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Chronic Kidney Disease - Effect of Rhubarb on Lipid Metabolism

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Short title: *Chronic kidney disease – effect of rhubarb on lipid metabolism*

Abstract: ***Objective**: To evaluate effect of rhubarb - A Chinese herbal medicine, with and without ACE inhibitor on lipid metabolism in patients with chronic kidney disease. Material and methods. 45 patients of chronic renal failure on conservative management were randomly allocated to three groups of 15 patients each. Group A was given ACE inhibitors. Group B was given Rhubarb and anti-hypertensive agents other than ACE inhibitors. Group C was given Rhubarb and ACE inhibitors. The patients were followed up and investigated for six months regularly at monthly interval. At every visit, patients were reevaluated for changes in weight, blood pressure, any signs and symptoms of progression of renal disease. Following parameters of all patients were estimated monthly:Hb, TLC, DLC, ESR, Urine C/E, Blood urea, Blood sugar, Serum calcium, Serum creatinine, 24 hour urinary volume and creatinine, Creatinine Clearance, Lipid profile. Results. Maximum improvement in lipid profile occurred in Group C followed by Group B. Least improvement was noted among Group A patients. In Group C, serum cholesterol, serum triglycerides, serum VLDL cholesterol decreased, serum HDL cholesterol increased significantly signifying beneficial effect of ACE inhibitor + rhubarb. Conclusions. There is beneficial effect of Rhubarb + ACE inhibitor on lipid profile in patients of chronic renal failure.***

Keywords: Chronic kidney disease, Rhubarb, Lipid Metabolism, Lipid profile

1. Introduction

Chronic kidney disease (CKD) is often result of hypertension and diabetes. Studies have shown that CKD is associated with increased risk of cardiovascular disease. [1]Dyslipidemiais one of the several factors that have been implicated in increased cardiovascular risk associated with CKD and also in progression of renal damage. [2,3]Cholesterol lowering drugs have been used for many decades with high side effects such as myopathy, liver damage, leucopenia. Synthetic drugs interfere with many biochemical reactions in human metabolism. [4]People with CKD are at increased risk of side effects from cholesterol lowering drugs due to reduced renal excretion, polypharmacy and multiple co-morbidities. [1,5]Therefore, we need a natural lipid lowering medicine with minimal side effects and maximumtherapeutic effect.

Prevention of progression of chronic kidney disease is attempted via a low protein, low phosphate diet. Angiotensin converting enzyme (ACE) inhibitors are widely used along with measures to control problems such as acidosis, electrolyte imbalance and anemia.[6] Traditional Chinese medicine in the form of herbal decoctions has been used extensively in the treatment of uraemic patients for many years and remains cornerstone of treatment in rural areas of China. [7]Rhubarb (Rheum officinale), a Chinese herb has been found effective in preventing progression of chronic kidney disease. [7,8]The aim of this study is to evaluate the effect of rhubarb on lipid metabolism in patients of chronic kidney disease.

2. Material and Methods

This study was carried on 45 patients of chronic renal failure after taking informed consent. None of these patients was on any renal replacement therapy in the form of either maintenance dialysis or renal transplantation.

Inclusion and exclusion criteria

CRF patients with GFR > 20 ml/min were included. However, patients with obstructive uropathy and collagen vascular disease were excluded from the study.

2.1 Methods

Patients were randomly allocated to three groups of 15 patients each. Group A was given ACE inhibitors. Group B was given Rhubarb and anti-hypertensive agents other than ACE inhibitors. Group C was given Rhubarb and ACE inhibitors. All the patients were put on protein and phosphorus restricted diet. Calcium supplementation was done. The patients were followed up for six months regularly at monthly interval. At every visit, patients were reevaluated for changes in weight, blood pressure, any signs and symptoms of progression of renal disease. Lipid profile of patients was estimated monthly along with Hb, TLC, DLC, ESR, Urine C/E, Blood urea, Blood sugar, Serum calcium, Serum creatinine, 24 hour urinary volume, creatinine, Creatinine Clearance.

2.2 Statistical analysis

The various parametes obtained were subjected to paired‘t’ test (within the same group) and unpaired‘t’ test (between two groups).

3. Result

15 (9 M, 6F) patients mean aged 46 years (range 23 – 68 years) were of Group A, 15 (12 M, 3F) patients mean age 46 years (range 21 – 76 years) were of Group B, 15 (6 M, 9 F) patients mean age 45 years (range 15 – 65 years) were of Group C. Clinical features found in patients were general weakness, body aches, gastrointestinal complaints in the form of nausea, vomiting and hiccoughs; dyspnoea on exertion, decreased appetite, swelling over body. Anaemia, hypertension and fluid overload were other common findings. Maximum improvement in symptoms occurred in Group C followed by Group B. Least improvement was noted among Group A patients.

Causes of chronic renal failure in Group A, B and C were Chronic glomerulonephritis (26.6 %, 33.3 %, 26.6 %), Hypertensive nephropathy (13.3 %, 20 %, 20 %), Diabetic nephropathy (26.6 %, 6.6 %, 46.6 %), Chronic pyelonephritis (26.6 %, 20 %, 0 %)and Polycystic Kidney Disease (6.6 %, 13.3 %, 6.6 %) respectively.

There was no significant difference between haematological profile of patients in Group A, B and C. Blood urea increased in Group A and B but the change was not significant ($p>0.05$). In Group C, blood urea decreased significantly after 6 months as compared to baseline ($p < 0.05$) and as compared to Group A ($p<0.05$), signifying beneficial effect of ACE inhibitor + rhubarb.

Rise in serum creatinine in Group A and B was not significant meaning that serum creatinine levels remained static over 6 months period in Group A and B respectively. In Group C, serum creatinine declined significantly as compared to baseline ($p<0.01$) and as compared to Group A ($p < 0.01$) after six months of study.

GFR fell in Group A over 6 months, fall being significant statistically ($p < 0.05$). In Group B, GFR showed improvement but rise was not significant ($p>0.05$). As compared to Group A, rise in GFR was significant ($p < 0.05$). In Group C, GFR rose significantly over 6 months as compared to baseline ($p < 0.05$) and as compared to Group A ($p < 0.001$). Serum Calcium rose significantly in Group C as compared to baseline ($p < 0.001$) whereas in Group A & B change was not significant statistically.

Serum Cholesterol significantly decreased in Group B ($p < 0.01$) and Group C ($p < 0.001$). Change was not significant in Group A ($p>0.05$). Fall in Serum triglycerides was statistically significant in Group A ($p<0.01$), Group B ($p < 0.05$) and Group C ($p < 0.001$). Serum VLDL cholesterol fell significantly in Group B ($p < 0.05$) and Group C ($p < 0.001$). In Group C, decrease was statistically significant as compared to Group A ($p<0.05$). Serum LDL Cholesterol rose significantly in Group B ($p < 0.001$) but the change was not significant in Group A& C ($p>0.05$). Serum HDL Cholesterol increased significantly in both Group B ($p < 0.001$) and Group C ($p < 0.001$), but change was not significant in Group A ($p>0.05$), possibly indicating beneficial effect of rhubarb in improving lipid profile.

4. Discussion

It is widely believed that once there has been sufficient initial damage, no matter what the cause, renal failure inevitably progresses. [9] To slow the progression of chronic renal failure and amelioration of uraemic symptoms protein restriction (0.6 g protein/kg/day) [10, 11] phosphate restriction (5-10 mg/kg/day) and calcium supplementation [12, 13] is used. Progression of renal disease in humans is slowed by adequate control of hypertension. [10,14] ACE inhibitors and Ca channel blockers are renoprotective. [14]Becker and colleagues demonstrated the potential capacity of the ACE inhibitor to slow the rate of progression of chronic renal failure, even in patients with very low glomerular filtration rates. The protective effect of enalapril was independent of blood pressure control. [10]

Out of various chemical components of rhubarb, Anthraquinones – Rhein[15] and Emodin [16], Stilbenes [17, 18] and Chromones [17] improve lipid disorders. There is a synergistic effect among these components.

Study of lipid profile showed that serum cholesterol decreased more in patients being given Rhubarb. This cholesterol lowering effect of rhubarb was also seen in animal model of chronic renal failure. [19, 20]

Serum triglyceride showed maximum decrease in patients receiving Rhubarb. This is in agreement with study conducted to study effect of rhubarb on lipid abnormalities in chronic renal failure. [21]

Rhubarb lowered serum VLDL cholesterol significantly as was previously shown in another study conducted in China. [21]

Rhubarb has equivocal effect on levels of serum LDL cholesterol. Similar results were reported by Leishi Li and coworkers in their prospective trial. [22]

Serum HDL cholesterol was significantly increased by rhubarb in patients of chronic renal failure. This beneficial effect of rhubarb was also seen in animal model of CRF and other studies in CRF patients. [21,23,24]

Thus rhubarb exerted a beneficial effect in improving lipid profile. This finding is in agreement with results of other studies.[19,20] Abnormal lipid metabolism causes progressive loss of renal functions because increased lipids cause increased mesangial cell proliferation, mesangial matrix and glomerular macrophages.[25] Thus, improvement in renal profile caused by rhubarb might be helpful in preventing the development of glomerulsclerosis.

The clinical trial on chronic renal diseases conducted by us clearly showed that the improvement of lipid profile is more marked with rhubarb than with ACE inhibitors. Although the modes of action of these two drugs differ, one

presumably working largely through the regulation of glomerular hemodynamics and the other mainly via the metabolic pathway, nevertheless they both exert beneficial effects on the progression of chronic renal failure. Our study also clearly demonstrated that their therapeutic effects are additive.

5. Conclusion

On the basis of the results of the present study it can be concluded that rhubarb had a beneficial effect on lipid profile of patients. Moreover, the beneficial effect was more when rhubarb was used in combination with ACE inhibitors. However, because of small number of patients and short follow up, further studies with longer follow up and larger number of patients are warranted which will help in establishing the role of this treatment modality in management of patients of chronic renal failure.

6. Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1

S. no	Parameter	Group	Baseline(a) Mean ± S.D.	3 months(b) Mean ± S.D.	6 months(c) Mean ± S.D.	p value paired (a)vs(b)	p value paired (a)vs(c)
1	Blood urea (mg %)	A B C pA/ B p A / C	88.33±38.84 84.40±28.63 70.53±28.52 N.S. N.S.	98.20±51.36 86.33±48.37 65.00±23.60 N.S. N.S.	103.00±56.06 95.67±49.76 52.93±27.18 N.S. < 0.05	N. S. N. S. N. S.	N. S. N. S. <0.05
2	Serum Creatinine (mg %)	A B C p A/ B p A / C	2.59±1.32 2.47±1.27 2.47±0.99 N.S. N.S.	3.41±2.03 2.64±1.76 1.70±0.98 < 0.05 < 0.05	3.84±2.49 2.73±1.71 1.49±0.77 N.S. < 0.01	N. S. N. S. <0.05	N. S. N. S. <0.01
3	Glomerular filtration rate (ml/min.)	A B C p A/ B p A / C	35.73±16.16 32.13±10.33 43.87±24.12 N.S. N.S.	32.80±11.72 33.07±14.30 57.53±29.40 N.S. < 0.05	24.33±10.72 37.53±21.90 59.47±24.37 <0.05 < 0.01	N. S. N. S. <0.05	N. S. N. S. <0.01
4	Serum Calcium (mg %)	A B C p A/ B p A / C	8.83±0.69 8.73±0.84 8.06±1.13 N.S. < 0.05	8.83±0.61 8.79±0.55 8.80±0.65 N.S. N.S.	8.81±1.13 8.77±0.45 9.25±0.52 N.S. N.S.	N. S. N. S. <0.05	N. S. N. S. <0.01
5	Serum Cholesterol (mg %)	A B C p A/ B p A / C	193.53±40.80 183.93±31.59 212.47±46.77 N.S. N.S.	196.87±40.28 185.00±35.01 185.13±32.54 N.S. N.S.	182.93±39.13 170.53±28.09 184.20±36.07 N.S. N.S.	N. S. N.S. <0.01	N. S. <0.01 <0.001
6	Serum Triglycerides (mg %)	A B C p A/ B p A / C	155.60±19.36 163.60±23.04 177.13±41.28 N.S. N.S.	144.53±22.35 151.47±23.69 166.60±37.11 N.S. N.S.	146.40±16.02 142.67±22.10 149.87±28.94 N.S. N.S.	N. S. N.S. N.S.	<0.01 <0.05 <0.001
7	Serum VLDL Cholesterol (mg %)	A B C p A/ B p A / C	28.87±6.48 34.93±9.35 43.87±15.20 N.S. <0.01	28.33±6.74 32.40±9.91 39.13±11.42 N.S. <0.01	28.93±6.41 30.33±8.35 36.20±11.03 N.S. <0.05	N. S. N.S. <0.01	N.S. <0.05 <0.001
8	Serum LDL Cholesterol (mg %)	A B C p A/ B p A / C	89.07±20.63 92.27±27.92 103.73±26.94 N.S. N.S.	86.53±17.14 99.00±29.91 102.60±26.64 N.S. N.S.	86.60±18.06 100.40±30.45 106.00±26.31 N.S. N.S.	N. S. <0.01 N.S.	N.S. <0.001 N.S.
9	Serum HDL Cholesterol (mg %)	A B C p A/ B p A / C	44.20±2.86 40.80±8.27 41.20±4.48 N.S. N.S.	44.20±4.23 42.47±8.40 44.07±4.80 N.S. N.S.	43.47±2.88 44.80±8.57 45.93±4.77 N.S. N.S.	N. S. <0.05 <0.001	N.S. <0.001 <0.001

P value unpaired Group A versus Group B = p A/B, P value unpaired Group A versus Group C = p A/C