

Research Article

REVIEW OF HEALTH STATUS AND LEVEL OF SATISFACTION OF CUSTOMERS WITH CKD USING RENADYL™: RESULTS OF A SURVEY

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ABSTRACT

Background: As global population ages, epidemiology shifts to chronic diseases – obesity, diabetes, hypertension – that spiral out of control and contribute to growing rates of kidney disease, likely to cause a major health crisis in the near future. In many regions of the world, these diseases are left without any care. The nephrology community needs to look into alternatives. This survey study was aimed to collect information about the quality of life and health status of past and current customers using Renadyl™, a probiotic dietary supplement for kidney health. **Methods:** Survey questionnaires along with stamped and addressed return envelopes were mailed out to 523 current and 475 former customers of Renadyl™ from Kibow Biotech Inc. Results were tabulated and analyzed using SAS V9.2 and MS Excel. **Results:** A total of 147 responses were received (16% response rate, 57 female, 84 male, age 7-94 years). Majority was over 50 years of age, retired, in at least stage III of kidney disease, with one or several comorbid conditions. Overwhelming majority (over 75%) was satisfied with safety, perceived efficacy and performance of Renadyl™, and with Kibow's services. **Conclusions:** Safety of Renadyl™ in all stages of CKD and with a variety of comorbid conditions, established in prior studies, was corroborated. It does not interfere with any other medical treatments, including dialysis. At the same time, it provides at least some beneficial effect with regard to the overall quality of life and maintaining or improving kidney health in particular. Further, adequately powered studies are warranted.

Keywords: Chronic Kidney Disease, Probiotics, Renadyl™, Survey

INTRODUCTION

In recent years, the general awareness of the rising global prevalence of kidney disease has been steadily growing among the medical and public health professionals [1-3]. Kidney disease is the eighth leading cause of death in the U.S. [4], with close to 600,000 End-Stage Renal Disease (ESRD) patients (most of them on dialysis) and more than 20 million in earlier stages of Chronic Kidney Disease (CKD) [5]. As the population ages, the epidemiology shifts to chronic metabolic diseases, such as obesity, diabetes and high blood pressure, all contributing factors to kidney disease. It is likely that people in the U.S. and globally will have a major health crisis in kidney disease. The annual cost of ESRD, according to U.S. Renal Data Systems, is \$50 billion, while that of CKD, in Medicare patients only, is another \$45.5 billion. In May of 2013, *Lancet* published a special issue on "Global Kidney Disease", with a series of articles focusing on its various aspects [6-11].

The awareness of probiotics, a component of many dietary supplements, has been rapidly spreading both in the academic research community and in society at large. 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). They are predominantly found in fermented dairy foods such as yogurt, kefir, and cheese, as well as other fermented foods. Given that the use of dietary supplements helps to save costs and to avoid unnecessary expenditures in other conditions (See Figure 1), the potential to do the same in CKD is significant.

The role of the digestive system^[12], as well as inflammation^[13] and oxidative stress^[14, 15] in kidney disease progression has been emphasized by researchers in the past decade. Current data have highlighted an integrated and perhaps a causal relationship between the observed clinical outcomes and the role of an activated immune system in uremia^[16]. In recent years, *Kidney International* reviewed the role of microbial imbalance (dysbiosis) in KD and the extent to which the gut microbial population might play a permissive role in the generation or assist in the degradation (perhaps even both) of many of the uremic toxins^[16, 17].

This expansion of the awareness and use of probiotics has raced ahead of the scientific basis for the mechanisms by which they impact health. Nevertheless, they are increasingly utilized in clinical settings. A simple search of the NIH *clinicaltrials.gov* registry for “probiotics” brought up 548 clinical studies^[18]. As their safety and health benefits are established, it is reasonable to anticipate that probiotic bacteria will be incorporated into a growing number of clinical regimens, either on their own or as an adjunct/part of a combined treatment, including the kidney disease.

Over the past 15 years, the potential utilization of oral sorbents and probiotics as complementary strategy for CKD has continuously been explored, both *in vitro* and *in vivo*,^[19] in rat and mini pig animal trials^[20,21], in veterinary trials^[22], and in human clinical trials with CKD stages III and IV patients^[23-26]. The first patented and proprietary probiotic product formulation to maintain kidney health was developed in 2009 – KibowBiotics® (now Renadyl™, Kibow Biotech, Inc., Newtown Square, PA, USA), containing *S.thermophilus* KB 19, *L.acidophilus* KB 27 and *B.longum* KB 31 strains, a total of 45 billion colony forming units (CFU) per capsule. It uses “enteric toxin removal technology” to specifically target and reduce several uremic toxins that diffuse from circulating blood across the bowel and contribute to CKD. Throughout the entire R&D process, Renadyl™ has shown the ability to utilize various nitrogenous uremic toxins as nutrients for growth of the beneficial gut microbial population, thus keeping the toxins from accumulating to highly toxic levels in patients with CKD. Unlike many untested probiotic supplements available on the market, Renadyl™ has the advantage of having proven scientific validity^[19-26]. The results of the most recent human clinical study in ESRD patients (CKD stage V) on haemodialysis, has been published^[27]. This randomized clinical trial clearly indicated that Renadyl™ was safe to use in patients undergoing haemodialysis treatment, although due to insufficiently powered sample size, efficacy in ESRD remains to be established definitively in the future, adequately powered studies^[27].

After 4 years of Renadyl™ being available for purchase, a certain base of long-term repeat customers has been established and continues to grow, attracting more interested people at a steady rate. Given the overwhelmingly positive feedback from these customers, a need to systematize this anecdotal evidence became apparent. The aim of this survey study was to collect information about the quality of life and health status of the customers that had been using Renadyl™. The results of a customer satisfaction survey conducted in the fall of 2013 are reported below.

METHODS

A survey questionnaire was designed, using the combined expertise gleaned both from experience in medical/healthcare professions, including public health, and from sociological training and social science research methods (See the full questionnaire in Table 1)^[28-30].

Table 1: Survey questionnaire

DEMOGRAPHY		1	2	3	4	5	6
Gender		M	F				
Employment status:		Employed	Unemployed	Self-employed	Retired	Other: Please list	
Age:		30-39	40-49	50-59	60-69	70-79	80+
EPIDEMIOLOGY		1	2	3	4	5	6
1	In which stage of chronic kidney disease (CKD) are you now?	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	
2	Are you undergoing Kidney Dialysis?	Yes	No	2a: If yes, how long have you been on dialysis? __			
3	From which conditions other than CKD are you currently suffering?	Obesity	Type I or II diabetes	Heart disease	Hyper-tension	Other: list	
4	How long have you been suffering from Kidney disease?	< 1 year	1-3 years	3-5 years	5-10 years	>10 years	
5	What was your age at onset of kidney disease?	<20	21-30	31-40	41-50	51-60	61-70
QUALITY OF LIFE QUESTIONS		1	2	3	4	5	
6	Generally, how would you rate your health?	Poor	Fair	Good	Very good	Excellent	
7	Compared to 1 year ago, rate your health generally now	Much worse	Worse	Same	Better	A lot better	
DAILY ACTIVITIES QUESTIONS: Does your health hinder you from:		1		2		3	
8	Vigorous activities (running, lifting heavy objects, strenuous sports)	To a large extent		Hinders a little		Not at all	
9	Moving furniture (tables & chairs), cleaning & sweeping the floors	To a large extent		Hinders a little		Not at all	

10	Carrying groceries	To a large extent	Hinders a little	Not at all
11	Climbing several flights of stairs	To a large extent	Hinders a little	Not at all
11a	<i>(Skip If previous answer is 3)</i> Climbing 1 flight of stairs	To a large extent	Hinders a little	Not at all
12	Bending, kneeling or attempting to stop moving	To a large extent	Hinders a little	Not at all
13	Walking for more than a mile	To a large extent	Hinders a little	Not at all
14	Walking several blocks	To a large extent	Hinders a little	Not at all
14a	<i>(Skip If previous answer is 3)</i> Walking for 1 block	To a large extent	Hinders a little	Not at all
15	Bathing and dressing on your own	To a large extent	Hinders a little	Not at all
HOW YOU FELT DURING THE PAST 8 WEEKS		1	2	
16	During the past 8 weeks, have you at any time experienced any problems with your work or other daily activities as a result of your health?			
0.1	Had to cut down on the amount of time spent at work or/and other activities	Yes	No	
0.2	Have been unable to finish what you wanted to finish	Yes	No	
0.3	Have been unable to perform your task or activities freely	Yes	No	
0.4	Had difficulties performing task/activities or had to use extra effort to do the same task/activities you used to do	Yes	No	
17	During the past 8 weeks, have you had any problems with	Yes	No	

	your work or other daily activities as a result of emotions (depression/anxiety)?						
0.1	You have had to cut down on the amount of time spent at work or/and other activities	Yes	No				
0.2	You have not been able to finish what you wanted to finish	Yes	No				
0.3	You have been unable to perform your task or/and activities as carefully as you usually do.	Yes	No				
For the past 8 weeks, to what extent/how much:		1	2	3	4	5	6
18	Did physical/emotional health interfere with normal social activities with family, friends, neighbors or groups?	Very large extent	Moderately	Slightly	Seldom	Not at all	
19	Bodily pain you experienced?	Very severe	Severe	Moderate	Mild	Very mild	No pain
20	Did pain interfere with your normal daily activities (both at work and home)?	Large extent	Significant extent	Moderately	Slightly	Not at all	
HOW YOU FELT DURING THE PAST 4 WEEKS		1	2	3	4		
21	For each question, please give the answer that comes to your mind first. Please circle accordingly.						
0.1	Did you feel full of pep?	All the time	Most of the time	Sometimes	Not at all		
0.2	Did you feel nervous?	All the time	Most of the time	Sometimes	Not at all		

0.3	Did you feel so down that you always thought that nothing could make you feel better?	All the time	Most of the time	Sometimes	Not at all
0.4	Did you feel calm and peaceful?	All the time	Most of the time	Sometimes	Not at all
0.5	Did you feel energetic?	All the time	Most of the time	Sometimes	Not at all
0.6	Did you feel disheartened and discouraged?	All the time	Most of the time	Sometimes	Not at all
0.7	Did you feel tired?	All the time	Most of the time	Sometimes	Not at all
0.8	Did you feel happy?	All the time	Most of the time	Sometimes	Not at all
0.9	Did you feel exhausted?	All the time	Most of the time	Sometimes	Not at all
22	To what extent has your physical health or emotional problems interfered with your social activities in the past 8 weeks?	All the time	Most of the time	Sometimes	Not at all
SELF-EVALUATION OF HEALTH AND DEPENDENCY		1	2	3	4
23	For each of the following questions, circle the answer that best applies to you.				
0.1	I seem to get sick easier than other people	Very true	Somewhat true	Somewhat true	Very untrue
0.2	I am as healthy as anybody that I know.	Very true	Somewhat true	Somewhat true	Very untrue
0.3	I expect my health to deteriorate	Very true	Somewhat true	Somewhat true	Very untrue
0.4	My health is in excellent condition	Very true	Somewhat true	Somewhat true	Very untrue
24	I depend on (Circle accordingly):				
0.1	My partner	Very true	Somewhat true	Somewhat true	Very untrue
0.2	My family and friends	Very true	Somewhat true	Somewhat true	Very untrue
0.3	My caregivers	Very true	Somewhat true	Somewhat true	Very untrue
0.4	Other social workers or/and medical staff	Very true	Somewhat true	Somewhat true	Very untrue

TREATMENT EXPECTATIONS							
		1	2	3	4	5	
25	What type of medications are you currently using to control your illness?	Hypertension drugs (diuretics, ACE blockers)	Painkillers/ Analgesics	Diabetic drugs	Metformin	Others: specify	
		1	2	3	4		
26	To what extent are you satisfied with your current therapy?	Very Unsatisfied	Unsatisfied	Satisfied	Very satisfied		
27	To what extent are you involved in the choice your own medications?	Not at all	Not much	Some choice	Very much		
28	To what extent are you involved in the decision to go on dialysis?	Not at all	Not much	Some choice	Very much		
29	The goal of kidney disease management is to delay progression of the disease and to control your signs and symptoms. How effective would you rate your current therapy?	Not at all	A little effective	Somewhat effective	Very effective		
		1	2	3	4	5	6
30	How much do the side effects of your current medications affect you?	Intolerable	Too many	Most of my daily routine	Some of my daily routine	Don't affect me	No side effects
31	Expectations of ideal treatment for kidney disease	1	2	3	4		
0.1	The presence of side effects	Very unimportant	Unimportant	Important	Very important		
0.2	The use of low dosage of drugs	Very unimportant	Unimportant	Important	Very important		
0.3	Ease of self-administration	Very unimportant	Unimportant	Important	Very important		
0.4	Fast relief of symptoms (less than a week)	Very unimportant	Unimportant	Important	Very important		
0.5	Sustained efficacy over time	Very unimportant	Unimportant	Important	Very important		
0.6	Cost of	Very unimportant	Unimportant	Important	Very important		

	treatment			ant		important	
0.7	Self-administration of medication	Very unimportant		Unimportant	Important		Very important
QUESTIONS ABOUT RENADYL™		1	2	3	4	5	6
32	How did you come to know about Renadyl™?	Healthcare professionals	Family and friends	Internet	Tradeshows/conferences	Others: specify	
33	How satisfied are you about the current Renadyl™ product offering from Kibow?	Very unsatisfied	Unsatisfied	Satisfied	Very satisfied		
34	In your opinion, how important are dietary supplements in managing kidney health?	Very unimportant	Unimportant	Important	Very important		
35	If you have taken Renadyl, how much did the side effects affect you?	Intolerable	Too many	Most of my daily routine	Some of my daily routine	Didn't affect me	No side effects
PERCEPTION OF RENADYL™							
36	Level of agree/disagreement that Renadyl helps with your condition:	1	2	3	4		
0.1	Improvement in kidney function (levels of urea [BUN] and creatinine)?	Strongly disagree		Disagree	Agree		Strongly agree
0.2	Better sense of well-being (mood, energy level, physical fitness)?	Strongly disagree		Disagree	Agree		Strongly agree
0.3	Reductions in severity/frequency of signs and symptoms?	Strongly disagree		Disagree	Agree		Strongly agree
0.4	Would you recommend Renadyl to a friend?	Strongly disagree		Disagree	Agree		Strongly agree
SATISFACTION WITH KIBOW'S PRODUCTS AND SERVICES							
37	How satisfied are you with regard to:	1	2	3	4		
0.1	Overall customer	Very satisfied		Unsatisfied	Satisfied		Very satisfied

	service quality and understanding of your concerns?				
0.2	Quality of product shipped? Please skip if never ordered Kibow's product	Very satisfied	Unsatisfied	Satisfied	Very satisfied
0.3	The price for value given by Renadyl?	Very satisfied	Unsatisfied	Satisfied	Very satisfied
0.4	Product efficacy in maintaining or improving kidney health?	Very satisfied	Unsatisfied	Satisfied	Very satisfied

To ensure the internal validity of the questionnaire, internal controls were used, such as question rephrasing and repetition (eg, question 22 rephrases the preceding question 18). Nearly one thousand surveys were mailed out to all of the current customers as of September 11, 2013 (n=523), as well as to those customers that have ordered in the past, but whose last order was in 2012 (n=475). As an incentive to complete the survey, all respondents were offered a 25% discount on their next order of Renadyl™. We indicated September 30th as the preferred response date, but we continued collecting the incoming surveys until the end of October.

Out of 998 questionnaires mailed, 66 were either returned to sender by the U.S. Postal Service (n=49, mostly due to insufficient address information or inability to forward the mailing), or were excluded from the sample for other reasons: because the addressees had obtained a transplant kidney (n=2), had passed away (n=3), had given the product to their pets with kidney issues (n=4), were healthcare professionals who had purchased on behalf others (n=2) or simply mailed in the filled-out questionnaire significantly later than we had originally asked. The final sample size was 932 potential respondents.

The results were tabulated and analyzed both by Kibow staff and by a professional academic statistician (for the purposes of external, independent validation). SAS software V9.2, as well as MS Excel have been used to analyze all survey results.

RESULTS

Of 932 potential respondents, n=147 returned their questionnaires, a rate of 16%. Subsequently, n=89 (61%) respondents claimed the offered discount, while n=58 (39%) respondents did not. All results are reported below, and percentages refer to a fraction of the total number of respondents (n=147), unless otherwise indicated.

Demographics

The demographics of the sample population are presented in Table 2.

Over three quarters (n=113, 77%) of respondents were at least 50 years old, almost two thirds (n=97, 66%) – at least 60 years old. Males (n=84, 57%) outnumbered females (n=57, 39%) by 47%. Over one half (n=79, 54%) of respondents were retired, another third (n=50, 34%) – employed or self-employed.

Majority of respondents were either in CKD Stages III and IV (n=84, 57%) or in ESRD (stage V) – n=25 (17%). Only one CKD Stage IV respondent indicated receiving dialysis

treatment. Of those in ESRD, 64% (n=17) were on dialysis. From among those, 35% (n=6) have been in treatment for less than a year and 29% (n=5) – between 1 and 5 years.

Table 2: Demographic characteristics (n=147)

Age	Median	70 yrs	
	Range	7 to 94 yrs	
	>50 yrs old	113 (77%)	
	>60 yrs old	97 (66%)	
	Missing data	26 (18%)	
Gender	Female	57 (39%)	
	Male	84 (57%)	
	Missing data	6 (4%)	
Employment	Employed	50 (34%)	
	Retired	79 (54%)	
	Unemployed.	13 (9%)	
	High school	1 (1%)	
	Missing data	4 (3%)	
Disease status	CKD-I	15 (10%)	
	CKD-II	9 (6%)	
	CKD-III	44 (30%)	
	CKD-IV	40 (27%)	
	ESRD	25 (17%)	
	No CKD	8 (5%)	
	Missing data	6 (4%)	
Dialysis status	On dialysis	ESRD	16 (11%)
		CKD-IV	1 (1%)
	Not on dialysis	ESRD	9 (6%)
		CKD	121 (82%)
Dialysis duration [Missing – 4(3%)]	<1 yr	6 (4%)	35%
	<5 yrs	5 (3%)	29%
	<10 yrs	1 (1%)	6%
	<15 yrs	1 (1%)	6%
	Total	17(12%)	100%

Epidemiology

The epidemiological characteristics (questions 1-5) of the study population are presented in Table 3.

One-fifth (21%) of respondents had been suffering from CKD for over 10 years (n=31), just over a quarter (27%) – between 5 and 10 years (n=40), almost one-half (44%) – between 1 and 5 years (n=64), with only 4% diagnosed with CKD less than a year prior to taking the survey (n=6). The majority of respondents (71%) indicated the age of onset as being after the

age of 50 (n=105), with almost half (48%) – after the age of 60 (n=70). Only 13% experienced onset of the disease prior to the age of 40 (n=19).

Comorbidity

As expected, the majority of CKD patients suffered from either hypertension (40%) or diabetes (10%), or both simultaneously (25%), the two leading risk factors for CKD. Moreover, 12% suffered from obesity, a significant risk factor for both diabetes and hypertension (indeed, 90% of respondents suffering from obesity also suffered from either or both conditions). Heart disease was a problem for 18% of respondents, in 85% of the cases also comorbid with either/both hypertension or/and diabetes. Only 8% of respondents did not suffer from any other medical conditions. Some of the other conditions that respondents reported include cancer (4%), stroke (1%), various mental, developmental, or neurological conditions (6%, incl. depression/anxiety, bipolar, eating disorder, Alzheimer's, 4p syndrome, fibromyalgia), autoimmune or endocrine problems (8%, incl. hyper para-/hypothyroidism, lupus, celiac, asthma), skeletal/joint problems (6%, incl. osteoarthritis, osteoporosis, knee replacements, back issues), metabolic problems (3%, incl. high cholesterol, low haemoglobin, metabolic syndrome, gout).

General health perceptions and functioning

Physical functioning

The majority (63%) reported their health as being good, and only 5% – as poor (questions 6-16, table 4).

Compared to a year before, 82% reported stable or improved health, while 16% reported decrease in their health status. The overwhelming majority (82%) reported at least some difficulty with vigorous activities, including running, lifting heavy objects, and sports, and 73% - with climbing several flights of stairs. In the latter group, 49% also reported at least some difficulty with climbing even one flight of stairs.

Approximately a half of respondents had at least some difficulty with doing daily chores: bending, kneeling or stopping their movement (63%), walking for more than a mile (60%), moving chairs/table or sweeping/cleaning the floor (57%), carrying groceries (48%), or walking several blocks (53%). In the latter group, 35% also reported at least some difficulty with walking even 1 block. Only 25% had any trouble bathing or dressing on their own.

Role Functioning

Over 8 weeks preceding survey completion, 39% reduced time spent at work or doing other activities, 37% were unable to finish what they wanted, and 41% were unable to perform their activities freely due to their health issues. More than half (56%) needed to spend extra effort to perform activities they had been able to perform easily in the past.

Mental health

Over the same 8 weeks, approximately one-quarter to one-third of respondents had to reduce their time spent at work or doing other activities (23%), were unable to finish what they wanted (25%), and were unable to perform activities as carefully as usually (31%) due to emotional issues, i.e. depression or anxiety. (Please see Table 5 for the results presented in this section.)

Table 3: Epidemiological characteristics (n=147)

1: Onset of CKD	>10 yrs	31 (21%)
	6-10 yrs	40 (27%)
	4-5 yrs	29 (20%)
	1-3 yrs	35 (24%)
	<1 yrs	6 (4%)
	No CKD	6 (4%)
2: Age of CKD onset	<20 yrs	7 (5%)
	21-30 yrs	4 (3%)
	31-40 yrs	8 (5%)
	41-50 yrs	16 (11%)
	51-60 yrs	35 (24%)
	61-70 yrs	39 (27%)
	71+	31 (21%)
	No CKD	6 (4%)
3: Number of health conditions	Median	2
	Range	0-7
4: Medical conditions (self-reported)	Hypertension (HTN)	95 (65%)
	Diabetes (DM)	51 (35%)
	Heart disease (HD)	27 (18%)
	Obesity (OW)	18 (12%)
	Autoimmune/endocrine ^a	11 (7%)
	Skeletal/joints ^b	9 (6%)
	Psycho/neuro/develop ^c	9 (6%)
	Cancers ^d	6 (4%)
	Metabolic issues ^e	5 (3%)
	None	12 (8%)
Missing data	11 (7%)	
5: Comorbidity	HTN and DM	36 (25%)
	HTN and HD	21 (14%)
	HTN and OW	14 (10%)
	DM and HD	12 (8%)
	DM and OW	10 (7%)

^aHypothyroidism (4), asthma (2), lupus (1), celiac (1), CVID (1), sarcoid (1), Addison's (1)^bOsteoarthritis (3), knee problems (3), back problems (2), osteoporosis (1)^cFibromyalgia/fatigue (2), vertigo (2), Alzheimer's (1), eating disorder (1), bipolar (1), depression/anxiety/insomnia (1), 4p syndrome (1)^dLung (1), prostate (1), leukaemia (1), mantle cell lymphoma (1), Crohn's disease (1), unknown (1)^eHypercholesterolemia (2), low haemoglobin (1), metabolic syndrome (1), gout (1)

Table 4: Quality of life/Daily activities (n=147)

6: Self-rating of health	Poor	7 (4.8%)	
	Fair	46 (31.3%)	
	Very/Good	92 (62.6%)	
	Missing data	1 (0.7%)	
7: Compared to yr. ago	Much/Worse	24 (16.3%)	
	Same	65 (44.2%)	
	Much/Better	56 (38.1%)	
	Missing data	2 (1.4%)	
Health as hindrance for daily activities:^a	To a large extent	A little	Not at all
8: Vigorous activities	68 (46%)	52 (35%)	25 (17%)
9: Furniture/sweeping	39 (27%)	45 (31%)	61 (41%)
10: Carrying groceries	28 (19%)	43 (29%)	73 (50%)
11: Climbing stairs	47 (32%)	60 (41%)	38 (26%)
11a: - 1 flight of stairs ^b	21 (14%)	51 (35%)	32 (22%)
12: Bending/kneeling	30 (20%)	62 (42%)	53 (36%)
13: Walking >1 mile	54 (37%)	34 (23%)	58 (39%)
14: Walking few blocks	42 (29%)	36 (24%)	68 (46%)
14a: - 1 block ^b	19 (13%)	33 (22%)	21 (14%)
15: Bathing/dressing	10 (7%)	27 (18%)	108(73%)
Past 8 weeks (health):	Yes	No	Missing
16.1 Time (work/activities)	58 (39%)	87 (59%)	2 (1.4%)
16.2 Unable to finish	55 (37%)	91 (62%)	1 (0.7%)
16.3 Unable to perform	61 (41%)	84 (57%)	2 (1.4%)
16.4 Extra effort needed	83 (56%)	60 (41%)	4 (2.7%)

^a Missing values: 1 (0.7%) or 2 (1.4%) for most questions in this group (Q8-15), except Q11a and Q14a – 6 (4%).

^b For questions 11a and 14a, those responding “Not at all” to 11 and 14, respectively, were instructed to skip. So Q11a did not apply to 38 (26%) and Q14a – to 68 (46%) of the respondents.

Table 5: Emotional fitness/Pain (n=147)

Past 8wks (emotions):	Yes	No	Missing
17.1 Time (work/activities)	34 (23%)	112 (76%)	1 (0.7%)
17.2 Unable to finish	37 (25%)	103 (70%)	7 (4.8%)
17.3 Unable to perform	46 (31%)	97 (66%)	4 (2.7%)
18: Health as interference with social activities	Very much		18 (12%)
	Moderate/slight/seldom		82 (56%)
	Not at all		46 (31%)
	Missing		1 (0.7%)
19: Bodily pain	Severe/Very		17 (11%)
	Moderate/mild		62 (42%)
	Very mild/none		67 (46%)
	Missing		1 (0.7%)
20: Pain as interference with daily activities	Very much		20(13.6%)
	Moderate/slight		69(47.0%)
	Not at all		57(38.7%)
	Missing		1 (0.7%)
Past 4 weeks feeling: ^a	Always	Sometimes	Not at all
21.1 Full of pep	32 (22%)	80 (54%)	32 (22%)
21.2 Nervous	12 (8%)	71 (48%)	63 (43%)
21.3 Down	6 (4%)	50 (34%)	88 (60%)
21.4 Calm	80 (54%)	62 (42%)	3 (2%)
21.5 Energetic	38 (26%)	83 (56%)	25 (17%)
21.6 Discouraged	10 (7%)	90 (61%)	45 (31%)
21.7 Tired	48 (33%)	88 (60%)	10 (7%)
21.8 Happy	86 (59%)	53 (36%)	6 (4%)
21.9 Exhausted	30 (20%)	98 (67%)	18 (12%)
22: Health as interference with social activities (past 8 wks)	Very much		18 (12%)
	Moderate/slight/seldom		82 (56%)
	Not at all		46 (31%)
	Missing		1 (0.7%)

^aMissing values: 1 (0.7%) or 2 (1.4%) for most questions in this group (Q21.1-Q21.9), except Q21.1 and Q21.3 – 3 (2%).

In the 4 preceding weeks, the majority felt “calm” (54%) and “happy” (59%) most or all of the time; “full of pep” (54%) and “energetic” (56%), but also “tired” (60%), “exhausted” (67%), “discouraged” (61%) – sometimes; and did NOT feel “down” (60%) at all. Only a minority felt “nervous” (8%), “down” (4%), and “discouraged” (7%) most or all of the time, while only a very small minority did not feel calm (2%) or happy (4%) at all – mutually reinforcing results (internal validity). Also mutually reinforcing was that one-fifth did not feel full of pep (22%) or energetic (17%) at all, while roughly the same proportion felt exhausted (20%) or tired (33%) most or all of the time. (See question 21 in Table 5.)

Social functioning

Also, the respondents reported that in those 8 weeks their physical and emotional issues interfered with their social activities either to a very large extent (12%), moderately or slightly (56%), or not at all (31%, Question 18). These results were corroborated by similar responses to question 22 (a measure of internal validity) – physical/emotional issues affected social activities most or all of the time (14%), only sometimes (48%) or not at all (37%). (Please see table 5)

Pain

Only 11% experienced severe pain in the preceding 8 weeks, while 42% experienced moderate to mild pain and 46% - very mild to no pain at all. Approximately the same proportions reported that the extent to which their pain interfered with their daily activities both at work (if applicable) and home was significant (14%), moderate or slight (47%), or not at all (39%).

Health perceptions – comparative and dependency

Three-quarters (75%) thought they didn’t get sick easier than other people, but 66% – that their health was not in excellent condition, and 52% – that they were not as healthy as anybody they knew. Over one-half (56%) expected their health to deteriorate. About one-half depended on their partners (50%) or other family and friends (44%) for assistance, and only one-fifth – on other caregivers (20%) or other social work/medical staff (19%). (Please see Table 6.)

Table 6: Self-evaluation of health/dependency (n=147)

Health	True	Untrue	Missing
23.1: Get sick easier than others	34 (23%)	110 (75%)	3 (2%)
23.2: Healthy as anybody	68 (46%)	76 (52%)	3 (2%)
23.3: Expect health to deteriorate	82 (56%)	61 (41%)	4 (3%)
23.4: Health is excellent	48 (33%)	97 (66%)	2 (2%)
Dependency	Depend	Do not	Missing
24.1: On partner	74 (50%)	61 (41%)	12 (8%)
24.2: On family and friends	64 (44%)	81 (55%)	2 (2%)
24.3: On caregivers	29 (20%)	106 (72%)	12 (8%)
24.4: On social work/medical staff	28 (19%)	109 (74%)	10 (7%)

Satisfaction

Satisfaction with medications

The majority took medications (question 25) for hypertension (n=65, 44%), diabetes (n=9, 6%), or both (n=37, 25%), which corresponds to the epidemiology of these conditions (Table 3). Some (n=20, 14%) also took medication for pain relief, quarter of whom (n=5) took *only*

pain medicine. Another n=12 (8%) respondents did not take *any* medication at all. Those taking medications reported no side effects from (n=44, 30%) or not being affected by (n=50, 34%) any of them, while n=41 (28%) – only some of their daily routine being affected (question 30).

Heart/cardiovascular disease medications were also prominent among other medications taken (n=16, 11%), roughly corresponding to the epidemiology of such conditions (Table 3). A sizeable minority also took some variety of nutritional supplements and herbs (n=14, 10%), as well as vitamins and microelements (n=13, 9%), usually prescribed by naturopathic physicians or nutritionists. A few respondents also took medications for such metabolically related to CKD conditions as parathyroid/thyroid excess or insufficiency (n=10, 7%), elevated cholesterol (n=7, 5%), elevated phosphate (n=6, 4%), potassium insufficiency (n=4, 3%), urinary/prostate issues (n=4, 3%), gastrointestinal issues (n=4, 3%), and gout (n=3, 2%).

Treatment satisfaction and expectations

The overwhelming majority was satisfied or very satisfied (82%) with the current therapy (question 26), and considered it to be somewhat or very effective (87%, question 29). The majority felt they had some (33%) or very much (43%) choice with regard to their medications, while only 7% thought they had no choice at all, which usually meant that their survival depended on the medications (question 27). Slightly more than half thought they had some (16%) or very much (44%) choice with regard to the decision whether to start dialysis or not. Another 14% did not have to consider this decision yet, due to their pre-dialysis status (question 28, please see Table 7 for Q26-31).

As far as the expectations from an ideal treatment for kidney disease, the majority considered side effects (85%), dosage (82%), ease of self-administration (88%), fast relief of symptoms (78%), sustained efficacy over time (89%), and even cost of treatment (84%) to be ultimately unimportant, valuing their health higher than any of these factors. Nevertheless, preference for low dosage (12%), lower cost of treatment (10%) and fast relief of symptoms (less than a week) (15%) were considered to be relatively more important, while ease of administration (5%) and sustained efficacy (3%) – relatively less important factors.

Satisfaction with Renadyl™ and Kibow Biotech

An overwhelming majority (92%) of respondents learned about Renadyl™ from their healthcare professionals (42%), internet (33%) or family and friends (16%). Those selecting “other” as their source of information (6%), usually learned about the product from some health-related literature – health/herbal newsletter, journal or magazine, or a book. A few even found out about Renadyl™ through their veterinarian, when their pet started taking Azodyl™, our veterinary formulation licensed for distribution to Vétoquinol SA (www.vetoquinolusa.com). Please see Table 8 for all results presented in this section.

An overwhelming majority of respondents (88% and 95%, respectively) were satisfied (52%) or very satisfied (35%) with the current product offering from Kibow and considered dietary supplements to be important (32%) or very important (63%) for managing kidney health.

Virtually all respondents (98%, n=144 out of 147) reported either not having experienced any side effects from Renadyl™ (67%), or, if experienced any, not having been affected (25%) or affected only mildly (5%) by them.

Approximately a quarter of respondents indicated their agreement that Renadyl™ had helped improve their kidney function and sense of well-being (73% each), and reduce severity and frequency of signs and symptoms (74%). An overwhelming majority indicated that they would recommend the product to a friend (88%), and a few had already done so.

Table 7: Treatment satisfaction (n=147)

	Very unsatisfied/ None	Unsatisfied/ Not much	Satisfied/ Somewhat	Very satisfied/ Very much	Missing data
26: Satisfaction with current therapy	3 (2%)	17 (12%)	92 (63%)	29 (20%)	6 (4%)
27: Involvement in medication choice	11 (7%)	20 (14%)	48 (33%)	63 (43%)	5 (3%)
28: Involvement in decision about dialysis	24 (16%)	8 (5%)	23 (16%)	65 (44%)	27 (18%) ^a
29: Effectiveness of current therapy	4 (3%)	9 (6%)	69 (47%)	59 (40%)	6 (4%)

^aOf those, 21 (14%) – Not applicable

30: Current medications' side effects	Too many	3 (2%)
	Most routine	2 (1.4%)
	Much routine	1 (0.7%)
	Some routine	41 (28%)
	Don't affect	50 (34%)
	No effects	44 (30%)
	Missing data	5 (4%)

Expectations from ideal CKD treatment	Unimportant	Important	Missing
31.1: Presence of side effects	125 (85%)	11 (7%)	11 (7%)
31.2: Low dosage of drugs	120 (82%)	17 (12%)	10 (7%)
31.3: Ease of self-administration	129 (88%)	8 (5%)	10 (7%)
31.4: Fast relief of symptoms (<1 week)	115 (78%)	22 (15%)	10 (7%)
31.5: Sustained efficacy over time	131 (89%)	6 (3%)	11 (7%)
31.6: Cost of treatment	123 (84%)	14 (10%)	10 (7%)
31.7: Self-administration of medication	129 (88%)	8 (5%)	10 (7%)

An overwhelming majority reported their satisfaction with Kibow's overall quality of service/understanding their concerns (94%), the quality of the product shipped (89%), and the efficacy of the product in maintaining or improving kidney health (78%). The biggest issue by far was the price of Renadyl™: 22% reported their dissatisfaction and 3% – strong dissatisfaction with the cost. Even in this case, 66% indicated they were satisfied (52%) or very satisfied (14%). Still, those satisfied frequently added comments suggesting that they would have liked the price to be lower.

Table 8: Renadyl™/Kibow Biotech (n=147)

32: Learned about Renadyl™	Professionals	62 (42%)		
[Missing – 1 (0.7%)]	Internet	49 (33%)		
	Family/friends	24 (16%)		
	Other literature	9 (6%)		
	Conferences/shows	2 (1%)		
33: Satisfaction with Renadyl™	Very/Satisfied	129 (88%)		
[Missing – 9(6%)]	Not sure	1 (0.7%)		
	Very/Unsatisfied	8 (5%)		
34: Dietary supplements in kidney health	Very/Important	139 (95%)		
	Very/Unimportant	6 (4%)		
	Missing	2(1.4%)		
35: Side effects of Renadyl™	No side effects	99 (67%)		
	Didn't affect	37 (25%)		
	Affected mildly	8 (5%)		
	Missing data	3 (2%)		
Renadyl's efficacy	Agree	Disagree	Not sure	Missing data
36.1: Improves kidney function (BUN/creatinine levels)	108 (73%)	17 (12%)	2 (1.4%)	20 (14%)
36.2: Increased sense of well-being (mood, energy, fitness)	107 (73%)	18 (12%)	3 (2%)	19 (13%)
36.3: Reduced severity/frequency of signs/symptoms	109 (74%)	16 (11%)	2 (1.4%)	20 (14%)
36.4: Would recommend to a friend	130 (88%)	7 (5%)	1 (0.7%)	9 (6%)
37.1: Customer service quality	138 (94%)	1 (0.7%)	2 (1.4%)	6 (4%)
37.2: Quality of shipped product	131 (89%)	3 (2%)	1 (0.7%)	12 (8%)
37.3: Price for value of Renadyl™	97 (66%)	36 (24%)	2 (1.4%)	12 (8%)
37.4: Product efficacy	114 (78%)	10 (7%)	1 (0.7%)	22 (15%)

DISCUSSION

Overall, the results can be described as overwhelmingly positive. The participants' feedback conveys high level of satisfaction with the product formulation, its safety and perceived efficacy, as well as customer service at Kibow. The results also describe the expected significant variation in the health status of customers using Renadyl™, depending on the stage of kidney disease, number of comorbidities, age and other salient factors. In assessing the presented results, particularly related to physical health (questions 6-16, table 4), it is

important to keep in mind that the demographics and epidemiological profile of respondents, particularly their age, often became the most important determining factor influencing their responses (as was frequently indicated by the respondents' own comments). In assessing the results related to emotional/mental health (questions 17-22, table 5), both physical health and social status (eg availability of life partners and/or family and friends as caregivers) were likely significant contributing factors to the variation in outcome.

Health-related quality of life (QOL) is an important measure of how disease affects patients' lives. While it is known that dialysis patients have decreased QOL relative to healthy individuals, fairly little is known about QOL of CKD patients in pre-dialysis stages I-IV, before renal replacement therapy^[31]. Therefore, the current survey study may be seen as belonging with other efforts to fill that particular gap in our knowledge. Moreover, given the increasing evidence that probiotics have a significant role to play in improving QOL in a variety of conditions, such as, for instance, colorectal cancer^[32], cystic fibrosis^[33], or a variety of gastrointestinal, immune and metabolic conditions^[34,35], the authors wanted to obtain some basic measurement of the effect of Renadyl™ on customers with CKD.

The internal validity of the survey questionnaire was a significant strength in this study. To ensure the internal validity of the questionnaire, several controls were deliberately incorporated, such as rephrasing and repetition of questions (eg question 22 rephrases the preceding question 18). In addition, data analysis itself provided additional corroboration in support of internal validity. Specifically, in reporting their feelings (question 21), the respondents provided mutually reinforcing results by reporting low levels of emotional distress (21.2, 21.3, 21.6) and high levels of positive affect (21.4, 21.8). Also mutually reinforcing, the proportion of the respondents reporting lack of energy (21.1, 21.5) was approximately equivalent to that reporting high levels of exhaustion (21.7, 21.9). The correspondence between the responses about current medications (question 25) and the epidemiological profile of the respondents (Table 3) added another dimension to internal validation.

Uncertainty about the external validity, or representativeness, was among the major limitations of the study. Inevitably, the sample used in this survey was selected according to convenience – all of the current customers of Kibow, plus some of the recent yet inactive customers. This was not a truly random sample, because Kibow's customers represent a self-selected sample of kidney disease patients who already view alternative medicine more broadly and dietary supplements, including probiotics, more specifically either in a positive light or at least with suspended disbelief. In other words, there was no possibility to control for placebo effect. In comparison with the estimates based on the results of NHANES III, in the current sample CKD stages IV and V are overrepresented, stage III relatively underrepresented, while stage I and II – significantly under represented^[36]. This is understandable, however, as in stages I and II the signs and symptoms of CKD are either still absent or very mild, and thus undiagnosed.

In addition, all of the results were self-reported, as is common for survey methods, which also presents limits with regard to ability to ascertain the accuracy of such observations. At the same time, this can also be considered as one of survey methodology's strengths, since there is no other practically useful way to easily and unobtrusively capture individuals' perceptions and subjective experiences, which are important factors to consider in any therapeutic situation.

Methodological Limitations

Response rate

The response rate of 16% may seem low at the first glance – depending on the context, survey response rates can reach 60 or 70% or higher. Usually, however, that requires several waves of reminders and additional efforts to increase the rate of response. In this particular

case, it being a *customer satisfaction* survey, not a randomized and controlled clinical study, only one wave of responses was collected – reminders were not sent and only the responses received within the first month and a half were included in the analysis, because there is also some evidence that different waves may have different characteristics and make the results actually *less* representative^[37].

Age is a significant factor and has been shown in prior research to affect the response rate^[38, 39]. Considering that the customer population is skewed toward the elderly, CKD being a chronic disease with an onset late in life, this also helps explain the relatively low response rate. Moreover, self-administered survey questionnaires permit the respondents to examine the questions prior to making the decision about participation, thus influencing the latter due to negative emotions connected to the topic (eg, fear of revealing personal information) or to perceived high burden of the questions (eg, complicated reports of past behaviors, lookup of household records) and similar considerations^[40].

In other words, low response rate was to be expected, given the unique demographic makeup of the CKD population. Besides, in recent years, the basic inferential paradigm of survey research, which assumes 100 response rates on a probability sample, has been challenged^[40]. Survey designs seeking high response rates entail high costs, usually generated by repeated efforts to obtain access to sample units and to address any concerns of the sample persons^[41]. This customer satisfaction survey was limited with regard to funding access and was conducted at a minimal cost.

Non-response Bias

An important issue that is sometimes connected to the low response rate is the nonresponse bias. Low response rates are open to interpretation – the respondents may represent subgroups of the target population, some subgroups may have systematically failed to respond or responded at a lower rate, the results may be consequently biased to an unknown extent. Concern with bias is key if the survey content is differentially perceived by population subgroups and if the response rate is low^[37, 40].

In this particular case, potential subgroups can be identified as current vs. former customers, pre-dialysis (CKD stages I-IV) vs. dialysis (CKD stage V, usually). Among the respondents, 85 (58%) questionnaires were returned by the current customers, 31 (21%) – by the past customers, and another 31 (21%) were anonymous. It is understandable that the current customers would be expected to represent a larger fraction of the respondents, given that active contact is maintained with them. Many of the past customers, who had last ordered in 2012, may have relocated or may have been less motivated to fill out the questionnaire, not using the product any longer and not being able to take advantage of the incentive offered. More about incentive and its relevance will be discussed below. As far as dialysis vs. pre-dialysis patients, most customer using Renadyl™ tend to be overwhelmingly pre-dialysis (CKD Stages III and IV) patients. While dialysis patients can also benefit from using the product, the very fact of receiving dialysis may be a factor affecting their willingness to use or ability to afford the product.

However, response rates alone are not good indicators of non-response bias. It is a well-developed finding in the survey methodological literature that response rates by themselves are poor indicators of non-response bias^[42, 43]. The search for mechanisms that link nonresponse rates and nonresponse bias should focus on the level of individual measures and not on the level of the survey. To predict what survey estimates are most susceptible to nonresponse bias, we need to understand how each survey variable relates to causes of survey participation^[40]. It is also important to understand non-respondents – often the reasons for not returning the questionnaire include one of the following and more: never received it, never got around to it, too busy, forgot it or mislaid it, completed but never mailed, came at a

bad time (eg, ill), thought received it by mistake, seemed too long, not interested, never answer surveys^[43].

Incentive

The survey methodological literature offers a number of techniques to increase response rates, including, for example, pre-notification and incentives. However, none of these measures – including incentives – is reliably related to the magnitude of nonresponse differences^[40]. The use of incentives has become fairly common, and there is agreement that incentives, both monetary and non-monetary, increase overall response rates. The dilemma for survey researchers, then, is not *whether* to offer an incentive, but *what kind* of incentive, at what value, and when in the survey process to offer it. Generally, non-monetary incentives are less effective than monetary ones, and prepaid incentives are more effective than those conditional upon participation^[44, 45].

One of the reasons incentives may work is related to a norm of reciprocity, whereby the potential respondent feels obligated to respond or return the favor by completing the survey. The recipient of the incentive, having benefited, feels indebted to the giver. This obligation to return the favor is less contingent on the value of the benefit received, than on the ethical principle of helping those who have helped you. Viewed this way, an incentive valued not only for its perceived cash value, but also because it represents the thoughtfulness and genuine appreciation of the giver^[44].

This manner of thinking applied in the current study: since the respondents were, or had recently been, Kibow's active customers, a 25% discount on the next order of Renadyl™ was deemed an appropriate reward for taking the time to complete the questionnaire. As it were, only 61% of respondents (n=89) chose to take advantage of the discount. The other 40% included both past and current, active customers.

Ethical considerations

This *customer satisfaction* survey study can be classified as “minimal risk” research, which, in the *clinical* setting, usually receives expedited review from the Institutional Review Board (IRB), for which some or all elements of informed consent may be waived or modified, and in which vulnerable subjects including healthy children, incapacitated persons and prisoners may be permitted to enroll, even if a particular study does not hold out any direct benefit to them^[46].

CONCLUSIONS

Overall, the results indicate that Renadyl™ is safe to take in all stages of CKD, even with a variety of comorbid conditions, and does not interfere with any other medical treatments, including dialysis. At the same time, it provides at least some beneficial effect with regard to the overall quality of life and maintaining or improving kidney health in particular. Further adequately powered studies are warranted.

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