

The effect of Synbiotics on serum Indoxyl Sulfate in Maintenance Haemodialysis Patients

Thesis

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تأثير السينبيوتيك على مستوى الاندوكسيل سلفات في الدم في مرضى الاستصفاء الدموي

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

CKD	Chronic kidney disease.
AKI	Acute kidney injury.
kDa	Kilo Dalton.
ADMA	Asymmetric Dimethylarginine.
SDMA	Symmetric Dimethylarginine.
HPLC	High performance liquid chromatography.
NO	Nitric oxide.
PBUTs	Protein-bound uremic toxins.
HIF	Hypoxia-inducible factor .
EPO	Erythropoietin .
AGE	Advanced glycation end products .
NADPH	Nicotinamide Adenine Dinucleotide Phosphate .
PAA	Phenylacetic acid.
IAA	Indole acetic acid.
OAT	Organic acid transporters.
PC	P-cresol.
PTH	Parathyroid hormone.
RAS	Renin–angiotensin system.
ROS	Oxygen free radicals.
TMAO	Trimethylamine N-oxide.
GFR	Glomerular Filtration Rate.
PTC	Proximal tubular epithelial cells.
TGF	Tumour growth factor.
EPC	Endothelial progenitor cells.
Ang-II	Angiotensin-II.
CRS	Cardiorenal syndrome.
HD	Hemodialysis.
CV	Cardiovascular.

pH: Power of hydrogen.
ESRD: End stage renal disease.
TLRs.....: Toll-like receptors.
LPS: Lipopolysaccharides.
CRP: C-reactive protein.
Cr: Creatinine .
PD: Peritoneal dialysis.
IL: Interleukin.
Hb: Hemoglobin
BUN: Blood Urea Nitrogen
HTN.....: Hypertension
DM.....: Diabetes mellites
HCV.....: Hepatitis C virus
SBP: Systolic blood pressure.
DBP.....: Diastolic blood pressure.
GIS.....: Gastrointestinal symptoms

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Introduction

Inflammation is a multifactorial phenotype during CKD. Many factors such as decreased clearance of pro-inflammatory cytokines, oxidative stress, metabolic acidosis, infections, dialysis access problems and obesity contribute to inflammation. More recently, alterations in gut microbiota composition and intestinal barrier have been shown to be associated with inflammation and oxidative stress in CKD patients. Few studies have documented the composition of gut microbiota during CKD (***Maфра & Fouque, 2015***).

The imbalance in gut microbiota associated with alterations in colonic epithelium contributes to the accumulation of gut-derived uraemic toxins. Toxic gases, indoxyl sulphate (IS), p-cresyl sulphate (p-CS), amines, ammonia and trimethylamine n-oxide (TMAO) may be absorbed into the bloodstream and be responsible for systemic inflammation (***Maфра & Fouque, 2015***).

Among the uraemic retention solutes, protein-bound compounds such as the p-cresol conjugates p-cresyl sulphate (p-CS) and Indoxyl sulphate (IS) have attracted most interest in recent years due to their poor clearance by conventional dialysis and their potential toxicity (***Poveda et al., 2014***).

These protein-bound uraemic retention solutes originate from protein fermentation in the large intestine, including p-cresyl sulfate and indoxyl sulphate (**Meijers & Evenepoel, 2011**).

CKD enhances the protein fermentation process through a number of mechanisms including inefficient protein assimilation in the small intestine resulting in more protein entering the large intestine, prolonged colonic transit time, and increased luminal pH secondary to increased colonic urea diffusion, all of which contribute to the alteration of the bacterial composition of the microbiota specific to this population (**Meijers & Evenepoel, 2011**).

Several studies demonstrated direct associations between both p-cresyl sulphate and indoxyl sulfate and the overall mortality and cardiovascular disease in both CKD and end-stage renal disease (**Liabeuf et al., 2010**).

So far, Indoxyl sulfate, is considered to be a key player in increased glomerular sclerosis and progression of CKD (**Tumur et al., 2010**).

Indoxyl sulfate is also known as to be involved in the pathogenesis of atherosclerosis (**Lin et al., 2010**).

Some recent studies also demonstrated that the QTc interval was prolonged in early CKD patients with a higher serum IS levels (**Tang et al., 2015**).

Other recent studies suggest that indoxyl sulfate is associated with thrombosis of dialysis grafts after angioplasty. Probiotics are living organisms, administered as food components or supplements, which provide specific benefits by themselves, essentially by creating a more favourable balance in the composition of intestinal microbiota (**Vanholder & Glorieux, 2015**).

Prebiotics are non-digestible compounds improving the composition and/or function of the intestinal microbiota while Synbiotics contain a mixture of prebiotics and probiotics (**Vanholder & Glorieux, 2015**).

Lowering the production of these uremic toxins by manipulating bacterial composition of the microbiota and/or colonic transit time therefore represents a promising therapeutic strategy. (**Rossi et al., 2012**).

Prebiotics, probiotics and synbiotics could play a role in reducing the generation of uraemic toxins, but the results of clinical studies have been deceiving, with sometimes contradictory results.

In a review by **Rossi et al.**, there were 11 interventions that administered probiotics using an array of different species and strains. Nine of these studies saw a decreasing trend in PCS and/or IS post-intervention, which all seven and four from five found significance, respectively (**Rossi et al., 2012**).

Also there were 13 interventions that used prebiotics with only one in the HD population. Twelve of these interventions observed a trend for a decrease in PCS and/or IS, but only eight of 11 reported a significant decrease in PCS and three out of five a significant decrease in IS (**Rossi et al., 2012**).

Aim of the work.

To study the possible effect of Synbiotics on serum Indoxyl Sulfate in maintenance hemodialysis patients.