REDUCED ALPHA-2 ANTIPLASMIN LEVELS IN NEPHROTIC SYNDROME

THESIS

Submitted for partial fulfillment of M.S. degree in internal medicine

By

Mohamed Abdel-Rahman Hassan El-Shayp

Supervised by

Prof. Dr. Wahid El-Said
Prof. of Internal Medicine and Nephrology

Prof. Dr. Mona Rafeek
Assit. Prof. of Clinical Pathology

Prof. Dr. Hany Ali Refaat
Assist. Prof. of Internal Medicine and Nephrology

Prof. Dr. Shadia Barakat
Assist. Prof. of Physiology

Dr. Khaled Abu-Seef
Lecturer of Internal Medicine and Nephrology

Faculty of Medicine
Ain Shams University
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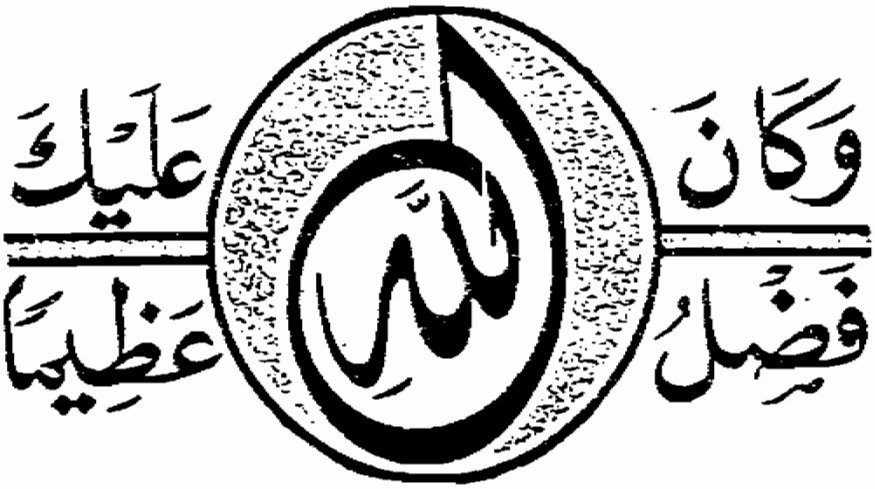
بسم الله الرحمن الرحيم



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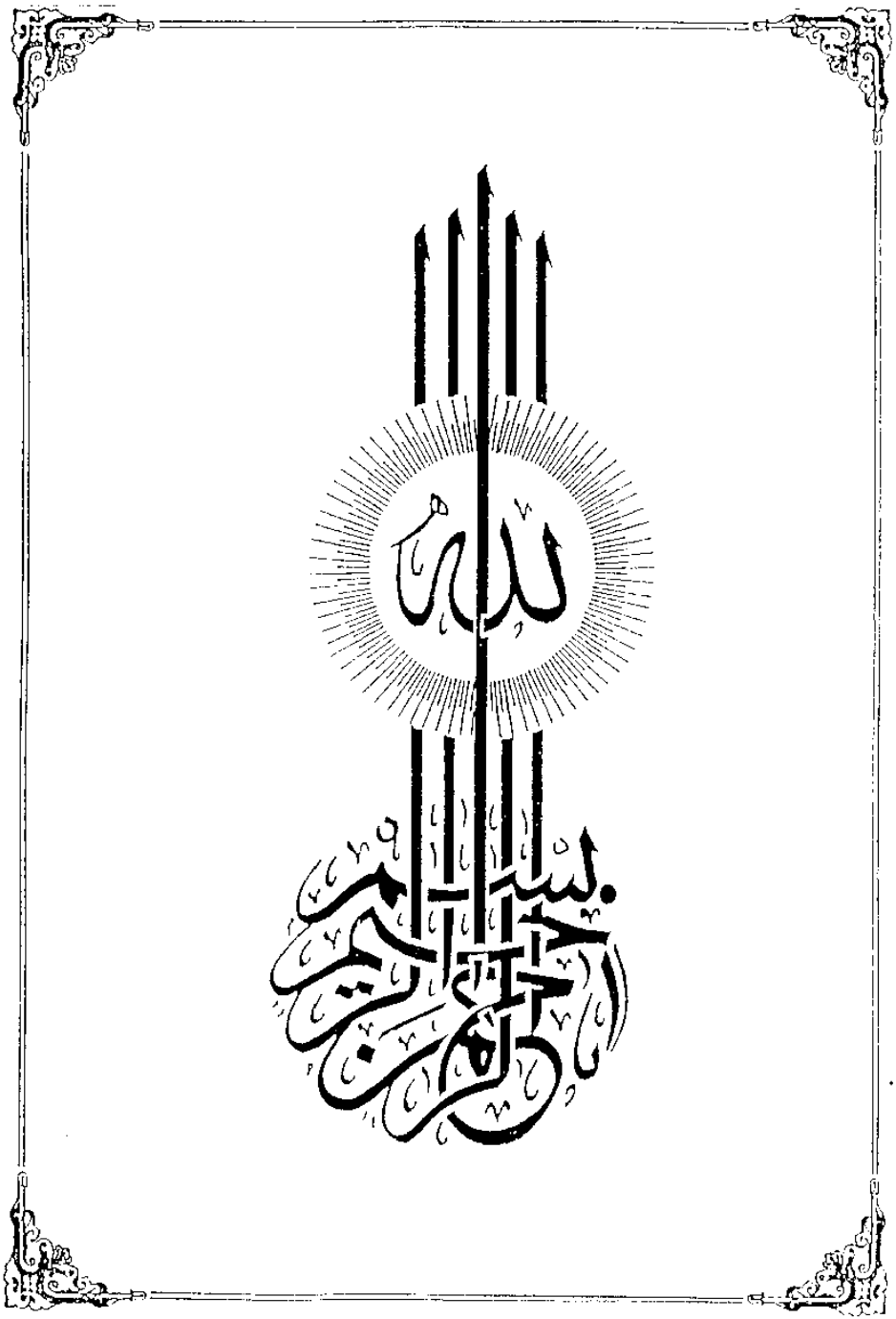

To My Mother

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LIST OF APPREVIATIONS:

α2 PI	: α2 plasmin inhibitor
α2 M	: α2 Macroglobulin
C1 inh.	: Complement component No. I inhibitor
AT III	: Antithrombin III
F.D.P.	: Fibrin Degradation Products
SGOT	: Serum Glutamic Oxaloacetic Transaminase
SGPT	: Serum Glutamic Pyruvic Transaminase
T.P.	: Total serum Proteins
t-PA	: Tissue plasminogen activator
G.N	: Golmerulonephritis
V.W.F.	: Von Willebrand Factor

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INTRODUCTION

AND

AIM OF THE WORK

Thromboembolic phenomena following nephrotic syndrome is a common complication ***(Liach et al., 1985)*** however not all patients with nephrotic get thrombosis, may be due to a protective mechanism as loss of clotting factors in urine as factor VIII ***(Epstein et al., 1976) IX (Handley et al., 1967) XII (Hikehiko et al., 1981).***

α2 antiplasmin which is a physiological inhibitor of the palsmin may be one of the physiological counterbalancing mechanisms to thrombosis in nephrotic syndrome when it is lost in appreciable amounts in urine among other proteins (non selective proteinuria) ***(Robert et al., 1985)***.

Many studies had focused attention on clotting factors, platelets, fibrinogen and other clotting parameters however α2 PI has received the least attention specially regarding its pathological role in thromboembolic tendency, this study is focused on the role of α2 PI in relation to thromboembolic phenomena in nephrotic syndrome.

Aim of Work:

Is to measure serum level of α2 PI as well as other renal function, s. proteins, urinary proteins/24 h., urinary F.D.P and s. fibrinogen in nephrotic patients and their relation to nephrotic patients with thrombosis.

REVIEW OF LITERATURE

NEPHROTIC SYNDROME

The association between proteinuria and oedema has been recognized for more than 200 years.

In ***1765, Domeinco Cotugno*** described a young soldier with massive oedema, and urine that coagulated "like the soft white of an egg" when it was heated over a fire. A century ago ***Richard Bright*** defined the nephrotic syndrome as combination of proteinuria and oedema with lesions in the kidney and hypo-proteinemia. Today, the term nephrotic syndrome is a clinical entity having multiple causes and characterized by increased glomerular permeability manifested by massive proteinuria and lipiduria. There is a variable tendency towards oedema, hypoalbuminaemia and hyperlipidamia. Protein excretion rates are usually in excess of 3.5 gm/24h. per 1.73 m^2 body surface area in the absence of depressed glomerular filtration rate ***(Schreiner, 1979)***.

Structure and Function of the Kidney:

Each normal adult kidney weighs approximately 150 g. contains between 800,000 and 1.4 million glomeruli distributed throughout the cortex, and receives about 10% of the resting cardiac output. Blood is delivered to the glomerular tuft via the afferent arteriole which breaks up into a knot of capillaries and subsequently reforms as the efferent arteriole. Filtration of the fluid phase of the blood from the capillary lumen to the urinary space depends on:

- The hydrostatic pressure in the capillaries, which is determined by the difference between afferent and efferent arteriolar pressures.
- The colloid osmotic pressure, which acts predominantly within the capillary as the ultrafiltrate in the urinary space is almost protein free.
- The ultrafiltration coefficient of the glomerular basement membrane.

A healthy adult has a glomerular filtration rate (GFR) of 100-200 ml ultrafiltrate/minute. Assuming a haematocrit of 50%, this is equivalent to filtration of 20% of the fluid phase of the blood on each passage through the kidney, most of which, of course, is reabsorbed in the tubules.

Thus, the glomeruli have evolved to allow relatively unimpeded passage of small molecular weight substances such as water, urea, creatinine, amino acids, glucose and elemental ions; those to be retained within the body have specific tubular reabsorption mechanism. Blood cells and large molecular weight substances, such as immunoglobulins and albumin, are effectively retained within the circulation. Nevertheless, up to 2 g/day of predominantly small molecular weight proteins (10-30 KD) may be filtered. Much of this protein is resorbed in the tubules leaving, at most, 150-200 mg/day to appear in the urine.

The capillary endothelium-the dimensions of the fenestrations between the endothelial cells prevent access to the glomerular basement membrane by the formed contact with its capillary surface.

The glomerular basement membrane comprises several proteins. The central lamina densa, containing predominantly type IV collagen, is structured in a lattice-like array and probably acts as a size selective barrier, allowing free passage of molecules with a radius of less than 19°A, while completely preventing filtration of molecules greater than 42°A. The two laminae are (externa and interna), which lie on either side of the lamina densa, are composed of highly negatively charged molecules, notably heparin sulphate proteoglycan, which retard similarly charged anionic molecules, particularly albumin.

The glomerular epithelium imparts a further physical hurdle, though the ultrastructure of the slit pore membrane (the apparent space between the interdigitations of the foot processes) also leaves "gaps" approaching 40°A in their maximal dimension ***(Collin Short, 1991).***

Classification and Causes:

A) Idiopathic primary nephrotic syndrome due to primary glomerular disease.
B) Secondary nephrotic syndrome in which the glomerular lesion arises as a complication of other diseases.

A) Idiopathic Primary Nephrotic Syndrome:

A histopathological classification of lesions found in idiopathic nephrotic syndrome due to primary glomerular disease as detected by light, electron, and immunofluorescent microscopical examinations of renal biopsy specimens ***(Habib et al., 1979).***

1) Minimal change lesion (lipid nephrosis):

The glomeruli looks more or less normal when examined by light microscopy ***(Earley et al., 1979)***. On examination by electron microscopy, there is fusion of foot processes of the glomerular epithelial cells (podocytes) over the surface of B.M..

The basement membrane itself is of normal thickness and contains no deposits.

The visceral epithelial cells may be swollen and have enlarged nuclei, but there is no cell proliferation, inflammatory infillate, fibrosis or fibrin deposits. This change in the epithelial cell foot process is the predominant abnormality, and hence the condition is named minimal lesion nephrotic syndrome ***(Goggino, 1982).***

2) Mesangial proliferative glomerulonephritis:

It is usually defined by light microscopic picture. The glomeruli are characterized by definite but variable degrees of increase in cellularity of the mesangium, usually affecting all lobules of glomeruli to an equal degree ***(Waldherr et al., 1987)***.

3) Focal glomerular sclerosis:

By light microscopy the lesions are found to be affecting a variable minority of the glomeruli, often those in the deeper, juxta medullary cortex ***(Bohle et al., 1974)***.

The individual glomerular lesion consists of a segmental sclerosis with an increase in mesangial matrix usually spreading form glomerular hilus ***(White et al., 1973)***.

Hyaline material is characteristically deposited in the subendothelial areas of the affected loops ***(Hyman and Burkholder 1973)***. Another characteristic finding is the presence of a clear zone or halo, overlying the sclerotic segment and between the basement membrane and the vertical epithelial cell.

4) Membranous glomerulopathy:

The characteristic light microscopic feature in this type is the presence of a diffuse and uniform thickening of the capillary wall, usually without any significant proliferation of endothelial, mesangial or epithelial cells ***(Jones, 1957)***.

5) Membrane-proliferative G.N.:

Mesangio-capillary G.N.

There is a prominent increase in mesangial cellularity together with circumferential extention of mesangial cells and cytoplasm into the peripheral capillary wall. These changes lead to appearance of a thickened and reduplicated (Tram-Track) capillary wall by light microscopy ***(Heptinstall 1974)***.

Secondary Nephrotic Syndrome:

Nephrotic syndrome associated with specific etiological events or in which glomerular disease arises as a complication of other diseases ***(Glassock et al; 1987)***.