Possible Pathways of Gut Microbiome Modulation by Probiotics in Chronic Kidney Disease

Natarajan Ranganathan[1], Usha Vyas[1]
[1]Kibow Biotech Inc., Newtown Square ,PA 19073

INTRODUCTION

Chronic Kidney Disease (CKD) affects over 200 million people worldwide. CKD patients accumulate various uremic toxins in the blood, of which many are derived or produced by the pathogenic gut microbes. Advanced CKD alters the composition and functions of the intestinal microbiome. Colonic microbiota are increasingly acknowledged to be an important source of uremic toxins. p-Cresyl sulfate, Indoxyl sulfate and Trimethylamine N-oxide (TMAO) are currently attracting much attention as renovascular toxins. CKD is also associated with high levels of systemic inflammation and small intestinal bacterial overgrowth (SIBO) due to bacterial translocation and an imbalanced gut microflora called gut dysbiosis. Pathobionts outweigh the good bacteria in CKD gut. Probiotics can help alleviate all of these by various mechanisms.

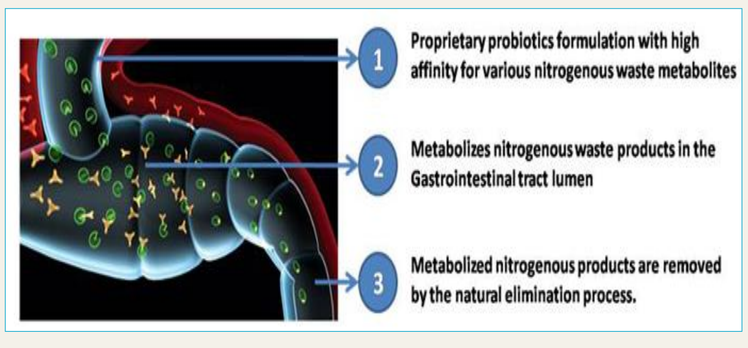
METHODS

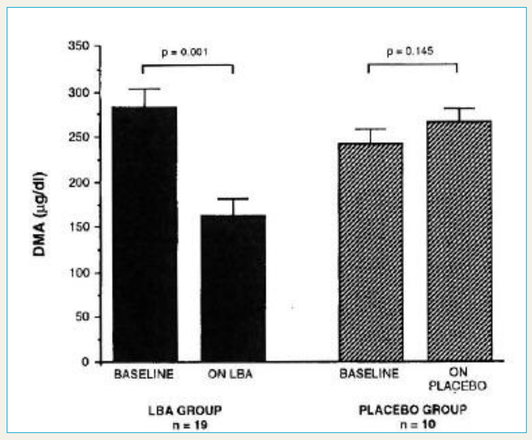
Probiotic bacteria benefit human health in various ways. We reviewed data from various scientific groups which are working towards understanding the role of the gut microbiome in CKD. This poster presentation is a review summary of the possible ways in which probiotic bacteria can benefit CKD population.

RESULTS

Published data have shown that in CKD patients probiotics work by three different mechanisms.

1) Specific strains of probiotic bacteria can metabolize the accumulated nitrogenous wastes thereby reducing serum levels of uremic toxins and also reduce SIBO [1,2,3,4].

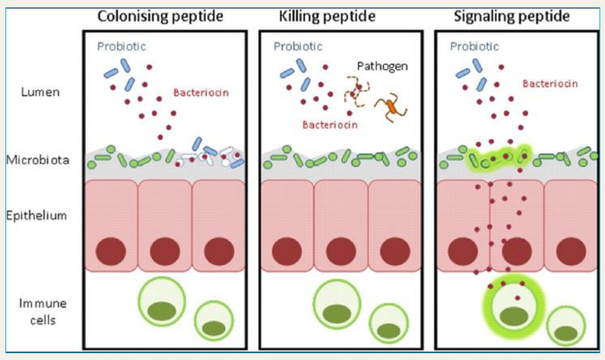


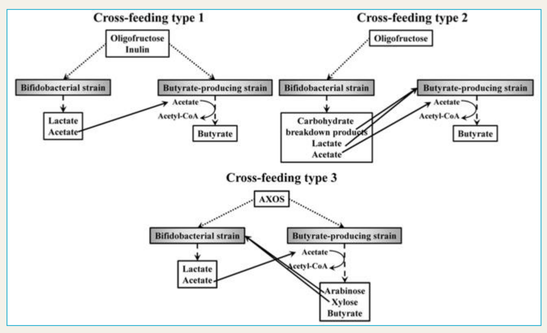


Serum dimethylamine (DMA) levels (mean ± SEM) at baseline (before any treatment) and while 'on' treatment (either LBA or placebo). First group (solid bars) consisted of 19 patients with chronic kidney failure on dialysis and were given active *L. acidophilus* (LBA). Second group (hatched bars) consisted of 10 different patients with chronic kidney failure also on dialysis who were given placebo.

RESULTS contd....

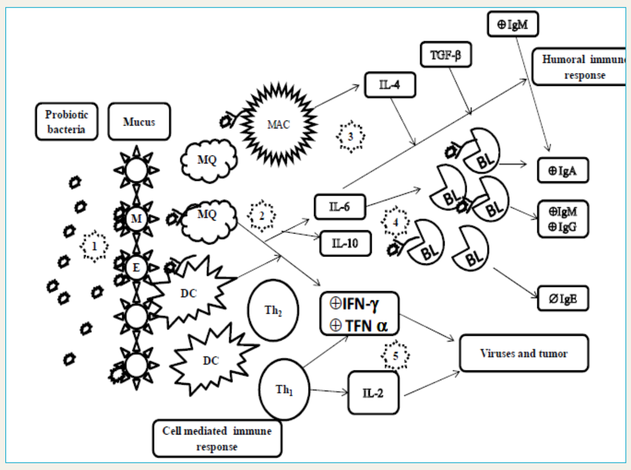
2)Several of these probiotic Lactobacilli and S thermophilus produce a wide range of bacteriocins which are small, ribosomally-synthesized peptides with narrow or broad spectrum antimicrobial activity against both gram positive and gram negative pathogens residing in the gut. The pathogens are competively excluded and reduction of these pathogenic bacteria in the gut leads to repair of the gut barrier integrity[5]. Probiotic Bifidobacteria promote the growth of butyrate producers. Butyrate is the energy source for colonocytes and increased levels of butyrate can restore intestinal barrier integrity[6].





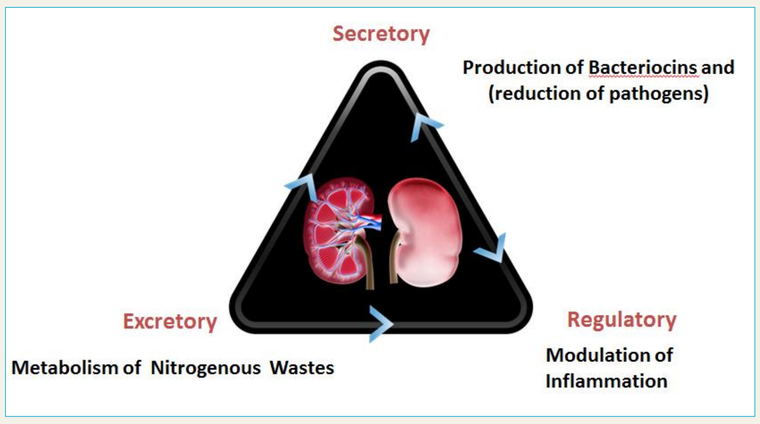
RESULTS contd.....

3) The third mechanism is the effect of probiotic bacteria on inflammatory markers and cytokines. Oxidative stress and inflammation influence the development and subsequent progression of CKD. The microbial derived uremic toxin indoxyl sulfate exacerbates reactive oxygen species production and inflammation in 3T3-L1 adipose cells. Probiotics have the potential to modulate and regulate the immune response. Probiotic bacteria lower levels of proinflammatory markers like IL-1B, IL-6, C reactive protein (CRP) and TNFα and up regulate levels of anti-inflammatory markers like IL-10 [7].



- **Hypothesised mechanism of immunomodulation by probiotics.** (1). Interaction of probiotic bacteria with epithelial cells (E) or M cells (M) or the Dendritic cells (DC) results in the internalization of the bacteria or its components. (2). This interaction stimulates the release of IL-6 by epithelial cells and stimulates macrophages (MQ) and dendritic cells to produce TNF-α and IFN-γ. (3). Mast cells (MAC) or also stimulated to produce the cytokine IL-4, which together with IL-6 and TGF-β induce the T-independent switch from IgM to IgA on the surface of B lymphocytes (BL), thereby enhancing the production of IgA. (4). IL-6 favours the clonal expansion of IgA B lymphocytes. There is also an associated increase in the production of antibodies such as IgM, IgG and reduced secretion of IgE. (5). Th1 cells produce pro-inflammatory cytokines such as IFNγ, TNFα and IL-2, which stimulate the phagocytosis and destruction of microbial pathogens and induce macrophages, natural killer cells and cytotoxic T-lymphocytes to kill viruses and tumors (Galdeano et al. 2007).

SUMMARY/CONCLUSIONS



An increasing body of evidence indicates that crosstalk between host and microbiota is pathophysiologically relevant in patients with chronic kidney disease (CKD). Interactions are bidirectional; on the one hand, uremia affects both the composition and metabolism of the gut microbiota and, on the other hand, important uremic toxins originate from microbial metabolism. Probiotics work by different mechanisms and benefit CKD patients by removing uremic toxins, restoring gut barrier integrity, reducing inflammation, and re-balancing the gut microbiome.

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