Amino Acid Abnormalities In Pediatric Patients with Chronic Renal Failure &Vascular Effect of L-Arginine Supplementation

Thesis Submitted for Partial Fulfillment of M.D. Degree in Medical Human Genetics

By

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DEDICATION TO

My dear father who wished to see me a doctor but died before it becomes true

My dear mother for her great care, kindness, and help

My helpful & supportive family

قالوا سبحانك لا علم لنا إلا ما علمتنا

إنك أنت العليم الحكيم

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List of Abbreviations

AA	Amino acid
ADMA	Asymmetric dimethylarginine
ATP	Adenosine triphosphate
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BCAA	Branched-chain amino acids
BCKA	Branched-chain keto acids
BH4	Tetrahydrobiopterin
BMI	Body mass index
Ca	Calcium
cAMP	Cyclic adenosine monophosphate
CAPD	Continuous ambulatory peritoneal dialysis
CBC	Complete blood count
cGMP	Cyclic guanosine monophosphate
CKD	Chronic kidney disease
COX	Cyclooxygenase
CRF	Chronic renal failure
CRP	C-reactive protein
CVD	Cardiovascular disease
DDAH	Dimethylarginine dimethylaminohydrolase
EAAs	Essential amino acids
EDD	Endothelium-dependent vasodilatation
ENDD	Endothelium non dependent vasodilatation
ESRD	End stage renal disease
FAA	Free amino acids
FMD	Flow mediated dilatation
GFR	Glomerular filtration rate
GMP	Guanosine monophosphate
GSH	Glutathione
GTP	Guanosine triphosphate
HD	Haemodialysis
HTN	Hypertension

IL-1	Interleukin 1
IL-6	Interleukin-6
LDL	Low-density lipoprotein
mRNA	Messenger RNA
MTHFR	Methylenetetrahydrofolate reductase
NO	Nitric oxide
NOS	NO synthases
oxLDL	Oxidized LDL
P	Phosphate
PDGF	Platelet derived growth factor
RBC	Red blood cells
ROS	Reactive oxygen species
SDMA	Symmetric dimethylarginine
SMC	Smooth muscle cells

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Introduction

The uremic syndrome is a complex condition that results from an accumulation of multiple waste compounds, combined with failure of the endocrine and homeostatic functions of the kidney in end-stage chronic renal failure (CRF) patients ***(Brunini et al., 2006A).***

In Jamaican children, the cumulative annual incidence of chronic renal failure is 3.2 per million children aged < 12 years. The incidence is likely underestimated as some children may have been undiagnosed and/or not referred. Glomerulonephritis is the commonest cause of chronic renal failure (50%) followed by obstructive uropathy, reflux nephropathy, renal dysplasia and chronic pyelonephritis. Mortality rate among CRF patients is 65% ***(Miller and Williams, 2002).***

Tawfik et al., 2002, stated that primary renal disease tends to account for a relatively small proportion of the etiologies of renal impairment in Egyptian children. Most of the cases encountered in their study suffered functional renal impairment secondary to severe dehydration or sepsis. Presence of congenital abnormalities of the gastrointestinal tract, heart or urinary tract, increased the possibility of suffering from impaired renal function approximately 9 times. Delays in seeking medical advice increased the risk substantially.

Malnutrition is a common pathological condition which exacerbates cardiovascular morbidity and mortality in CRF patients ***(Da Silva et al., 2005 and Brunin et al., 2006A***). The underlying mechanisms in CRF malnutrition have not been completely clarified. Inadequate diet and a state of persistent catabolism play major roles ***(Brunini et al.,***

2006A). Also protein metabolism changes with loss of renal function resulting in deterioration of nutritional status ***(Ivarsen et al., 2001).***

Levels of plasma and intracellular amino acids are significant early indicators of protein metabolism and nutritional status assessment ***(Brunini et al., 2006A and Chuang et al., 2006***). Many of the characteristic alterations in the plasma amino acid profile that are observed in chronic end-stage renal disease are already present in mild renal insufficiency. Progressive loss of renal function generally results in increasing abnormalities; these changes in plasma amino acid concentrations were usually linear with reduction in glomerular filtration rate GFR (***Laidlaw et al., 1994).***

Plasma protein and amino acid concentrations have been reported to be abnormal in patients with chronic renal failure, whether on conservative or regular dialysis treatment ***(Perfumo et al., 1986, Ceballos et al., 1990, Suliman et al., 1999 and Suliman et al., 2002).*** These abnormalities may be related to impaired protein and amino acid metabolism, to dietary deficiencies of calories and proteins, or to amino acid and protein losses due to peritoneal dialysis or hemodialysis ***(Perfumo et al., 1986).*** Moreover, branched-chain amino acids are moderately decreased only in the advanced stage of renal failure and this may be, at least in part, nutritional in origin (**Ceballos et al., 1990**). Also increased protein degradation may be the cause of increased plasma concentration of nonessential amino acids in malnourished chronic renal patients ***(Ivarsen et al., 2001).***

Increased cardiovascular mortality and morbidity is well recognized in adults with CRF. The adverse impact of CRF on cardiovascular mortality and morbidity in the young is however even greater with a 500 times higher rate of

cardiovascular deaths than a control population. The initiation of vascular damage begins very early during the course of CRF, and involves the vascular endothelium. L-Arginine is the substrate for nitric oxide (NO) synthase and has been shown to increase endothelial function in animal models and in clinical studies of subjects with hypercholesterolemia and coronary artery disease. So L-arginine supplementation in children with CRF might increase NO bioavailability ***(Bennett-Richards, et al., 2002A).***

Aim of the work

The aim of this work is to

- Detect the abnormalities in plasma amino acids in pediatric patients with chronic renal failure on regular hemodialysis .
- Assess the vascular function in children with chronic renal failure following oral L-arginine supplementation.
- Assess the vascular function in children with chronic renal failure and correlate it with L-arginine aminoacid.

I. Amino Acids

Amino acid structure:

There are twenty amino acids (AA) that are commonly found in proteins. Each amino acid has a similar, yet unique structure. The common AA are known as alpha AA because they have a primary amino group (-NH2) and a carboxylic acid group (-COOH) as substitutes of the alpha carbon atoms (figure 1). Proline is an exception because it has a secondary amino group (-NH-), for uniformity it is also treated as alpha-amino acid ***(Osuri, 2003).***

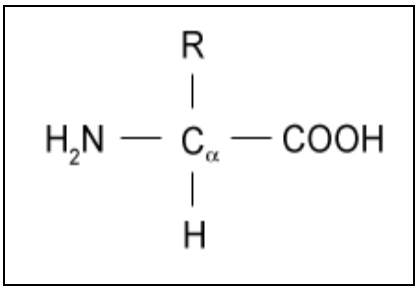

Figure 1: General structure of alpha - amino acid ***(Osuri, 2003).***

Each AA has a different side chain (or R group). The side chains vary greatly in their complexity and properties. The side chain of glycine is simply a hydrogen. The side chain of tryptophan is based on the aromatic, bicyclic indole group ***(Gorga, 2007).***

General properties:

The amino and carboxylic acid groups of AA readily ionize. At a pH (~7.4), the amino groups are protonated and the carboxyl acid groups are in their conjugate base (carboxylate) form, this shows that an AA that can act as an