RELATION OF URIC ACID AND HYPERTENSION IN CHRONIC KIDNEY DISEASE AND DIALYSIS PATIENTS

Thesis

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List of Abbreviations

Abb.	Full term
ACEIs	*Angiotensin- converting enzyme inhibitor.*
ATP	*Adenosine triphosphat .*
B.M.I	*Body mass index*
BP	*blood pressure.*
BUN	*Blood urea nitrogen.*
CKD	*Chronic kidney disease.*
CO	*Cardiac output.*
CV	*Cardiovascular.*
D.B.P	*Diastolic blood pressure.*
DASH diet	*Dietary approaches to stop hypertension.*
ECV	*Extracellular volume.*
EET	*Epoxyeicosatrienoic acid.*
EKG/ECG	*Electrocardiogram.*
eNO	*Endothelial nitric oxide.*
eNOS	*Endothelial nitric oxide synthase .*
ESRD	*End-stage renal disease.*
ET-١	*Endothelin.*
GFR	*Glomerular filtration rate.*
GI	*Glycemic index.*
H.S	*Highly significant.*
Hb%	*Hemoglobin level.*
HD	*Hemodialysis.*
HDL	*High density lipoprotein*
HTN	*Hypertension.*
JNC٧	*Joint national commete*
K/DOQI	*Kidney disease outcomes quality initiative.*
LDL	*Low density lipoprotein*
LVH	*Left Ventricular hypertrophy.*

LVMI	*Left Ventricular Mass Index.*
MAP	*Mean arterial pressure.*
N.s	*Non-significant.*
NAD+	*Nicotinamid adenine dinucleotide.*
NKF	*National kidney foundation.*
NOS	*Nitric oxide synthase.*
PGC	*Intra-glomerular pressure.*
PTH	parathyroid hormone
QA	*Single nephron blood flow.*
RA	*Afferent arteriolar resistance.*
RAS	*Renin-angiotensin- system.*
RE	*Efferent arteriolar resistance.*
RF	*Renal failure.*
ROS	*Reactive oxygen species.*
RRT	*Renal replacement therapy.*
S.B.P	*Systolic blood pressure.*
S.D	*Standard devation.*
SNGFR	*Single-nephron GFR.*
SUA	*Serum uric acid.*
Thai	Thailand
TSH	*Thyroid stimulation hormone*
VR	*Venous return.*
XO	*xanthine oxidase.*

INTRODUCTION

Many years ago, Sir Alfred Garrod in the ١٨٠٠s provided the first evidence that gout was associated with increased levels of uric acid in the blood **(Garrod, ١٨٤٨).**

Shortly thereafter, Frederick Akbar Mohamed first described essential hypertension, and noted that it was often associated with gout. Writing in the Lancet, he said: "People who are subject to this high blood pressure frequently belong to gouty families or have themselves suffered from the symptoms of the disease **(Mohamed, ١٨٧٩).**

After that, many papers reported on the association of gout with hypertension, obesity, and cardiovascular disease. Indeed, in the days before effective therapy was available to lower serum uric acid, more than ٧٠٪ of patients with gout were obese, more than ٥٠٪ had hypertension, nearly all had some degree of renal disease (and ١٠٪ to ٢٥٪ died of it) and approximately ٩٠٪ developed some degree of heart disease (and ٢٠٪ died of a cardiac complication) **(Breckenridge, ١٩٦٦).**

Thus, gout seemed to be a major risk factor for cardiovascular disease. And clinically evident gout is only the tip of the iceberg. Many patients have hyperuricemia (uric acid > ٧,٠ mg/dL in men and > ٦,٥ mg/dL in women) but do not have gout. Studies in people with "asymptomatic

hyperuricemia" have also demonstrated a remarkable association with hypertension, obesity, metabolic syndrome, kidney disease, and cardiovascular disease **(Johnson et al., ٢٠٠٥).**

Several epidemiologic studies have tried to determine if uric acid is an independent risk factor for cardiovascular disease, some found that it was, but others did not. The inability to resolve these issues, coupled with the lack of a mechanism by which uric acid might cause cardiovascular disease, has up to now led most authorities to conclude that uric acid is not a true risk factor for cardiovascular disease **(Culleton et al., ١٩٩٩).**

In other studies in rats, experimental hyperuricemia (induced by oxonic acid) was also associated with the development of mild renal disease, characterized by mild proteinuria, renal arteriolar changes, glomerular hypertrophy, tubulointerstitial fibrosis, and eventually glomerulosclerosis **(Nakagawa et al., ٢٠٠٣).**

Interestingly, when hyperuricemia was induced in rats with preexisting renal disease (ie, in which one entire kidney and two thirds of the other kidney had been removed), their renal lesions were dramatically worse than in similar rats without hyperuricemia. This suggests that the hyperuricemia may not only cause renal disease, but may also exacerbate preexistent renal disease **(Kang et al., ٢٠٠٢).**

The mechanism by which uric acid might cause renal disease was revealed by micropuncture studies, which demonstrated that elevated uric acid (٣,١ ± ٠,٢ mg/dL) caused glomerular hypertension and cortical vasoconstriction. These changes would be expected to induce glomerular damage and tubular ischemia. In addition, uric acid stimulated inflammatory mediators in vascular cells, including C-reactive protein and monocyte chemoattractant protein and vasoconstrictive factors such as thromboxane **(Sanchez-Lozada et al., ٢٠٠٢).**

Recent studies in humans also suggest that uric acid is a true risk factor for kidney disease. Numerous recent papers have reported elevated uric acid is an independent risk factor for kidney disease in the general population١ and in patients with preexistent renal disease **(Toprak et al., ٢٠٠٦).**

Elevated uric acid has also been reported to be more common in patients with diabetes with progressive renal disease. While earlier studies have reported mixed results from lowering uric acid in patients with renal disease. A recent clinical study found that lowering uric acid in patients with renal disease and asymptomatic hyperuricemia resulted in less progression of their renal disease **(Siu et al., ٢٠٠٦).**

AIM OF THE WORK

To study incidence of hyperuricemia in patients with chronic kidney disease and dialysis patients and its relation to hypertension.

Chapter (١):

URIC ACID

Physiology of uric acid and uric acid metabolism

Hyperuricemia can be the consequence of increased uric acid production or decreased excretion. Any cause for decreased glomerular filtration, tubular excretion or increased reabsorption would result in an elevated serum uric acid. Increased serum uric acid has been found to predict the development of renal insufficiency in individuals with normal renal function **(Johnson et al., ٢٠٠٣).**

Uric acid, a product of purine metabolism, is degraded in most mammals by the hepatic enzyme, urate oxidase (uricase), to allantoin, which is freely excreted in the urine **(Richard et al., ٢٠٠٣).**

Uric acid is the final product of purine metabolism in humans. The kidneys excrete approximately two-thirds of the uric acid that is produced daily (**Shihping et al., ٢٠٠٤).**

The serum uric acid concentration is determined largely by the rate of purine metabolism and the efficiency of renal clearance. Therefore, significant amounts of uric acid may accumulate in patients approaching end-stage renal disease (ESRD) (**Shihping et al., ٢٠٠٤)**

Uric acid production has been associated with triglyceride level, and postulated to purine metabolism in triglycerides biosynthesis pathways. Excess purine intake and endogenous production due to glucose intake endure the elevation of uric acid levels **(Kuo Hong et al., ٢٠٠٥).**

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion (**Baker et al., ٢٠٠٥).**

A reduction in glomerular filtration rate (GFR) increases serum uric acid, although a significant compensatory increase in gastrointestinal excretion occurs **(Richard et al., ٢٠٠٣)**.

Sources of uric acid

In many instances, people have elevated uric acid levels for hereditary reasons. Diet may also be a factor. Purines are found in high amounts in animal internal organ food products, such as liver. A moderate amount of purine is also contained in beef, pork, poultry, fish and seafood (**Choi, ٢٠٠٤).**

Examples of high purine sources include: sweetbreads, anchovies, sardines, liver, beef kidneys, brains, herring, mackerel, scallops, game meats, and gravy. Moderate intake of purine-containing food is not associated with an increased risk of gout **(Choi, ٢٠٠٤).**