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A Prospective Randomised Case Control Study on the Role of Probiotics in Controlling Chronic Kidney Disease Progression

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To study the role of probiotics in controlling chronic kidney disease progression.
Sample: To correlate renal parameters like creatinine, urea, uric acid, PCR in patients with chronic kidney disease.
Study Design: It is a Prospective case control study
Place and Duration of the Study: Department of Nephrology, Santhiram Medical college and General Hospital, between December 2020 – May 2021.
Methodology: We included 150 patients with chronic kidney disease from in and out patient departments. In this study patients are divided into two groups; case and control group. Control group is treated with normal conventional therapy whereas the case group is treated with conventional therapy along with probiotics. The lab parameters like creatinine, PCR, urea, uric acid were analyzed before and after the therapy in both groups.
Results: The lab parameters were analyzed by paired student`s t- test and the p value of these

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parameters were found to be in control group creatinine ranges from (4.42+/- 2.84 to 3.54+/- 2.73) and in case/ interventional group creatinine ranges from (5.13+/-2.43 to 2.29+/-1.57) shows <0.001. It shows significant improvement in these parameters in both control and case group. CKD stages were analyzed by Chi- square test, the p value of CKD stages in case group was found to be <0.0001 and in control group it was found to be 0.03.

Conclusion: It shows that there is significant improvement is found in both interventional (case) and non-interventional (control) groups. But more betterment is observed in case group than in control group. Hence probiotics are used as a natural bio-treatment to control the progression of CKD and improves the quality of life.

Keywords: Chronic kidney disease; protein – to – creatinine ratio; probiotics; creatinine.

1. INTRODUCTION

CKD is becoming a major worldwide health issue. The present burden of disease might be due to change of the underlying pathogenicity of CKD.

Chronic kidney disease has been subdivided into 5 stages.

Stage 1: normal eGFR >90 ml/ min/1.73 m2 and persistent albuminuria
Stage 2: EGFR between 60-89 ml/min/1.73m2
Stage 3: EGFR between 30-59 ml/min/ 1.73 m2
Stage 4: EGFR between 15 - 29 ml/min/1.73m2
Stage 5: EGFR <15 ml/min/1.73m^2 [1]

Kidneys are physiological highly active with high oxygen requirement. In CKD earlier, interstitial capillaries become increasingly permeable (kidney capillary leak syndrome) sense that many plasma proteins that normally never reached the renal interstitium are able to do so and activate an inflammatory responses [2]. Chronic kidney disease can be an illustration of another chronic illnesses that are causing end organ renal damage, such as Diabetes mellitus and hypertension [3].

Lifestyle modifications such as weight reduction, exercise and dietary manipulations can be effective. Approaches to control hypertension by means of dietary salt restrictions and diets rich in Fruit and Vegetables and low in saturated fat have been recommended [4]. Hence the application of probiotics to decline the progression of CKD is an emerging area of medicine and a new hope for the CKD patients [5]. The term "probiotics" was introduced in 1965 by Lilly and Stillwell. Probiotics were defined as microbially derived factors that stimulate the growth of other organisms. In 1989, Roy Fuller emphasized the requirement of viability for probiotics and introduced the idea that they have a beneficial effect on the host. Species of lactobacillus and bifidobacterium are most commonly used as probiotics, but the yeast saccharomyces cerevisiae and some *E. coli* and bacillus species are also used as probiotics [6].

The dose needed for probiotics varies greatly depending on the strain and product. Although many over-the-counter products delivery in the range of 1 to 10 billion CFU/dose, some products have been shown to be efficacious at lower levels while some require a substantially higher levels [7]. The mechanism of action of probiotics includes few steps such as inhibition of adhesion, immunomodulation, production of antimicrobial substances, modification of toxin -and toxin receptors, competition for nutrients, reduction in bacterial translocation and anti-inflammatory signalling with the epithelium [8]. Probiotics have been proven that it is possible to enhance both innate and adaptive arms of the host immune system [9]. Probiotic strains have the ability to promote the differentiation of B cells and increase the production of secretory Ig A. Polymeric Ig A sticks to the mucus layer overlying the gut epithelium and binds to pathogenic microorganisms, thereby reducing their ability to gain access to endothelial cells. Other probiotic strains stimulate the innate immune system by signalling to dendritic cells which then travel to mesenteric lymph nodes where the induce regulatory T cells and the production of anti-inflammatory cytokines (interleukin-10 and transforming growth factor β) [6]. The first aim of administering probiotics during CKD is URS removal [10]. Therefore as the production of URS, mainly generated by protein degradation, could not be completely blocked by a low protein diet, reducing the conversion of amino acids into tri methylamine n oxide, p- cresyl sulfate or indoxyl sulphate by modelling intestinal microbiota could be considered as an additional beneficial intervention [11]. Because of the potential beneficial effects of probiotics (reducing

inflammation and uremic toxins) it is possible that renal function improve during treatment. However studies performed in CKD used the markers such as serum urea, uric acid, PCR, creatinine. Probiotic supplementation is generally preferred over food sources because of high potassium, Phosphorus, Sodium and sugar content of any food containing probiotics. The hypothesis being tested is that specially formulated probiotic dietary supplement product comprised of defined and tested microbial strains may afford Reno protection and possibly alleviate the symptoms of uremic syndrome. Health Promotion is the leading theme in the probiotic concept which implies that there should be no adverse effects linked to an intake of probiotics [12].

2. METHODOLOGY

A prospective randomized case control study which involves two groups such as case and control. Control group is treated with the normal conventional therapy whereas the case group is treated with the conventional therapy along with probiotics. The study was conducted in nephrology department of a tertiary Care Hospital, for a period of six months and this study was included the patients of all ages. The data was collected from the case sheets, the patient reports who had meeting the nephrology department with CKD symptoms, interviews with reporting persons or clinicians, patients or patient Guardians, use of past medication history, which was generally obtained from past prescriptions. The study was conducted in Santhiram Medical College and General Hospital, Nandyal, after the approval of Institution human ethics committee at Santhiram Medical College and General Hospital, Nandyal this study was initiated. During the study period of six months of this study the total sample size was 150 patients this study included patients attending in nephrology in and out patient department are included in the study and the patients who had kidney transplantation and pregnant and lactating women or excluded from the study. The necessary information was collected by interviewing the patients using the patient data profile form.

The results were analyzed and tabulated statistically by using SPSS (statistical package for social science) Chi-square test is used to compare the analyzed the stages and the P value of case group is < 0.001 is statistically taken as significant and the P value of control group is 0.03 is taken as significant. Paired student T test is used to analyze the lab parameters. The P value of lab parameters creatinine, urea, uric acid, PCR in case group are found to be <0.001 and the p-value of lab parameters of creatinine, urea, uric acid, PCR in control group were found to be < 0.001 both are statistically significant but the probiotics are more significant.

3. RESULTS AND DISCUSSION

The prospective observational study was conducted for a period of six months from December 2020 – May 2021 in all outpatient and inpatient departments at a tertiary care teaching hospital, Nandyal

6.1 TREATMENTCHART

Casegroup	Controlgroup
Antibiotics	Antibiotics
Proton pump inhibitors	Proton pump inhibitors
VitaminD3must	VitaminD3must
Multivitamin supplements	Multivitamin supplements
Nutritional supplements	Nutritional supplements
Iron supplements	Iron supplements
Diuretics	Diuretics
Probiotics	

3.1 Probiotic: T. Auxipro Composition

Streptococcus thermophillus - 4.5billioncfu Lactobacillus acidophilus –4.5 billion cfu Bifidobacterium longum – 4.5 billion cfu Bacillus coagulants–1.5billioncfu
Fructooligosaccharides-100mg

Among total CKD patients, 72% are males and remaining 28% are females. It shows that males are more likely to suffer from kidney failure sooner than women.

More than 60% of the CKD patients are in between the age groups of 40-50 and 50-60. Hence greater than 40 years age people are more prone to CKD condition.

Among 150 members who are suffering with CKD, about 68% of the patients are hypertensive and diabetic. Hence hypertension along with diabetes would more likely prone to CKD than hypertension and diabetes alone.

Among 150 CKD patients, 41.3% of patients have 6-8gms/dl of HB levels and 37.3% of patients have HB levels of 8-10gms/dl.

Table 1. Gender wise distribution of CKD patients

Category	No. of Patients	Percentage (%)
Males	108	72%
Females	42	28%

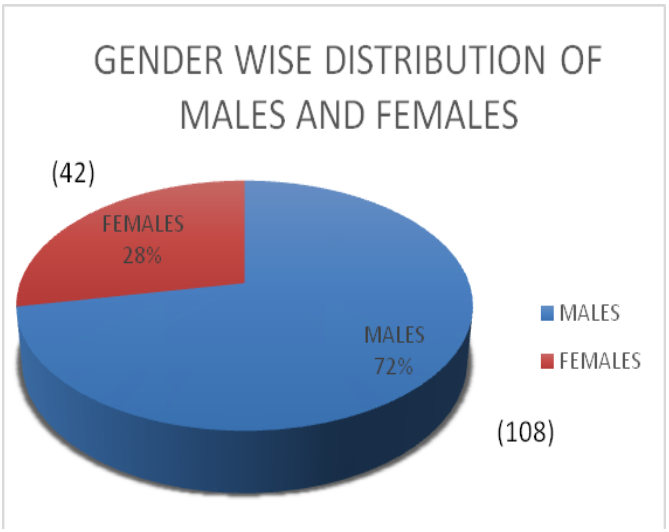

Fig. 1. Pie chart showing gender wise distribution

Table 2. Age groups of CKD patients

Age group	No. of patients	Percentage
0-20	2	1.33%
20-30	8	5.33%
30-40	18	12%
40-50	48	32%
50-60	44	29.33%
60-70	18	12%
70-80	11	7.33%
80-90	1	0.66
90-100	0	0

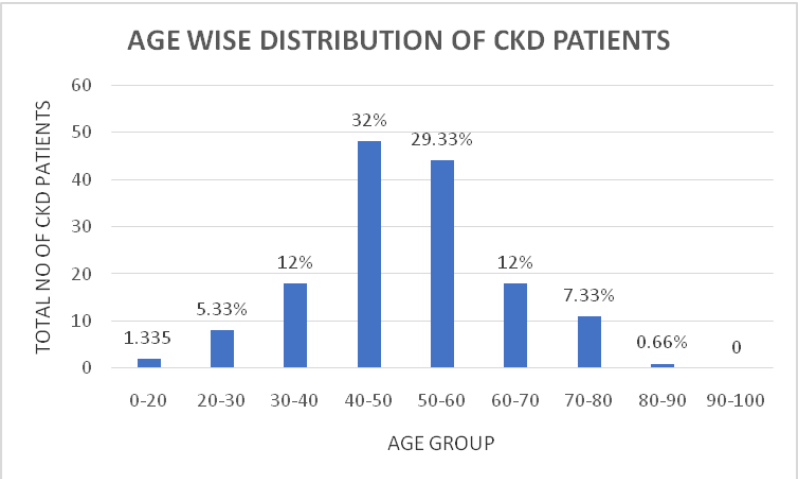

Fig. 2. Age wise distribution of CKD patients

Table 3. HTN and DM in CKD patients

Category	No. of patients	Percentage
HYPERTENSION	18	12%
DIABETES	11	7.33%
HTN +DM	102	68%
OTHERS	19	12.66%

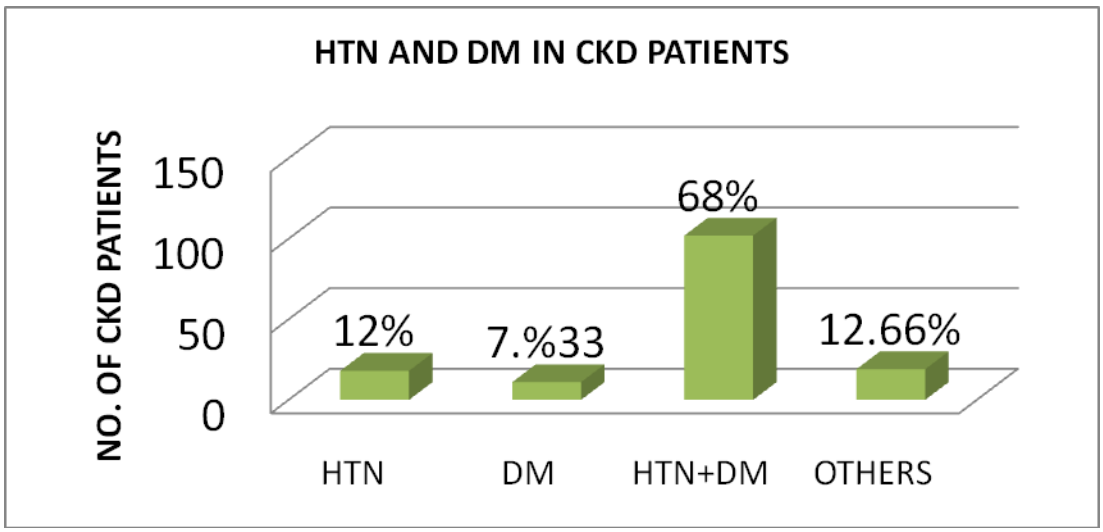

Fig. 3. HTN and DM in CKD Patients

Table 4. Haemoglobin levels of CKD patients

Hblevels	No. of patients	Percentage
HB:6-8gms/dl	62	41.3%
HB:8-10gms/dl	56	37.3%
HB:10-12gms/dl	20	13.3%
HB:12-14gms/dl	12	8%

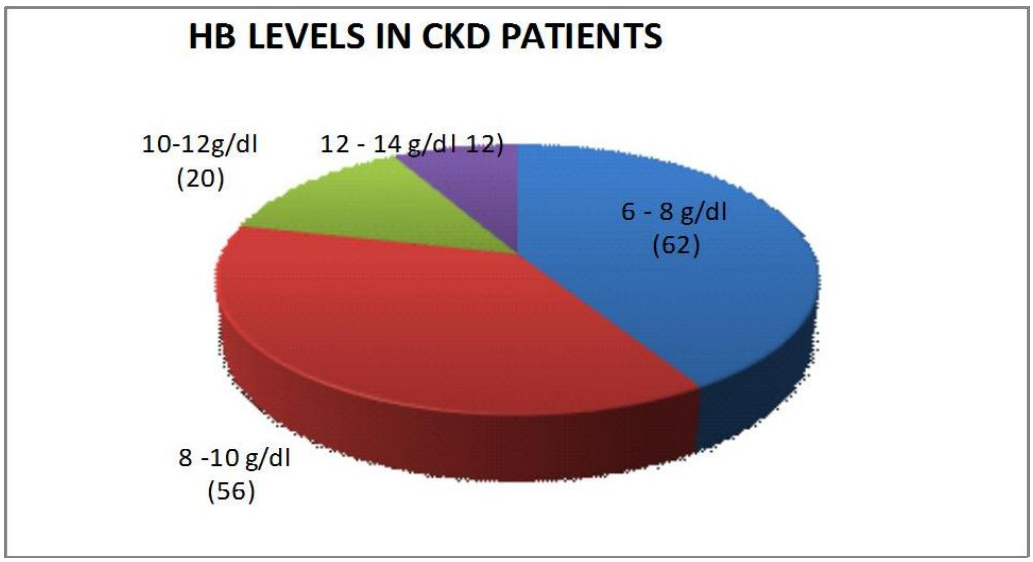

Fig. 4. Haemoglobin levels in CKD patients

Table 5. Lab parameters before and after the therapy with probiotics in interventional group and before and with the normal conventional therapy in non- interventional group

	Interventional group				Non-interventional group			
Parameters	**Before therapy**	**%**	**After Therapy**	**%**	**Before Therapy**	**%**	**After Therapy**	**%**
CREATININE								
0.6-1.5	5	6.66	50	66.6	3	4	7	9.33
1.5-2.4	7	9.33	10	13.3	5	6.66	9	12
2.4-3.3	7	9.33	6	8	6	8	12	16
3.3-4.2	8	10.66	5	6.6	11	14.6	14	18.6
4.2-5.1	10	13.33	2	2.6	19	25.3	16	21.33
>5.1	38	50.66	2	2.6	31	41.3	17	22.67
UREA								
13-43	3	4	55	73.33	5	6.66	10	13.33
43-73	37	49.33	15	20	6	8	13	17.3
73-103	15	20	5	6.66	14	18.6	15	20
103-133	9	12	0	0	17	22.6	17	22.6
>133	11	14.66	0	0	33	44	20	26.7
URIC ACID								
3.2-7.2	14	18.66	55	73.3	5	6.66	10	13.33
7.2-11.2	57	76	15	20	21	28	13	17.33
11.2-15.2	3	4	3	4	23	30.6	22	29.3
15.2-19.2	1	1.33	2	2.6	26	34.6	30	40
PCR								
0.1-0.2	5	6.66	45	60	2	2.66	12	16
0.2-2	8	10.66	15	20	13	17.33	14	18.6
2-3.8	8	10.66	9	12	18	24	16	21.3
3.8-5.6	9	12	3	4	20	26.6	16	21.3
5.6-7.4	10	13.33	3	4	22	29.3	17	22.6
>7.4	35	46.66	0	0	0	0	0	0

Table 6. Lab parameters with and without the treatment of probiotics

Parameters with and Without Probiotics Treatment				
Parameters	**Probiotics given**	**%**	**Probiotics not given**	**%**
CREATININE				
0.6-1.5	50	66.6%	7	9.33%%
1.5-2.4	10	13.3%	9	12%
2.4-3.3	6	8%	12	16%
3.3-4.2	5	3.8 %	14	18.6%
4.2-5.1	2	6.6 %	16	21.33%
>5.1	2	2.6 %	17	22.67%
UREA				
13-43	55	73.33 %	10	13.33%
43-73	15	20 %	13	17.33%
73-103	5	6.66 %	15	20%
103-133	0	0	17	22.7%
>133	0	0	20	26.7%
URIC ACID				
3.2-7.2	55	73.33 %	10	13.33 %
7.2-11.2	15	20 %	13	17.33 %
11.2-15.2	3	4 %	22	29.33 %
15.2-19.2	2	2.66 %	30	40 %
PCR				
0.1-0.2	45	60 %	12	16 %

Parameters with and Without Probiotics Treatment				
Parameters	**Probiotics given**	**%**	**Probiotics not given**	**%**
0.2-2	15	20 %	14	18.66 %
2-3.8	9	12 %	16	21.33 %
3.8-5.6	3	4 %	16	21.33 %
5.6-7.4	3	4 %	17	22.66 %

During CKD, the potential utilization of therapies modulating the gut microbiota such as probiotics has emerged as an attractive strategy to reduce URS and improve CVD. Probiotics when administered in adequate amounts, confer a health benefit on the host'. the modification of the intestinal microbiota in CKD strongly increases transformation of amino acids into URS, e.g., indoxyl-sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine noxide (TMAO)1 among others. Increased intestinal concentration of uremic toxins may lead to microbial dysbiosis and pathobionts overgrowth. Pathobionts trigger the intestinal immune system toward a proinflammatory response by preferentially activating Th17-Th7 cells and increasing the production of lipopolysaccharides (LPSs), a major component of the outer membrane of Gram-negative bacteria. Thus, dysbiosis also contributes to an increase in intestinal permeability by disrupting the colonic epithelial tight junction, which may subsequently lead to translocation of LPS and bacteria into the host's internal environment. It is therefore possible that the modification of intestinal microbiota in CKD might be involved in insulin resistance and dyslipidemia through increased LPS production, modified carbohydrate fermentation or bile acid level and composition. Given that gut-derived uremic toxins, inflammation and insulin resistance contribute to progression of CKD.

4. CONCLUSION

CKD is a chronic health issue with a high economic burden on patients and health care and is associated with decreased quality of life. Hence probiotics are used to improve the condition.

In this study, the patients are divided in to two groups; case /interventional group and control/ non interventional group. Control group is treated with normal conventional therapy whereas the case group is treated with convention therapy along with probiotics.

By using probiotics the renal parameters such as creatinine, urea, uric acid, PCR were improved.

In case group before the treatment with probiotics approximately 5-10% of patients have normal levels of these parameters and after the treatment with probiotics, approximately 50-60%of patients reaches to normal levels of these parameters.

In control group before the treatment approximately 5% of patients have normal levels of these parameters and after the treatment approximately 10-15% of patients reaches to normal levels of these parameters.

The lab parameters were analyzed by paired students t-test and the p- valve of these parameters in both groups were found to be < 0.001. It shows significant improvement in these parameters both in case and control group. CKD stages were analyzed by Chi-square test, the p-value of CKD stages in case group was found to be < 0.0001 and in control group it was found to be 0.03. It shows that there is significant improvement in both groups, but more betterment is observed in case group than in control group.

So, the application of probiotics in kidney health is an emerging area of medicine and probiotics are cost effective easily available which impacts low cost burden on patients. Hence probiotics are used as a natural bio-treatment along with dietary probiotic foods to control the progression of CKD condition and improves the quality of life.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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