ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 12, pp. 22428-22434, December, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

REDUCING RATE OF RENAL DETERIORATION IN A LOW RESOURCE SETTING IN DEVELOPING COUNTRY-A FOLLOW UP STUDY FROM SOUTH INDIA

Anitha Rani A[1]., Vijay Viswanathan*[2]., Jaiganesh. M[3]., Hemanga Barman[3] and Vanjinathan[3]

[1]Kidney Department, Prof. M. Viswanathan Diabetes Research Centre
[2]M.V. Hospital for Diabetes & Prof. M. Viswanathan Diabetes Research Centre, (WHO Collaborating Centre for Research, Education and Training in Diabetes),
[3]Consultant Diabetologist, M.V. Hospital for Diabetes

DOI: http://dx.doi.org/10.24327/ijrsr.2017.0812.1266

ARTICLE INFO

Article History:

Received 05th September, 2017
Received in revised form 08th October, 2017
Accepted 10th November, 2017
Published online 28st December, 2017

Key Words:

Renal deterioration, eGFR,
Diabetic Kidney Disease, KDIGO

ABSTRACT

Objective: To determine the reducing rate of renal deterioration in a low resource setting among Indian Patients with CKD due to Diabetic kidney disease. **Methods:** A Prospective follow-up study was conducted among T2DM patients attended outpatient clinic over a period of one year in a tertiary care hospital. A total of 236 T2DM patients fall under Moderate Risk (MR) and High Risk (HR) categories (KDIGO classification) were included. Patients were randomized in to two groups. Group I (n = 121), received routine care of treatment and group II (n = 115) received an intensive blood pressure, lipids and glycemic control along with educational reinforcement with regular follow up. **Results:** All biochemical parameters were similar at baseline in both groups. However a significant reduction was observed at the end of follow-up period in BMI ($p<0.0001$), Systolic BP ($p<0.0001$), Diastolic BP ($p<0.0001$), HbA1c ($p<0.0001$), creatinine ($p=0.004$), Urea ($p<0.0001$), Total-cholesterol ($p =0.0009$), LDL-cholesterol (<0.005), HDL-Cholesterol ($p=0.003$) and increased eGFR ($p<0.0001$), in group II when compared to group I. At baseline in Group I, 58 and 63 patients and Group II, 56 and 59 patients were in MR and HR category. At the end of follow-up period, 30.35 % of patients become normo-albuminuric, in group II from MR category. In group I, 20.68% of subjects progressed from MR to HR and 17.46% progressed from HR to VHR category, whereas in Group II none of the patients progressed from MR to HR. Similarly in Group I, 12.69 % of HR patients were converted to MR, where as in Group II, higher percentage of HR (20.33%) patients were converted to MR category. **Conclusion:** Study finding highlighted that intensive multi factorial intervention can lower the risk of diabetic nephropathy among T2DM patients who are at higher risk and a combined intensified management strategy is superior over conventional therapy.

INTRODUCTION

Diabetes Mellitus is a complex disorder which often combined with dyslipidemia, hypertension, and adiposity in addition with hyperglycemia, which leads to higher risk of micro and macro vascular complications. In the past decades a number of studies focused on the intervention for risk factors have recommended multifactorial treatment for these common disorders (1). It is expected that the global prevalence of diabetes will reach 642 million by 2040 (2). Nearly 40 percent of the individuals with diabetes will develop CKD (Chronic Kidney Disease), (3) and significant number of individuals will developed End Stage Renal Disease (ESRD). With the increasing number of newer agents under development which targets newly identified mechanistic pathway which underlies diabetic kidney disease (DKD). It is timely to reflect on what has been learned in order to better optimize both the care of affected patients as well as provide a road map for future research.

The onset of microalbuminuria is a typical characteristic of Diabetic nephropathy, which further progress to overt proteinuria. The adverse renal and cardiovascular risks can be reduced through reducing microalbuminuria (4 - 6). ACE inhibitors (Angiotensin-converting enzyme) and ARBs (angiotensin II receptor blocker) were established as a first line drugs, which prevents the development and progression of

Corresponding author:* **Vijay Viswanathan
M.V. Hospital for Diabetes & Prof. M. Viswanathan Diabetes Research Centre, (WHO Collaborating Centre for Research, Education and Training in Diabetes),

Diabetic nephropathy through reducing microalbuminuria. There are many drugs which effectively reduce proteinuria in diabetic nephropathy and among these drugs cilnidipine (4th generation calcium channel blocker) is a distinctive dihydropyridine derivative. In patients with diabetes, the sympathetic nervous activity is enhanced which resulted in constriction of the efferent arterioles and increased intraglomerular pressure (7). Cilnidipin dilates both afferent and efferent arteriole through its effect on N – type calcium channels, which to the greater extent decreases the urinary albumin as well as protein excretion (8,9). As the mechanism of action is different in both ACE inhibitors and cilnidipine in reducing the microalbumin, both can be combined to obtain the benefit of both classes of drugs.

Microalbuminuria is considered as a primary and early marker for micro vascular complications unfold the risk of progression of CKD. For CKD the earlier KDOQI (Kidney Disease Outcomes Quality Initiative) classification categorizes the stages of CKD based on eGFR alone (10). As albumin is considered as an independent predictor for ESRD, the new classification scheme KDIGO (Kidney Disease Improving Global Outcome) (11), combines albumin and eGFR category, which influences the treatment regimens. Further the different colour codes (Green - Low Risk, Yellow - Moderate Risk, orange - High Risk and red - Very High Risk) in KDIGO classification, specifies the risk based on the degree of albuminuria and eGFR. Thus main objective of the present study was to determine the reducing rate of renal deterioration among diabetic patients in moderately increased risk (MR) and high risk (HR) category of KDIGO classification in a low resource setting among Indian Patients with CKD due to Diabetic kidney disease.

Research design and methods

The hospital based prospective follow up study was conducted among patients with T2DM, who attended the outpatient Diabetes clinic over a period of one year (January 2016 to June 2017) in a tertiary care hospital in India. Present study included all T2DM patients aged between 25 – 60 years (both genders) with diabetic duration above 5 years, hypertension, persistent micro or macro albuminuria. Patients who falls in MR (yellow colour) and HR (Orange colour) categories (CKD stage 2 & 3) of KDIGO classification (11) were included in the study. KDIGO classification is based on eGFR and albuminuria and categorized in to low risk (LR), Moderate risk (MR), High risk (HR) and Very High risk (VHR) groups. MR includes A1G3a, A2G1, A2G2 and HR includes A1G3b, A2G3a, A3G1, and A3G2 accordingly (Fig 1).

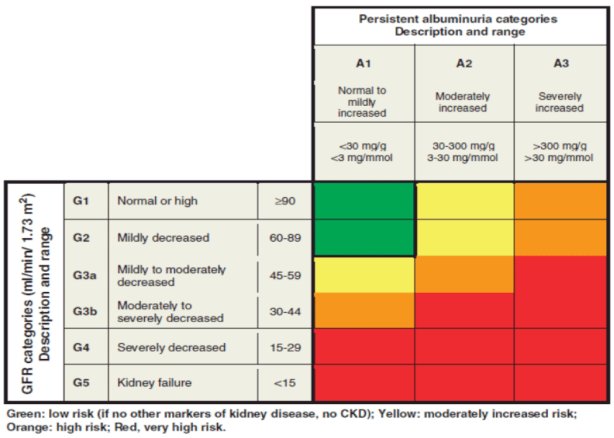

Figure 1 Prognosis of CKD by GRF and Albuminuria (11)

Patients with type1 diabetes and gestational diabetes, normal blood pressure (BP), eGFR <30 ml/min, and those with incomplete laboratory data, in consistent micro and macro albuminuria, urinary tract infection and lactating women were excluded from the study. Further patients don't follow the medication and who were not on regular follow up were excluded from the study.

All the patients included in the study were screened for laboratory investigations, medications, demographic and anthropometric details such as age, gender, duration of diabetes, duration of hypertension, family history of diabetes and family history of nephropathy were recorded and Body Mass Index (BMI) was calculated. All the subjects were on treatment with oral hypoglycemic agents and or with Insulin and known hypertensive's were on antihypertensive medication. Biochemical parameters such as fasting and postprandial glucose, HbA1c, lipid profile, urea, creatinine, urinary protein and urinary albumin values were recorded. All biochemical parameters were estimated using BS400 biochemistry auto analyzer, HbA1c was measured using HPLC method using variant turbo equipment (Bio-Rad). Serum creatinine was estimated by Jaffe's kinetic method, urinary albumin was estimated by immuno-turbidimetric procedure. Urinary protein was determined using pyrogallol method. EGFR was calculated based on CKD - EPI equation, developed in 2009 (12) and intended to be more generalizable across various clinical settings.

Based on the inclusion and exclusion criteria, a total of 264 patients in MR and HR categories based on KDIGO classification with dyslipidemia and hypertension were recruited in the study. Based on the randomization chart, patients were assigned to control group and intensive group. Group I (control group: n= 131) received routine care in the diabetic clinic, and in Group II (intervention group: n=133), to control BP, lipids and micro/ macroalbuminuria, β blockers, statins (Atorvastatin 10mg) ARB and cilnidipin was recommended to achieve target Bp of 140/ 80mmHg and lipids (Total Cholesterol <200 mg/dl, LDL <100 mg/dl, HDL >40 mg/dl, Triglyceride <150 mg/dl). Apart from this for intervention group, well trained diabetic educators, counsellors and dieticians reinforced the diabetic education on physical activity and dietary habits. The primary focus is on medication adherence and lifestyle modification through health eating habits and physical activity. Goal setting, problem solving and planning in advance for regular follow-up visits along with telephonic reminders were majorly focused for these patients. A total of 28 patients were excluded from the study due to lost follow up and lack of medication adherence, which ended in 121 patients in control group and 115 patients in intervention group. Ethical clearance from the institutional ethics committee was obtained.

Statistical analysis

The results were presented as mean ± standard deviation (SD) and percentage. Chi-square test was used to compare the dichotomous/categorical variables. The unpaired *t*-test was used to compare two means. One-way analysis of variance was used to detect significant differences in the mean values. $P < 0.05$ was considered significant. All the analysis was carried

out using Statistical Package for Social Sciences version 16 (Chicago, Inc., USA).

RESULTS

The final analysis was done with the data of 236 type 2 diabetic patients in MR and HR categories based on KDIGO classification with dyslipidemia and hypertension and they were followed up for the period of one year. Of 236 patents, 115 patents were followed up intensively. The demographic, anthropometric details of the study population were presented in table 1. In both the groups' majority of the participants were males with the diabetic duration of 12.2 and 11.5 years in group I and Group II, respectively. Majority of the patients were on mixed diet (non vegetarians). Presence of family history of diabetes (group I: 65.28 %; group II: 53.91%) family history of diabetic nephropathy (group I: 11.39 %; group II: 12.9 %) and smoking (group I: 21.7%; group II: 19.35 %) were presented in percentage for the study groups. Majority of the patients (52.06%) were on Oral hypoglycemic agent (OHA) in Group I, whereas 42.60 percent of the subjects were on combination of OHA and insulin in group II. The anti hypertensive treatment plan for both group was also presented in table 1.

Table 1 Demographic characteristics of the study groups at baseline

Characteristic		Group I (n = 121)	Group II (n = 115)
Ages (yrs)*		56.98 ± 8.28	58.24±7.51
Gender (M:F)*		78:43	62:53
Duration of diabetes (yrs)*		12.2 ± 5.62	11.5 ± 4.95
Duration of hypertension (yrs)*		5.89 ± 6.13	5.6± 3.14
Family history of diabetes		72 (59.50)	62 (53.91)
Food habits vegetarians/ non vegetarians		63 (52.06)	63 (54.78)
Smoking		17 (21.7)	12 (19.35)
Family History of Diabetic nephropathy		9 (11.39)	8 (12.9)
Antidiabetic treatment	OHA	63 (52.06)	41 (35.65)
	Insulin	20 (16.52)	25 (21.73)
	OHA + Insulin	38 (31.40)	49 (42.60)
Anti hypertensive treatment	ARB	29 (23.96)	-
	ACEI	13 (10.74)	-
	Diuretics	9 (7.43)	
	ARB with Cilnidipin	25 (20.66)	101 (87.82)
	Cilnidipin	-	14 (12.17)
	ARB with amlodipin	23 (19.00)	-
	ARB/ ACEI with Diuretics	22 (18.18)	-
	α – blockers	10 (8.26)	14 (12.17)
	β – blockers	38 (31.40)	115 (100)
	Others	85 (70.24)	78 (67.82)
	N acetyl cysteine		
Lipid lowering drug	Atorvastatin	42 (34.7)	115 (100)
	Other statins	79 (62.3)	-

*values are presented in mean ± SD; Values are in n (%).

At baseline significant difference was not observed in all the biochemical parameters, among the study groups (Table 2). However at the end of the follow up period (12 months), significant difference was observed between control and intervention group in parameters such as, BMI ($p<0.0001$), Systolic BP ($p <0.0001$), Diastolic BP ($p<0.0001$), HbA1c ($p<0.0001$), serum creatinine ($p=0.004$), eGFR ($p <0.0001$), Urea ($p <0.0001$), Total cholesterol ($p =0.0009$), LDL cholesterol (<0.005), HDL Cholesterol ($p = 0.003$) (Table 3.)

Table 2 Comparison of biochemical parameters in the study groups at baseline

Group Variables	Group I (n=121)	Group II (n=115)
BMI (Kg/m^2)	28.02±2.35	27.63±1.24
Systolic BP (mmHg)	151.32±13.84	149.91±13.07
Diastolic BP (mmHg)	90.82±6.40	89.73±6.81
HbA1c %	8.69±1.74	8.37±1.69
Creatinine (mg/dl)	1.48±0.73	1.54±0.95
eGFR ml/min/1.73sqm body surface area.	52.5±8.59	53.74±4.21
Urea (mg/dl)	57.97±37.27	56.00±34.74
Total Cholesterol (mg/dl)	236.86±61.43	239.16±63.08
LDL – cholesterol (mg/dl)	124±33.89	130.53±38.5
HDL – cholesterol (mg/dl)	36.89±14.93	35.37±14.42
Triglyceride (mg/dl)	189.32±83.16	178.47±86.27

Table 3 Comparison of biochemical parameters in the study groups at the end of follow up period

Group Variables	Group I (n=121)	Group II (n=115)
BMI (Kg/m^2)	28.43±2.54	27.08±1.56***
Systolic BP (mmHg)	135.88±21.37	120.86±20.50***
Diastolic BP (mmHg)	80.572±6.98	76.78±7.07***
HbA1c %	9.46±1.7	7.6±0.87***
Creatinine (mg/dl)	1.5±0.60	1.27±0.62 **
eGFR ml/min/1.73sqm body surface area.	41.92±11.66	65.09±4.53***
Urea (mg/dl)	46.90±38.24	37.58±21.01***
Total Cholesterol (mg/dl)	188.10±42.32	172.56±26.09**
LDL – cholesterol (mg/dl)	95.68±27.95	87.07±17.26*
HDL – cholesterol (mg/dl)	40.67±16.62	46.88±15.65*
Triglyceride (mg/dl)	147.44±51.26	140.54±44.92

A p vale < 0.05 is considered statistically significant. P<0.05*, P< 0.001**, P< 0.0001***

In the present study, during the follow up period of 3rd, 6th and 12th month, the risk factors such as HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, systolic and diastolic blood pressure in intensive group (group II) showed downward trend and eGFR improved (fig 2.), whereas in the control group (group I) all the risk factors increased and eGFR decreased.

Based on KDIGO chart, at the base line 58 (47.93%) and 56 (48.69%) patients were in moderate risk category and 63 (52.06%) and 59 (51.30%) patients were in high risk category in Group I and Group II respectively (Fig 3.). At end of the follow up period, in group I, 10.7% of patients become normo albuminuric, whereas in group II higher percentage (30.35%) of patients becomes normo albuminuric from MR category. In group I, 20.68% (n=12) of subjects progressed from MR to HR and 17.46% (n=11) progressed from HR to VHR category, where as in Group II none of the patients progressed from MR to HR and only 8.47% (n=5) of patients progressed from HR to VHR category. Similarly in Group I, 12.69 % of HR patients were converted in to MR, where as in Group II, higher percentage of HR (20.33%) patients were converted in to MR category.

DISCUSSION

Diabetes is the commonest cause of ESRD (End Stage renal disease) worldwide, nearly in 20-40% of the ESRD patients it is considered as the etiological factor. Among T2DM patients, microalbuminuria is a known predictor of poor renal outcome (13 - 15). If T2DM patients with microalbuminuria were left untreated, it progress to macroalbuminuria and overt diabetic nephropathy.

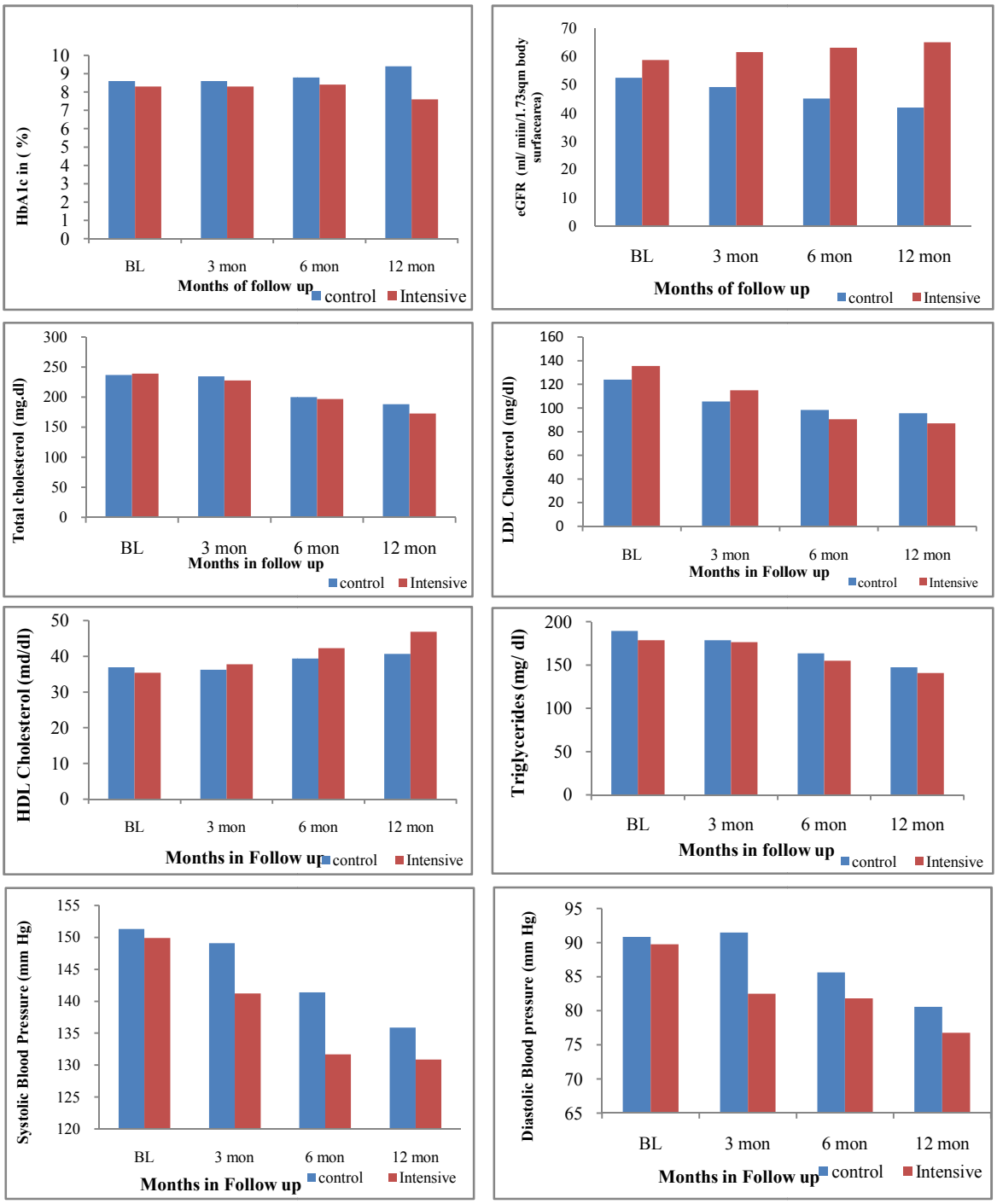

Figure 2 Changes in the selected risk factors during the follow-up period in the study group

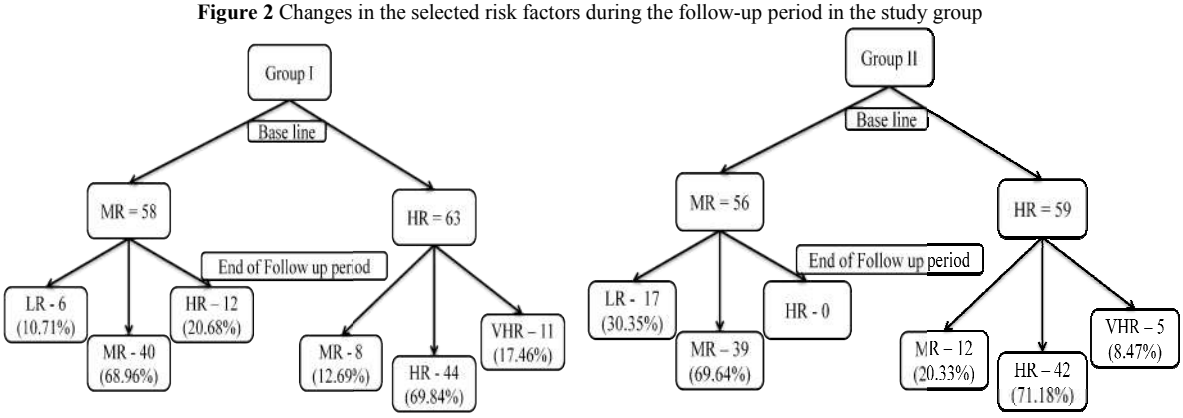

Figure 3 KDIGO risk categories at the end of the follow up period in both the groups

A combined and intensified management strategy is superior to a conventional treatment. In the present study all the biochemical parameters were similar at baseline but differ significantly at the end of the follow up period in group II, which shows that in intensive follow up was superior to conventional therapy in maintaining and controlling, Blood pressure, Triglyceride, total cholesterol, LDL, HDL and glycated hemoglobin. During the study period, the risk factors in group II has reduced primarily because of the intensive treatment along with the reinforcement of patient's education. In past decade, a large number of prospective studies highlighted the list of modifiable risk factors for vascular complications, which includes hyperglycaemia, hypertension, dyslipidemia and smoking. Earlier studies highlighted that the effective reduction in blood pressure and the lipid lowering is evident after a year (16 - 20). However the effect on hyperglycaemia on diabetes-related end points occur even later (21). T2DM patients with uncontrolled diabetes and Bp are at the higher risk of developing diabetic nephropathy. In a study conducted by Vijay et al., 2012, highlighted that age, prolonged duration of diabetes, increased systolic blood pressure, poor glycaemic control and presence of retinopathy were significantly associated with the progression of diabetic nephropathy (22). In an earlier study renal risk was stratified using eGFR and albuminuria, and the finding showed that there is significant association between the Diabetic retinopathy and the renal risk categories (23). Many surveys emphasized the slow progress in reaching the treatment goals in preventing the vascular complications related to diabetes (24, 25). Thus, the effective early intervention may prevent the risk factor for vascular complications.

Present study finding showed that Group II did better than the Group I, however in both the groups the intake of ACEI/ARB is almost similar on top of this the intervention group (group II) has got cilnidipin. Therefore probably cilnidipin is providing additional benefit in addition with ACEI/ARB in reducing eGFR. Thus confirms intensive follow up along with the appropriate treatment plan leads to better improvement in eGFR. The difference in drugs and their combination may also contribute to the long term outcome. Further along with the treatment plan tight monitoring of dietary habits, physical activities and medication adherence reduces the renal deterioration. Fujita *et al*. emphasizes the use of ACE inhibitor along with cilnidipine, and compared it with amlodipin and highlighted that the subjects treated with cilnidipine shows more decrease in protrinuria than those patients treated with amlodipine (26). The current study finding is in line with the study conducted by Hatta et al., (27), among CKD patients, cilnidipine shows anti hypertensive effect, along with the reduction in proteinuria. In a study conducted among the proteinuric hypertensive patients, amlodipin shows significant increase in protrinuria whereas increase was suppressed in cilnidipine group (28). Likewise, significant reduction of urinary protein excretion and serum triglyceride among patients with diabetes was observed using cilnidipin (29).

Potential treatment plans are available to prevent micro vascular and macro vascular complications among T2DM patients. Specifically, there exist evidence for the benefit of single factor intervention, to control of lipids, glucose and hypertension using a regular aspirin (30, 31). There is, perhaps the limited literature on the effect of multifactorial intervention and its application in clinical practice, on micro vascular complications among T2DM patients. Present study intended to address this gap through intensive multifactorial intervention against the routine care of treatment. The early and continuous intervention focused on reducing the risk factors is essential among the subjects with diabetes who are at moderate and high risk category based on KDIGO classification (includes both albuminuria and eGFR). Intervention is focused on the lifestyle modification through physical activity (regular exercise) and dietary modifications (reduction in dietary fat intake) and medications aimed to control HbA1c (<7%), Blood pressure (< 140/80mmHg) and lipids (Total Chol <200 mg/dl, LDL <100 mg/dl, HDL >40 mg/dl, Triglyceride <150 mg/dl). It is based on the current study finding and the earlier evidence from Steno 2 study that it may be possible to achieve the higher benefits through utilizing the supplementary evidence based approach.

CONCLUSION

The quality of diabetes care in developing countries like India still remains in a suboptimal level, in spite of the availability of the effective treatment plans and preventive strategies for comorbid conditions of diabetes. The present study highlights the importance of multifactorial interventions in clinical practice and the potential benefits in terms of methodological application of the existing knowledge. Thus it is possible to prevent progression of Diabetic kidney disease even in a low resource setting if adequate multi- factorial measures are taken to control diabetes, Bp and lipids. The intensive multi factorial intervention can lower the risk of diabetic nephropathy. It is recommended that the policy makers in healthcare sectors should focused on the intervention based on the multiple risk factor in T2DM patients who are in high risk is cost effective.

Conflicts of interest

There are no conflicts of interest in the study

Authors' contributions: AR was involved in study design, data collection, interpretation and preparation of manuscript. VV was involved in study design, treatment plan, interpretation and review of the final version of manuscript. JG, HB and VN were responsible for the treatment plan of the patients.

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How to cite this article:

Anitha Rani A *et al*.2017, Reducing Rate of Renal Deterioration In A Low Resource Setting In Developing Country-A Follow Up Study From South India. *Int J Recent Sci Res.* 8(12), pp. 22428-22434.
DOI: http://dx.doi.org/10.24327/ijrsr.2017.0812.1266

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