Effect of hemodialysis membrane pore size on homocysteine level in children with chronic renal failure.

Thesis

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بسم الله الرحمن الرحيم

وعلمك ما لم تكن تعلم وكان فضل الله

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Abstract

Hyperhomocysteinemia is a putative risk factor for cardiovascular disease in the hemodialysis population. Modifications of the dialysis regimen may result in a better removal of Hcy. We examined the effect of dialyzer membrane pore size on Hcy levels in pediatric hemodialysis patients. The study included twenty patients with ESRD on regular hemodialysis with the mean age (±SD) of 11±2.56 years. Plasma Hcy before and after dialysis were measured both on low-flux dialysis and 12 weeks after conversion to high-flux membranes. Despite the absence of significant reduction in predialysis homocysteine levels , high-flux dialysis was associated with improvement in important cardiovascular risk factors including anemia , hypertension and hyperphosphatemia.

Key words: Chronic renal failure ; cardiovascular risk ; dialyzer membrane; hemodialysis; high-flux; Homocysteine ; low-flux.

Contents

List of abbreviations

ABD	Adynamic bone disease
ACE	Angiotensin Converting Enzyme
ADH	Antidiuretic hormone
ADMA	Asymmetric dimethylarginine
ADP	Adenosine diphosphate
AKI	Acute kidney injury
ALP	Alkaline phosphatase
anti-GBM	Anti–glomerular basement membrane
ATN	Acute tubular necrosis
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BHMT	Betaine homocysteine methyltransferase
BMI	Body mass index
BW	Body weight
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosohate
CBS	Cystathionine β-synthase
CGL	Cystathionine γ-lyase
cGMP	Cyclic guanosine monophosphate\
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CRF	Chronic renal failure
CRI	Chronic renal insufficiency
C_{UF}	Ultrafiltration coefficient
CVD	Cardiovascular disease
DMG	Dimethlyglycine
EBV	Epstein-Barr virus
eCrCl	Estimated creatinine clearance
eNOS	Endothelial nitric oxide synthase
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
Hcy	Homocysteine
HD	Hemodialysis
HUS	Hemolytic uremic syndrome
IGF-1	Insulin like growth factor 1
IGFBP	Insulin like growth factor binding protein
IHD	Ischemic heart disease
IVC	Inferior vena cava
LDL	Low-density lipoprotein
MAT	methionine adenosyltransferase
MBGN	Membranoproliferative glomerulonephritis
MBP	Mean blood pressure in mmHg
MeTHF	Methyltetrahydrofolate
MS	Methionine synthase
MT	Methyltransferase
MTHFR	Methylenetetra-hydrofolate reductase
NKF-K/DOQI	National Kidney Foundation's- Kidney Disease Outcomes Quality Initiative

PD	Peritoneal dialysis
PDUR	Postdialytic urea rebound
PGE2	Prostaglandin E2
PGI2	Prostacyclin
PTFE	Polytetrafluoroethylene
PTH	Parathyroid hormone
RAA	Renin–angiotensin–aldosterone axis
RBC	Red blood cell
RDA	Recommended dietary allowance
rhGH	Recombinant human growth hormone
rHuEPO	Recombinant human erythropoietin
ROS	Reactive oxygen species
RRT	Renal replacement therapy
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
SER	Serine
THF	Tetrahydrofolate
TXA2	Thromboxan A2
UF	Ultrafiltration
UKM	Urea kinetic modeling
VDRL	Venereal Disease Research Laboratory

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Introduction and aim of the work

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Introduction

End-stage renal disease (ESRD) is defined as the phase when the patient's renal dysfunction has progressed to the point at which homeostasis and ultimately survival cannot be sustained with native renal function, and either dialysis or renal transplantation is required ***(Vogt and Avner, 2007).***

Cardiovascular disease (CVD) is highly prevalent in end stage renal disease population and is the predominant cause of death ***(David et al., 2005).*** Throughout the last decade, it was realized that the major killer in chronic dialysis patients was not uremia per se but CVD. A cardiac cause accounted for almost half of all causes of death and the rate of death was approximately 10 to 20 times higher than in the general population ***(Parekh et al., 2002).*** Unfortunately, children with ESRD share many risk factors for CVD**.** The combination of these risk factors including elevated homocysteine might be the reason for the development and acceleration of cardiac disease in pediatric ESRD ***(Mark, 2002).*** Several studies demonstrate a graded and independent association between Homocysteine and cardiovascular risk ***(Wald et al., 2002 and Klerk et al., 2002).***

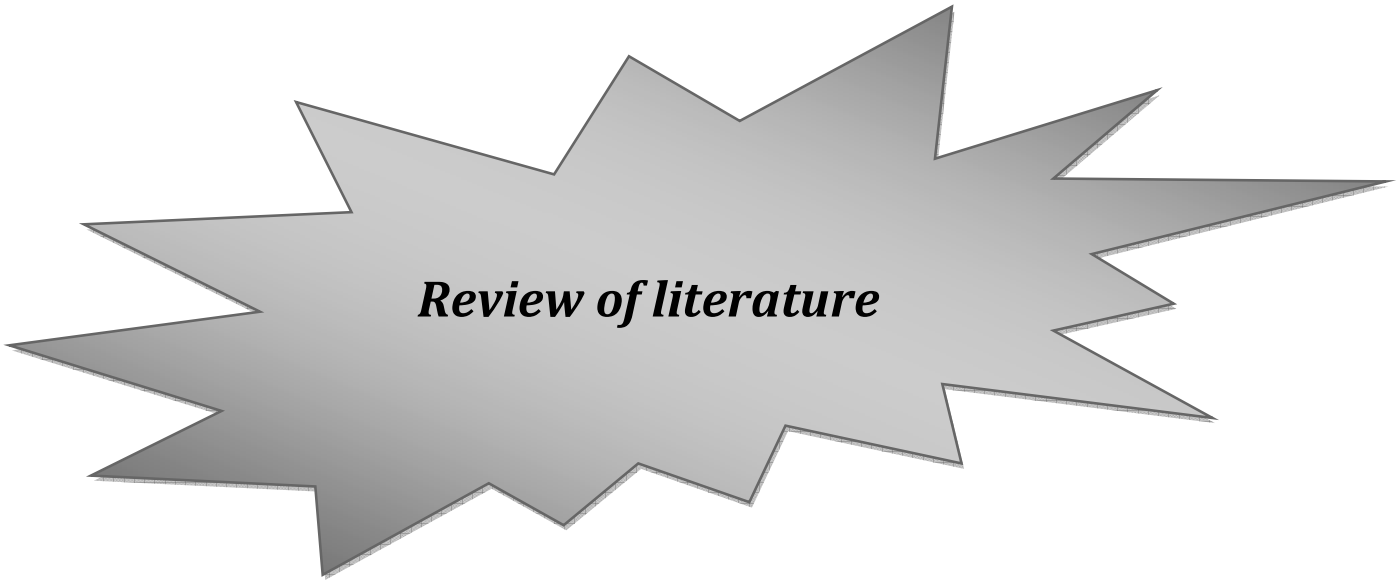
Homocysteine (Hcy) is a sulfur-containing amino acid produced in the metabolism of the essential amino acid methionine by methylation reactions involving the active form of methionine, s-adenosyl methionine (***Hankey & Eikelboom, 1999).*** Most of the early work on the causes of hyperhomocysteinemia focused on nutritional or genetic factors or impaired homocysteine removal by renal disease ***(Selhub et al., 2000).***

The totality of evidence from epidemiologic observations suggests an independent relationship between homocysteine and atherothrombotic vascular risk. It is quite plausible that the relationship between hyperhomocysteinemia and CVD is indirect, and is confounded by other factors (e.g., deficiencies of folate, vitamin B12, or vitamin B6 and renal insufficiency) that influence both homocysteine levels and cardiovascular risk ***(Sanjay et al., 2006).***

Aim of work

The aim of this study is to:

Compare the effect of dialysis with both low-flux and high-flux membranes on homocysteine level and its dialytic removal in pediatric patients with ESRD on regular hemodialysis.


Review of literature

Chapter 1
Renal Failure

The term "renal failure" means failure of renal excretory function owing to depression of glomemlar filtration rate (GFR) ***(Andreoli, 1999).***

Acute Renal Failure (ARF):

Introduction

Acute renal failure denotes the abrupt onset of renal dysfunction leading to the inability to regulate acid-base and electrolyte balance and to excrete wastes and fluid. Increased understanding of the pathophysiology and clinical spectrum of acute renal failure has led to a change in nomenclature of this condition to acute kidney injury (AKI), acknowledging that acute renal dysfunction occurs due to injurious endogenous or exogenous disease processes ***(Michael & Goldstein, 2008).***

Epidemiology

The epidemiologic importance of AKI as a public health problem is underscored by evidence showing that even a small reduction (0.3 mg/dL serum creatinine increase) in the renal function of hospitalized adult and pediatric patients is a risk factor for morbidity and mortality ***(Price et al., 2007).***

Although little data exist to describe the incidence of pediatric AKI, the prevalence of hospital and pediatric ICU-acquired AKI appears to be increasing, which may result from changes in diagnostic profiles over the last 10–20 years and increasing use of more invasive management to support critically ill children and higher illness severity of these patients ***(Vachvanichsanong et al., 2006).***

When requirement for some form of renal replacement therapy (RRT) as the strictest definition of AKI is used, its incidence in the PICU ranges from 1–2% ***(Bailey et al., 2007).***

In 2004, a consensus definition for AKI was proposed by the Acute Dialysis Quality Initiative: the RIFLE criteria (risk, injury, failure, loss, end-stage renal disease). The adult-derived RIFLE definition was modified, and then applied and validated in pediatric patients and renamed as the pediatric RIFLE (pRIFLE) criteria. pRIFLE stratifies AKI from mild (R, *risk*) to severe (F, *failure*) (Table 1) ***(Bellomo et al., 2004).***

Table 1 Pediatric RIFLE criteria definition of acute kidney injury

	Pediatric RIFLE criteria	
	Estimated CrCl (eCCl) [a]	Urine output
Risk	*eCrCl* decrease by 25%	<0.5ml/ kg/h for 8h
Injury	*eCrCl* decrease by 50%	<0.5mL/ kg/ h for 16 h
Failure	*eCrCl* decrease by 75% or *eCrCl* <35mL/ min/1.73 m_2	<0.3mL/ kg/ h for 24 h Or anuric for 12 h
Loss	Persistent failure >4 weeks.	
End stage	End stage renal disease. (persistent failure >3 months	

[a] Estimated creatinine clearance calculation is discussed later.

(Bellomo et al., 2004)

Etiology and Pathophysiology of AKI

A recent pediatric retrospective study revealed that the most common causes of AKI in a tertiary health care center were renal ischemia, nephrotoxic medication use, and sepsis***(Hui-Stickle et al., 2005).*** Each of these conditions cause AKI via different mechanisms.They lead to a final common pathway of acute tubular necrosis (ATN), characterized by renal tubular epithelial cell death. Table 2 lists common causes of AKI.

I. Prerenal AKI

Prerenal AKI refers to the abrupt decrease in GFR following renal hypoperfusion, as shown in table 2 ***(Michael &Goldstein, 2008).***

In the setting of this decreased renal perfusion, several adaptive responses come into play, aiming at maintaining GFR and restoring intravascular volume via neurohormonal mechanisms. Decreased renal perfusion leads to increase in adrenergic activity and stimulation of the renin–angiotensin–aldosterone (RAA) axis and antidiuretic hormone (ADH) release ***(Devarajan, 2005).*** The increase in adrenergic activity leads to systemic vasoconstriction, thereby increasing blood pressure. Stimulation of the RAA system leads to reabsorption of salt and water. Increase in systemic ADH leads to retention of water by the collecting tubule. Each of these mechanisms favors the maintenance of intravascular volume and systemic blood pressure and thus maintaining GFR ***(Lameire et al., 2005).***