Study of the Effect of Probiotics on Serum IndoxylSulphate in Haemodialysis Patients

Thesis

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Contents

Abstract

Chronic kidney disease (CKD) is a worldwide health problem that has many clinical outcomes and affecting the patients due to accumulation of uremic toxins.Many classifications for uremic toxins based on different aspects specially bounding to plasma proteins and molecular size are well known now and affect the mechanism and module of replacement therapy that fit End stage renal disease(ESRD) patients.Indoxyl sulphate(IS) is a protein bound uremic toxin that has many deleterious effects on cardiovascular system with deterioration of kidney functions,It is believed that gut kidney axis has main role for production of IS and so targeting gut microbiota and modifying the dysbiotic content in CKD patients can help in decreasing IS.Probiotics are emerging strategy in clinical life and appear to be effective in targeting IS.

Methodology: Study conducted on 92 ESRD patients on regular HD from January/2017 to March/2017 and patients divided to two groups : intervention group receiving probiotics regimen for 6 weeks while control group receiving placebo for the same period.
Results show reduction of IS (14±22.71 µg/ml vs 3.6±14.33 µg/ml,Pvalue 0.02) in intervention group vs control group respectively,reduction in serum phosphorus,CRP,lipid profile was recorded.
conclusion : Probiotics cause reduction in IS with reduction in phosphorus,CRP,lipid profile with no reported side effects

Key Words :

Chronic kidney disease(ckd),indoxyl sulphate, probiotics, protein bound uremic toxins

List of Abbreviations

AHL : Acetyl homoserine lactone

AHR : Aryl hydrocarbon receptor

cAMP : Adenosine 3',5'-cyclic monophosphate

CKD : Chronic Kidney Disease

COX-2 : Cyclooxygenase 2

CREB : camp response element binding protein

CVD : Cardio-Vascular Disease

DCM : Dilated cardiomyopathy

DNA : Deoxyribonucleic acid

ERK1/2 : Extracellular Signal-Regulated Kinases 1 and 2
Extracellularly-Regulated Kinase-1 and -2

FAO : Food and Agriculture Organization

FGF23 : Fibroblast growth factor 23

FOXP3 : Forkhead box p3

GFR : Glomerular filtration rate

GPR : G protein–coupled receptors

GIT : Gastrointestinal tract

GABA : Gamma-aminobutyric acid

GALT : Gut-associated lymphoid tissue

IS : IndoxylSulphate

IBD : Inflammatory bowel disease

IgA	**:**	Immunoglobulin A
IBD	**:**	Irritable bowel disease
KDIGO	**:**	Kidney Disease Intiative Global Outcome
Keap1	**:**	Kelch-like ECH protein-1
LVH	**:**	Left ventricular hypertrophy
MAPK	**:**	Mitogen-activated protein kinase
MAMPs	**:**	Microbeassociated molecular patterns
NADPH	**:**	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
(NF)-κB p65	**:**	Nuclear factor
Nox4	**:**	NADPH oxidase-4
Nrf2	**:**	NF erthroid-2-derived factor-2
NOD1	**:**	Nucleotide-Binding Oligomerization Domain 1
NF-B	**:**	Nuclear Factor- B
OAT	**:**	Organic anion transporters
PCS	**:**	P-CresylSulphate
PTC	**:**	Proximal tubular epithelial cells
PTH	**:**	Parathyroid hormone
PBUTs	**:**	Protein bound uremic toxins
PWV	**:**	Pulse wave velocity
PRR	**:**	Pattern recognition receptors

ROS	**:**	Reactive oxygen species
RAS	**:**	Renin-angiotensin system
RRT	**:**	Renal replacement therapy
SULT	**:**	Sulphotransferase
SLCO4C1	**:**	A gene on chromosome 5q21.2 that encodes a protein which mediates Na+-independent transport
SCFAs	**:**	short-chain fatty acids
TGF	**:**	Transforming growth factor
UC	**:**	Ulcerative colitis
WHO	**:**	World health organization
1,25-D3	**:**	1,25-dihydroxyvitamin D3

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Introduction

In recent years, an appreciation for the role of the gut microbiota in health and disease has gained momentum, with microbial modulating therapies emerging in mainstream medicine. Within the discipline of Nephrology, the evidence supporting the role of the kidney-gut axis in uremia is building. In fact, it is now clear that the dysbiotic gut microbiota observed in chronic kidney disease (CKD)produce key nephrovascular toxins, indoxylsulphate (IS) and p-cresol sulphate (PCS). There is convincing evidence demonstrating dose dependent nephro- and cardiovascular toxicities ofIS and PCS in both in vitro and animal studies ***(Vaziri et al., 2013).***

Uremic patients show greatly increased counts of both aerobic (approximately 10^6 bacteria/ml) and anaerobic (approximately10^7 bacteria/ml) organisms in the duodenum and jejunum, normally not colonized heavily by bacteria in healthy persons. Lower intestinalcolonic microbial flora which counts (approximately 10^{12}) has also been shown to be altered in patients with CKD ***(Vaziri et al., 2013).***

Hida et al., 1996 studied the colonic composition of microbiota in healthy controls and hemodialysis patients. Analysis ofthe fecal microbiota revealed a disturbed

composition of the microbiota characterized by an overgrowth of aerobic bacteria. Although this study did not show a significant difference in the total number of bacteria, the number of aerobic bacteria, such as Enterobacteria and Enterococci species, was approximately 100 times higher in hemodialysis patients.

The gastrointestinal system is at the interphase between the blood and the potentially toxic contents of the gut. Histologic changes, including reduction of villous height, elongation of the crypts, and infiltration of lamina propria with inflammatory cells are noted in CKD. Uremia increases intestinal permeability in patients with CKD. The disruption of colonic epithelial tight junction could subsequently lead to translocation ofbacteriaacross the intestinal wall.Hemodialysis induced systemic circulatory stress and recurrent regional ischemia may also damage the mechanical barrier of the gut that promote intestinal dysbiosis contributing to the leaky gut in CKD ***(Wang et al., 2012).***

Certain intestinal bacteria can generate uremic toxins that are absorbed into the blood and are normally cleared by the kidney. Proteinfermentation by gut microbiota

results in the generation of different metabolites, including phenols and indoles ***(Macfarlane and Macfarlane, 2012).***

Aronov et al., (2011)compare plasma from hemodialysis patients with and without colon and confirmed the colonic origin of indoxyl sulfate and p-cresol. These are prototype members of a large group of protein bound uremic toxins that are resistant to clearance by dialysis.

Barreto et al., (2009)showed that an elevated level of indoxyl sulfate is associated with vascular stiffness, aortic calcification, and higher cardiovascular mortality. Indoxyl sulfate is a potential vascular toxin that induces oxidative stress in endothelial cells, increases shedding of endothelial microparticles, impairs endothelial cell repair mechanism, and increases vascular smooth muscle cell proliferation.

A number of therapeutic opportunities for targetingIS and Pcs have been proposed, including inhibition of colonic bacterial biosynthesis (protein restriction and microbial modulating therapies), suppression of absorption (oral adsorbents), augmentation of clearance (enhanced dialysis) and modulation of cellular pathways (organic anion transporters and antioxidants). Many of these therapies remain limited to experimental studies,have unfavourable

side effects or a high cost burden preventing their translation to clinical research. In particular, oral adsorbents have been extensively studied, with promising improvements in both cardiovascular risk and kidney functionfollowing reductions in serum IS ***(Rossi et al., 2013).***

Probiotics are defined by the United Nations Food and Agriculture Organization and the World Health Organization as live microorganisms which when administered in adequate amounts confer a health benefit on the host. It exerts its effect through

- Acid and bile resistance to ensure survival through the uppergastrointestinal tract.
- Competitive exclusion ofindoxyl sulphate and p-cresol sulphate producing bacteria (through competition for essential nutrients and luminal and epithelial binding sites).
- Direct bacterial antagonism via inhibitory substance production (such as biosurfactants, hydrogen peroxide, and bacteriocins).
- Immunomodulation via immune cell activation resulting in indirectinhibition of pathogenic bacteria ***(Food and Agriculture Organsization: Guidelines for the evaluation of probiotics in food, 2002).***