

Study of Comparative Evaluation of Atorvastatin and Salicinol (*Salacia Roxburghii*) on GFR and Carotid Intima Media Thickness in Diabetic and Nondiabetic CKD Patients with Hypertension

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Abstract- Background: Most of the newer concepts in Nephrology developed in the 19th and 20th 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 ocean. We have ample of evidence that progression of renal failure can be slowed down but we still need more definite information 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 reduction in CIMT is possible.

OBJECTIVES: To study of comparative evaluation of atorvastatin and salicinol (*salacia roxburghii*) on GFR and CIMT in diabetic and nondiabetic 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 Nephrology ward from May 2014 to June 2015 were included in the study. Patient with acute MI, congestive heart failure, unstable angina, 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 nondiabetic treated patients.

RESULTS: Among total patients included in the study 35 were non diabetic and 45 were diabetic.

Mean serum creatinine at baseline study in diabetic & non-diabetic group were 4.3 ± 2.0 & 5.0 ± 1.6 & changes were statistically significant intra group. 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. 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 six month.

CONCLUSION: The male to female ratio was 2:1. Age of the patient ranged from 20yrs onward. No significant effect of the drug was seen on 24hrs urinary protein, blood pressure, hemoglobin & GFR. On comparison of non-diabetic and diabetic significant decrease (<0.05) in GFR were observed at the end of study. 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

I. INTRODUCTION

Hippocrates in 5th century B.C blamed malfunctioning kidney for 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 century. At the beginning of this century even the term Nephrology did not exist.

No one could foresee the introduction of medication such as diuretics. Antihypertensive agents and immunosuppressive drugs that have brought a scientific revolution in the treatment of 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 ocean.

We have ample of evidence that progression of renal failure can be slowed down but we still need more definite information whether established renal failure can be reversed. Retarding the progression of renal failure is one of the most important task 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 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 empathetic physician All possible areas shall be explored, where one can see even a slightest ray of hope new drugs for retardation or reversing the progression of renal failure of 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.

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 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 property the anti-inflammatory anti proteinuric and anti-atherosclerotic property of salicinol along with Adiponectin enhancing potential of salicinol has been evaluated in the present clinical trial.

The antidiabetic property of salacia species has been recognized since ancient time. The Ayurvedic practitioners of south India particularly Tamil Nadu and Kerala are using this plant for the treatment of diabetic complications like peripheral neuritis, 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 (Dubey 1994, Wani 2006, Singh 2007, Sharma 2007, Rajesh 2009).

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 micro vascular complication in diabetes cases. Since it is an Indian Plant it was decided to evaluate other dimensions of salacia particularly in the management of microvascular complication including antidiabetic antiatherogenic, 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

II. 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, myopathy. Non-compliant patient & those patient 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 patient were included in the study after signing of the written consent. Before starting the drugs a through history was taken and clinical examination was done.

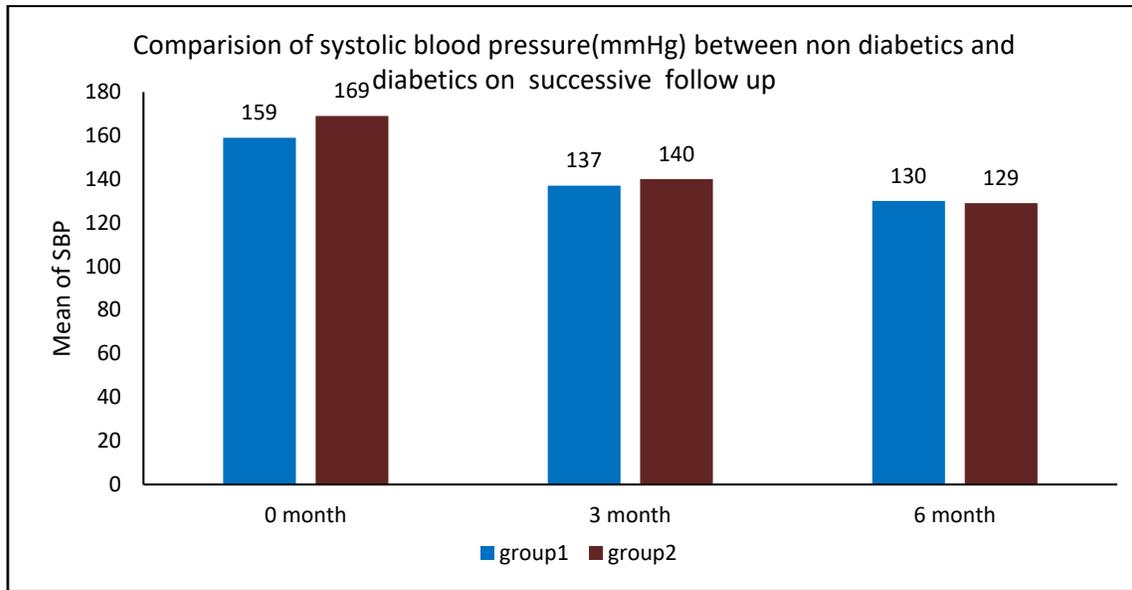
III. OBSERVATIONS

COMPARISON BETWEEN DIABETIC AND NON-DIABETIC (INTER GROUPS AND INTRA GROUPS)

Among total pt. included in the study 35 were non-diabetic and rest 45 were diabetic.

TABLE 1: Comparison of Systolic Blood pressure between groups and within group on successive follow up

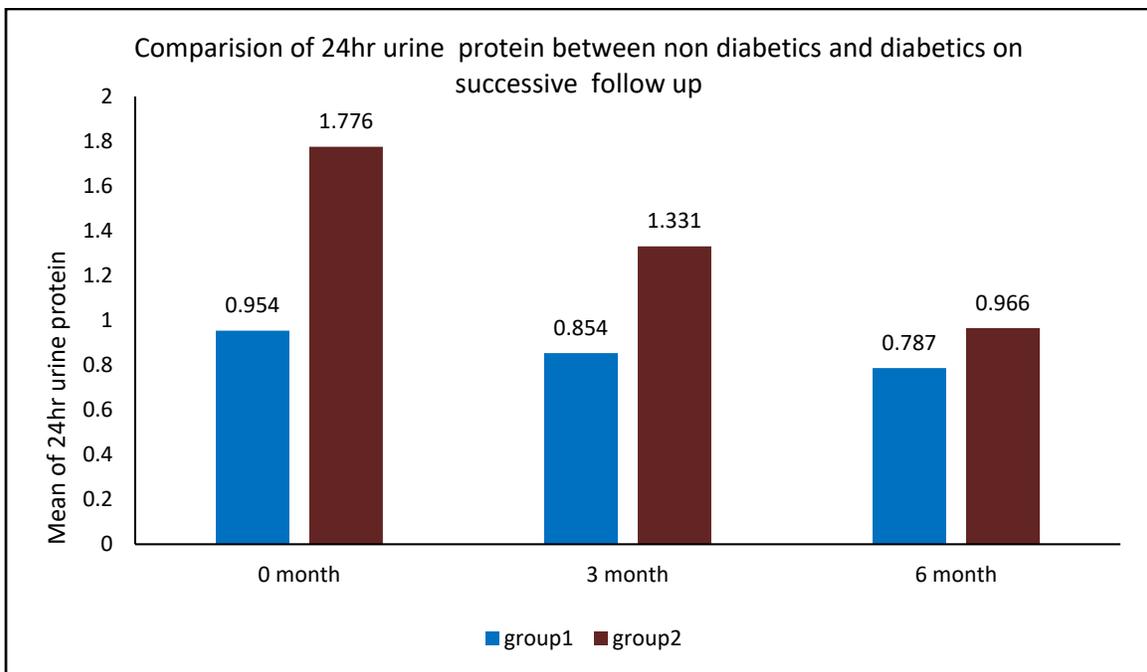
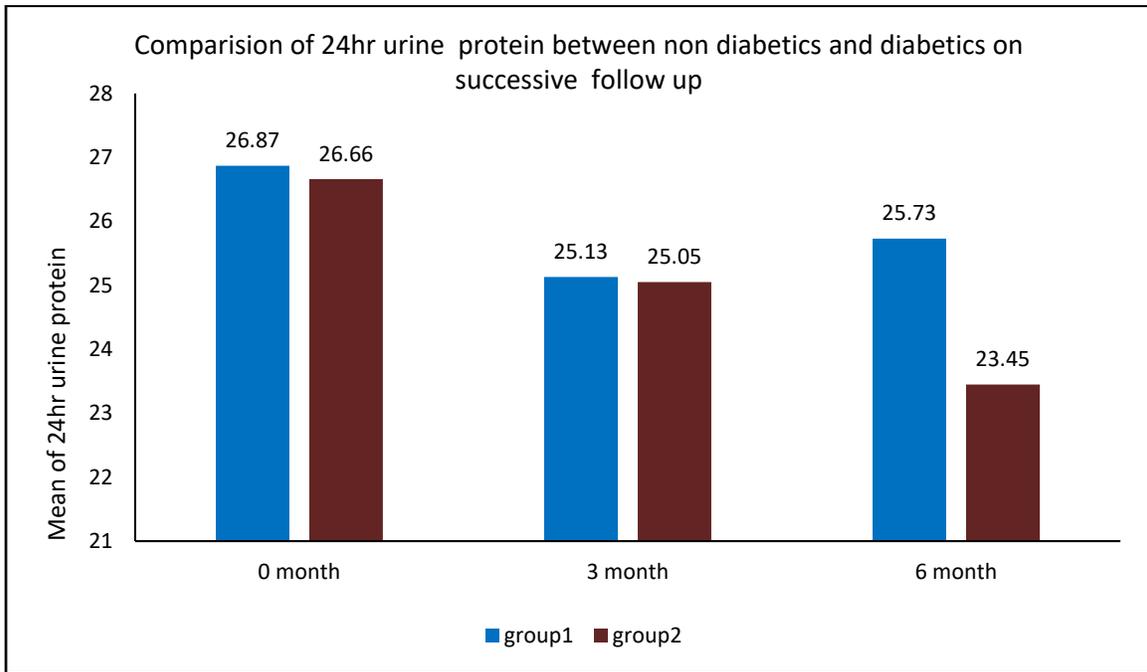
Group	Systolic Blood pressure (Mean+-SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Non Diabetic	159±18	137±8	130±6	11.160 P<0.001	9.430 P<0.001
Diabetic	169±19	140±8	129±5	15.395 P<0.001	16.375 P<0.001
t-value	-2.264	-1.589	0.067	-	-
p-value	0.026	0.116	0.947		



Mean Systolic blood pressure & diastolic blood pressure in non-diabetic at baseline was 159±18 & 96±8 while in diabetic baseline SBP and DBP in 169±19 & 97±9 SBP & DBP changes on subsequent visit were statistically significant.

Table 3: Comparison of 24hr urine protein between groups and within group on successive follow up

Group	24hr urine protein(Mean+SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	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		



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

Table 4: 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 month	6 month	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 were 5.0±1.6 & 4.4±2.0 in non-diabetic & diabetic group respectively. Changes were statistically significant at 6 months in non-diabetic group while at 3 & 6 months in diabetic group. On intergroup comparison, no statistically significant changes were found.

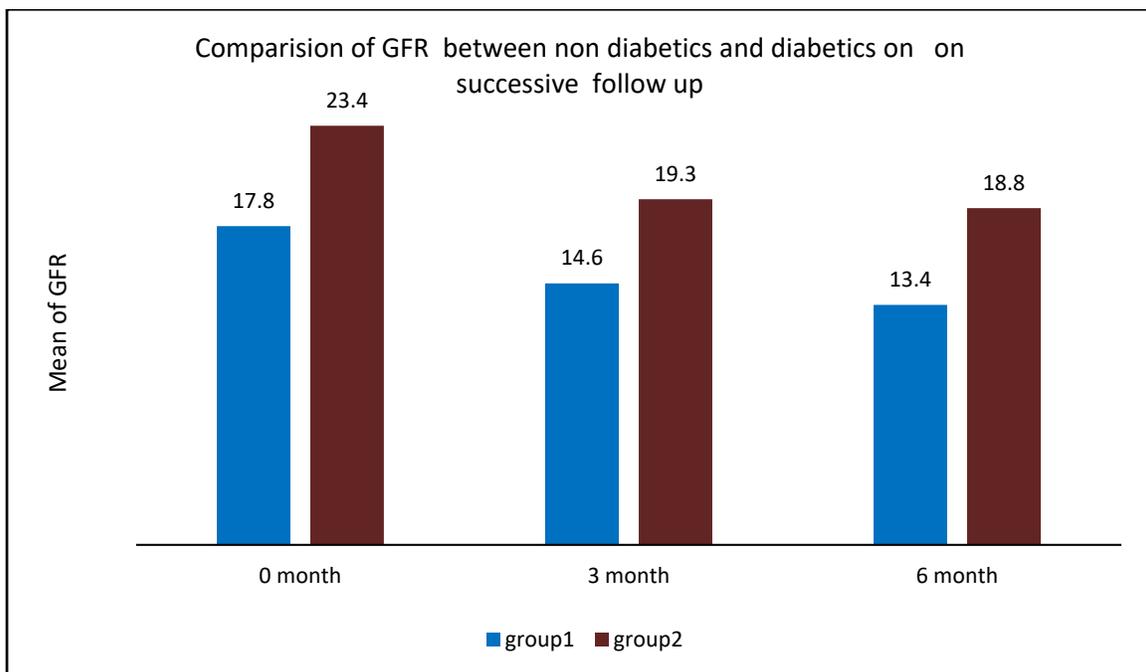
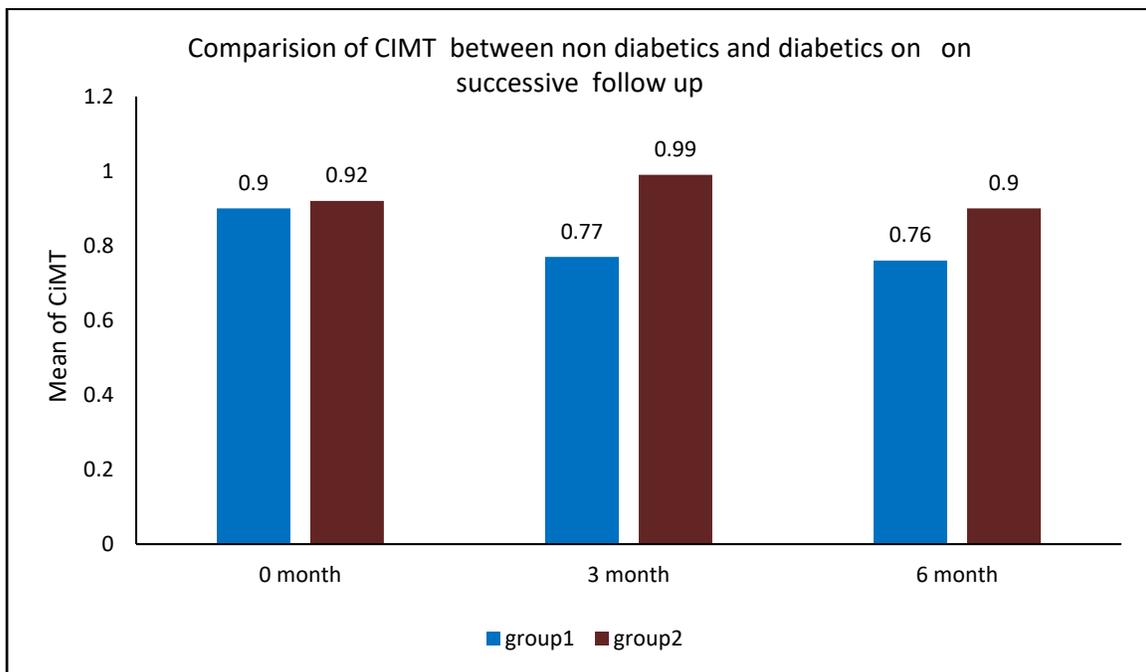
Table 24: Comparison of CIMT between groups and within group on successive follow

Group	cimt (Mean+SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	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 & diabetic at baseline was 0.90±0.07 & 0.92±0.07 and it was statistically significant on subsequent visit in non-diabetic, while on inter group comparison CIMT changes were statistically significant at 3 and 6 months.

Table 25: 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		



Mean GFR at baseline in non-diabetic & diabetic were 17.8 ± 13.7 & 23.4 ± 15.6 & was statistically significant at 3 and 6 months in diabetic and on intergroup comparison statistically significant changes found at three and six months.

Discussion

Due to rapid urbanization and industrialization, the incidence of diseases particularly Diabetes mellitus, Hypertension and CHD are increasing worldwide at an alarming rate. Due to 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 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 managements of

various mental and physical diseases. It is pertinent to mention here that we have extensive experience based knowledge but we are lacking with 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 new concepts and targets for the managements of chronic diseases. As in the present investigation, we are concentrating on the treatment modalities for

chronic kidney disease with hypertension with abnormal lipid profile.

Among 95 patients of chronic renal failure taken for study, Eighty patient of chronic renal failure with hypertension completed the six 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. Mean age of patient in various group were well matched & there was no significant statistical differences. Mean age of group-I was 53.9 yrs & Mean age of Group-II was 51.75

There was male preponderance in our patient. Overall 65% patients were male & 35% were female. In Group-I 62.3% patient were male while in Group-II 67.5% were male. The male predominance in our patient 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 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 & DBP in non-diabetic & diabetic group changes were not significant at the end of study.

on comparison of 24hrs urinary protein value changes In diabetic & non-diabetic were found to be insignificant at the end of study. Mean serum creatinine at baseline study in diabetic & non-diabetic group were 4.3 ± 2.0 & 5.0 ± 1.6 & 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.

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 six month.

Thus the beneficial effect of salicinol was observed and for further substantiating the finding by prospective study is recommended.

IV. 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. Forty patient, each were randomized to two groups. Group-I were on Atorvastatin & 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 20yrs onward. Majority of the patient were above 40yrs of age.

3. Commonest symptom was weakness in all the groups followed by anorexia, swelling over body, pallor & sleep disorders.

4. No significant effect of the drug was seen on 24hrs urinary protein, blood pressure, hemoglobin & GFR.

10. On comparison of non-diabetic and diabetic significant decrease (<0.05) in GFR were observed at the end of study.

11. 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 & carotid intima media thickness. However in this study the follow-up period was only six months which is relatively a short period to assess the effect of salicinol on GFR & CIMT which has a natural course running into years, A large prospective study is recommended to further establish the findings of this study.

REFERENCES

- [1] Agarwal R. Effects of statins on renal function. *Mayo Clin Proc* 2007; 82:1381-90.
- [2] Alexander, RW. (1994) Inflammation and coronary artery disease *N Engl J Med*. 331,468-469.
- [3] Beers, R.F. Jr. and Sizer IW: *Journal of Biological Chemistry* 195:133-140, 1952.
- [4] Callister TQ, Raggi P, Cooil B, et al. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. *N Engl J Med*.
- [5] Chakravarti, R et al., Antidiabetic and hypolipidemic potential of DRF-2519 a dual activator of PPAR α and PPAR γ . *Eur. j. pharmacol.*, 491, 195206; 2004.
- [6] Dunn M. J. and Hood, V. L "Prostaglandins and the kidney," *The American Journal of Physiology*, vol. 233, no. 3, pp. 169-184, 1977.
- [7] E. Saad, B. Charra, and D. S. C. Raj, "Hypertension control with daily dialysis," *Seminars in Dialysis*, vol. 17, no. 4, pp. 295-298, 2004.
- [8] Finn AV, Kolodgie FD, Virmani R. Correlation Between Carotid Intimal/Medial Thickness and Atherosclerosis. A Point of View From Pathology [published online ahead of print August 13, 2009]. *Arterioscler Thromb.*
- [9] Flamming et al., Genotoxicity testing of salacia oblonga extract. *Food and chemical toxicology* 44:1868- 1874, 2006.
- [10] G. Opelz and B. D'ohler, "Improved long-term outcomes after renal transplantation associated with blood pressure control," *American Journal of Transplantation*, vol. 5, no. 11, pp. 2725- 2731, 2005.
- [11] Gunal AI, S. Duman, M. Ozkahya et al., "Strict volume control normalizes hypertension in peritoneal dialysis patients," *American Journal of Kidney Diseases*, vol. 37, no. 3, pp. 588-593, 2001.
- [12] Howard G. Burke Gt., Szklo M, et al. Active and passive smoking are associated With increased carotid wall thickness. The Atherosclerosis Risk in Communities study. *Arch Intern Med*.
- [13] Isbel NM, Haluska B, Johnson DW, et al. Increased targeting of cardiovascular risk factors in patients with chronic kidney disease does not improve atheroma burden or cardiovascular function. *Am Heart J*. 2006;151:745-753.
- [14] Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*. 2009;20:223-228.
- [15] Johnson RJ, Rivivighn SD, Kim YG, et al. Reappraisal of the pathogenesis and consequence of hyperuricemia in hypertension, cardiovascular disease and renal disease. *Am J Kidney Dis*. 1999;33:225-234.
- [16] Kakkar P, Das B and Viswanathan PN.: A modified spectrophotometric assay of superoxide dismutase. *Ind. J of Biochem. Biophys.* (21): 130-32, 1984.

- [17] Lott JA, Lu CJ. Lipase isoforms and amylase isoenzymes assays and application in the diagnosis of acute pancreatitis. *Clin. Chem.* 1991; 37:361.
- [18] Israelian-Konarakis Z, Reaven PD. Peroxisome proliferator-activated receptor α and atherosclerosis: from basic mechanisms to clinical implications. *Cardiol Rev*; 13:240-6; 2005.
- [19] Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int.* 2003;63:1121—1129.
- [20] Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular disease in the community. *J Am Coll Cardiol.*
- [21] National Kidney Foundation. K/DOQI kidney disease outcome quality initiative. *Am J Kidney Dis.*
- [22] Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. *Prog Cardiovasc Dis*; 15:289-329; 1972.
- [23] O'Brien MM, Gonzales R, Shroyer AL, et al. Modest serum creatinine elevation affects adverse outcome after general surgery. *Kidney Int.* 2002;62:585—592.
- [24] Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Annals of Biochemistry* 1979 (95): 351-58.
- [25] Preston E, Ellis MR, Kulinskaya E, Davies AH, Brown EA. Association between carotid artery intima-media thickness and cardiovascular risk factors in CKD. *Am J Kidney Dis.*
- [26] R. Agarwal and R. R. Lewis, "Prediction of hypertension in chronic hemodialysis patients," *Kidney International*, vol. 60, no. 5, pp. 1982-1989, 2001.
- [27] Studer M, Briel M, Leimenstoll B, et al. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med.* 2005;165:725-730.
- [28] Taal MW, Brenner BM. Renal risk scores: Progress and prospects. *Kidney Int.*
- [29] Tanaka T, Yamamoto J, Iwasaki S, Asaba H, Hamura H, Ikeda Y, Watanabe M,
- [30] U S Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, Md, USA, 2010.
- [31] Vaziri ND, Moradi H. Mechanisms of dyslipidemia of chronic renal failure. *Hemodial Int.* 2006;10:1-7.
- [32] Vaziri ND, Sato T, Liang K. Molecular mechanisms of altered cholesterol metabolism in rats with spontaneous focal glomerulosclerosis. *Kidney Int.*
- [33] Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med.* 2002; 137:563—570.
- [34] Yamagishi S, Matsui T, Nakamura K. Atorvastatin and diabetic vascular complications. *Curr Pharm Des* 2006; 12:1549-54.
- [35] Yamagishi S, Matsui T. Advanced glycation end products (AGEs), oxidative stress and diabetic nephropathy. *Oxid Med Cell Longev* 2010; 3:1-8.
- [36] Zhao Y, Marcel YL. Serum albumin is a significant intermediate in cholesterol transfer between cells and lipoproteins. *Biochemistry.* 1996;35:7174-7180.
- [37] Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*; 97: 1784-89; 2000.

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