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Bifidobacteria longum- Probiotic therapy for the treatment of hyperphosphatemia in end stage renal disease patients

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Abstract
Elevated serum phosphorus is a predictable accompaniment of end-stage renal disease (ESRD) in the absence or even with supplementation of phosphate binders. Because of hyperphosphatemia these patients typically require oral phosphate binders for life-long phosphorus management, in addition to dietary restrictions and maintenance dialysis. Recently, Bifidobacteria, drew attention as an experimental treatment for hyperphosphatemia. The capsulated powder of bifidobacteria reduces intestinal phosphate absorption by inhibiting the sodium-phosphate transporter in the gastrointestinal tract, also a positive correlation between serum Phosphorus levels and intestinal pH was observed. In conclusion, the mechanism for the Phosphorus-lowering effect of bifidobacteria is supposed as follows: CKD conditions increase aerobic bacteria which hydrolyze urea into ammonia. Elevated pH decreases ionization of intestinal calcium (Ca) which leads to an increase in free phosphate ions through reduction of Ca phosphate crystal precipitation. Administered bifidobacteria metabolize carbohydrates to produce SCFAs, (short chain fatty acids) resulting in acidification of the intestinal lumen. The resulting low intestinal pH increases Ca ionization, which binds with free phosphate ions as an intrinsic Phosphate binder, resulting in the reduction of serum Phosphorus levels. The purpose of this study is to report on new findings regarding bifidobacteria novel effects and to review the possibility of repurposing this powder for hyperphosphatemia treatment in dialysis patients by elucidating its safety and efficacy profiles along with its synergistic clinical benefits.

Keywords: Hyperphosphatemia, Dialysis, Bifidobacterium Longum, Short Chain Fatty Acids.

Introduction
Considering the clinical implications of uncontrolled hyperphosphatemia, maintenance of phosphorus concentrations within an optimum range is standard of care in this patient population. Recently, the epidemiologic associations between serum phosphorus and worse outcome have been extended to the general population [1-3] This becomes even more important in view of the increasing dietary phosphorus intake in the most diet due in large part to the greater consumption of foods processed with phosphate additives. A greater understanding of mechanisms and epidemiology of altered phosphorus metabolism and disease in CKD may help clarify the possible role of excess dietary phosphorus as a health risk factor in the general population [4, 5]. The kidneys play an essential role in the regulation of serum phosphorus concentration, ensuring that urinary phosphorus excretion matches the net absorption of phosphorus from the gastrointestinal tract. In the presence of normal kidney function, fasting serum phosphorus is maintained within a tight range despite wide fluctuations in dietary phosphorus intake through variations in the urinary phosphorus excretion [6]. These considerations are important because of the evidence that the phosphorus content of the today's diet has been increasing, mostly due to increased consumption of foods processed with phosphate additives [7, 8]. Due to the important role of the kidneys in maintaining phosphorus homeostasis, an elevated serum phosphorus concentration is a common manifestation of advanced chronic kidney disease (CKD) which can lead to substantial health problems in this population, most importantly bone and cardiovascular disease (CVD) [9-11]. Moreover, several longitudinal studies have linked hyperphosphatemia with CKD progression. Thus as Chronic kidney disease itself is a great health problem, it also precipitates Cardiac problems, which are fatal due to high serum level of Phosphate in renal patients.

Therefore, an unknown proportion of people whose death and disability attributed to CVD have kidney disease as well.Because the kidneys are major regulators of phosphorus in the body and are responsible for maintaining its serum concentrations within the physiologic range, it is not surprising that when renal function begins to decline, this homeostasis is disrupted and serum phosphorus begins to increase [12, 13]. An increase in serum phosphorus causes parathyroid hyperplasia leading to secondary hyperparathyroidism and ultimately bone disease. Currently, however, it is clearly recognized that these bone abnormalities are manifestations of disturbed mineral metabolism also affecting extra-skeletal sites (vascular calcifications) and therefore the term "CKD-mineral and bone disorder" is now frequently used to describe this syndrome, which is very prevalent in CKD and dialysis patients [14, 15]. India is experiencing a rapid health transition with large and rising burdens of chronic diseases, which are estimated to account for 53% of all deaths and 44% of disability adjusted life years lost in 2005 [16-18]. Changes in lifestyle and urbanization resulted in obesity, hypertension and diabetes, which are associated with increased risk of CKD [19]. The exact prevalence of CKD in India is not clear in the absence of regular national registry data and provided only by small observational studies or personal experiences, and the quality of data is quiet uneven [20-23]. For a long time, it has been presumed that nearly 100,000 new patients with ESRD in India require renal replacement therapy every year based on data from tertiary referral centres, with a potential to underestimate the true prevalence of CKD, which was defined as estimated glomerular filtration rate (GFR) less than 80 ml/min by MDRD (Modification of diet in renal diseases) formula [24-26]. On basis of the recent survey of the ICMR (Indian Council of Medical Research), it is estimated that prevalence of diabetes in adults is 6.8% & 11.8% in rural and urban areas, respectively. Moreover, prevalence of hyper-tension has been reported to range from 20– 40% and 12–17% in urban and rural adults, respectively…

The Probiotic Therapy

Bifidobacterium longum is a gram-positive, catalase negative, rod-shaped bacterium present in the human gastrointestinal tract and one of the 32 species that belong to the genus *Bifidobacterium*. It is a micro-aero tolerant anaerobe and considered to be one of the earliest colonizers of the gastrointestinal tract of infants [27]. *B. longum* is non-pathogenic and is often added to food products for its beneficial probiotic health effects. By creating acidity in the intestinal medium, this bacteria significantly retards the absorption of Phosphorus from the gut and also increases excretion by making phosphorus soluble in the medium. (Strid *et al*., 2012, Strid *et al*. 2013 and Hammer *et al*., 2009) [28]. The capsulated powder of bifidobacteria reduces intestinal phosphate absorption by inhibiting the sodium-phosphate transporter in the gastrointestinal tract, also a positive correlation between serum Phosphorus levels and intestinal pH was observed. In conclusion, the mechanism for the Phosphorus-lowering effect of bifidobacteria is supposed as follows: CKD conditions increase aerobic bacteria which hydrolyze urea into ammonia. Elevated pH decreases ionization of intestinal calcium (Ca) which leads to an increase in free phosphate ions through reduction of Ca phosphate crystal precipitation. Administered bifidobacteria metabolize carbohydrates to produce SCFAs, (short chain fatty acids mainly acetic acid) resulting in acidification of the intestinal lumen. The resulting low intestinal pH increases Ca ionization, which binds with free phosphate ions as an intrinsic Phosphate binder, resulting in the reduction of serum Phosphorus levels. In order to enable *Bifidobacteria* to reach the intestine, a colony-forming unit of *Bifidobacterium longum* JBL01, a strain of human *Bifidobacteria*, measuring 2.0 × 10 [9], combined with 0.11 g of oligosaccharides (lactulose and raffinose) as a stimulant to bacteria proliferation, were encapsulated in a gastro-resistant seamless capsule (B capsule, Morishita Jintan Co., Ltd, Osaka, Japan.

Objectives of the Work

- Based on these studies following objectives are drawn-
- To assess the initial serum Phosphorus level of the patients.
- To study Effect of supplementing Bifidobacteria Longum in powder form in gastro-resistant seamless capsule on Serum Phosphorus Level of hemodialysis patients.
- To study the effect of this supplementation on prevalence of complications of Hyperphosphatemia.
- To study the side –effects of this supplementation on patients.
- To study the effect of supplementation on Lipid profile of the patents.
- To study the placebo effect of supplementation on these biochemical parameters
- To assess the initial level of Calcium in serum of patients, because when the serum Phosphorus level gets high, simultaneously the serum Calcium level gets low, this induced hypocalcaemia has many adverse effects on body as CVD related problems.
- To assess the initial Total Lipid profile of the patients as hyperphosphatemia and parallel hypocalcaemia has dyslipidemia –precipitating effect.
- To assess the initial level of C- reactive protein, because higher serum Phosphorus level increases sensitivity and incidences of repeated infections. This causes higher level of C- reactive proteins.
- To assess the serum level of Creatinine as this bio-indicator reflects the severity of CKD, because the excretion of Creatinine is hampered in chronic renal disorder and co- related with the severity of the disease.
- Hemoglobin gm% values was assessed by using Hemoglobinometer, as in CKD absence of REF
- (Renal Erythropoietin Factor) precipitates severe anaemia. Also the other parameters were measured as they are also affected.
- To assess the total serum level of Parathyroid hormone, because elevated Phosphorus level changed the status of this very hormone or vice versa.
- To assess the serum gm% level of Albumin as in CKD, albuminuria is commonly seen symptom, related with the severity and blood's osmotic pressure changes related complications.
- To assess the serum status of enzyme -Creatine Kinase as the serum level of this enzyme indicates the condition of

Cardiac Health, because chronic renal disease precipitates Ca precipitation on Cardiac soft tissues, thus Atherosclerosis and other Cardiac related ill effects are observed..

- To study the effect of supplementation on parathyroid hormone status of the hemodialysis patients,
- To study the side –effects of Bifidum Longum supplementation on patients.
- To study the effect of supplementation on C - reactive protein of the patients.
- To study the effect of supplementation on serum level Creatine Kinase of the patients.

Materials & Methods

- This study was carried out on CKD-V patients before initiation of dialysis therapy in nephrology department of the Subha Dubey's Hospital for two year period from Oct, 2012 to Sep, 2015. At first, CKD-V Stage patients were selected randomly according to inclusion criteria, then relevant history was taken and physical examination was carried out after taking permission of subjects. All the formalities related to medical ethics was followed. Relevant following investigations were done.
- 51 CKD patients were selected randomly by contacting various clinics of nephrology in CG during the study duration of 3 years. Their criteria of selection was their serum phosphorus level, that was essentially should be above 7 mg% (hyperphosphatemia).They were divided in three groups, but the demographic data of all the three groups was tried to kept matching in all parameters, also all are hospitalized patients, so their diet was almost same, with low phosphorus containing foods, medicines and phosphate binders were all same. So, the only point of difference was intervention of probiotic in the experimental group.

(a) Control group (19) patients – no intervention was given

(b) Experimental group (19) patients – Intervention of *Bifidobacterium longum* JBL01, a strain of human *Bifidobacteria*, measuring 2.0 × 10 [9], combined with 0.11 g of oligosaccharides (lactulose and raffinose) as a stimulant to bacteria proliferation, were encapsulated in a gastro-resistant seamless capsule (B capsule, Morishita Jintan Co., Ltd, Osaka, Japan). *Bifidobacteria* can survive in this gastro-resistant capsule even in a solution of 1.2 pH at 37 °C for 120 min. Duration of intervention 3-4 weeks.

(c) Placebo group- (19) patients –they were given capsule just like the intervention dose of probiotic for about the same period and on the same time.

- Biochemical Estimation Done-
- Estimation of Serum Calcium was done by OCPC (Ortho-Cresolphthalein Complexone) method by using the kit of "Lab Care" in auto analyzer, model no-Star 21 Plus. 1 ml vial of reagent was mixed with 0.5 ml serum. The calcium in the patient serum/plasma reacts with OCPC to form a purple colored complex. The intensity of the color is directly proportional to the concentration of calcium in the sample. The concentration is measured colorimetrically at a wavelength of 578nm (550 – 590nm) and compared with that of a standard.
- Estimation of serum Phosphorus was also done by using kit of Lab care and by using auto analyser, models no Star 21 Plus. In the reaction, inorganic phosphorus reacts with ammonium molybdate in an acidic solution to form a colored phosphomolybdate complex. The system monitors the change in absorbance at 365 nm at a fixed time interval. This change in absorbance is directly proportional to the concentration of phosphorus in the sample.
- Serum Creatinine level was measured by using kit of MERCK company, in auto-analyser. Creatinine in a protein free solution reacts with Alkaline Picrate and produces a red colour complex, which is measured calorimetrically at 520 nm.
- C-reactive protein was assessed by using kit of Span Diagnostics, reagent kit, Surat [code 25934] used for in vitro detection of C - reactive protein (CRP) in human sera in auto-analyser by agglutination method.50 micro ml serum was mixed with 1 ml reagent, clumping was indication of positive test.
- Hemoglobin gm% values was assessed by using Hemoglobinometer, also other parameters were
- Assessed by using by using 5 Part Hematology Analyser, BC-5000 of Mindray company.
- The HbA1c values were all were estimated, as higher Serum Glucose is strong etiological factor for diabetes and a correlation was observed among HbA1c values and serum creatinine level to assess the level of severity of CKD with status of diabetes.
- Serum Albumin gm% was assessed because in renal disorders albuminuria is common, and serum Albumin level gets low parallel to the severity of the disease. The level was assessed by using autonalayser, model no 121 star, with the use of diagnostic kit for albumin analysis of Span company. Also total protein gm% level was assessed by using the Kit of the same company, because it is expected that total protein status is also significantly reduced in CKD.
- Those blood samples, which were found positive for C-reactive protein were sent to Ranbaxy Lab, Bombay via local sample collecting centre and were again qualitatively analysed. About 11 samples were sent outside, we analysed remaining samples ourselves and compare the results. We also got the same trend of serum values. The results were compared with the normal serum values. Qualitative and semi quantitative rapid latex slide test was used. We used kit of Span diagnostics, mixed 50 micro ml serum with 1 drop of reagent and within 6 seconds the result was read.
- As Serum Creatine Kinase is bio-indicator of cardiac damage-so quantitative analysis of this enzyme is done to assess the severity of the cardiac damage. For analysis Kit of Tecko Diagnosis was used, for assessment kinetic method was adopted. Sample value of 50 micro ml serum was mixed with reconstituted reagent with buffer, at 37 Ç, and the absorbance was read at 340nm, the time interval was 30 seconds.

- Estimation of lipid profile- Chema Diagnostica Qualigens fine chemicals a division of Glaxo India Ltd.

2. Span diagnostic limited, Surat, India.

(a) Cholesterol Estimation Kit (one step method of Wybenga and Plleggi) (Catalog No. – 25924)

(b) HDL Estimation Kit (One step method of Wybenga and Plleggi) (Catalog No.–25924)

(c) Triglyceride Estimation Kit (Enzymatic colorimetric method GPO–PAP liquid stable single regent) (Catalog No. 77034 (6×250 ml)).

- Estimation of Parathyroid Hormone- By Mini Vidas (Biometric Company) Model XT-55, by using Kit of Merrimack Company.
- Bifidobacteria Longum was purchased from Alibaba.com, made by Unique Biotech Limited and 25 kgs pack was supplied by dr Ratna Sudha. Six subjects use another preparation.(JBL01 (B-HD capsule, Morishita Jintan Co., Ltd., Japan)
- Thus, to improve the composition of disturbed micro flora and alleviate faecal impaction, B capsules containing *B. longum* JBL01 were administered orally.
- The intervention dosage for powder ranged from 2 gms to 4 grams /day, with the average daily dose of approximately 2.5 gms. (BB 536) In a randomized, double-blind, placebo-controlled cross-over trial, 9 patients undergoing haemodialysis who had serum phosphorus levels > 6.0 mg/dL despite binder therapy were randomly assigned to placebo or Bifida bacteria for 8 weeks. Powder and placebo were packaged in identical capsules.
- PATIENT'S PROFILE- once capsule daily for 4 weeks in 9 patients receiving HD [age: 62.2 ± 9.8 years; 4 males, 5 females; 5 diabetes mellitus (DM), 4 non-DM; HD duration: 9.3 ± 7.0 years; serum albumin levels: 3.9 ± 0.3 g/dL; serum corrected calcium (Ca) levels: 7.1 ± 0.8 mg/dL; serum P levels: 6.7 ± 0.6 mg/dL; serum intact parathyroid hormone (PTH) levels: 363 ± 221 pg/mL].
- Results were compared with those of 9 HD patients who did not receive B capsules as a control group (age: 58.1 ± 15.6 years; 5males, 4 females; 3 DM, 6 non-DM; HD duration: 9.1 ± 6.8 years; serum albumin levels: 3.8 ± 0.3 g/dL; serum-corrected Ca levels: 9.0 ± 0.9 mg/dL; serum P levels: 7.0 ± 0.8 mg/dL; serum intact PTH levels: 219 ± 124 pg/mL).
- No patient had undergone treatment with *B. longum* preparations before participating in this study.
- The dose of drugs affecting P metabolism were fixed through the study period in the experimental (n=9, Placebo (n=4)and control group (n=9) -Ca carbonate: 2.79 ± 1.44 g, / sevelamer hydrochloride: 3.20 ± 2.94 g, / calcitriol injection: 1.67 ± 0.24 μg/week, ; maxacalcitol: 15.0 ± 4.1 μg/week, / oral alfacalcidol: 0.5 μg, / oral calcitriol: 0.38 μg,)

Observations

- Normal serum calcium value is 9-10.5 mg/dL, the observed value is 6.71mg/dL average, thus a significant hypocalcaemia is observed among the studied group.
- Normal serum values for phosphorus is 2.4-4.5 mg/Dl, but the observed value is 9.9 mg/dL, thus a significant hyperphosphatemia t value- 2.31 is observed in studied group.
- The normal serum creatinine level is 0.5-1.1mg/dL, but the estimated average level was >2.5 mg/dl, this was the basic criteria for the selection of patients included in this study.
- The normal CaXP value is 55mg /dL, The average observed value was bit high -62mg/dl, but in 23% subjects the value was observed extremely elevated (average-83-106mg/dl.)
- The GFR was observed <15 ml/min/1.73m2 before starting therapy.
- The Hemoglobin gm/100 ml value was observed lower than normal. 93% of the studied subjects were having anaemia. (Average-8.33 gm%)
- The hematocrit value was normal (31%), also the size of RBCs were observed normal in hemogram-85 $mm^{2.}$.Thus the patients had normocytic – normochromic anaemia.
- The 23% of the CRD had HbA1c values 8.11, 77% of these diabetic-CKD patients were females.
- Nyco Cord U-Albumin test and the Afinion ACR test results showed -271ug/day Albumin excretion and <5.4 mg albumin/mmol creatinine Excretion ratio. These values biochemically proved the severe stage of CKD.
- Cardiovascular Events*:* We have collected the technical information from the cardiologists-the following cardiovascular events were observed in CKD patients-Ischemic Heart Disease (IHD), Arrhythmia, Left ventricular hypertrophy (LVH), Congestive Heart Failure (CCF). We included clinical and ECG and Radiological criteria to define cardiac events. Guidance was taken by Dr D. Aggrawal, Cardiologist, Sanjivini Hospital, Bilaspur in this concern.
- Serum c-reactive protein initially was 3.6 mg/L, the normal value is 1.0 to 3.0 mg/L.
- The parathyroid hormones serum value is 413 ± 79 pgm/mL. (Normal level 55 pgm/mL)
- Serum Level of Creatine Kinase is 188U/L, normal value is 145-171 U/L.

Table 1: Relevant Biochemical Profile Changes after Intervention Period

Biochemistry	Normal Value	Subject	Controls	Placebo	T Value
Serum Phosphate	2.4-4.5 Mg/Dl,	6.3 Mg/Dl	9.9 Mg/Dl	8.9mg/Dl	0.904*,**
Serum Calcium	9-10.5 Mg/Dl	9.71mg/Dl	5.8mg/Dl	6.1 Mg/Dl	0.312*
Ca : P X Complex	55 Mg /Dl	62 Mg/Dl	56 Mg/Dl	53 Mg/Dl	0.133*
Creatinine	0.5-1.1mg/Dl,	1.5 Mg/Dl,	2.3 Mg/Dl	3.2 Mg/Dl	0.241*,**
C- Reactive Protein	1.0 To 3 Mg/L.	3.6 Mg/L,	4.5 Mg/L	4.2 Mg/L	0.411*,**
Parathyroid Hormone	38 Pgram/ Ml	71 P Gram/Ml	29.3 Pgram/Ml	33.7 P Gram/ Ml	0.942*,**
Serum Creatine Kinase	145-170 U/L	183 U/L	181 U/L	179 U/L	0.219* [0.005 -*0.001**]

Table 2: Effect of Probiotic Supplementation on Biochemistry-

Sr	Biochemistry	Initial Value	Post Supplementation Value	T Value
1	Serum Phosphate	9.9 Mg/Dl	6.3 Mg/Dl	0.417*
2	Serum Calcium	5.8mg/Dl	9.71mg/Dl	0.891*
3	Ca : P X Complex	56 Mg/Dl	62 Mg/Dl	0.484*,**
4	Creatinine	2.3 Mg/Dl	1.5 Mg/Dl,	0.243*
5	C- Reactive Protein	4.5 Mg/L	4.27 Mg/L,	Na
6	Parathyroid Hormone	29.3 Pgram/Ml	71 P Gram/Ml	0.347*
7	Serum Creatine Kinase	191 U/L	179 U/L	0.216*

At 0.005* And 0.001 Level**

Table 3: Initial Values of Serum Lipid Profile of Subjects

Age group	No. of Participants	Cholesterol	Triglyceride	HDL	LDL
37-40	8	2.02±0.33	0.95±0.29	0.29±0.06	1.46±0.24
41-44	6	2.07±0.25	1.63±0.38	0.27±0.08	1.49±0.19
45-48	8	1.50±0.35	1.11±0.39	0.31±0.07	0.98±0.31
49-52	6	1.83±0.26	1.24±0.37	0.30±0.09	1.29±0.22
53-56	8	1.88±0.25	1.87±0.28	0.34±0.07	1.17±0.19
57-60	6	1.76±0.22	1.76±0.46	0.27±0.05	1.13±0.17
60+	9	1.89±0.17	1.91±0.42	0.28±0.02	1.23±0.16

Table 4: Mean, SD & 't' Values of lipid profile of Intervention Group in comparison with controls *P<0.05 level, **P<0.01 level. SD Values showed in parenthesis

Lipid Constituents	(mean values)		Change in percent-age value	(df =38) t value
	Experimental Group (n=19)	Control Group (n=19)		
Cholesterol (mg/ml)	1.80 (±0.34)	1.85 (±0.17)	□ 3%	1.46 NS
Triglyceride (mg/ml)	1.49 (±0.36	1.92 (±0.29)	□ 22%	12.33*,**
HDL (mg/ml)	0.41 (±0.14)	0.29 (±0.02)	↑ 28%	16.08*,**
LDL (mg/ml)	1.17 (±0.36)	1.25 (±0.17)	□ 7%	(2.08)

NS = Not significant.

( ) significant at 1% level only.

- Serum P levels unexpectedly decreased significantly in the Third and fourth weeks due to oral administration of the Bifidum capsule. Serum P levels remained unchanged in the placebo and control group. Subsequently, serum P levels returned to original levels 4 weeks after the completion of oral treatment.
- The finding also suggests that kidney disease could potentially be seen as a useful prognostic marker for coronary heart disease."

Results & Conclusion

Thus, this functional probiotic powder can be a patient-convenient and inexpensive alternative or adjunctive therapy for phosphorus management in dialysis patients. We found a graded independent relation between higher levels of serum phosphate and the risk of cardiovascular events in people. Further well-designed, large-scale, long-term, comparative trials are needed to successfully repurpose Bifidobacteria for the new indication. Bifidobacteria treatment decreased serum phosphorus from 9.9 to 6.3 mg/dL (P =.02), and no significant changes occurred in the placebo group. Among patients who demonstrated more than 80% adherence based on routine pill counts, the fall in serum phosphorus was more pronounced, decreasing from 7.22 to 5.03 mg/dL. Positive effects were observed on serum C-peptide level also. Placebo group did not show any reduction on significant basis. Four patients had complains of mild diarrhoea, so their doses were reduced to half.Thus, this functional probiotic powder can be a patient-convenient and inexpensive alternative or adjunctive therapy for phosphorus management in dialysis patients. I found a graded independent relation between higher levels of serum phosphate and the risk of cardiovascular events in people. Further well-designed, large-scale, long-term, comparative trials are needed to successfully repurpose Bifidobacteria for the new indication. Lowered pH levels in the intestinal medium inhibit the overgrowth of aerobic and putrefactive bacteria, thus, bifidobacteria can also cause further reduction of intestinal pH through this mechanism. Under decreased intestinal pH conditions, Ca ionization increases. As an intrinsic P binder, increased Ca2+ binds with free phosphate ions, resulting in Ca phosphate crystal precipitation to reduce serum P levels.

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