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Management of Advanced Stages of Chronic Kidney Disease Patients with the Administration of Renadyl Capsule: A Single Center Pilot Study in Bangladesh

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Authors' contributions

This work was carried out in collaboration among all authors. Authors TR, HUR and FKM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors TR and MAH managed the analyses of the study. Authors TR, SG, MA, AIC and SA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Chronic kidney diseases become a public health concern as the rate of this diseases is increasing. Thus, the aim of the study was to evaluate the changes in key biomarkers in Bangladeshi CKD stages IV and V patients by using Renadyl capsule.
Study Design: Open label randomized placebo controlled clinical trial.
Methods: Data were collected from patients with CKD stage IV and V in 2017, in an out-patient setting in Kidney Foundation Hospital and Research Institute, Bangladesh. Patient's information, medical history and clinical data were also collected. Health condition of the patients was collected by using SF-36 QOL questionnaire. Data were analyzed using SPSS software version 23.0.

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Results: Administration of Renadyl capsule improved the clinical and biochemical data of the patients. Renadyl administration improved the filtration rate, kidney size, creatinine level, heart rate and liver function. Patient's physical and mental health was also improved.
Conclusion: Renadyl administration appeared to be safe among chronic kidney patients with improved kidney function. However, more clinical trials are suggested to determine the efficacy and effects of Renadyl.

Keywords: Chronic kidney diseases; Renadyl; kidney patients; Bangladesh.

1. INTRODUCTION

Chronic kidney disease (CKD) is one of the major public health concerns worldwide. Rapid progression of the severity of the disease is generally observed and patients undergo end-stage renal disease (ESRD) in the blinks of an eye and then the patients required either dialysis or transplantation for survival, both of which are considered to be a limited and costly option in many parts of the world and are left without any care [1]. Dialysis is a process that helps to remove the build-up toxin and metabolites like creatinine and blood urea nitrogen that damage kidneys cannot eliminate from the body. Alternatively, these nitrogenous wastes can be utilized by certain probiotics as nutrients and thereby aid in reducing waste load in the body. Many researchers have emphasized the role of digestive [2] and immune [3] functions in the progression of kidney disease. Over the past few decades, oral sorbents and probiotics have been used as medicine for CKD [4]. Some prior studies based on safety of this probiotic supplement showed beneficial effect in overall quality of life of its consumers and also help to maintain or improve kidney health [5,6]. Probiotics are defined by the Food and Agriculture Organization (FAO) and World Health Organization (WHO) as*, live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host* (2002) [7]. The concept that, microbial imbalance or dysbiosis took place in the gut microbiota of patients with CKD and might play a role in either the generation or degradation of uremic toxins [8]. Uremic syndrome consists of nitrogenous waste retention, deficiency in kidney-derived hormones, and reduced acid excretion, and, if untreated, may progress to coma and even death [6]. There are different probiotic supplements, currently available in the market for kidney patients but their safety is not tested yet. However, Renadyl was proved to be safe for dialysis patients in a recently conducted randomized clinical trial [9].

Several pilot human clinical trials have been conducted to determine the effects of daily consumption of probiotics on CKD signs and symptoms. This report presents preliminary data from a pilot study, conducted in Bangladesh among non-dialyzed stages IV and V CKD patients with the purpose to evaluate if this probiotic supplement could delay the progression of CKD to ESRD by improving or maintaining their quality of life. Therefore, the goal of this study was to evaluate changes in key biomarkers (primarily eGFR declined by 30% from baseline to 3 months) in CKD stages IV and V patients by using Renadyl.

2. METHODOLOGY

2.1 Study Design

It was an open label double blind and randomized placebo controlled clinical trial with a one to one arm 3 month study, conducted on patients with CKD stage IV and V in 2017, in an out-patient setting in Kidney Foundation Hospital and Research Institute (KFHRI), Bangladesh.

2.2 Sample Size, Inclusion/Exclusion Criteria and Ethical Permission

Maximum enrollment was 20 patients. Participants voluntarily enrolled in this study were prequalified and selected based on the inclusion criteria such as- age 18 to 75 years, were on CKD stage IV for at least 12 consecutive months, documented by their medical history and gave signed consent form to participate in the study. Patients with HIV/AIDS or liver disease, on any kind of antibiotics or anticoagulant therapy, active dependency on any drugs or alcohol, pregnancy, or lactation state, were excluded from the study.

We divided the patients into two groups randomly: Treatment group, a total of 12 patients (orally administered probiotic supplement, Renadyl from Ki Bow Biotech Inc) and control group, a total of another 12 patients (not

administered Renadyl). Each patient in treatment group was supposed to get three containers of Renadyl (60 capsules/container administered as 1 capsule twice a day) for three consecutive months. Nothing was administered for patients in control group. However, as we initially selected only 12 patients based on study protocol, we were unable to continue the study as only 4 out of 12 patients remained at the end of 2 months (Based on study protocol, the proposed four visits were as follows-baseline or visit 1, administered Renadyl for one month or visit 2, for two months or visit 3, and for 3 months or visit 4) and any further follow-up of patients could not be done.

Formal ethical permission for the study was taken from Kidney Foundation Hospital and Research Institute, Dhaka, Bangladesh.

2.3 Data Collection Procedure

Patient's demographic information including all co-morbidities, medications, any event or any changes or hospital admission during the study period were collected. Clinical data (history, physical exam, laboratory data and management including medication and supplements) were reviewed by nephrologist and clinical research team members. Following information were collected each month from baseline (visit 1) till 2nd month (visit 3): BP, heart rate, eGFR, Serum creatinine, Uric acid, Urine dip for protein, Hemoglobin, ACE/ ARB, any change of medications during the study, any event or hospital admission during the study. Liver function test and albumin at base line and visit 3 only.

During baseline data collection (visit 1), each patient in both groups was examined for sociodemographic data, modified SF-36 Quality of life form, and clinical data and all the baseline values were obtained. After 7 days of collecting baseline information, Renadyl capsule was provided to each patient in treatment group on the dose of 1 capsule twice daily after meals for the next three consecutive months and monthly measurement of the above mentioned parameters were recommended to both treatment and control group. However, nothing was administered to Control group and they were kept just to make comparison with patients on treatment group. Additionally, each patient was advised to come to the hospital every month for a follow up visit as long as they were taking Renadyl capsule. For the first two consecutive months, routine physical and biochemical examination as well as modified SF-36 QOL data were collected. Therefore, we could not collect any of those data two months after administration of Renadyl due to absence of participants in treatment group, and the study was discontinued at the end of 2 months (3 visits).

2.4 Statistical Analysis

Descriptive statistics were performed to determine the characteristics of the subject and the clinical and biochemical characteristics of patients. Continuous variables were presented as a Mean± Standard deviation. A chi-square test was performed to assess the relationships between subject's characteristics, clinical and biochemical parameters, and months of the study. Statistical Package for Social Sciences (SPSS) software was used for all statistical analysis and a p-value of less than 0.05 were considered as statistically significant.

3. RESULTS

Overall, baseline data collection was done for all 24 (100%) study participants (12 patients selected for treatment and 12 patients for control group). Of them, 16 (72%) patients (7 patients from treatment and 9 patients from control group) showed up during the 1st month or visit 2, and only 9 (38%) patients (4 patients from treatment and 5 from control) showed up during the 2nd month or visit 3. As no patients showed up from treatment group during the 3rd month or visit 4, the study was discontinued onwards.

Table 1 shows the demographics of patients who participated in this study. Of these 24 patients, the predominant sex was male, 18 (75%), both in treatment and control group. About half (50%) of the patients had an education level above HSC and 25% with below SSC. 33% of them were in service or business, 33% in other tasks, 25% housewife, and only 8% were unemployed. More than 70% had a family income of more than 20 thousand taka. Approximately 79% came from urban areas and 71% of patients were reported to have a history of hospital admission.

Table 2 shows the anthropometric and biochemical parameters among study participants. Average weight of patients was 67 kg with an SD of 8.5 kg. Average height was 163.5 cm with an SD of 6.3 cm, average BMI was 25 kg/m^2 with an SD of 3.2. Among all patients, 4% were in the "under-weight" range of less than 18.5 kg/m^2 , 46% were in the "Normal-

weight" category of 18.6 to 24.9kg/m^2, 42% were in the "over-weight" category of 25-29.9 kg/m^2, and 8% were in the "obese" range of more than 30 kg/m^2 [10]. Biochemical data revealed that, Sr. sodium level was in average, 137 mmol/L, Sr. K, 4.1 mmol/L, blood urea 16 mg/dl with an SD of 11 mg/dl and hemoglobin level was 10.8 mg/dl on average among all patients. No significant differences were observed while comparing anthropometric and biochemical parameters between treatment and control group over time except body weight. For treatment group, body weight increased from 68.8 kg (visit 1) to 69.5 kg (visit 3), while in control group, it remained constant. There were minute changes showed in Sr. Na, Sr. K, Sr. CO_2, Sr. Cl between both groups. Blood urea level increased in visit 2 which was again reduced in visit 3 and hemoglobin level was reduced in treatment group, it was increased in control group, however, no statistically significant differences were observed for these parameters.

Table 1. Demographics of patients

Parameters (n)	Categories	Frequency (%)
Gender	Male	18 (75)
	Female	6 (25)
Education (24)	Below SSC	6 (25)
	SSC-HSc	6 (25)
	Above HSc	12 (50)
Profession (24)	Agriculture	0 (0)
	Unemployed	2 (8)
	Service/Business	8 (33)
	Housewife	6 (25)
	Others	8 (33)
Monthly Income (24)	1000-5000 TK	1(4)
	5001-15000 TK	6 (25)
	15001-20000 TK	
	>20000 TK	17 (71)
Residence area (24)	Urban	19 (79)
	Rural	5 (21)
History of Hospital Admission (24)	Yes	17 (71)
	No	7 (29)

Data were collected from 24 patients, 18 males and 6 females with Chronic Kidney Disease, Stage IV, and V from the out-patients unit of Kidney Foundation Bangladesh. Values are frequency at baseline or visit 1 for demographics

Table 2. Anthropometric and biochemical parameters

Parameters	Mean ±SD (n)
Weight (kg)	66.6±8.5
Height (cm)	163.5±6.3
BMI (kg/m^2)	25.0±3.2
Underweight (BMI<18.5 kg/m^2)	1 (4%)
Normal (BMI 18.6-24.9 kg/m^2)	11 (46%)
Overweight (BMI 25-29.9 kg/m^2)	10 (42%)
Obese (BMI>30 kg/m^2)	2 (8%)
Sr. Na (mmol/L)	136.9±5.0
Sr. K (mmol/L)	4.1±0.5
Sr. Cl (mmol/L)	103.6±4.7
Sr. CO_2 (mmol/L)	25.4±3.3
Blood Urea (mg/dl)	16.1±10.9
UTP (mg/dl)	12.9±1.8
Hemoglobin (mg/dl)	10.8±1.4

Data were collected from 24 patients, 18 males and 6 females with Chronic Kidney Disease, Stage IV, and V from the out-patients unit of Kidney Foundation Bangladesh. Values are mean ±SD (n) for anthropometric and biochemical parameters

Table 3 demonstrates the clinical and biochemical parameters of participants over time. At baseline or visit 1, the clinical parameters of treatment and control groups look much similar but at visit 3, risks of health problems were lowered for treatment group. It was seen that blood pressure, Sr. Creatinine level, drug profile and size of kidney had been significantly increased in treatment group compared to control group. However, as only 4 patients remained in treatment group during Visit 3, we could not draw any interpretation of whether there is any improvement found among patients due to administration of Renadyl. Vital sign values during baseline data collection were as follows: About 92% (22) of total patients had blood pressure level <140/ 90 mm/Hg. About 92% (22) of patients had regular heart rate, 58% (14) of total patients eGFR within 29-15 ml/min/1.73 m^2 and 42% (10) within 14- 5 ml/min/1.73 m^2. Approximately, 83% (20) of patient's serum creatinine was 300- 500 mmol/L and 17% (4) of patient's serum creatinine was >500 mmol/L. About 54% (10) of patients' blood hemoglobin level was less than 10 mg/dl. More than 70% of patient's kidney size was > 9 cm. 100% taking Anti HTN drug, 64% phosphate binder, 47% vit.D3.

Table 3. Clinical and other biochemical parameters

Parameters (n)		Visit 1		Visit 2		Visit 3	
		Treatment	Control	Treatment	Control	Treatment	Control
Blood pressure (mmHg)	<140/90	11(50.0)	11(50.0)	7(100)	0(0)	4(100)	0(0)
	>140/90	1(50.0)	1(50.0)	5(83.3)	1(16.7)	2(50.0)	2(50.0)
Heart Rate	Regular	10(83.3)	12(100)	7(100)	7(100)	3(100)	4(100)
	Irregular	2(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)
eGFR (ml/min/1.73 m^2)	60-30	0 (0)	0(0)	0(0)	0(0)	0(0)	0(0)
	29-15	6(50.0)	8(66.7)	1(25.0)	3(75.0)	2(66.7)	0(0)
	<14.5	6(50.0)	4(33.3)	2(33.3)	4(66.7)	1(33.3)	3(100)
Sr Creatinine (mmol/L)	300-500	10(83.3)	10(83.3)	4(57.1)	7(77.8)	1(50.0)	3(75.0)
	>500	2(16.7)	2(16.7)	3(42.9)	2(22.2)	1(50.0)	1(25.0)
Sr. Ca (mg/dl)	<2	0(0.0)	2(33.3)	0(0)	1(25.0)	1(100)	0(0)
	>2	7(100)	4(66.7)	5(100)	3(75.0)	0(0)	3(100)
Urine for Sugar	+	2(25.0)	2(66.7)	0(0)	1(25.0)	0(0)	0(0)
	++	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)
	+++	1(12.5)	0(0)	0(0)	1(25.0)	1(33.3)	0(0)
	Nil	5(62.5)	1(33.3)	6(100)	2(50.0)	2(66.7)	0(0)
Hemoglobin (mg/dl)	<8	1 (9.0)	0(0)	0(0)	0(0)	0(0)	0(0)
	8 to 10	5(45.5)	6(54.5)	3(42.9)	0(0)	1(33.3)	1(25.0)
	>10	5(45.5)	5(45.5)	4(57.1)	5(100)	2(66.7)	3(75.0)
Drug profile	Anti HTN	6(35.3)	11(64.7)	0(0)	1(100)	4(57.1)	3(42.9)
	Phosphate Binder	5 (45.5)	6(54.5)	4(44.4)	5(55.6)	4(80.0)	1(20.0)
	25 D3	3(37.5)	5(62.5)	2(100)	0(0)	4(80.0)	1(20.0)
	Others	3(50.0)	3(50.0)	0(0)	1(100)	3(75.0)	1(25.0)
Size of Kidney (cm)	<8	1(14.3)	0(0)	0(0)	0(0)	0(0)	0(0)
	8 to 9	4(57.1)	3(100)	0(0)	2(75.0)	1(100)	1(50.0)
	>9	2(28.6)	0(0)	3(100)	1(25.0)	0(0)	1(50.0)
Liver Function Test	Hbs Ag (+ve)	1 (14.3)	0(0)	1(25.0)	0(0)	1(50.0)	0(0)
	Hbs Ag (-ve)	6(85.7)	3(100)	3(75.0)	2(100)	1(50.0)	2(100)
CAD/MI	Yes	0 (0)	0(0)	1(25.0)	0(0)	0(0)	0(0)
	No	12(100)	12(100)	3(75.0)	3(100)	3(100)	1(100)
CVD Stroke	Yes	2 (16.7)	1(8.3)	0(0)	1(50.0)	0(0)	0(0)
	No	10(83.3)	11(91.7)	4(100)	1(50.0)	3(100)	1(100)

Data were collected from 24 patients, 18 males and 6 females with Chronic Kidney Disease, Stage IV, and V from the out-patients unit of Kidney Foundation Bangladesh. Values are frequencies with percent at three time points (month 0, 1, and 2) for clinical and biochemical parameters

Table 4 demonstrated different clinical parameters of patients in treatment group only who were administered with Renadyl. Compared to visit 1 (baseline), in visit 3, percentage of patients reported to have diabetics, nausea, anemia and irregular heart rate reduced and 100% of the patients were reported to have a blood pressure of <140/90 mmHg.

Table 4. Medical records for patients in treatment group

Parameters	Categories	Visit 1 (n=12)	Visit 2 (n=7)	Visit 3 (n=4)
		n (%)	n (%)	n (%)
Comorbidities	Diabetics	5 (41.7)	2 (28.6)	1 (25)
	HTN	5 (41.7)	4 (57.1)	2 (50)
	CGN	2 (16.7)	1 (14.3)	1 (25)
Problems	Loss of appetite	4 (33.3)	3 (42.9)	2 (50)
	Nausea/Vomiting	2 (16.7)	1 (14.3)	0 (0)
	Weakness	6 (50)	5 (71.4)	3 (75)
	Anemia	2 (16.7)	0 (0)	0 (0)
	Itching	2 (16.7)	2 (28.6)	1 (25)
	Shortness of breath	3 (25)	1 (14.3)	1 (25)
	Edema	2 (16.7)	1 (14.3)	1 (25)
	Others	5 (41.7)	3 (42.9)	3 (75)
Blood pressure (mmHg)	<140/90	11 (91.7)	7 (100)	4 (100)
	>140/90	1 (8.3)	0 (0)	0 (0)
Heart Rate	Regular	11 (91.7)	7 (100)	3 (100)
	Irregular	1 (8.3)	0 (0)	0 (0)
	60-30			
eGFR	29-15	6 (50)	1 (14.3)	2 (50)
(ml/min/1.73 m^2)	<14.5	6 (50)	3 (42.9)	1 (25)
CAD/MI	Yes	0 (0)	1 (14.3)	0 (0)
	No	12 (100)	6 (85.7)	4 (100)
CVD Stroke	Yes	0 (0)	0 (0)	0 (0)
	No	12 (100)	7 (100)	4 (100)

Data were collected from 12 cases, 10males and 2females at month 0, 6 males and 1 female at month 1 and 3 males and 1 female at month 2 with Chronic Kidney Disease, Stage IV, and V from the out-patients unit of Kidney Foundation Bangladesh. Values are frequency and percentage at three time points for clinical parameters

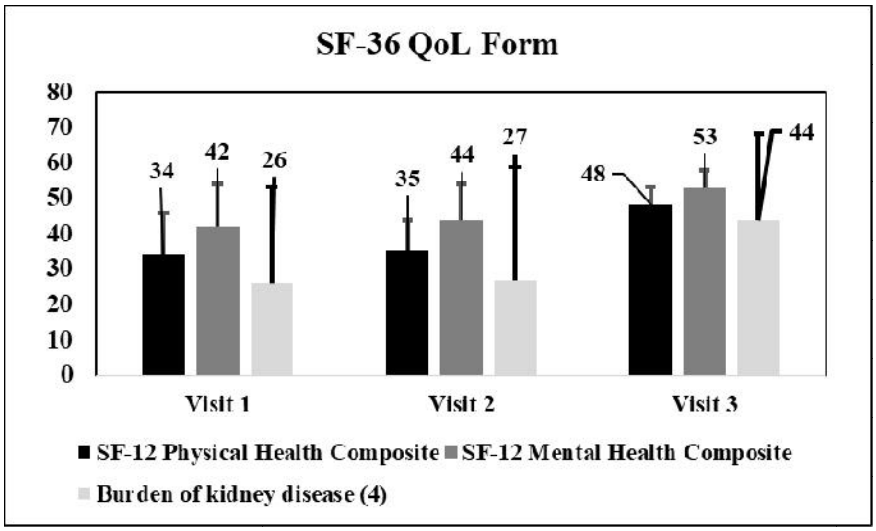

Fig. 1. Assessment of SF-36 QoL (Quality of life) Form over time

Fig. 1 demonstrated the health status of study patients through using SF-36 form, Kidney Disease Quality of Life (KD-QoL). In case of KD-QoL, during visit 1 (baseline), the two domain "physical health composite" score was 34±12 and "mental health composite" score was 42±12 and in visit 3, these were 48±5 and 53±5 respectively. Here, a lower score indicates malnourished patients. The mean score for burden of kidney disease was 26±27 and 44±24. SF-36 KDQoL form was composed of 36 questions and studies showed that, a low KD-QoL score in advanced stage of CKD patients is associated with increased risk of hospitalization and death. In general, KD-QoL score is a 5-scale composite score: Physical & mental health composite, symptoms, burden and effects of kidney disease and it is a good way of assessing morbidity and mortality among patients. Due to lack of response, the other three components of KD-QoL (problems, symptoms, and effects of CKD) could not be measured.

4. DISCUSSION

The present study was observational in nature where no significantly negative changes were found in the key biomarkers of advanced staged CKD patients, even after 2 months administration of Renadyl, a probiotic supplement. Therefore, biochemical data revealed that, serum blood urea, was slightly reduced, that can be stated as a beneficial effect, as it is a type of uremic toxin that may increase the overall toxin load and further deteriorate the condition of patients. Similar effect was found in other countries among a large group of CKD patients. [11,12] where it was reported that, supplementation of probiotic or dietary fiber intake significantly reduced the level of serum urea [13-15]. Therefore, it is important to reduce serum urea as it produces uremic toxins by diffusion that leads to the erosion of the epithelial barrier and produces inflammation [16,17]. Inflammation and oxidative stress in CKD patients are strongly associated with cardiovascular diseases comorbidity [18,19]. A clinical trial on rats discovered that life span of uremic rats was prolonged due to the use of probiotic mixture (*Lactobacilli*, *Bifidobacterium* and *S. thermophilus*) [20]. The main mechanism of probiotic on CKD patients are modulating of the gut microbiota and improving the intestinal mucosal barrier [21,22].

Probiotic therapy might play a positive role in reducing the inflammation and oxidative stress among CKD patients. Some other studies found that, symbiotic supplementation (probiotic with prebiotic) also improved the condition of CKD patients through reducing the concentration of inflammation markers and delay the progression of CKD [23,24]. However, the effectiveness of probiotics on non-dialysis patients was not well investigated [25]. In the present study, although attempts were taken to assess the overall clinical and biochemical data of a small Bangladeshi advanced stage CKD cohort for 3 months of Renadyl (probiotic) administration, no significant differences were observed in any other biochemical or clinical parameters over time and no study patients had experienced any cardiac attack or stroke from baseline till visit 3 (except one patient in visit 2). Hypertension and diabetes were considered as the major risk factors for CKD worldwide [26]. Therefore, in this study, a smaller number of patients in treatment group were reported to have anemia, nausea, and diabetics in visit 3. Yet, it might be the effect of decreasing the number of patients in treatment group over time, so we could not reach to any decision.

Quality of Life (QoL) was assessed using an interviewer administered 36-item Short Form Health Survey (SF-36) questionnaire [27]. The KDQOL-36 is comprised of five subscales calculated separately: 1) SF-12 physical component summary (PCS), 2) SF-12 mental component summary (MCS), 3) burden of kidney disease, 4) symptoms of kidney disease, and 5) effects of kidney disease. The two domains in SF-36, PCS used for assessing physical health status and MCS used for assessing emotional and psychological function contribute to the total QoL score [28]. It is an easy to use tool that can be used in the outcome assessment programs for dialysis patients [29]. It is also a clinically adequate and inexpensive method that gives a balanced estimation of nutritional status in dialysis patients [30]. In the present study, it was observed that, compared to baseline or visit 1, Renadyl administration improves the quality of life of study patients which was similar to many studies [26,31]. However, data could be collected from 22 patients in visit 1, 15 patients in visit 2 and only 7 patients in visit 3 from both treatment and control group and therefore, we could not make any decision on whether it actually improved their quality of life.

The main limitation of this study was drop out of patients over time for which we could not perform all three visits to each patient after initiation of

this supplement. The main reason for patient drop-out was shift to another hospital or another nephrologist. Therefore, there were some strength of this study, e.g., ours was the very first study of Renadyl administration among advanced Bangladeshi CKD patients. Along with demographic and clinical data, our study for the 1st time used SF-36 QoL form to assess the health status of CKD patients in this country.

5. CONCLUSION

In the present study, attempts were made to see whether there were any significant differences in the key biomarkers of Bangladeshi CKD stage IV and V patients, 3 months after Renadyl administration which appeared to be safe as no adverse effects were found in the study cohort after the initiation of the supplement The aim was to ameliorate the progression of further damage of their kidney function as not all Bangladeshi ESRD patients are lucky enough to get access to dialysis and once diagnosed, die before getting any kind of renal replacement therapy (RRT) within a short period of time due to rapid progression of CKD. Hence, results from KD-QOL assessment showed that, patients overall physical and psychological status improved over time, which could be considered as one of the positive outcomes, found from this pilot study. Though, efficacy could not be confirmed definitively, primarily due to small sample size and low statistical power. Further studies are warranted with a larger sample size.

DISCLAIMER

The Renadyl capsule container and the protocol, used for this research was provided by “Ki Bow Biotech Inc (Passionate about your health). There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Patients gave signed consent form to participate in the study.

ETHICAL APPROVAL

Formal ethical permission for the study was taken from Kidney Foundation Hospital and Research Institute, Dhaka, Bangladesh.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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