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Concept and Potential of Enteric Dialysis® - Treating the Cause of Dysbiosis and not the Symptoms in Chronic Kidney Diseases (CKD)

Natarajan Ranganathan*

Kibow Biotech Inc, Newtown Square, Pennsylvania, USA

Abstract

The primary goal of this invited commentary is to update recent scientific progress, understanding, knowledge gained and also several clinical advances made since the very first review that was published from our commercial efforts in the year 2012 (Title: Probiotics, Prebiotics and Synbiotics: Gut and Beyond in Gastroenterology Research and Practice). The use of probiotics and prebiotics is generally well recognized towards digestive, gut and immune health. However, Kibow Biotech is a R&D Biotech company involved in novel and niche application of probiotics and prebiotics as a dietary supplement in stabilization of Gut Microbiome towards Chronic Kidney Disease (CKD).

Keywords: Enteric dialysis; Dysbiosis; CKD; Probiotics; Prebiotics; Gut microbiome; GFR reduction

Commentary

Since our first review article on this subject matter, several other reviews have been published as of now [1-9]. All of these independent reviews in various scientific journals reflect on various topics such as gut Microbiome, its dysbiosis, impact of the altered intestinal characteristics including small bowel bacterial overgrowth, newer uremic toxins, adsorbent drugs and several observational small scale clinical studies from Kibow [10-14] and a host of others (all of these are referenced in the review articles).

This commentary is mainly written to connect various aspects of scientific understanding with greater emphasis on the health economics and potential of probiotics and prebiotics towards CKD applications both in developed and developing countries. Hence, with all humility, the author has undertaken to revisit and review the subject matter and thus help offer his independent views in connecting the failing **KI**dney function by the **BOW**el as was originally conceived by the distinguished thought leader of Renal Sciences - Dr Eli A Friedman [15,16]. Out of this concept was born **"KIBOW"** in the year 1997 and the concept is now being more scientifically researched, commercially validated and realized as **"Gut and Kidney connection"**.

Chronic kidney disease

General awareness of the rising global prevalence of kidney disease has been steadily growing among medical and public health professionals [17-19]. Kidney disease is the eighth leading cause of death in the U.S. [20], with approximately 600,000 patients in end-stage renal disease (ESRD, most receiving dialysis) and over 26 million in earlier stages of chronic kidney disease (CKD) [21]. As the population continues to age and the epidemiological shift from acute infectious to chronic metabolic diseases progresses, contributing factors to kidney disease (obesity, diabetes, and hypertension) become epidemic. Kidney disease may turn into a major health crisis in the USA and globally. Existing worldwide statistical data on the incidence and prevalence of kidney disease and kidney failure, the resulting mortality, the high cost of treatment, and associated socioeconomic and political consequences present a compelling and urgent need for an effective, easy to use and affordable alternative adjunct treatment modality to be available to the global kidney patient population. A latest research by the George Institute for Health published in the Lancet [22] shows that every year over two million people globally die as they do not have access to treatment for kidney failure (dialysis or transplantation). Despite ongoing R&D drug developments by several pharma/biotech firms, the use of dietary supplements is also a promising and inexpensive approach and should be included in any strategy to reduce the likelihood of such epidemic CKD crisis.

The uremic syndrome

It is said to consist of nitrogenous waste retention, deficiency in kidney derived hormones such as erythropoietin and vitamin D (anemia and renal osteodystrophy), the enzyme renin, and reduced acid excretion with acidosis. Untreated uremia may progress to coma and eventual death. Toxicity due to the accumulation of various uremic toxins (recent findings and literature reports to include Indoxyl Sulfate and para-Cresyl Sulfate in particular) is a concern for CKD and ESRD patient populations. Concentrations of uremic solutes have been shown to increase as the disease progresses from CKD to ESRD [23]. The European Toxin workgroup (EUTOX) has classified many uremic toxins based on their molecular weights and their protein binding property [24]. Though urea is generally nontoxic, it can degrade to the highly toxic cyanate, which, in turn, binds to proteins by carbamylation, including serum albumin, and modifies them. Recent studies by Berg et al. [25] have shown that carbamylated serum albumin is a risk factor for mortality in patients with kidney failure. As early as 1998, it was shown that CKD patients are at a higher risk of cardiovascular problems. Death due to cardiovascular disease is higher by 10 to 20 times in these patients as compared with the general population [26]. CKD and ESRD patients have high morbidity and mortality rate due to uremic cardiomyopathy [27]. Uremic toxins in CKD patients burden the cardiovascular system and lead to progression of cardiovascular disease [28]. Increased levels of uremic toxins also cause dysregulation of the Gut Microbiome (Dysbiosis) which in turn promotes inflammation and oxidative stress. This further accelerates the progression of CKD symptoms including progressive decline of the GFR to End Stage Renal Disease requiring dialysis. Therefore, some believe it to be necessary to

***Corresponding author:** Natarajan Ranganathan, Kibow Biotech Inc, 4781 West Chester Pike, Newtown Square, PA 19073, USA, Tel: 610-353-5130; Fax: 610-353-5110; E-mail: rangan@kibowbiotech.com

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reduce the levels of urea in chronic renal failure patients by medication or other interventions and strategies, such as a probiotic therapy (some representatives of the lactic acid bacteria population have the capacity to metabolize urea). Probiotics and prebiotics have for centuries been reported to enhance intestinal health [29]. Scientific proof has now been obtained that confirms their positive effects on human health in general [30]. Recently, the application of probiotics/prebiotics in various diseases has intensified, as understanding of how the gut microbiota shapes human health and how their composition changes significantly in any disease conditions causing more inflammation and more so in CKD progression [31].

Probiotics

They 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). Probiotics are characterized and named according to its Genus, Species and Strains. In addition, only those well characterized and precisely defined strains possessing specific health benefits are classified as Probiotics. Probiotics are quantified as Colony Forming Units (CFU, generally billions of CFU/gm).

Prebiotics

They 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 confers benefits upon host well-being and health [32]". Well known examples of prebiotics include inulin, oligofructose, galacto-oligosaccharide, lactulose [33], xylo-oligosaccharides [34] and Beta-glucans [35]. The combination of probiotics and prebiotics is generally known as **Synbiotics**. They now appear with increasing frequency in various foods, beverages, supplements, and are readily utilized in alternative and complementary medical practice strategies. Due to direct consumer advertising, the average population has been convinced of the positive role that probiotics play in health and disease. This has led to marketing and consumption of a number of probiotic supplements available for purchase online or in pharmacies without their benefit being scientifically proven in a rigorous clinical trial. Probiotic microbes are predominantly found in fermented dairy foods such as yogurt, kefir, cheese and other fermented foods. The expansion of our awareness and use of probiotics, however, has raced ahead of the scientific basis for the mechanisms by which they impact health. Probiotics are increasingly utilized in clinical settings. The role of digestive [36] and immune systems [7], as well as inflammatory [37] and oxidative stress [38,39] functions in the progression of inflammation and CKD 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.

Gut Microbiome

During coevolution with microbes, the human intestinal tract has been colonized by thousands of bacterial species [40,41]. Gut-borne microbes outnumber the human body cells by a factor of **ten** – i.e. >100 trillion versus 10 trillion [42]. Recent metagenomic analysis of human gut microbiota has revealed the presence of **3.3 million** genes, compared to **a mere 23,000** known human genes [43-45]. Microbial communities perform the majority of biochemical activities on the planet and play integral roles in human metabolism and immune homeostasis in human physiology and function [46]. Evidence for various beneficial roles of the intestinal microbiota and, concomitantly, probiotic microbes in human health and disease has been expanding rapidly in recent years [47-50]. Beneficial impacts have been noted for gastrointestinal disorders, functional bowel disorders, inflammatory bowel disease and ulcerative colitis, diarrhea, cardiovascular disorders, cancer, hepatic function, metabolic conditions including obesity/diabetes, lipid metabolism, neuropsychiatric disorders (depression and anxiety), chronic fatigue syndrome, autism, psychoneuroimmunity, and neurodermatology, immune function (incl. immunomodulation/inflammation), allergies and, autoimmune disorders.

Gut Dysbiosis, Leaky Gut Syndrome, Small Bowel Bacterial Overgrowth (SBBO) or Small Intestinal Bacterial Overgrowth (SIBO)

Since the recent advances and relevant discovery and knowledge gained from the complexity of Gut Microbiome, it is becoming more and more evident that CKD patients have a distinctly altered bacterial composition – also termed as Dysbiosis (less of the good microbes such as lactobacilli/Bifido species versus the Pathogens – that are the cause of dysbiosis). This altered intestinal microbial gut flora results in impaired barrier, structure and function causing the disruption on intestinal Epithelial Tight Junction. This is also referred to "leaky gut syndrome" and invariably related to almost all of the gut related diseases. CKD causes dysbiosis, bacterial conversion of urea into ammonia and several gut Microbiome produced toxins. This disrupts the enterocyte tight junctions, resulting in translocation of bacteria and toxins into systematic circulation resulting ultimately in increased inflammation. Small bowel bacterial overgrowth is a condition in which very large numbers of bacterial growth also occurs in the small intestine. Simenhoff and coworkers were the earliest researchers to report on the SBBO in dialysis patients [51,52]. They attributed this to increased toxicity of various amines like methylamine, dimethylamine, N,N-nitrosoamine including the recent finding of Trimethyl Amine (TMA) and its oxidation to Trimethyl Amine Oxide (TMAO). These researchers also demonstrated the "Biomodulation of the toxic and nutritional effects of small bowel bacterial overgrowth in end-stage kidney disease using freeze-dried Lactobacillus acidophilus". Unlike the large intestine, the small intestine does not have a high number of bacteria. When there are too many bacteria in the small intestine (SIBO), these organisms use up the nutrients that would otherwise be absorbed into the body. The breakdown of nutrients in the small intestine by the excess bacteria can also damage the intestinal lining. This can make it even harder for the body to absorb nutrients resulting in malnutrition, loss of body mass, increased inflammation/oxidative stress and ultimately resulting in poor quality of life among CKD patients.

Potential Therapeutic Future Interventions – Addressing the cause of Dysbiosis and not the symptoms

The kidney/s is a single organ system possessing three distinct functions. These are: **secretory** (hormonal), **regulatory** (homeostasis) and **excretory** (urinary elimination). The currently existing drug interventions address only the individual deficiencies on the pathophysiology and biochemical functions of the kidney. These three functions are in a dynamic equilibrium in any healthy individual and so is the Gut Microbiome with trillions of microbes.

In CKD patients there are profound changes in the colonic structure and function resulting in abnormal generation and absorption of toxins, dysbiosis, inflammation, impaired epithelial disarray as well as SBBO. Generally most of these patients are treated with one or more distinct drug therapies such as antibiotics, EPO, Vit D, ACE drugs or ARB inhibitors, K or PO_4 binders, diuretics etc., to address the

corresponding symptoms.

Using Ketoacids

Besides dietary changes, treatment of CKD has many components such as low protein diet, sufficient adequate calorie intake, plus vitamins and trace elements. When kidney function declines, protein recommendations are lowered to preserve kidney function and reduce uremic symptoms. In addition to reducing protein intake, amino and keto acid supplements can be given. The fact that many studies and clinical outcomes documenting a low protein diet with keto acids or essential amino acids and its effect on the slow progression of CKD is becoming more and more evident [53,54]. These supplements provide protein without overloading the diseased kidneys with too much phosphorus or urea that would come from foods. However, in the United States, these supplements are expensive and not routinely covered by insurance companies. Likewise it is also quite expensive for CKD patients who have little or no financial resources worldwide.

Using Kremezin

Oral charcoal sorbents like AST-120 (9 gm/day, about USD$270/month supply), manufactured by Kureha Chemical Industry Co Ltd and marketed as a drug under the brand name Kremezin is being used mainly in Japan and has been reported to have mixed clinical findings in other countries. Recently completed RCT of AST-120 in over 2000 patients in USA failed to show any improvement in progression of CKD [55]. The successful use of the same product as a drug in Japan may be attributed to the additional benefits derived from the daily consumption of fermented drinks (Yakult) and other fermented food product (Miso) as a part of daily diet among the Japanese population of patients. AST-120 has little affinity for urea but does bind with uric acid, creatinine, indole and phenol metabolites. In addition, it also possesses the negative impact in binding to several of the drugs that most of the CKD patients consume every day. AST-120 is a specially coated charcoal and possesses similar properties of activated charcoal in binding characteristics to scores of aromatics, steroidal and heterocyclic compounds.

Using Probiotics

Prebiotics, probiotics and synbiotics could also play a role in reducing the generation and elimination of uremic toxins, decreased inflammation, more so in conjunction with standard care of therapy according to individual CKD patient, nutritional needs and disease conditions. The modulation of the intestinal microbiota composition with the use of probiotics/prebiotics could potentially minimize the deleterious effects of its imbalance, thereby improving the health of the gastrointestinal tract, strengthening the immune system, restoring the bioavailability of micronutrients, exerting anti diabetic actions, improving dyslipidemia and allergic disorders, and reducing the risk of other health problems. The mechanism by which probiotics exert their favorable effects seems due to direct utilization of several uremic toxins (diffused from circulating blood into the colon) as nutrients for its own growth with its inherent capabilities of multiplying and doubling every 20 to 25 minutes. The increased growth of these gut microbes are then eliminated by the natural defecation process which has been referred to as **"Enteric Dialysis"** in this commentary (Figure 1).

In addition, probiotics change the intestinal pH, inhibit the growth of pathogens (through the production of antibacterial compounds, competitive exclusion of pathogens in receptor binding sites and competition for available nutrients), and suppression of mutagenic and carcinogenic processes and ultimately affords protection of the intestinal/gut barrier. Despite several reported observational or pilot scale/small scale studies, quality intervention trials investigating this novel treatment in CKD are still lacking in its full clinical validation. Hence, a well-designed RCT protocol with the power needed for subject enrollment and statistical significance changes in defined primary or secondary end points are needed. The published studies and as well the proposed "SYNERGY" [56] clinical trials are aimed to assess the effectiveness of synbiotics (co-administration of pre- and probiotics) as a potential treatment targeting the synthesis of uremic toxins, specifically, indoxyl sulfate (IS) and p-cresol sulfate (PCS). These and other biomarkers evaluated like doubling of the serum creatinine has been re-evaluated and being proposed with the general acceptance of GFR decline as an end point for clinical trials in CKD. The earlier end point "doubling of serum creatinine"- resulting in 50% or greater GFR reduction, is a late event in several CKD patients and also subject to several of the aforementioned variable subject matters discussed. It is also subject to enrolled patients primary disease status, diet, life style and several other factors including genetic makeup and dysbiosis of the gut Microbiome including inflammation and oxidative stress. Thus decrease of GFR of 30-40% can sufficiently reduce these inflammatory markers which will ultimately have a significant impact on the quality of life (QOL) in CKD patients. This also requires a long time of follow up and large sample size in clinical trials. Thus, there is a great interest in alternative GFR-based end point to shorten the duration of clinical trials, reduce sample size, and extend their conduct to patients with earlier stages of CKD.

New end points for CKD clinical trials gaining acceptance from US FDA, NKF and several nephrology professionals and renal health care providers/industries

"The US Food and Drug Administration currently accept halving of glomerular filtration rate GFR) assessed as doubling of serum creatinine level, as a surrogate end point for the development of kidney failure in clinical trials of kidney disease progression. A doubling of serum creatinine level generally is a late event in chronic kidney disease (CKD); thus, there is great interest in considering alternative end points for clinical trials to shorten their duration, reduce sample size, and extend their conduct to patients with earlier stages of CKD. However, the relationship between lesser declines in GFR and the subsequent development of kidney failure has not been well characterized. The National Kidney Foundation and Food and Drug Administration sponsored a scientific workshop to critically examine available data to determine whether alternative GFR-based end points have sufficiently strong relationships with important clinical outcomes of CKD to be used in clinical trials. Based on a series of meta-analyses of cohorts and clinical trials and simulations of trial designs and analytic methods, the workshop concluded that a confirmed decline in estimated GFR of 30% over 2 to 3 years may be an acceptable surrogate end point in some circumstances, but the pattern of treatment effects on GFR must be examined, specifically acute effects on estimated GFR. An estimated GFR decline of 40% may be more broadly acceptable than a 30% decline across a wider range of baseline GFRs and patterns of treatment effects on GFR. However, there are other circumstances in which these end points could lead to a reduction in statistical power or erroneous conclusions regarding benefits or harms of interventions. We encourage careful consideration of these alternative end points in the design of future clinical trials [57]".

Routine Dialysis Versus the concept of "Enteric Dialysis"

Previous research has suggested that longer dialysis sessions can provide benefits without increasing the risks of complications [58-

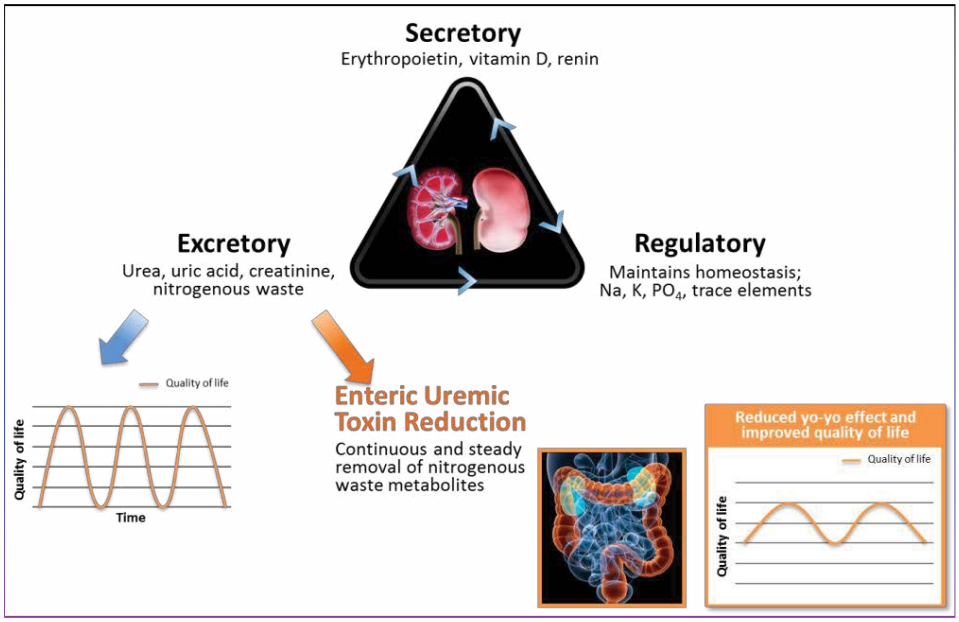

Figure 1: Treating the cause of dysbiosis not the symptoms using probiotics (Enteric Dialysis® – Registered trademark of Kibow Biotech Inc.).

60]. However, some nephrology professionals find this view highly debatable. (http://kidney.niddk.nih.gov/about/ResearchUpdates/KidneyWin13/1.aspx). The controversy centers on the invasive nature of hemo/peritoneal dialysis that has significant potential for causing greater infections and higher mortality, particularly when sessions are frequent. However, the use of a well-researched, clinically documented and safe probiotic/prebiotic dietary supplement formulation has the potential to safely perform continuous 24/7 uremic toxin removal and stabilize the gut Microbiome and its dysbiosis.

Summary

Global CKD is on the rise. Toxicity due to the accumulation of various uremic toxins includes several newer ones such as Indoxyl Sulfate, para-Cresyl Sulfate and many others. Concentrations of various uremic solutes have been shown to increase as the disease progresses from CKD to ESRD. Current hemo/peritoneal dialysis is only accessible in affluent countries wherever respective governmental healthcare provides treatment at little or no cost. Oral sorbents like Kremezin - an activated charcoal or even ketoacids are also expensive and not affordable by many, especially those living in poor and developing countries. CKD patients have an imbalanced or dysbiosis of gut microbiota with a higher number of pathobionts which produce toxic wastes like the indoles, phenols and the carcinogenic amines like methylamine, dimethylamine, N,N-nitrosoamine as a consequence of SIBO. The critical role of the gut Microbiome and its Dysbiosis in various diseases is garnering greater scientific scrutiny. In this emerging science and the use of pro and prebiotics to restore the imbalances in the gut Microbiome in CKD is indeed attracting several groups of nephrology research professionals from various countries. The recent USFDA/NKF guidance on the reduction of the GFR is indeed a newer clinical endpoint which could generally be used for proposed CKD clinical trials uniformly.

Using probiotics/prebiotics for the removal of uremic toxins like urea, uric acid, creatinine and the gut derived toxins like the indoles and phenols in the bowel; the so called concept of "Enteric Dialysis" is a revolutionary way and offers hope to Renal failure population. It is safe, inexpensive and provides an alternate option for CKD and ESRD patients worldwide. However, well designed multi-site additional RCT clinical trials need to be performed in order to document statistically significant data. Hence, the gut Microbiome modulation of dysbiosis with pro/prebiotics provides an attractive futuristic potential towards CKD patients and as well in several other health/disease conditions.

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Conflict of Interest

The author is one of the key founders of Kibow Biotech Inc, is employed as key management and scientific personnel and has substantial financial / business interest in the company.

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