International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 22-09-2018; Accepted: 25-10-2018
www.medicalsciencejournal.com
Volume 4; Issue 11; November 2018; Page No. 162-169

Study of comparative evaluation of Atorvastatin and Salacinol (*Salacia roxburghii*) on BMI, lipid profile and adiponectin level in diabetic and non-diabetic patient of chronic kidney disease with hypertension

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Abstract

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. 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 pilot clinical study was planned to explore the therapeutic potential of Salacinol 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 Salacinol (*Salacia roxburghii*) on BMI, Lipid profile and Adiponectin level in Diabetic and non-diabetic patient of chronic kidney disease with hypertension

Methods: The present study was conducted in the Department of General 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. 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. Subsequently patients were allocated to one of the two groups, the first group consisted of Diabetic patient treated with atorvastatin Salacinol and second group was of nondiabetic treated patients.

Results: Among total patients included in the study 35 were non diabetic and 45 were diabetic. On BMI comparison in diabetic & non-diabetic at the end of study, changes were found to be highly significant suggesting probably role of Salacinol as weight lowering agent. Mean LDL/ HDL ration in diabetic and non-diabetic at baseline were 4.61±0.49 and 4.49±0.59 and on intergroup comparison changes were statistically significant at three and six months. Mean cholesterol changes when compared diabetic & non-diabetic group were statistically insignificant at the end of study. Mean triglyceride level in diabetic & non-diabetic at baseline were 167.6±18.6 & 167.6±14.8 and on comparison with each other changes were statistically significant at six months. Mean adiponectin value at baseline in diabetic and non-diabetic were 5.32±1.53 and 4.22±1.58 and changes were statistically significant at 3 and 6 months in diabetic group and at 6 months in non-diabetic group. On Intergroup comparison changes were statistically significant at 3 and 6 months. However, changes were statistically significant even at baseline.

Conclusion: The male patients dominated over the female patients with a male to female ratio of 2:1. Age of the patient ranged from 20yrs onward. Majority of the patient were above 40yrs of age. Commonest symptom was weakness in all the groups followed by anorexia, swelling over body, pallor & sleep disorders. No significant effect of the drug was seen on 24hrs urinary protein, blood pressure, hemoglobin & GFR. In patient treated with Atorvastatin and Salacinol, the changes in Adiponectin level were statistically significant (<().()()l) at three and six months. On comparison of non-diabetic and diabetic significant decrease (<0.05) including BMI, LDL/ HDL ratio, triglyceride level were observed at the end of study.

Keywords: atorvastatin, salacinol (*Salacia roxburghii*), BMI

Introduction

Hippocrates in 5th century B.C 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 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 lock 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 Salacinol as anti-atherosclerotic agent by looking for if reduction in CIMT is possible.

In various experimental and clinical studies it has been demonstrated that salacia species containing Salacinol 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 Salacinol along with Adiponectin enhancing potential of Salacinol 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 various pharmacological action of salacia species are as under:

1. Salacia depresses cardiac angiotensin Π signaling of AT-1 receptors
2. Suppressor of overexpression of cardiac PPAR-a in diabetic heart
3. Salacia as PPAR-y agonists in diabetes mellitus and insulin resistance.
4. Salacia as PPAR-a agonists in the management of dyslipidemia
5. Salacia inhibits a-glucosidase
6. Salacia decreases postprandial glycaemia
7. Salacia inhibits aldose reductase
8. Salacia inhibits pancreatic lipase

In view of the need for the drugs to retard or reverse the progression of renal failure and atherosclerosis scavenging property and also in view of the unchartered wealth of traditional medicines which is found in India, this study was planned to explore the therapeutic potentials of the traditional medicines in case of chronic renal failure.

Material and Methods

The present study was conducted in the Department of General 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 2015 to June 2016 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. The patients were then subjected to baseline urine, hematological, biochemical and immunological investigation. All the patients were given strict dietary instruction and a diet chart was given for their reference. They were maintained on low protein 0.6mg/kg/day), low salt (s 5mg/day) as potassium restricted 40-60 meq/day) diet. A caloric intake of 30-35 kcal/kg body weight was planned. All of the patient were needed were given phosphate binders & none of the patient was taking ACE inhibitor. Subsequently patients were allocated randomly to one of the two groups, the first group consisted of patient treated with atorvastatin Salacinol and second group was treated with atorvastatin only.

The allocated drug was started and after a period of one month they were assessed for dietary control by asking them to recall their diet in last 24hrs and for any symptomatic improvement or deterioration as compared to the last visit. They were also examined thoroughly and baseline investigations were repeated on three & six months.

The drug used were Salacinol & Atorvastatin. Salacinol, is extract from *Salacia roxburghii* which is a climbing shrub or small tree found in evergreen forest of North Bengal, Assam, Sikkim & N.E.F.A. Ripe fruits are edible, common name satrangi saptachakra, swarnamala part used were root. This is antidiabetic drug used in the treatment of diabetes. It is also having anti-inflammatory and analgesic action. The stems have been used as anti-inflammatory cardiotonic, antidiabetic and anti-oxidant. It also acts on pro inflammatory cytokines IL-6, TNF-α and also hsCRP, thus reduces vascular inflammation and atherosclerotic process. Its major activity observed is that this drug exerted as an agonist for PPAR activated receptors resulting in insulin regulated gene transcription. The extract contains lgm of the drug which is divided into two dosage of 500mg each capsule with patient has to talces 1 capsule twice daily. Pre-clinical study were conducted in SRM University Chennai. Source of procurement is Tulsi pharma Bhadohi, U.P, which has been supported by Department of science and technology, Government of India. Another drug was Atorvastatin having a period role as lipid lowering agent. Its mechanism of action as competitive inhibitors of HMG-C0A.

The drug Salacinol were given free of cost since we have procured drug for research purposes, while patient bought atorvastatin on their own. Drugs sufficient in quantity for one month were distributed at the time of monthly visits.

Investigations

The following investigations were done at baseline, 3 months & 6 months.

1. Hematological investigation — These included estimation of hemoglobin by sahli's hemoglobin meter, TLC by Neubaurs chamber.
2. Biochemical Analysis
   - Blood sugar (fasting) (Varley, 1980)
   - Blood urea - diacetyl monoxine method (Varley, 1980)
   - Serum creatinine - Alkaline picrate method of Jaffe reaction (Varley, 1980)
   - Serum cholesterol — Timed end point method using cholesterol reagent.
   - Total serum protein — Biduret method (Varley, 1980)
   - Serum Albumin — dye binding capacity buffer method (Varley, 1980)
   - Serum calcium and phosphorous Direct calorimetry with complexing agents (Varley, 1980)
3. Urinalysis
   - Routine examination for urinary pH, albumin sugar and detailed microscopic study was done as described by (Varley, 1980).
   - Quantitative examination of 24hs urinary protein was done by Biduret method.
4. Radiological examination - Ultrasonography of abdomen for kidney size cortical thickness, cortico-medullary differentiation, pelvi-calyceal system Ureters urinary bladder and prostate was done in all patient.
5. Creatinine clearance were estimated by using cockroft-gault equation.
6. Carotid-intima-media thickness by non-invasive B-scan color Doppler.
7. Adiponectin destination was done by ELISA method in department of pathology IM>, BIIU Varanasi.

Sample Collection

Blood were drawn by 20G needle from the median cubital vein of patient with disposable syringe. Patients were healthy at the time of sample collection, without recent illness, infection, inflammation, tissue injuries. 10ml of blood was drawn for these tests. Sample can be refrigerated up to l week, frozen up to 3 months. Fasting sample should be drawn for best results. On follow up at three and six months, samples were taken using same methodology for routine investigations and other specific tests.

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		

Table 2: Comparison of DBP between groups and within group on successive follow up

Group	DBP (Mean+-SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Non diabetic	96±8	86±6	82±3	14.443P<0.001	9.483P<0.001
diabetic	97±9	88±6	83±3	11.969P<0.001	12.366P=0.001
t-value	-0.649	-1.810	-0.438	-	-
p-value	0.0518	<0.074	0.663		

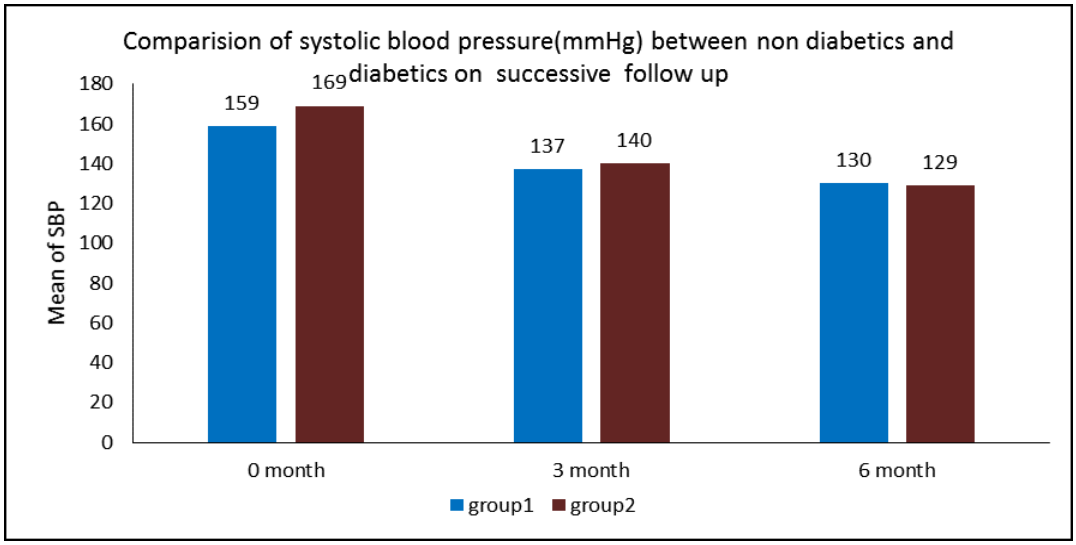

Fig 1

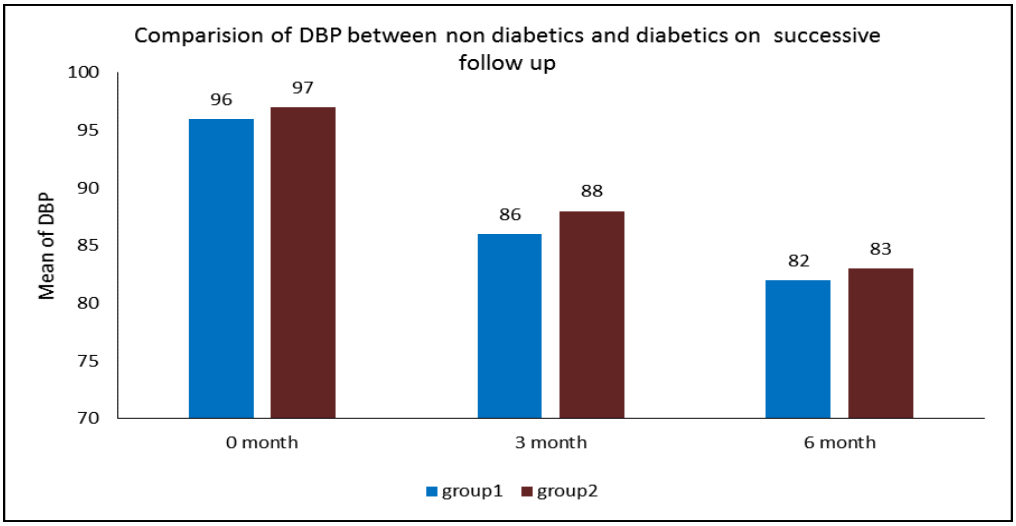

Fig 2

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 BMI between groups and within group on successive follow up

Group	BMI (Mean+-SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Non diabetic	26.87±1.78	25.13±586	25.73±2.10	1.541P<0.133	1.639P=0.110
diabetic	26.66±1.51	25.05±3.24	23.45±1.65	3.316P=0.001	5.199P<0.001
t-value	0.569	0.078	5.422	-	-
p-value	0.571	<0.001	<0.001		

Mean BMI at baseline in non-diabetic & diabetic were 26.87±1.78 & 26.66±1.51 respectively & changes were significant at 6 month in non-diabetic while at 3 & 6 months in diabetic group on comparison between two groups, differences are statistically significant at six months.

Table 4: 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		

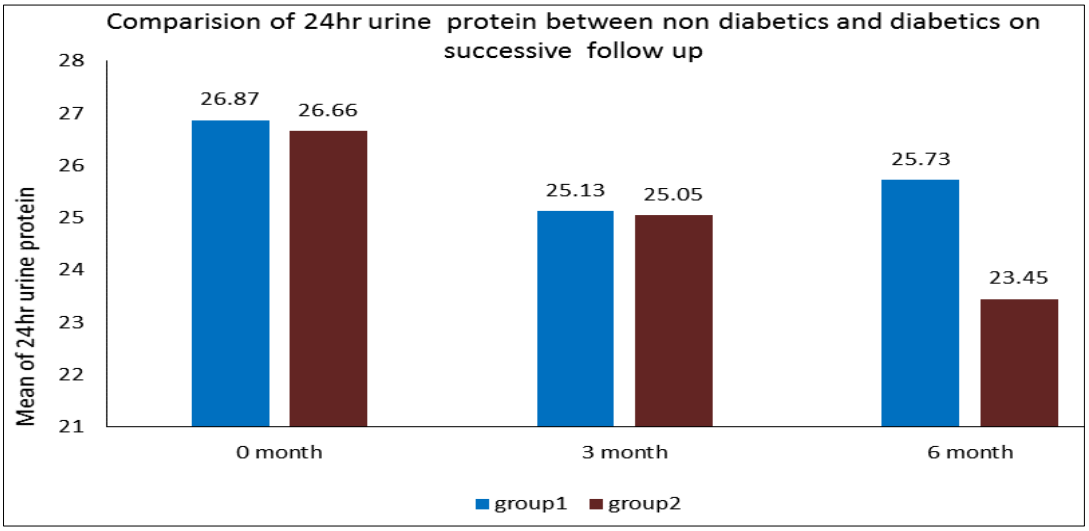

Fig 3

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 comparision, no statistically significant changes were found at the end of study.

Table 5: Comparison of LDL/HDL ratio between groups and within group on successive follow up

Group	LDL/HDL ratio (Mean + SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Non diabetic	4.49±0.59	3.47±0.48	2.66±0.55	-1.572P=0.125	-2.998P=0.005
diabetic	4.61±0.49	3.85±0.67	3.01±0.66	-2.736P=0.009	-3.240P=0.002
t-value	-0.991	-2.812	-2.523	-	-
p-value	0.325	0.006	0.014		

Mean LDL/HDL ration in non-diabetic & diabetic at baseline were 4.49+0.59 & 4.61+0.49 & were statistically significant at 3 month in both the group. It was also statistically significant on inter group comparison at 3 and 6 months.

Table 6: Comparison of cholesterol between groups and within group on successive follow up

Group	cholesterol (Mean + SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Non-diabetic	279.4±30.7	234.8±23.0	192.0±38.0	8.690 P<0.001	17.926 P<0.001
diabetic	285.8±21.8	246.7±22.2	186.4±15.7	9.345P<0.001	22.812P<0.001
t-value	-1.093	-2.343	0.896	-	-
p-value	0.278	0.022	0.373		

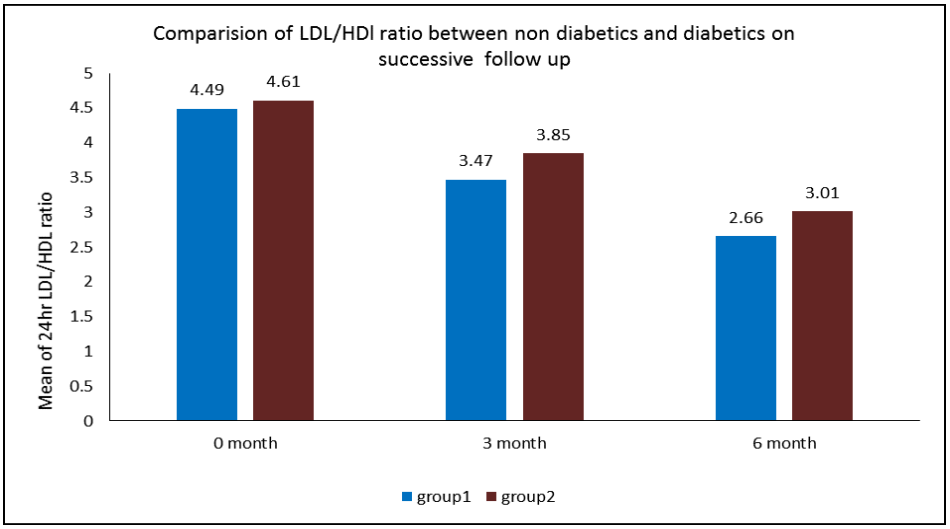

Fig 4

Mean cholesterol in non-diabetic & diabetic group at baseline were & 285.8±21.8 and were statistically significant on subsequent visit' but on intergroup comparison, no statistically significant changes were found.

Table 7: Comparison of Adiponectin between groups and within group on successive follow

Group	Adiponectin (Mean+SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
diabetic	5.32±1.53	5.88±1.41	6.82.±1.12	7.422 P<0.001	10.134P<0.001
Non-diabetic	4.22±1.58	4.32±1.58	4.11±1.27	1.342 P=0.165	2.118P=0.041
t-value	2.997	4.965	9.721	-	-
p-value	0.004	<0.001	<0.001		

Mean adiponectin value at baseline in diabetic and non-diabetic were 5.32±1.53 and 4.22±1.58 and changes were statistically significant at 3 and 6 months in diabetic group and at 6 months in non-diabetic group. On Intergroup comparison changes were statistically significant at 3 and 6 months. However, changes were statistically significant even at baseline.

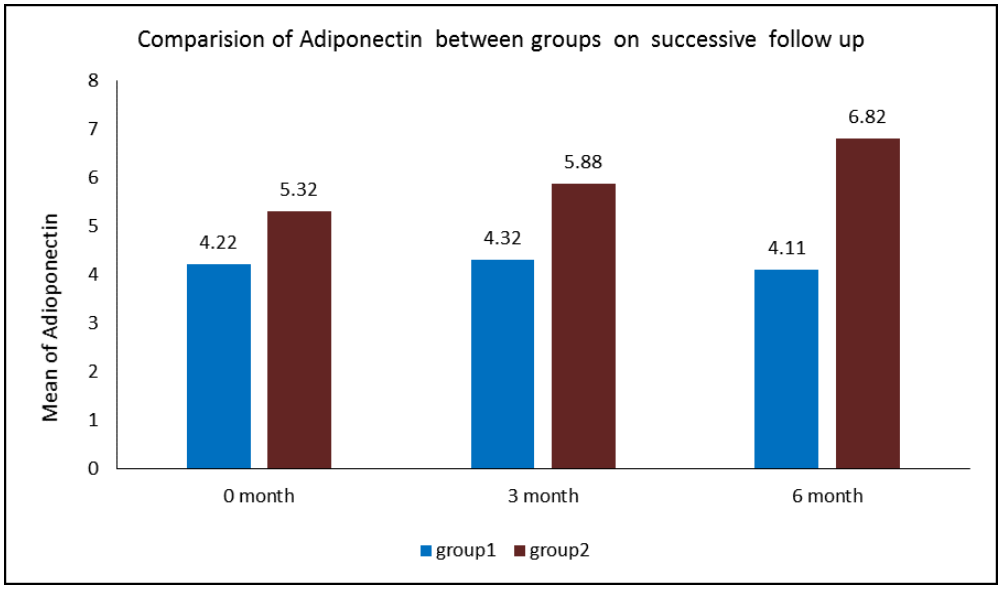

Fig 5

Table 8: Comparison of Triglyceride between groups and within group on successive follow up

Group	Triglyceride (Mean + SD)			Within the group comparison paired 't' test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Non-diabetic	167.6±14.8	134.9±22.9	115.8±20.5	9.170P<0.001	16.029P<0.001
diabetic	167.6±18.6	127.4±12.7	108.5±11.1	18.433P<0.001	23.843P<0.001
t-value	-0.017	1.848	2.023	-	-
p-value	0.986	0.068	0.046		

Mean Triglyceride at baseline in non-diabetic & diabetic group were 167.6±14.8 & 167.6±18.6 and changes ware statistically significant at 6 months inter & inter group comparison.

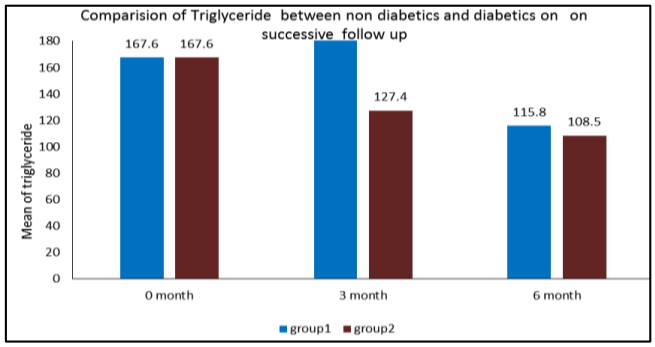

Fig 6

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. 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. 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 Yrs. There was male preponderance in our patient. Overall 65% patients were male & 35% were female. In Group-1 623% 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. Most common presenting features was the subjective feeling of weakness in 100% of patients in all groups Other common symptoms were anorexia, edema. nausea & vomiting sleep disorder. On comparison of SBP & DBP in non-diabetic & diabetic group changes were not significant at the end of study. On BMI comparison in diabetic & non-diabetic at the end of study, changes were found to be highly significant suggesting probably role of Salacinol as weight lowering agent. 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 Salacinol in diabetic group as for as renal impairment progression is related. Mean LDL/ HDL ration in diabetic and non-diabetic at baseline were 4.61±0.49 and 4.49±0.59 and on intergroup comparison changes were statistically significant at three and six months. Mean cholesterol changes when compared diabetic & non-diabetic group were statistically insignificant at the end of study. Mean triglyceride level in diabetic & non-diabetic at baseline were

167.6±18.6 & 167.6±14.8 and on comparison with each other changes were statistically significant at six months. Thus the beneficial effect of Salacinol was observed and for further substantiating the finding by prospective study is recommended.

Summary and Conclusion

Present study was conducted at the Department of Nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi between the period of May 2015 to June 2016. Eighty patient of mild to moderate chronic renal failure were included in the study. The salient features of this study are The male patients dominated over the female patients with a male to female ratio of 2:1. Age of the patient ranged from 20yrs onward. Majority of the patient were above 40yrs of age. Commonest symptom was weakness in all the groups followed by anorexia, swelling over body, pallor & sleep disorders. No significant effect of the drug was seen on 24hrs urinary protein, blood pressure, hemoglobin & GFR. In patient treated with Atorvastatin and Salacinol BMI (Body mass index) showed significant decrease (<0.05) on 3 rd and six months. Patient treated with Atorvastatin and Salacinol lipid profile including LDL/HDI, ratio. serum total cholesterol & triglyceride showed significant decrease (<0.05) at three months and at the end of study. In patient treated with Atorvastatin and Salacinol, the changes in Adiponectin level were statistically significant (<().()()l) at three and six months. Thus on overall favorable effect of Salacinol was seen with respect to decrease in lipid profile parameter, Adiponectin, and BMI. However in this study the follow-up period was only six months which is relatively a short period to assess the effect of Salacinol 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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