Ranganathan, J Nephrol Ther 2018, 8:5
DOI: 10.4172/2161-0959.1000319

Journal of Nephrology & Therapeutics

Commentary Open Access

Reality of "Enteric Dialysis ®" with Probiotics and Prebiotics to Delay the Need of Conventional Dialysis

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Received date: September 14, 2018; **Accepted date:** September 17, 2018; **Published date:** September 30, 2018

Abstract

Probiotics and prebiotics are generally used for gut, immune and digestive health. However, we have been looking outside the box for the use of probiotics and prebiotics toward help in maintaining healthy kidney function. The gut microbiome is unfavorably altered (i.e., Dysbiosis) in individuals with renal impairment, promoting progressive renal failure, persistent systemic inflammation, and small bowel bacterial overgrowth (SBBO). A probiotic that delays the progression of kidney failure would have enormous impact as millions of individuals worldwide suffer from chronic kidney disease and, not all individuals; especially in low income countries have access to chronic dialysis care. Probiotics have demonstrated their ability to remove uremic toxins, and early studies indicate the slowing of renal disease progression. The role of probiotics in managing renal failure is not yet clearly defined, but the data thus far, suggest that probiotics will prove to play a significant role in chronic kidney disease management.

Keywords: Enteric dialysis; Probiotics; Prebiotics; Dysbiosis; eGFR; Gut microbiome

Introduction

The original concept "WILL THE BOWEL BE THE KIDNEY OF THE FUTURE?" was formally proposed by Dr. Eli A. Friedman (Prof Emeritus, Renal Sciences, Downstate Medical Center, State University of New York, Brooklyn, NY) and discussed in a two hour symposium. This was held at the International Society of Artificial Intestinal Organ Congress on August 04, 1999 in Edinburgh, Scotland, with three distinguished international nephrologists and reviewer of this article (Figure 1).

Figure 1: L to R: Dr. Carl Kjellstrand, Karolinska Institute, Sweden, Dr. Tatsumo Tsunaka, Tokyo Women's Medical University, Tokyo, Japan, Dr. Natarajan Ranganathan, Founder, Kibow Biotech, Inc., Pennsylvania USA, and Dr. Eli A. Friedman Distinguished Professor of Renal Science, State University of New York, Downstate Medical Center, New York, USA.

Since then this concept has been the prime mission and goal of the reviewer of this article who is also the founder of Kibow Biotech, Inc. All of the work accomplished in the past two decades can be viewed in the form of various poster presentations presented at many nephrology related annual/biennial meetings (ASN, WCN). This can be found at https://www.kibowbiotech.com/rd/. In addition, several peer reviewed articles in various medical/scientific journals can also be viewed at https://www.kibowbiotech.com/journal-publications/. The reviewer published his earlier commentary titled "Concept and Potential of Enteric Dialysis® - Treating the Cause of Dysbiosis and not the Symptoms in Chronic Kidney Diseases (CKD)" in this journal in 2015 (doi:10.4172/2161-0959.1000209). Since then exponential advances have been made related to the modulation of the gut microbiome with pro/prebiotics towards alleviating dysbiosis, inflammation and potential benefits on improving Quality of Life (QoL) among these patients. This review article is a continuation of the earlier published commentary and to update the recent developments in this field.

The gut microbiome includes those bacteria that inhabit the entire intestinal tract and is an extraordinary complex and dynamic conglomerate of bacteria. During coevolution with microbes, the human intestinal tract has been colonized by thousands of bacterial species [1,2]. Gut-borne microbes outnumber the human body cells by a factor of ten [3]. Recent metagenomics analysis of human gut microbiota has revealed the presence of 3.3 million genes, compared to a mere 23,000 known human genes [4-6]. in healthy individuals, the phyla Bacteroidetes and Firmicutes contribute >90% of all species. Microbiotic composition varies considerably in different sections of the gastrointestinal tract; and function changes according to gut location as well as the gender, sex, race, and diet of the host [7]. A large degree of diversity exists even among healthy individuals [8]. The microbiota contains unique and specific enzymes and biochemical pathways to increase energy extraction from food, metabolism of undigested carbohydrates, and the biosynthesis of vitamins [5,9]. In addition, the microbiome produces antimicrobial compounds [10-12] and provides a physical barrier protecting the host from pathogen invasion. Intestinal mucosa development and the host immune system are also dependent on the gut microbiome [13-15].

The critical role of the gut microbiome in human health and disease has only recently been identified [16], prompting considerable interest

in using prebiotics and probiotics to modulate the gut microbiome to improve health and treat disease. Beneficial effects of probiotics have been demonstrated in antibiotic-associated diarrhea [17], bacterial vaginosis [18], hypertension [19], dyslipidemia [20], inflammatory bowel disease [21], obesity [22], cancer [23], and lactose intolerance [24]. Hundreds of products exist that are commercially available in multiple formulations as foods, beverages, and dietary supplements. Millions of individuals utilize these products, or feed them to their animals [25], without medical supervision even when vigorous scientific evidence for their efficacy may be lacking [25,26].

Chronic Kidney Disease (CKD) patients have an imbalance of their gut microbiome [27], and they too have benefitted from the positive effect of probiotics. In kidney failure, multiple factors are associated with progressive disease including underlying kidney disease, systemic hypertension, diet [28], digestive [29] and immune systems [30], the production of inflammatory substances [31], and the existence of oxidative stress [32,33]. An activated immune system may also play a role in progressive uremia [34]. Many of these factors may be modified by probiotic use.

A sufficiently powered, randomized placebo-controlled human trial using a non-creatinine measure of renal function has yet to be accomplished with CKD progression, as an outcome measure as discussed in the two meta-analysis [35,36]. However, ample studies ranging from open label, double blind-randomized placebo controlled trial, open label randomized placebo controlled trial, randomized double blind placebo controlled cross-over trial and dose escalation trials exist, suggesting that probiotic supplementation is helpful in CKD patients by correcting gut microbial imbalance, delaying kidney failure progression [37-40] reducing levels of inflammatory markers, improving iron status, stabilizing parahormone levels and even decreasing the risk for proteinuric kidney disease [41-43].

Recent papers report meta-analyses of probiotic use in patients with CKD. These analyses confirm beneficial effects on uremic toxins [35,36], inflammation, and gastrointestinal symptoms [35], but not preservation of kidney function (Table 1). However, variations in probiotic supplement used, study design, underlying kidney disease, and absence of baseline kidney function determinations has limited the value of meta-analyses [35,36,44].

Parameters assessed	**CKD (J Nephropathol 2018; 7(3):106-114**	**ESRD patients on Dialysis (2018. Digestive Diseases and Sciences. https://doi.org/10.1007/s10620-018-5243-9)**
Total articles searched for	491	491
Number of articles omitted based on study design,article type,population,outcome of interest	427	427
Number of articles for which full length review was conducted	64	64
Number of articles further omitted	59	52
Number of articles finally selected	5	7
Number of Patients studied	161	178
Probiotic course	4 weeks to 6 months	2 weeks to 6 months
Levels of serum creatinine	No significant decrease	Potential benefits
eGFR	No significant decrease	Potential benefits
Levels of p-cresol	Significant decrease	Potential benefits
Infectious complications	None	Potential benefits
C reactive protein (CRP) (Inflammation)	Potential benefits	Significant decrease
TNF-a	Potential benefits	No significant decrease
Serum albumin	Potential benefits	No significant decrease
Protein bound uremic toxins (PBUT)	Potential benefits	Significant decrease
GI symptoms	Potential benefits	Significant improvement
Conclusion	Meta-analysis findings suggest potential beneficial effects of probiotics on uremic toxins. Short term tratment with probiotics did not change serum creatinine or eGFR significantly. Long term effects on CKD progression and uremic toxins are required.	Meta-analysis findings suggests potential beneficial effects of probiotics on uremic toxins, inflammation and GI symptoms. Further large scale clinical studies are required to assess its benefits on other clinical outcomes including patient mortality.

NOTE: Both meta-analysis papers have cited Kibow Biotech's clinical trial with positive outcomes. Clinical outcomes depend on the strain specificity of probiotics. Strains used by Kibow Biotech Inc. are specific in their ability to metabolize uremic toxins, reduce gut dysbiosis and improve Quality of Life (QOL) in patients taking our synbiotic dietary supplement Renadyl TM which has been clinically validated like a drug.

Table 1: Meta-analysis of probiotics in CKD and ESRD patients.

In this review, we focus on using probiotics to restore a metabolically balanced gastrointestinal tract in CKD patients and, most importantly, to decelerate CKD progression.

Chronic kidney disease

Chronic kidney disease is a global public health issue and rising worldwide as indicated by increases in attributable deaths, and incidence and prevalence of end-stage renal disease [45]. Approximately 500,000 U.S. patients are enrolled in chronic dialysis programs. Over 26 million individuals are in earlier stages of CKD [46]. Diabetes, hypertension, and vascular disease frequently all play a role in the development of CKD and are rampant in the United States [47] and in many areas of the world [48]. CKD is a major risk factor for cardiovascular disease [49]. The potential impact of probiotics to delay the need for dialysis is immense in view of the large numbers of CKD patients worldwide [48].

Probiotics

The Food and Agriculture Organization (FAO) and World Health Organization (WHO) define probiotics as live microorganisms that when administered in adequate amounts, confer a health benefit to the host [50]. Probiotics are predominantly found in fermented dairy products such as yogurt, kefir, cheese and other fermented foods. Naming and characterization of probiotics are according to genus, species, and strain. Only those well characterized and precisely defined strains possessing specific health benefits are classified as probiotics. As live organisms, probiotics are sensitive to temperature, light exposure, and moisture. In the United States, the Food and Drug Administration (FDA) provides, when appropriate, generally regarded as safe (GRAS) designations (i.e., GRAS certified) [51].

Beneficial or therapeutic properties depend on bacterial strain. Many strains produce bacteriocins, namely lactacin and bisin that inhibit the growth of pathogenic bacteria [52-54]. Specific strains may modulate gut inflammation lowering the levels of pro-inflammatory biomarkers, such as IL-1β and C-reactive protein and increasing middle molecules, such as IL-6 and TNF-α, that up-regulate the levels of anti-inflammatory markers like IL-10 [55-59].

Different strains of Lactobacillus acidophilus provide unique beneficial effects. For example, supplementation with L. acidophilus NCFM® tends to increase specific serum IgA after oral vaccination [58]; and significantly reduces the incidence and duration of fever, upper respiratory infection symptoms, and antibiotic use compared to a placebo in children with cold or influenza symptoms [60]. A proprietary strain of Lactobacillus acidophilus LA-05® has the ability to reduce lactose intolerance and diarrhea associated with antibiotic use [61-64]. Multiple organisms (Lactobacillus acidophilus LA05® and Bifidobacterium lactis BB-12®) have been combined with good therapeutic effect for treatment of inflammatory bowel disease [21]. At times, single-strain probiotics have been reported as more preserving of renal function [44].

Prebiotics

Prebiotics are defined as non-digestible, but fermentable, foods/ingredients that allow specific changes, both in the composition and/or activity, in the gastrointestinal microflora that confer benefits upon a host's well-being and health [65]. Well known examples of prebiotics include inulin, oligofructose, galactooligosaccharides, lactulose [66] xylooligosaccharides [67] and beta-glucans [68]. Many commercial products with purported health benefits are available that are derived from plant sources such as chicory, Jerusalem artichoke, mushrooms, larch wood, oats, barley, and wheat. All currently known prebiotics are non-digestible carbohydrates and classified as fibers, but not all fibers are prebiotic [69].

Prebiotics confer health benefits to the host by targeting bifidobacteria and lactobacilli over potentially harmful proteolytic and putrefactive bacteria. Unlike probiotics, prebiotics are highly stable over a long period of time and resistant to the surrounding environment, (Table 2). Prebiotics are often combined with probiotics, and the combination is referred to as a synbiotic.

Probiotic		**Prebiotic**
Type	Living organisms	Inanimate
Heat Sensitivity	Mostly heat sensitive	Heat stable
Stability	Viable organism numbers decrease over time	Long shelf life
pH Stability	Targeted release through pH sensitive capsule coating	pH stable

Table 2: The difference between probiotics and prebiotics.

Kidney failure

Kidney failure results in the accumulation of many metabolic waste products. Uremic retention solutes include the protein-bound uremic toxins indoxyl sulfate and p-cresyl sulfate that are associated with an increased mortality, but are also nephrotoxic thereby promoting a further deterioration in renal function, and also the growth of harmful bacteria [70]. Trimethylamine-N-oxide, associated with accelerated atherosclerosis and all-cause mortality [71,72], accumulates and is known to suppress/reverse cholesterol transport. The retention of urea has been generally regarded as non-toxic, but degradation to highly toxic cyanate can occur that binds to proteins, including albumin, by carbamylation. High carbamylated serum albumin concentrations are a mortality risk [73]. Excessive blood urea nitrogen concentrations have been shown to be associated with an increased risk for diabetes mellitus [74], as well as engendering multiple other toxicities [75]. Urea concentrations can be decreased by probiotic administration [44]. Amine production has been noted to be reduced by the use of probiotics [76], as well as levels of indoxyl sulfate and p-cresyl sulfate [35,36].

Urea itself induces molecular changes related to disruption of the protective intestinal barrier. Second, urea is at the origin of the generation of cyanate, ammonia and carbamylated compounds, which as such all have been linked to biological changes.

Vaziri et al. [77] tested the impact of urea on the integrity of the intestinal epithelial barrier. Previous studies by the same authors in CKD or in the presence of uremic plasma had demonstrated a disruption of intestinal barrier functions, potentially impairing the protection against leakage of intestinal content such as pro-inflammatory endotoxin into the body [78,79]. At the molecular level, this derangement was attributed to a decrease in expression of tight junction proteins [78,79].

Cyanate is a free radical that is in equilibrium with urea. Generally, it is accepted that 0.8% of the molar concentration of urea is converted into cyanate. Probably due to the increased availability of urea, cyanate levels are also elevated in CKD [80]. Cyanate induces carbamylation. Carbamylated compounds interfere with organ and body functions through multiple mechanisms. Carbamylated proteins activate mesangial cells into a profibrogenic prototype, with a potential to play a role in the progression of kidney failure [81]. Indoxyl sulfate and p-cresyl sulfate are generated by the pathogenic gut microbes. Both have a toxic role to play in vascular and renal disease progression [82].

Dysbiosis of the gut is a term for microbial imbalance or maladaptation of the gut microbiome. CKD causes dysbiosis as the colon is altered, so that higher quantities of pathogenic microbes and lower quantities of beneficial microbes are present [27,83-85], (Figure 2).

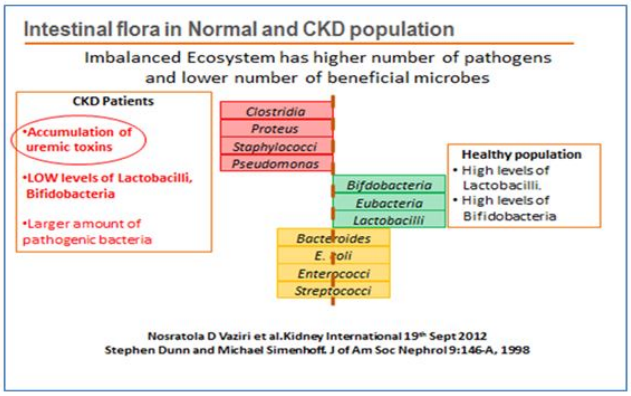

Figure 2: Gut microbiota in normal and CKD populations.

The dysbiotic organisms can outnumber protective species such as lactobacilli and are prone to generate uremic toxins by fermentation [27]. Pathogenic bacteria also convert urea into ammonia that disrupts enterocyte tight junction. The structure and function of the gut barrier wall is then compromised. This transformation is commonly known as "leaky gut syndrome" and is related to a variety of gastrointestinal tract diseases [30]. The resulting translocation of bacteria or bacterial products into the circulation, probably plays a role in persistent systemic inflammation [84,85]. The elevated levels of C-reactive protein and proinflammatory cytokines, as well as multiple other markers of systemic inflammation found in renal failure patients is regarded as evidence for ongoing systemic inflammation. Chronic inflammatory states are known to predispose to the development of atherosclerotic cardiovascular disease [86].

Small bowel abnormalities are also seen in CKD patients. Disproportionate numbers of small bowel organisms is termed small bowel bacterial overgrowth (SBBO) [87]. SBBO will result in the metabolism of nutrients [88] that would otherwise be utilized by the host. The breakdown of these nutrients in the small intestine may damage the intestinal lining [89], making it more difficult for the host to absorb nutrients. Malnutrition can result with the loss of body mass [90] and is associated with inflammation/oxidative stress [91]. The bio-modulation of SBBO in kidney failure patients can be reversed by the administration of Lactobacillus acidophilus [92].

The benefits noted with prebiotic and probiotic use to retard CKD progression may be the result of reducing the levels of nephrotoxic substances, and by reducing systemic inflammation [70,93].

Determination of kidney function in probiotic studies

Measuring renal function using only creatinine-based determinations in probiotic studies may not be an accurate measure of renal function. Unfortunately, renal function determinations reported in probiotic randomized controlled trials have only used creatinine-based equations for measuring GFR (i.e., eGFR) [35,36,44]. By using a gold standard measurement for renal function with an exogenous filtration marker, such as iothalamate or iohexol (i.e., mGFR), renal outcomes could be precisely measured [94]. The beneficial effect of probiotic administration on renal function, when determined by mGFR measurement, may exceed what a creatinine-based determination (i.e. eGFR) would indicate [95]. Thus, a true improvement in renal function could be masked when only creatinine-based measurements are used at a time when renal function is deteriorating.

Manipulation of the gut-kidney axis by prebiotics/probiotics and intestinal sorbents

The role of gut health in CKD is known as the gut-kidney axis, in view of the link between gut microbiota and clinical outcomes in CKD patients. Therapeutic products that are reported to positively affect the intestinal status include prebiotics/probiotics and intestinal sorbents. Probiotics that are utilized for their positive effect on renal function, or to reverse the accumulation of uremic toxins are most commonly members of the genera Lactobacillus, Bifidobacterium, and Streptococcus that typically produce lactic acid allowing them to predominate over pathogenic microorganisms. The mechanisms by which probiotics exert their favorable effect are likely owing to the direct utilization of uremic toxins, as nutrients for gut microbial growth [96]. The gut microbes stimulated by prebiotic/probiotic administration are ultimately eliminated by defecation restoring a dysbiotic gut microbiome to a healthier state-a process that has been referred to as enteric dialysis® [97].

- **Renadyl**™ (Kibow Biotech) is the most studied probiotic in renal failure patients. It is a probiotic/prebiotic formulation (i.e., a synbiotic) that has undergone study in in vitro models, animal models (rats, mini-pigs, cats, and dogs) [97-100], and clinical trials in humans (CKD III and IV, and dialysis patients). Studies indicate that Renadyl™ is able in advanced stages of CKD, to catabolize and remove uremic toxins and preserve renal function (Figure 3) [38,39,101-104]. Reduction in levels of urea in 63% of patients given our first generation product called "Kibow Biotics" was seen

[38]. The present newer formulation has been optimized to address middle molecules with a changed proprietary formulation. We have planned a multisite clinical trial on CKD IV patients to obtain statistically significant data on other uremic toxins like indoxyl sulfate, p-cresyl sulfate and trimethylamine –n-oxide. These have also been cited in the meta-analysis on CKD and ESRD patients (Table 1). A recent article 105 also shows the connections between GI and Renal disorders. Certainly, inflammation plays a significant role in many complications of CKD. The related studies that confirmed the role of defective intestinal mucosal barrier in the inflammation observed in CKD patients along with the effects of probiotics -/prebiotic treatment on specific inflammatory markers in CKD patients should be referred in a more extensive way (how many patients, which markers of inflammation were evaluated, what was the degree of decrease of the above markers). We have observed decrease in CRP when CKD patients were given Renadyl in our studies 103. We did not carry out studies for SBBO. However Simenoff and his team 92 saw a reduction in Nitrosamines, Dimethyl nitrosamines , Tri Methyl Amine Oxide (TMAO) when patients with SBBO were fed L acidophilus NCFM and Lebenin. The FDA/NKF guideline mandates the primary endpoints in CKD treatments/therapies is to reduce the decline of GFR by 30% (40% is preferred). Bearing this in mind we carried out our third bienneial survey. Of the 600 customers to whom we sent the survey questionnaire, 213 (35%) responded. The GFR values before and after taking Renadyl was analyzed statistically at the Mount Sinai school of medicine. The highest impact on GFR was an increase of 65, and the largest decrease in GFR was -43. The average change in GFR for a survey participant was an increase of 3.55 mL/min/1.73 m^2. The average baseline eGFR of the study respondent was close to 30 mL/min/1.73 m^2. We used this as a baseline for the three year GFR assessment as stated by the guideline. The average increase in eGFR was 3.5 mL/min/1.73 m^2 dividing that by the average time of three years the respondents took the product, gives an average per year increase in GFR of 2.90 mL/min. The normal progression of CKD based on the 2017 study conducted by Tsai and his group107, would lead to a decrease in 4.42 mL/min/1.73 m^2 per year. Using this as the normal progression, the FDA/NKF preferred guideline would reduce the decline in GFR by 40%, so the annual decrease in GFR would be 2.6 mL/min per year.

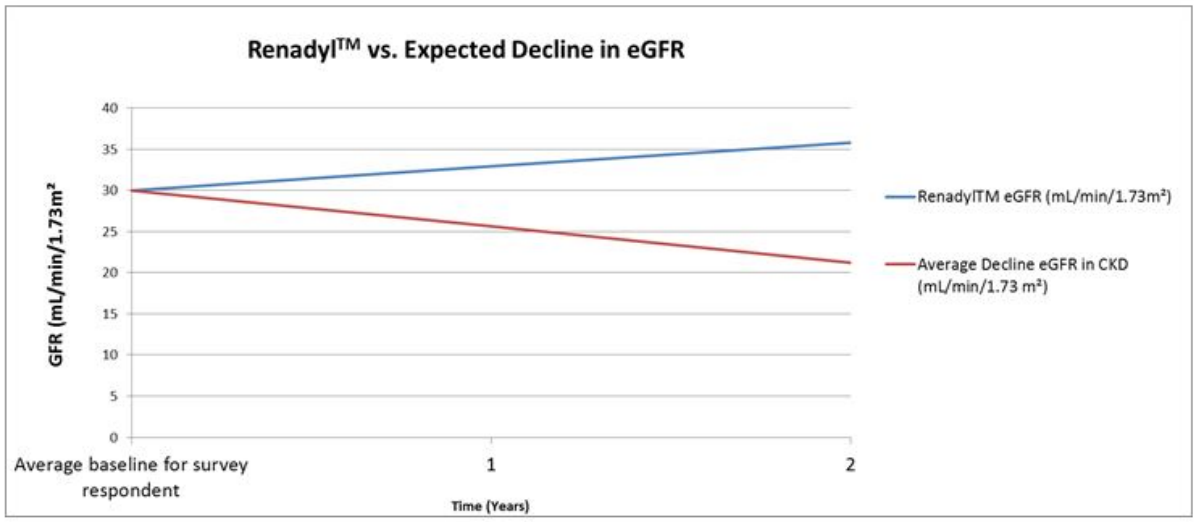

Figure 3: ™ Impact of Renadyl ™ on eGFR [106] compared to Expected Decline in CKD [107].

Animal studies (5/6th nephrectomized rats, minipigs, cats, dogs and large zoo animals) have also confirmed the ability of Renadyl™ to reduce uremic toxins [97-100]. An improved quality of life has also been reported with its use [108-110], including a recent survey where 88% of survey respondents indicated an improvement in their overall quality of life [110]. There are three specifically chosen probiotic microbial strains in Renadyl™ (S thermophilus-KB19, L acidophilus-KB27, B longum-KB31) that probably function synergistically in the gut by three mechanisms: (1) SBBO is reduced. Bacteriocins are produced, namely lactacin and bisin, that inhibit the growth of pathogenic bacteria [52-54]. This, in turn, leads to the reduced generation of gut-related uremic toxins [92,111]. (2) Uremic toxins are catabolized. S thermophilus-KB19 catabolizes urea, uric acid and creatinine. L acidophilus-KB27 catabolizes uric acid and decreases production of dimethylamine, trimethylamine, TMAO and nitrosamines. B longum-KB31 catabolizes creatinine and reduces levels of protein bound uremic toxins like indoles, phenols and cresols [102-105,108]. (3) Inflammation in the gut is modulated. There is a reduction in pro-inflammatory bio markers like IL-1β, C-reactive protein, IL-6 and TNF-α, positive impact on several oxidative markers and up regulation of anti-inflammatory markers like IL-10 [32-36, 55-59].

Large-scale randomized placebo-controlled intervention trials investigating Renadyl™ in CKD are still lacking but are planned and will include non-creatinine-based measurements of renal function to account for the non-renal elimination of creatinine possible with probiotic use.

Several other probiotic containing products such as VSL#3® (VSL Pharmaceuticals, MD, USA), Familack (Zist Takhmir, Iran) and Probinul-neutro® (Saninforma, Italy) have been used as investigational products in assessing various parameters related to evaluating GFR96,

oxalate absorption and urinary excretion [112], and other toxins like p-cresyl sulfate and indoxy sulfate[113], blood urea levels [114] and plasma p-cresol concentrations [115].

Multiple other probiotic-containing preparations, not always proprietary products, have been used in renal investigations making it difficult at times to determine the specific bacterial strain and dose studied. This heterogeneity between studies would reduce the ability to compare, evaluate, analyze, and duplicate previous studies [97]. Previously reported studies have not only indicated that probiotic use in kidney failure patients can retard the progression of chronic kidney disease but is without significant adverse reactions [36,106,110,116,117].

Sorbents

As early as 1932, Pendelton and West [118] showed that urea could migrate from plasma to the intestinal lumen. This led to the interest of using various techniques to remove the intestinal urea. In 1964 Yatzidis [119] for the first time fed charcoal as an oral sorbent to adsorb urea from the intestinal lumen. Administered in oral doses of 20 to 50 g daily, Yatzidis was able to manage patients with end-stage renal failure for 4 to 20 months without resorting to dialytic methods. Following this sorbent-like oxystarch used by Giordano [120], Sparks [121] and Friedman [122-124] also used sorbents for uremia.

Promising additional data indicating that gastrointestinal sorbents can bind to and remove in feces, clinically important amounts of nitrogenous wastes are provided by a series of investigations using oxidized starch (oxystarch) and oxidized cellulose (oxycellulose) performed by Giordano and associates [120]. In a double blind starch-oxystarch full balance study reported by Friedman et al. [123] seven uremic patients (creatinine clearances of 6 to 30 ml/min) were fed 29g of oxystarch or starch daily in four equal doses added to a diet containing 40 to 50 g of protein and 2 to 4 g of salt. Blood urea nitrogen levels fell 33% during oxystarch treatment from a mean of 93.1 mg/100 ml to a mean of 62.1 mg/l00 ml. There was no significant change in serum creatinine, plasma amino acid, uric acid and plasma glucose levels during oxystarch ingestion [124].

- Kremezin® /AST-120 (Kureha Chemical Industries) is a high purity porous carbon adsorbent utilized to absorb and remove uremic toxins from the gut by excreting the toxins with the feces. The product is widely used in Japan but has not been approved for use in the United States as strong evidence for its efficacy is lacking [125,126]. Kremezin® has little affinity for urea but does bind to uric acid, creatinine, and indole and phenol metabolites [127]. A disadvantage to its use is its binding with many drugs [128]. Sevelamer and chitosan are also sorbents studied in renal failure patients. Neither has been shown to preserve renal function, but chitosan has been shown in hemodialysis patients to decrease indoxyl sulphate levels and oxidative stress parameters [129-131].

Conclusion

In Chronic kidney patients there are scores of known and unknown uremic toxins such as urea, uric acid, creatinine (Millimolar concentrations), several other metabolites such as indoxyl sulfate, para-cresyl sulfate, oxalate, TMAO and others (Nano molar concentration), and some of them as protein bound uremic metabolites and difficult to remove by conventional dialysis. These are attributed mainly as cardiovascular toxins resulting in greater dysbiosis and ultimately increasing the cause of mortality in CKD patients. In addition recently, urea, which was previously considered a relatively non-toxic surrogate marker, has made a comeback as an important toxin "comeback of the century". It has been reported that higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus. It may increase insulin resistance and suppress insulin secretion. Thus urea, creatinine, uric acid and scores of other gut generated toxins arising from protein putrefaction in CKD patients can be addressed by the "Enteric Dialysis®" technology with Probiotics / Prebiotics to delay the need for conventional dialysis with standard care of therapy according to individual CKD patients (Figure 4).

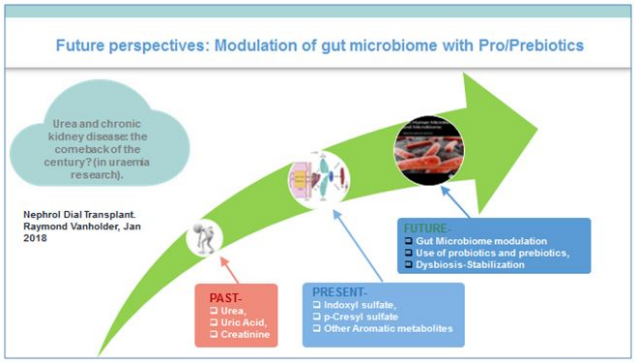

Figure 4: Modulation of gut microbiome with probiotics and prebiotics.

The gut microbiome in uremia has attracted considerable recent interest, as it has been noted that a dysbiotic gut microbiome exists in many CKD patients. The use of probiotics to modulate an unhealthy gut microbiome is a promising intervention giving their easy availability, innocuous nature, potential to reverse multiple CKD-associated metabolic derangements, and ability to preserve renal function. While additional confirmatory studies are awaiting to confirm the role probiotics will serve in the management of chronic kidney disease, we feel that the evidence thus far for beneficial effects is strong enough that probiotic use can be comfortably recommended and may well delay the need for dialysis. The potential impact of a probiotic that preserves renal function, in those with CKD would be considerable in view of the numbers of patients worldwide who have CKD, and especially in low income countries where dialysis care is unavailable. "Enteric Dialysis" using probiotics /prebiotics is a revolutionary manner for removal of uremic toxins and restoring the gut microbiome in the renal failure population.

Disclosures

Dr. N. Ranganathan is the founder of Kibow Biotech, Inc. and its chief scientist. Dr. Eli Friedman has been the chairman of the Scientific Advisory Board of Kibow Biotech, Inc. and has no financial interest in the company.

Acknowledgement

The authors wish to express their deep appreciation and sincere thanks to R&D colleagues-Usha Vyas, Anthony Irvin, Pari Ranganathan, and Dr. Daniel Lawson for their help in discussions and formatting this article. A very special thanks to Dr. Kenneth D Lempert, who further extended helped in this manuscript draft.

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