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

Thesis

Submitted for partial fulfillment of MD Degree in Internal Medicine

Presented by

Norhan Nagdy Madbouli
M.B.B.CH. Faculty of medicine, Ain Shams University

Supervised by

Prof. Dr. Yasser Soliman Ahmed
Professor of Internal Medicine and Nephrology
Faculty of medicine, Ain shams university

Prof. Dr. Eman Ibrahim Sarhaan
Professor of Internal Medicine& Nephrology
Faculty of medicine, Ain shams university

Prof. Dr. Nayra Shaker Mehanna
Professor of Dairy and Food Microbiology
National Research Center

Dr. Mohammed Saeed Hassan
Lecturer of Internal Medicine and Nephrology
Faculty of medicine, Ain shams university

Dr. Mostafa Abd-El Nasier Abd-El Gawad
Lecturer of Internal Medicine and Nephrology
Faculty of medicine, Ain shams university

Faculty of Medicine
Ain Shams University
2018

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

رسالة

توطئة للحصول علي درجة الدكتوراه فى الامراض الباطنية

مقدمة من

الطبيبة/ نورهان نجدي مدبولي

بكالريوس الطب والجراحة –ماجيستير الامراض الباطنية

تحت إشراف

أ.د/ ياسر سليمان أحمد

أستاذ امراض الكلى والباطنة العامة

كلية الطب- جامعة عين شمس

أ.د/ ايمان ابراهيم سرحان

أستاذ امراض الكلى والباطنه العامه

كلية الطب- جامعة عين شمس

ا.د.نايرا شاكر مهنا

أستاذ الميكروبيولوجي والصناعات الغذائيه

المركز القومي للبحوث

د.محمد سعيد حسن

مدرس أمراض الكلى و الباطنه العامة

كليه الطب-جامعة عين شمس

د.مصطفى عبد النصير عبد الجواد

مدرس أمراض الكلى و الباطنه العامة

كليه الطب-جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١٨

سورة البقرة الآية: ٣٢

First and foremost thanks to ALLAH, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to ***Prof. Dr. Yasser Soliman Ahmed,*** *Professor of Internal Medicine and Nephrology, Ain Shams University, for his close supervision, valuable instructions, continuous help, patience, advices and guidance. He has generously devoted much of his time and effort for planning and supervision of this study. It was a great honor to me to work under his direct supervision.*

I wish to express my great thanks and gratitude to ***Prof. Dr. Eman Ibrahim Sarhaan,*** *Professor of Internal Medicine& Nephrology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude to ***Prof. Dr. Nayra Shaker Mehanna,*** *Professor of Dairy and Food Microbiology, National Research Center, for her kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude to ***Dr. Mohammed Saeed Hassan,*** *Lecturer of Internal Medicine and Nephrology, Ain Shams University,, for his kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude to ***Dr. Mostafa Abd-El Nasier Abd-El Gawad,*** *Lecturer of Internal Medicine and Nephrologyy, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.*

Finally I would present all my appreciations to my patients without them, this work could not have been completed.

Contents

Subjects **Page**

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

List of Table

List of Figures

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 ***(Mafra & 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 ***(Mafra &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.