Effect of Metabolic Acidosis on Immunoregulation in Prevalent Hemodialysis Patients

Thesis

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List of Abbreviations

Abb.	Full term
ABGs	Arterial blood gases
ACEI	Angiotensin-converting enzyme inhibitor
AKI	Acute kidney injury
ANCA	Antineutrophil cytoplasmic antibody
APC	Antigen Presenting Cells
ARB	Angiotensin II receptor blocker
BAL	Bronchoalveolar lavages
BP	Blood pressure
CARS	Compensatory anti inflammatory response syndrome
CD	Crohn's disease
CK	Creatinine Kinase
CKD	Chronic kidney disease
CT	Computed tomography
CTL	Cytotoxic T lymphocytes
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
EAE	Experimental autoimmune encephalomyelitis
eGFR	Estimated glomerular filtration
ESRD	End stage renal disease
GFR	Glomerular filtration rate
GWAS	Genome-wide association studies
HD	Haemodialysis
IBD	Inflammatory bowel disease
IFN	Interferon
IgA	Immunoglobulin A
IL	Interleukins
IQWiG	Institute for Quality and Efficiency in Health Care

List of Abbreviations Cont...

Abb.	Full term
Jak	Janus kinase
KDOQI	Kidney Disease Outcomes Quality Initiative
KTx	Kidney transplantation
LPSs	Lipopolysaccharides
MBD	Mineral bone disease
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTB	Mycobacterium tuberculosis
NSAIDs	Non-steroidal anti-inflammatory drugs
PAMPs	Pathogen-associated molecular patterns
PBMCs	Peripheral blood mononuclear cells
PD	Peritoneal Dialysis
PMCs	Polymorphonuclear cells
PRRs	Pathogen recognition receptors
PTH	Parathyroid hormone
pTreg	Peripherally derived T regulatory
RA	Rheumatoid Arthritis
RBC	Red blood cells
RRT	Renal replacement therapy
SLE	Systemic Lupus Erythtomatosis
SS	Systemic Sclerosis
STAT	Signal transducer and activator of transcription
T1D	Type 1 diabetes
TB	Tubercle bacillus
Tfh	Follicular T helper
TGF	Transforming growth factor
Th	T helper

List of Abbreviations Cont...

Abb.	Full term

Tregs..... Regulatory T cells
UACR ..... Urinary albumin: creatinine ratio
UC.....Ulcerative colitis

INTRODUCTION

End stage renal disease (ESRD) is defined as irreversible decline in kidney function that is severe enough to be fatal in the absence of hemodialysis (HD) or transplantation. ESRD is included under stage 5 of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) classification of chronic kidney disease, where it refers to persons with an estimated glomerular filtration (eGFR) rate less than 15 mL per minute per 1.73 m2 body surface area ***(Cheng et al., 2018).***

Metabolic acidosis is disturbances in the homeostasis of plasma acidity characterized by an increase in the hydrogen ion concentration in the systemic circulation. Acidosis is a common complication of chronic kidney disease (CKD), which can cause patients to lose lean body mass by preventing the activation of adaptive responses that maintain protein stores ***(Yan et al., 2017)***. Some effects of acidosis include negative nitrogen balance, muscle wasting, protein catabolism, increased corticosteroid, and parathyroid hormone production ***(Kraut and Madias, 2011).***

The (KDOQI) recommended maintaining predialysis serum bicarbonate at ≥22 mEq/L ***(National Kidney Foundation, 2000).***

In patients with renal failure, the systemic concentrations of both pro-inflammatory - and anti inflammatory cytokines are

several times higher than concentrations in healthy individuals due to both decreased renal clearance and increased production of cytokines ***(Esmeralda et al., 2017).***

Interleukin 10 (IL-10) is a cytokine with potent anti-inflammatory properties that plays a central role in limiting host immune response to pathogens, thereby preventing damage to the host and maintaining normal tissue homeostasis. Dysregulation of IL-10 is associated with enhanced immunopathology in response to infection as well as increased risk for development of many autoimmune diseases ***(Shankar and Genhong, 2012).***

HD results in activation of cytokines, which can induce protein catabolism and promote apoptosis ***(Michel et al., 2010)***. Low IL-10 level has been associated with low requirement of EPO (Erythropoeitin) in HD patients ***(Attia et al., 2010).***

High levels of interleukins (ILs) and presence of metabolic acidosis are described as independent risk factors for morbidity and mortality in these patients. Although regular hemodialysis causes decreased levels of mortality in ESRD, it is considered a condition associated with inflammation ***(Ori et al., 2013).***

AIM OF THE WORK

The aim of this study is to evaluate the relationship between IL-10 and serum bicarbonate and metabolic acidosis in prevalent hemodialysis patients and evaluate the effect of correction of metabolic acidosis on IL10 levels.

Chapter 1

END STAGE RENAL DISEASE (ESRD)

Introduction:

The renal system consists of the kidney, ureters, and the urethra. (Fig. 1) The overall function of the system filters approximately 200 liters of fluid a day from renal blood flow which allows for toxins, metabolic waste products, and excess ion to be excreted while keeping essential substances in the blood ***(Faiz and Ifeanyichukwu, 2019).***

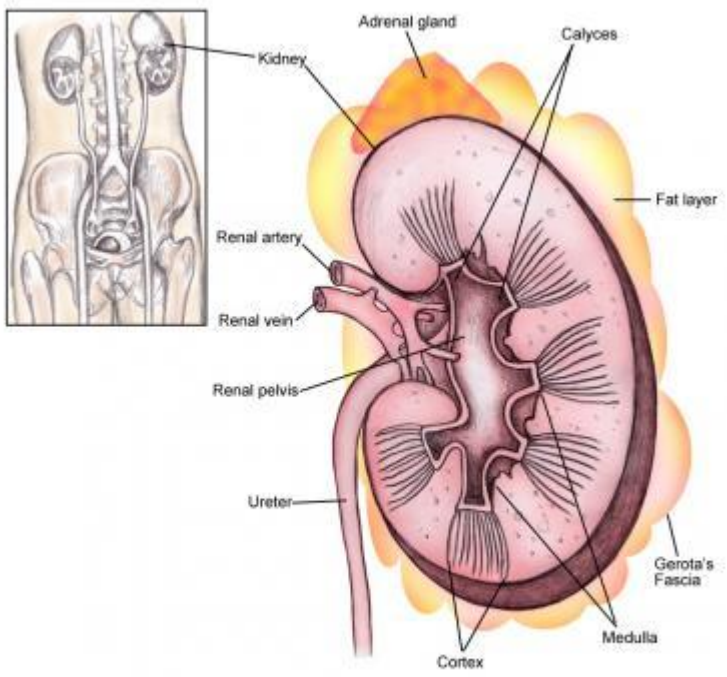

Figure (1): Normal renal system ***(Charbel et al., 2017).***

The kidney regulates plasma osmolarity by modulating the amount of water, solutes, and electrolytes in the blood ***(Jiatong et al., 2020).*** It ensures long term acid-base balance ***(Hamm et al., 2015)*** and also produces erythropoietin which stimulates the production of red blood cell ***(Tomokazu et al., 2015).*** It also produces renin for blood pressure regulation ***(Matthew et al., 2015)*** and carries out the conversion of vitamin D to its active form ***(Antonio and Michal, 2013).***

Chronic kidney disease (CKD) is the presence of kidney damage with urinary albumin excretion of over 29 mg/day or decreased kidney function with glomerular filtration rate (GFR) less than 60mL/min/1.73m^2 for three or more months ***(Faiz and Ifeanyichukwu, 2019).*** The presence of both of these factors along with abnormalities of kidney structure (Fig. 2) or function for greater than three months signifies CKD. End-stage renal disease, moreover, is defined as a GFR less than 15mL/min ***(Scott et al., 2018).***

The incidence and prevalence of CKD have risen dramatically, partly due to the increasing prevalence of diabetes and hypertension ***(Mallika et al., 2016).*** CKD is a significant global public health problem with poor prognosis, it is associated with high rates of morbidity and mortality and elevated health care costs ***(Carrero et al., 2017).***

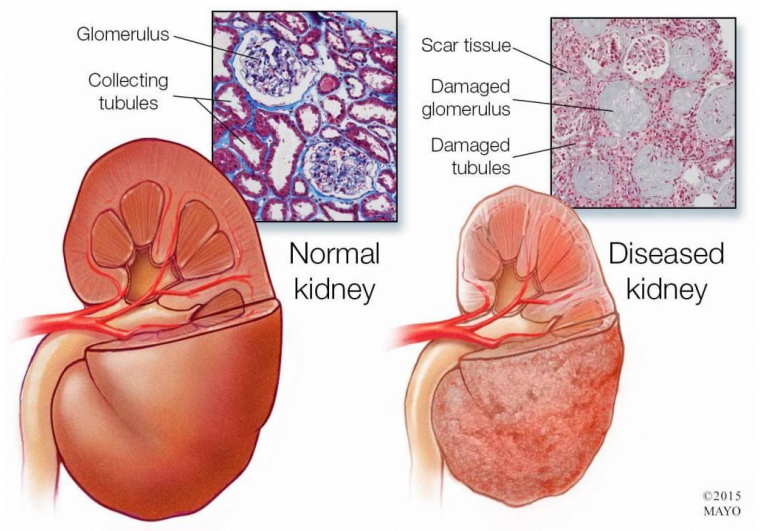

Figure (2): Normal and diseased kidney ***(Beka, 2018).***

Stages of CKD:

The stages of CKD are classified as follows (Table 1)

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)
- Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m^2)
- Stage 3b: Moderate reduction in GFR (30-44 mL/min/1.73 m^2)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)
- Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis)

(KDIGO, 2012)