and non-diabetic group at baseline was 23.4 ± 15.6 and 17.8 ± 13.7. On intergroup comparison, changes were statistically significant at 3 and 6 months. **Conclusion:** The male to female ratio was 2:1. Age of the patient ranged from 20 years onwards. No significant effect of the drug was seen on 24 hours urinary protein, blood pressure, hemoglobin and GFR. On comparison of non-diabetic and diabetic significant decreases (<0.05) in GFR were observed at the end of the study. On comparison of non-diabetic and diabetic highly significant decrease (<0.001) in CIMT were observed at 3 months and at the end of the study.

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INTRODUCTION

Hippocrates in the 5th century BC blamed malfunctioning kidney tor certain signs and symptoms. He commented that suppression of urine was a sign and could be followed by smell of urine in the breath, coma, and convulsions since then our understanding of nephrology has had revolutionary changes. Most of the newer concepts in nephrology developed in the 19th and 20th centuries. At the beginning of this century, even the term nephrology did not exist.[1-3] No one could foresee the introduction of medication, such as diuretics. Antihypertensive agents and immunosuppressive drugs have brought a scientific revolution in the treatment of ol renal diseases. These considerations make one humble, and one wonders whether our current management of renal disease will look any better to future Nephrologists at the end of the next century. Progression of renal failure is an area of nephrology where our understanding has improved appreciably in the last century, but still, our knowledge is like a drop in the ocean.[4] We have ample evidence that the progression of renal failure can be slowed down, but we still need more definite information on whether established renal failure can be reversed. Retarding the progression of renal failure is one of the most important tasks for the nephrologists as it not only improves the quality of life of the patient but also delays the development of end-stage renal disease, This also forestalls the considerable financial burden of dialysis, transplantation and immunosuppressive drugs. Progression of renal failure cannot only viewed as a scientific or medical problem, and patients cannot be viewed as merely an organism with an increasingly less efficient excretory apparatus; dealing with such patients needs compassionate attention by an empathetic physician. All possible areas shall be explored, where one can see even the slightest ray of hope new drugs for retardation or reversing the progression of renal failure. It is with this motive that we looked towards traditional medicines, which have followers of allopathic system mostly received step-motherly treatment from the of medicine.[5,6] This pilot clinical study was planned to explore the therapeutic potential of salicinol in retardation of chronic kidney disease progression and anti-atherosclerotic property by looking for if a reduction in CIMT is possible. In various experimental and clinical studies, it has been demonstrated that *Salacia* species containing salicinol has shown anti-inflammatory, Anti proteinuric and hypolipidemic action with improvement in endothelial dysfunction. With these properties the anti-inflammatory, antiproteinuric, and anti-atherosclerotic property of salicinol along with adiponectin enhancing the potential of salicinol has been evaluated in the present clinical trial. The antidiabetic property of *Salacia* species has been recognized since ancient times. The *Ayurvedic* practitioners of south India, particularly Tamil Nadu and Kerala, are using this plant for the treatment of diabetic complications like peripheral neuritis, and diabetic gangrene. The scientific evaluation on Salacia species was conducted at BHU by Dubey *et al*. (1993) and reported its antidiabetic property and its role in diabetic complications.[23] The findings were confirmed in collaborative studies in 2005. The antidiabetic and anti-inflammatory activity of *Salacia* was studied by Syed Ismail and Elango (1997) at the Tamil Nadu University. The aldose reductase and a-glucosidase inhibitory property were reported by Patricia *et al.* (2005) and Yuhao Li (2004). But no worker could study the role of *Salacia* species in the prevention and management of microvascular complications in diabetes cases.[7-9] Since it is an Indian plant, it was decided te evaluate other dimensions of *Salacia*, particularly in the management of microvascular complications, including antidiabetic anti-atherogenic, antioxidant, and anti-inflammatory properties. The pre-clinical and clinical studies were carried out with the view to prove the anti-atherogenic, hypolipidemic, and anti-obesity properties of *Salacia* species. Antioxidant properties were also determined.[10-14]

MATERIAL AND METHODS

The present study was conducted in the Department of nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Eighty patients of mild to moderate stable chronic renal failure with hypertension attending nephrology OPD or admitted in nephrology ward from May 2011 to June 2012 were included in the study. Patient with acute MI, congestive heart failure, unstable angina, and myopathy. Non-compliant patients and those patients taking medicines for their disease, which is known to improve lipid profile (lipid-lowering agent other than atorvastatin), were excluded from the study. Initially, patients were explained in detail about the experimental nature of the drugs and plan of study, and only willing patients were included in the study after signing of the written consent. Before starting the drugs, a thorough history was taken, and a clinical examination was done.

OBSERVATIONS

Comparison between Diabetic and Non-Diabetic (Inter Groups and Intra Groups)

Among total patients included in study 35 were non-diabetic, and rest 45 were diabetic (Table 1 and Figure 1).

Table 1: Comparison of systolic blood pressure between groups and within group on successive follow-up

Group	Systolic blood pressure (mean ± SD)			Within the group, comparison paired t-test	
	0 months	**3 months**	**6 months**	**0 *vs* 3**	**0 *vs* 6**
Non diabetic	159		± 18 137 ± 8 130 ± 6	11.160 p <0.001	9.430 p <0.001
Diabetic	169		± 19 140 ± 8 129 ± 5	15.395 p <0.001	16.375 p <0.001
t value	-2.264	-1.589	0.067	-	-
p value	0.026	0.116	0.947		

Table 2: Comparison of 24 hours urine protein between groups and within group on successive follow up

Group	24 hr urine protein (mean ± SD)			Within the group, comparison paired t-test	
	0 months	**3 months**	**6 months**	**0 *vs* 3**	**0 *vs* 6**
Non-diabetic	0.954 ± 1.101	0.854 ± 0.882	0.787 ± 0.818	1.548 p = 0.133	1.639 p = 0.110
Diabetic	1.776 ± 1.446	0.966 ± 0.990	0.966 ± 0.686	3.316 p <0.001	5.199 p <0.001
t-value	-2.780	-2.231	-1.058	-	-
p-value	0.007	0.029	0.293		

Table 3: Comparison of Creatinine between groups and within-group on successive follow-up

Group	Creatinine (mean ± SD)			Within the group, comparison paired t-test	
	0 month	**3 months**	**6 months**	**0 *vs* 3**	**0 *vs* 6**
Non-diabetic	5.0 ± 1.6	5.6 ± 1.7	6.2 ± 2.1	-1.572 p = 0.125	-2.998 p = 0.005
Diabetic	4.3 ± 2.0	3.51 ± 0.47	2.68 ± 0.51	-2.736 p = 0.009	-3.240 p = 0.002
t value	1.546	1.463	1.942	-	-
p value	0.126	0.148	0.058		

Mean serum creatinine at baseline study was 5.0 ± 1.6 and 4.4 ± 2.0 in the non-diabetic and diabetic group, respectively. Changes were statistically significant at 6 months in the non-diabetic group while at 3 and 6 months in the diabetic group. On intergroup comparison, no statistically significant changes were found.

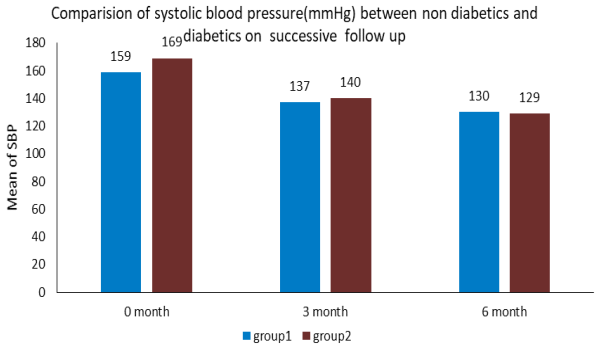

Figure 1: Comparison of systolic blood pressure (mmhg) between non diabetics and diabetics on successive follow up

Mean systolic blood pressure and diastolic blood pressure in non-diabetic at baseline was 159 ± 18 and 96 ± 8. In contrast, in diabetic baseline SBP and DBP in 169 ± 19 and 97 ± 9 SBP and DBP changes on the subsequent visit were statistically significant.

Mean 24 hours urinary protein in non-diabetic and diabetic at baseline were 0.954 ± 1.101 and 1.776 ± 1.446 and were statistically significant on a subsequent visit in the diabetic group. On intergroup comparison, no statistically significant changes were found at the end of the study.

Mean GFR at baseline in non-diabetic and diabetic were 17.8 ± 13.7 and 23.4 ± 15.6 and was statistically significant at 3 and 6 months in diabetic and on intergroup

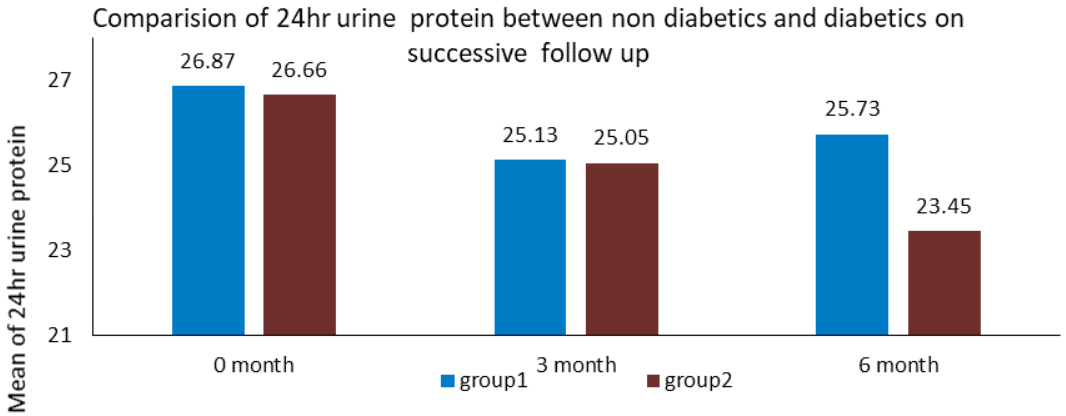

Figure 2: Comparison of 24 hr urine protein between non diabetics and diabetics on successive follow up

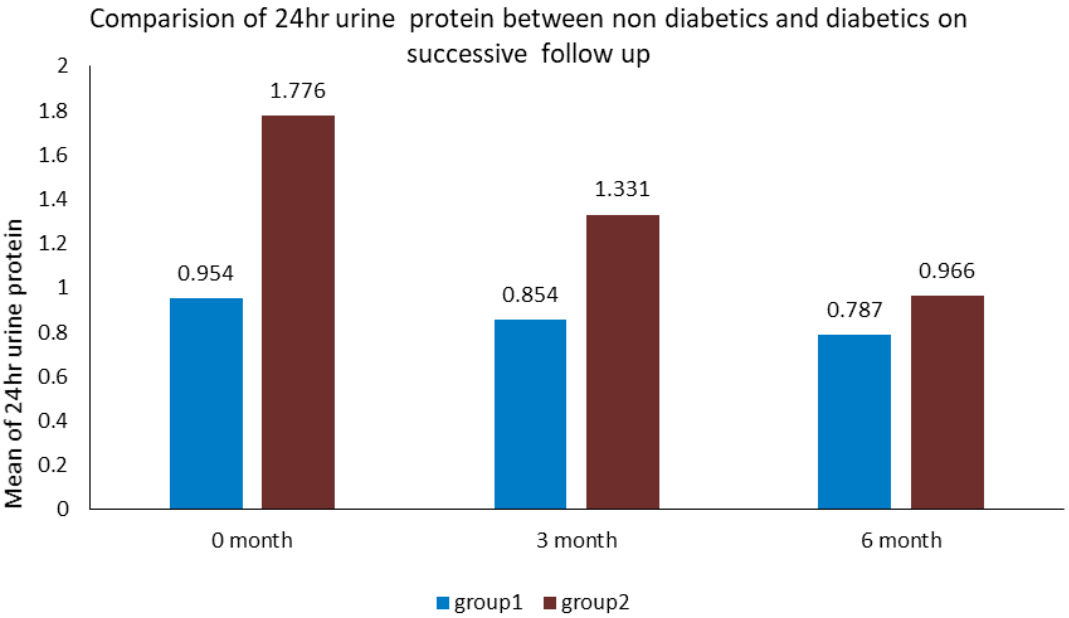

Figure 3: Comparison of 24 hr urine protein between non diabetics and diabetics on successive follow up

Table 4: Comparison of CIMT between groups and within group on successive follow

	CIMT (mean + SD)			**Within the group comparison paired 't' test**	
Group	**0 months**	**3 months**	**6 months**	**0 *vs* 3**	**0 *vs* 6**
Non-diabetic	0.90 ± 0.07	0.77 ± 0.06	0.76. ± 0.06	7.965 p < 0.001	8.158 p < 0.001
Diabetic	0.92 ± 0.07	0.99 ± 0.13	0.90 ± 0.11	-3.095 p = 0.003	.707 p = 0.483
t value	-1.044	-8.854	-6.824	-	-
p value	0.300	<0.001	<0.001		

Mean CIMT in non-diabetic and diabetic at baseline was 0.90 ± 0.07 and 0.92 ± 0.07, and it was statistically significant on a subsequent visit in non-diabetic, while on intergroup comparison CIMT changes were statistically significant at 3 and 6 months.

Table 5: Comparison of GFR between groups and within-group on successive follow-up

Group	GFR (Mean+SD)			Within the group, comparison paired t-test	
	0 month	**3 month**	**6 month**	**0 vs 3**	**0 vs 6**
Non-diabetic	17.8 ± 13.7	14.6 ± 7.9	13.4. ± 7.4	1.333 p = 0.191	1.728 p = 0.093
diabetic	23.4 ± 15.6	19.3 ± 11.4	18.8 ± 11.0	3.748 p <0.001	3.684 p <0.001
t-value	-1.657	-2.059	-2.483	-	-
p-value	0.102	0.043	0.015		

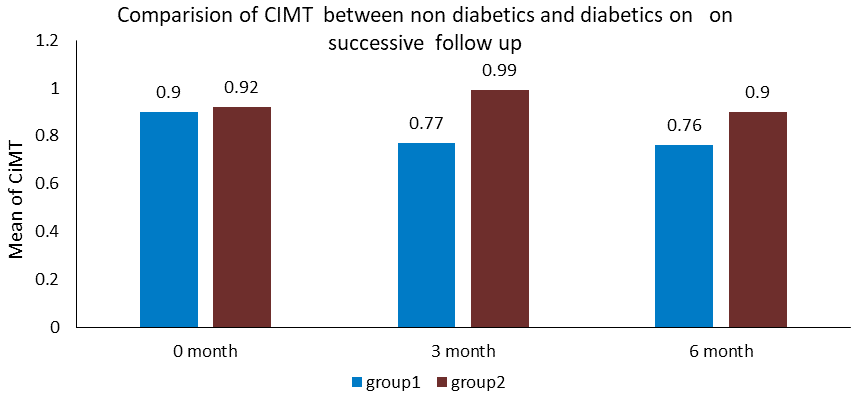

Figure 4: Comparison of CIMT between diabetics and diabetics on an successive follow up

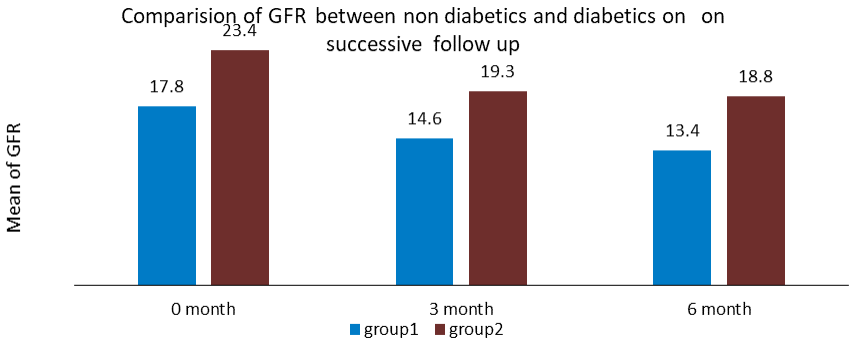

Figure 5: Comparison of CIMT between diabetics and diabetics on an successive follow up

comparison statistically significant changes found at three and six months (Figures 2-5 and Tables 2-5).

DISCUSSION

Due to rapid urbanization and industrialization, the incidence of diseases particularly diabetes mellitus, hypertension, and CHD are increasing worldwide at an alarming rate.[30,31] Due to the remarkable risk profile of modern synthetic agents, there is an urgent need to develop eco-friendly and bio-friendly plant-based products to replace synthetic chemicals since the chronic disease is a lifelong process. India has a rich national heritage in the form of plant-based remedies. These plants have shown pharmacological therapeutic potentials in the prevention and management of various mental and physical diseases.[15-19] It is pertinent to mention here that we have extensive experience-based knowledge, but we lack evidence-based scientific documentation required for global acceptance of these natural products. Recently World Health Organization has provided guidelines for validation of these plant origin products for its global acceptance. There is an urgent need to focus on new concepts and

targets for the management of chronic diseases. As in the present investigation, we are concentrating on the treatment modalities for chronic kidney disease with hypertension with an abnormal lipid profile. Among 95 patients of chronic renal failure taken for study, eighty patient of chronic renal failure with hypertension completed the 6 months follow-up and were finally included in the study. Group I consisted of forty patients treated with salicinol and atorvastatin. Group II consisted of forty patients treated with Atorvastatin only., Age of patient ranged from 20 years onwards. The mean age of patients in the various group were well matched, and there was no significant statistical differences. The mean age of group I was 53.9 years, and the mean age of group II was 51.75. There was a male preponderance in our patient. Overall, 65% of patients were male and 35% were female. In Group-1, 623% of patients were male while in group II, 67.5% were male. The male predominance in our patients is probably a reflection of male dominance in the social structure of our society. We have a society where male children are more cared for, and the adult male is the bread earner of the family. So. probably male patient are brought for the treatment to the hospital more frequently. On comparison of SBP and DBP in non-diabetic & diabetic group changes were not significant at the end of study.on comparison of 24 hours urinary protein value changes In diabetic and non-diabetic were found to be insignificant at the end of study[20] Mean serum creatinine at baseline study in diabetic and non-diabetic group were 4.3 ± 2.0 and 5.0 ± 1.6 and changes were statistically significant intra group, but on intergroup comparison changes were insignificant suggesting probably no specific role of salicinol in diabetic group as for as renal impairment progression is related. Mean CIMT in diabetic and non-diabetic at baseline were 0.92 ± 0.07 and 0.90 ± 0.07 and when comparing both changes were statistically significant at three month and six months suggesting CIMT regression more in diabetic group compared to non-diabetic [21-25]. Mean GFR in diabetic and non-diabetic group at baseline were 23.4 ± 15.6 and 17.8 ± 13.7. On intergroup comparison changes were statistically significant at three month and at 6 months. Thus, the beneficial effect of salicinol was observed and for further substantiating the finding by prospective study is recommended.[26-29]

SUMMARY AND CONCLUSION

Present study entitled "Study of Comparative evaluation of atorvastatin and salicinol (*Salacia Roxburghii*) on GFR and carotid intima media thickness in patient of chronic kidney disease with hypertension", was conducted at the Department of nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, between the period of May 2011 to June 2012. Eighty patient of mild to moderate chronic renal failure were included in the study. 40 patient, each were randomized to two groups. Group I were on atorvastatin and salicinol while group II were kept on atorvastatin only. The salient features of this study are:

1. The male patients dominated over the female patients with a male to female ratio of 2:1.
2. Age of the patient ranged from 20 years onward. Majority of the patient were above 40 years of age.
3. Commonest symptom was weakness in all the groups followed by anorexia, swelling over body, pallor, and sleep disorders.
4. No significant effect of the drug was seen on 24 hours urinary protein, blood pressure, hemoglobin, and GFR.
5. On comparison of non-diabetic and diabetic significant decrease (<0.05) in GFR were observed at the end of study.
6. On comparison of non-diabetic and diabetic highly significant decrease (<0.001) in CIMT were observed at three months and at the end of study.

Thus, on overall favorable effect of salicinol was seen with respect to decrease in serum creatinine and carotid intima media thickness. However, in this study the follow-up period was only 6 months which is relatively a short period to assess the effect of salicinol on GFR and CIMT which has a natural course running into years, a large prospective study is recommended to further establish the findings of this study.

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