THE PATTERNS OF PROTEINURIA IN DIABETES MELLITUS

Thesis

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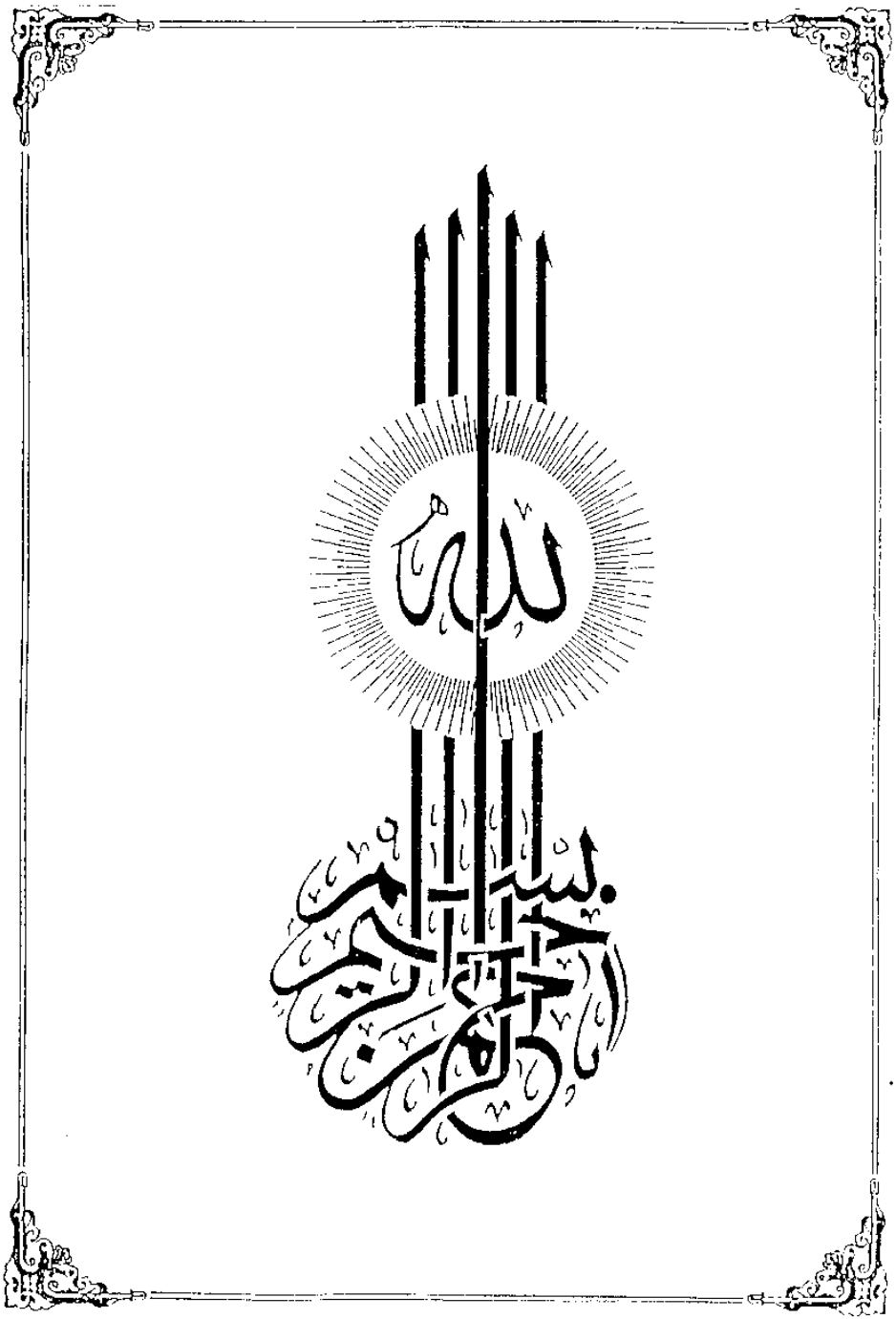
بسم الله الرحمن الرحيم

"وقل رب زدني علما"

صدق الله العظيم



THIS THESIS IS DEDICATED

TO MY BELOVED PARENTS AND

TO MY LOVELY DAUGHTER, HEND

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ABBREVIATIONS USED

ADH	Antidiuretic hormone
AER	Albumin excretion rate
A/G	Albumin/Globulins
dL	Decilitre
D.M.	Diabetes mellitus
GBM	Glomerular basement membrane
GD	Gestational Diabetes
GFR	Glomerular filtration rate
Hb	Hemoglobin
HLA	Human leucocytic antigen
ICA	Islet cell antibody
IDD	Insulin dependent diabetics
Ig	Immunoglobulin
IGT	Impaired glucose tolerance
L	Litre
min.	Minute
MR	Mesangial regions
MW	Molecular weight
N	Normality
NC	Normal controls
ND	Not detected
NIDD	Non-insulin-dependent diabetics
NP	Normal pregnants
OHA	Oral hyperglycemic agent
P	Probability value
PD	Pregnant diabetics
SD	Standard deviation
SE	Standard error
TBG	Thyroid binding globulin
WHO	World health organisation.
y	Year.

CONTENTS

1.INTRODUCTION
&
AIM OF THE WORK

INTRODUCTION

In humans, there are 2 kidneys located in the retroperitoneal space. Each kidney is about 12 cm in length and weighs about 150 g. The functional unit of the kidney is the nephron. There are about one million nephrons in each kidney, each consists of a glomerulus and a urinary tubule divided into several segments; the proximal convoluted tubule, the descending and ascending limbs of the loop of Henle, the distal convoluted tubule and the collecting tubule of Bellini ***(Tietz, 1987).***

Functions of the kidney

The main function of the kidney is to keep the volume and composition of extracellular fluid within normal limits. This is achieved through a balance between glomerular filtration and tubular reabsorption or excretion. The hydrostatic pressure imported to the blood by the heart forces the protein free filtrate of plasma through the walls of the glomerular capillaries. Electrostatic factors also serve to retard the filtration of plasma proteins, especially albumin ***(Harris, 1987).***

1. Excretory function: the function of the tubules is to modify the glomerular filtrate by excretion of the waste products, such as urea, retention and reabsorption of necessary materials, such as water, glucose and some electrolytes, as well as the addition of substances by a process of secretion, such as renin, erythropoietin and vitamin D. These secreted substances are

important to the metabolism of other body tissues. During the passage through the loop of Henle, further diminution in the volume occurs. The final adjustment occurs in the distal tubules and particularly in the collecting ducts where water is reabsorbed in the presence of antidiuretic hormone (ADH), secreted by the anterior labe of the pituitary gland to produce a concentrated urine of about 1.5 litres daily.

2. Regulatory function: The kidney plays a major role in homeostasis. Some substances are reabsorbed from the tubular lumen and others are secreted into it by the tubular cells.

3. Renal regulation of acid-base and water balance:

If cells are to function normally, the pH of the extracellular fluid must be maintained beween 7.35 and 7.45. About one hundred and seventy litres of water are filtered daily but only 1.5 litres of urine are produced in 24 hours. Over 168 litres of water are reabsorbed by the renal tubules. The proximal convoluted tubule is freely permeable to water, no osmotic gradient between it and the blood perfusing the renal cortex can be maintained. The reabsorption of 70% of the filtered sodium results in the diffusion of 70% of the filtered water out of the tubular lumen. Sodium is freely filtered at the glomeruli and reabsorbed by the tubules. About 99% or more of the filtered load of sodium is reabsorbed. Potassium is freely filtered at the glomeruli. Normally about 5% of the filtered load is

excreted. The active reabsorption of glucose, amino acids and other substances in the proximal tubule also contributes to water reabsorption ***(Andraoli et al., 1978).***

4. Endocrine function: The endocrine function of the kidney may be regarded either as primary, because the kidney is an endocrine organ producing hormones as prostaglandins, or as secondary, becasue the kidney is a site where some hormones produced elsewhere are activated. Also, the kidney is a site of degradation of insulin. The kidneys have an important role in vitamin D metabolism ***(Gowenlock et al., 1988).***

Plasma Proteins

There are different proteins in the human body, some soluble in fluids within or outside the cells and others insoluble. The soluble proteins of the extracellular fluids are easily available for investigation. The plasma proteins move between the blood and other extracellular fluids by active transport, as well as by passive diffusion. When cells are damaged, soluble proteins normally in cells or on their surfaces may also be presented in extracellular fluid. All plasma proteins are synthesized by the liver except γ globulins. Most of the proteins of urine and spinal fluid are derived from plasma ***(Tietz, 1987).***

The proteins of the plasma are actually a very complex mixture which includes not only simple proteins but also mixed

or conjugated proteins, such as glycoproteins and various types of lipoproteins. The serum proteins include albumin, globulins and fibrinogen. Fibrinogen is mostly removed in the clotting process in serum preparation. Plasma proteins are separated and estimated by electrophoresis into five major fractions; albumin (42 to 58%), α_1-globulins (2.5-7%), α_2 globulins (7-13%), β-globulins (8-14%) and γ-globulins (12-22%), while the total plasma protein concentration in humans ranges from 6.4-8.3 gldl ***(Ritzmann and Finney, 1983).*** The concentration of total plasma proteins may vary because of changes in the volume of plasma water or changes in the amounts of individual proteins. Decrease in the volume of plasma water (hemoconcentration) causes the concentration of all proteins to be increased to the same degree. This hyperproteinemia is seen in dehydration as in severe vomiting. Addison's disease, or diabetic acidosis.

Increase in the volume of plasma water (hemodilution), on the other hand, causes a decrease in the concentrations of all proteins. This hypoproteinuria occurs in water intoxication or salt retention syndromes, during massive intravenous infusions, and physiologically when a person is recumbent. A recumbent position decreases the total proteins concentration by 0.3-0.5 g/dl. ***(Whicher, 1983).***

Albumin

Albumin which is the most abundant protein in the human

plasma (3.2-5.5 g/dl), is synthesized mainly in the liver. Albumin molecule contains no carbohydrate and is not stored in parenchymal cells. Little albumin is filtered through the kidney glomeruli, and most of that is reabsorbed by the proximal tubule cells and degraded by their lysosomal enzymes into fragments that are returned to the circulation. Albumin has a molecular weight of 66,000 daltons; this relatively small size makes it a useful indicator of the integrity of glomerular and other membranes. Albumin is an anion at pH 7.4. Albumin chief biological functions are to transport and store a wide variety of ligands, to maintain the plasma oncotic pressure and to serve as a source of endogenous amino acids.

Albumin forms such a large proportion of the total proteins that low serum albumin levels (hypoalbuminemia) often causes hypoproteinemia. Hypoalbuminemia is very common in many diseases and results from one or more of the following factors: 1- increased catabolism; 2 - reduced absorption of amino acids; 3 - impaired synthesis; 4 - protein loss due to nephrotic syndrome, chromic glomerulonephritis or diabetes. When plasma albumin level is below 2.5 g/dl, the low plasma oncotic pressure allows water to move out of the blood capillaries into the tissues causing edema. Hyperalbuminemia is of little diagnostic significance except in dehydration.

The albumin region obtained by electrophoresis at pH 8.6, includes glycoproteins and mucopolysaccharides, in addition to

albumin. Congenital absence of albumin, analbuminemia, is asymptomatic except for occasional slight edema ***(Laurell, 1985).***

Globulins

Globulins consist of α_1-, α_2-, β- and γ-fractions.

Alpha$_1$ Globulins: α_1-globulins comprise several protein fractions which are α_1-antitrypsin, α_1-lipoprotein, α_1-glycoprotein, α_1-fetoprotein, prothrombin and thyroid-binding glubulin (TBG).

Alpha$_1$ antitrypsin is an acute phase reactant and its deficiency is associated with lung and liver diseases ***(Johnson, 1983)***. Alpha$_1$ fetoprotein is the principal fetal protein ***(Tietz, 1983).***

Alpha$_2$ Globulins: α_2 globulins comprise many protein fractions which are α_2-macroglobulin, haptoglobin, ceruloplasmin, α_2 lipoproteins and erythropoietin. Haptoglobin binds free hemoglobin in serum and is an acute phase reactant ***(Davides, 1975).***

Beta Globulins: β-globulins comprise many protein fractions such as transferrin and β-lipoprotein.

Transferrin (siderophilin) is the principal plasma protein for transport of iron. Transferrin has a molecular weight of

77.000. Its concentration in adult serum ranges from 0.2-0.4 g/dl. Plasma levels of transferrin are regulated by availability of iron, since in iron deficiency states plasma levels rise and, upon successful treatment with iron, return to normal levels.

Transferrin is synthesized in the liver and to a smaller extent in the reticuloendothelial system and also in the endocrine glands, such as testes and ovaries. Transferrin is a negative acute phase reactant, and low levels will occur along with low levels of albumin, prealbumin, and β-lipoprotein, in inflammation or malignancy. Other causes of low plasma levels are chronic liver diseases, malnutrition and protein loss, as in the nephrotic syndrome. High levels of transferrin occur in iron deficiency, pregnancy and during estrogen administration ***(Collins, 1982).***

β_2-microglobulin has a molecular weight of 11,800. Its concentration in adult serum ranges from 0.1 to 0.2 mg/dl. The small size of the β_2-microglobulin allows its passage through the glomerular membrane but most of it is reabsorbed. High plasma levels occur in renal failure, inflammation, and neoplams, especially those associated with β-lymphocytes. The level of β_2-microglobulin is useful to test the renal tubular function, particulary in kidney transplant patients ***(Woo et al., 1981).***

Gamma Globulins:

Electrophoretic gamma region contains most of the