Probiotic Dietary Supplementation in Chronic Kidney Disease Patients (CKD III and IV)-Preliminary Observations and Combined Data Analysis of a 6-month Pilot Scale, Randomized, Double Blind and Crossover Study Design in Argentina, Canada, Nigeria and USA.

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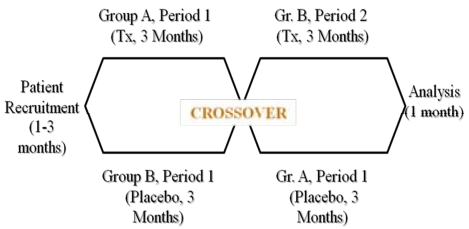
Background

Current thinking holds that retained "toxic " concentrations of nitrogenous wastes (azotemia), deficient kidney –derived hormones (erythropoietin, vitamin D), and unexcreted acid in totality comprise the uremic syndrome characterized by fatigue, acidosis, and anemia. Depending on its underlying cause, untreated uremia may progress to coma and eventual death. Previous experience suggests that oral administration of a scientifically based probiotic product formulation, containing selected microbial strains, may act as a complimentary adjunct by extending renoprotection via intraintestinal extraction of toxic solutes in patients with CKD stages III and IV. We report a pilot study as a component of registered trial NCT00760162.

Methods

This study was a prospective, randomized, double blind, crossover, placebo-controlled, 6-month trial of probiotic bacteria conducted in four countries, at six institutions, on 46 outpatients with CKD stages III and IV: USA (n=10), Canada (n=13), Nigeria (n=15), and Argentina(n=8). Primary endpoints included effect on hematologic, biochemical, fecal variables (only at the Canadian site), and general well being assessed by Quality of Life (QOL) criteria form. Outcomes were compared using biochemical parameters including: blood urea nitrogen (BUN), serum creatinine and uric acid, plus C – reactive protein (CRP) as an indication of active inflammation. QOL was scored on a subjective scale of 1 to 10 as a secondary parameter.

Design



Results

Average levels by treatment period

* KB – Kibow Biotics® ** PL – Placebo

1. Argentina

Pt. no.	Age	Sex	Diabet (Y/N)	Treat. Seq.	Creatinine KB*	Creatinine PL**	Creatinine KB-PL	Uric Acid KB	Uric Acid PL	Uric Acid KB-PL	BUN KB	BUN PL	BUN KB-PL
1	21	M	N	PL-KB	461	439	22	416	335	81	39.2	34.4	4.8
2	62	M	Y	PL-KB	346	381	-35	412	456	-44	65.1	86.6	-21.5
3	63	M	Y	KB-PL	254	236	17	559	547	12	52.5	46.9	5.6
4	73	M	Y	KB-PL	262	271	-9	462	517	-56	32.1	34.9	-2.8
5	57	F	N	PL-KB	286	275	11	389	412	-24	28.9	27.7	1.2
6	48	F	N	PL-KB	293	281	12	468	440	28	36.1	30.9	5.2
7	62	M	Y	PL-KB	321	342	-21	428	474	-46	39.9	50.0	-10.1
8	74	M	N	KB-PL	273	290	-16	593	482	111	34.3	38.9	-4.6

2. Canada

Pt. no.	Age	Sex	Diabet (Y/N)	Treat. Seq.	Creatinine KB	Creatinine PL	Creatinine KB-PL	Uric Acid KB	Uric Acid PL	Uric Acid KB-PL	BUN KB	BUN PL	BUN KB-PL
1	45	M	N	KB-PL	401	488	-87	396	430	-34	16.9	19.7	-2.8
2	57	M	N	PL-KB	280	278	2	519	482	37	16.8	17.5	-0.7
3	55	M	N	KB-PL	308	304	4	473	461	12	16.0	17.1	-1.1
4	51	M	N	PL-KB	277	310	-33	748	692	56	21.7	27.9	-6.2
5	48	M	N	KB-PL	592	729	-137	325	375	50	25.2	33.7	-8.5
6	50	F	N	PL-KB	473	459	14	641	606	35	33.6	33.1	0.5
7	70	M	Y	KB-PL	482	607	-125	514	500	14	22.0	26.8	-4.8
8	50	F	N	PL-KB	376	393	-17	596	532	64	20.5	21.6	-1.1
9	56	M	N	PL-KB	285	264	21	646	506	140	15.7	14.5	1.2
10	61	M	N	KB-PL	383	404	-21	520	544	-24	21.2	23.8	-2.6
11	47	F	N	PL-KB	783	630	153	344	379	-35	27.8	32.6	-4.8
12	40	F	N	PL-KB	637	491	146	481	488	-7	43.8	38.1	5.7
13	68	M	Y	PL-KB	217	218	-1	620	590	30	18.8	20.8	-2.0

3. Nigeria

Pt. no.	Age	Sex	Diabet (Y/N)	Treat. Seq.	Creatinine KB	Creatinine PL	Creatinine KB-PL	Uric Acid KB	Uric Acid PL	Uric Acid KB-PL	BUN KB	BUN PL	BUN KB-PL
1	57	F	N	PL-KB	462	441	21	512	500	12	12.1	13.3	-1.2
2	40	M	N	KB-PL	1534	2178	-643	512	630	-119	43.1	57.4	-14.3
3	67	M	N	KB-PL	905	1535	-630	517	517	0	25.3	54.4	-29.1
4	49	M	Y	PL-KB	589	469	120	484	438	46	28.9	25.0	3.9
5	28	F	N	PL-KB	327	389	-63	550	508	43	12.5	15.6	-3.1
6	46	M	N	KB-PL	243	205	37	559	482	77	8.5	7.3	1.2
7	42	M	Y	PL-KB	247	177	71	571	523	48	14.4	9.5	4.9
8	68	F	N	PL-KB	414	382	32	597	498	99	30.5	28.0	2.5
9	46	M	N	KB-PL	286	275	11	512	498	14	11.8	10.9	0.9
10	58	M	N	PL-KB	388	383	6	515	539	-24	18.0	16.6	1.4
11	29	F	Y	KB-PL	205	161	44	636	517	119	10.7	9.1	1.6
12	51	M	N	PL-KB	495	459	36	442	494	-52	16.7	25.0	-8.3
13	61	M	Y	PL-KB	359	372	-13	592	601	-9	16.1	18.3	-2.2
14	44	F	Y	KB-PL	496	555	-60	432	541	-109	18.4	20.4	-2.0
15	61	F	Y	KB-PL	143	135	8	724	565	159	13.6	9.4	4.2

4. USA

Pt. no.	Age	Sex	Treat. Seq.	Creatinine KB	Creatinine PL	Creatinine KB-PL	Uric Acid KB	Uric Acid PL	Uric Acid KB-PL	BUN KB	BUN PL	BUN KB-PL
		NYVA										
1	61	M	KB-PL	357	314	43	541	515	27	14.8	14.8	0
2	56	M	PL-KB	265	277	-12	446	440	6	10.8	9.5	1.3
3			KB-PL	306	357	-50	648	559	89	26.1	24.9	1.2
4			KB-PL	239	349	-111	555	488	67	24.4	28.6	-4.2
5	70	M	PL-KB	186	203	-18	454	446	8	10.5	12.6	-2.1
6			PL-KB	301	295	6	375	351	24	19.6	23	-3.4
		SUNY										
7	76	F	KB-PL	197	186	12	531	521	10	15.4	15.6	-0.2
8	40	M	KB-PL	248	224	24	672	613	59	17.6	14.4	3.2
9	68	F	PL-KB	336	287	49	538	639	-101	32.3	32.3	0
10	64	F	PL-KB	354	348	6	323	537	-214	15.6	17.4	-1.8

Quality of life ratings (by site and by treatment period)

Pt. no.	Canada KB	Canada PL	Canada KB-PL	Argentina KB	Argentina PL	Argentina KB-PL	Nigeria KB	Nigeria PL	Nigeria KB-PL	USA KB	USA PL	USA KB-PL
1	5	5	0	10	8	2	8	6	2	9	7	2
2	8	7	1	9	8	1	7	3	4	8	8	0
3	8	6	2	9	6	3	4	6	-2	8	5	3
4	7	6	1	10	7	3	8	6	2	6	6	0
5	6	5	1	7	7	0	9	7	2	9	6	3
6	7	6	1	8	7	1	9	6	3	9	7	2
7	7	7	0	9	8	1	8	7	1	8	7	1
8	7.5	7	0.5	10	7	3	7	5	2	8	7	2
9	10	5	5				8	7	1	10	8	2
10	10	7.5	2.5				8	7	1	8	7	1
11	10	9	1				9	9	0			
12	5	2	3				7	6	1			
13	8	7	1				7	5	2			
14							5	4	1			
15							7	4	3			
Average changes:			1.46			1.75			1.53			1.60

Summary

Summary: Percentages of patients showing improvement.

Site	# of patients	# of patients with decreased levels (%)			# of patients with improved quality of life ratings (%)
		Creatinine	Uric acid	BUN	
Argentina	8	4 (50)	4 (50)	4 (50)	7 (88)
Canada	13	7 (54)	4 (31)	13 (77)	11 (85)
Nigeria	15	5 (33)	5 (33)	7 (47)	13 (87)
USA	10	4 (40)	2 (20)	5 (50)	8 (80)
Totals	46	20 (43)	15 (33)	29 (63)	39 (85)

Oral ingestion of probiotics (90Billion cfu/day) was well tolerated and safe during the entire six month clinical trial at all clinical study sites. Among 46 CKD III and IV patients from all four sites, BUN decreased in 29 patients (63% with a probability of >95%) while creatinine values decreased in 20 patients (43% with no significant statistical difference) and uric acid levels decreased in 15 patients (33% with no significant statistical significance). Almost all subjects expressed a subjective sense of substantive overall improvement in perceived quality of life (86% with a probability of >95%) determined from patient diaries. Mild physical complaints including bloating, flatulence and/or diarrhea were observed in 10 study patients who completed the six month clinical trial at all sites. These symptoms were noticed only during the first three weeks of administration of probiotics and did not recur.

Conclusion

A preliminary clinical trial of oral administration of probiotics to patients with CKD stages III and IV discerned significant reduction of BUN along with enhanced well being without serious adverse effects. Use of bowel-based toxic solute extraction by the chosen probiotic product formulation is supported by this positive preliminary trial. Specific strains of orally administered probiotic bacteria metabolized nitrogenous wastes were well tolerated for up to six months. At all 4 sites, comprising 46 patients, QOL and BUN levels showed significant outcome difference ($p<0.05$) between placebo and probiotic treatment periods. A major limitation of this trial is its small size that may have precluded detection of changes in biochemical or hematologic changes in other variables that might have been evident in larger cohorts. Extension of the evaluation of this probiotic bacterial mixture will include a dose escalation trial in a similar prospective, placebo controlled, and double blind study site.