VALUE OF URINARY INTESTINAL ALKALINE PHOSPHATASE AS A SPECIFIC PROXIMAL TUBULAR MARKER IN DIABETIC NEPHROPATHY

THESIS
SUBMITTED FOR PARTIAL FULFILMENT OF
M.S. Degree in
CLINICAL AND CHEMICAL PATHOLOGY
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بسم الله الرحمن الرحيم

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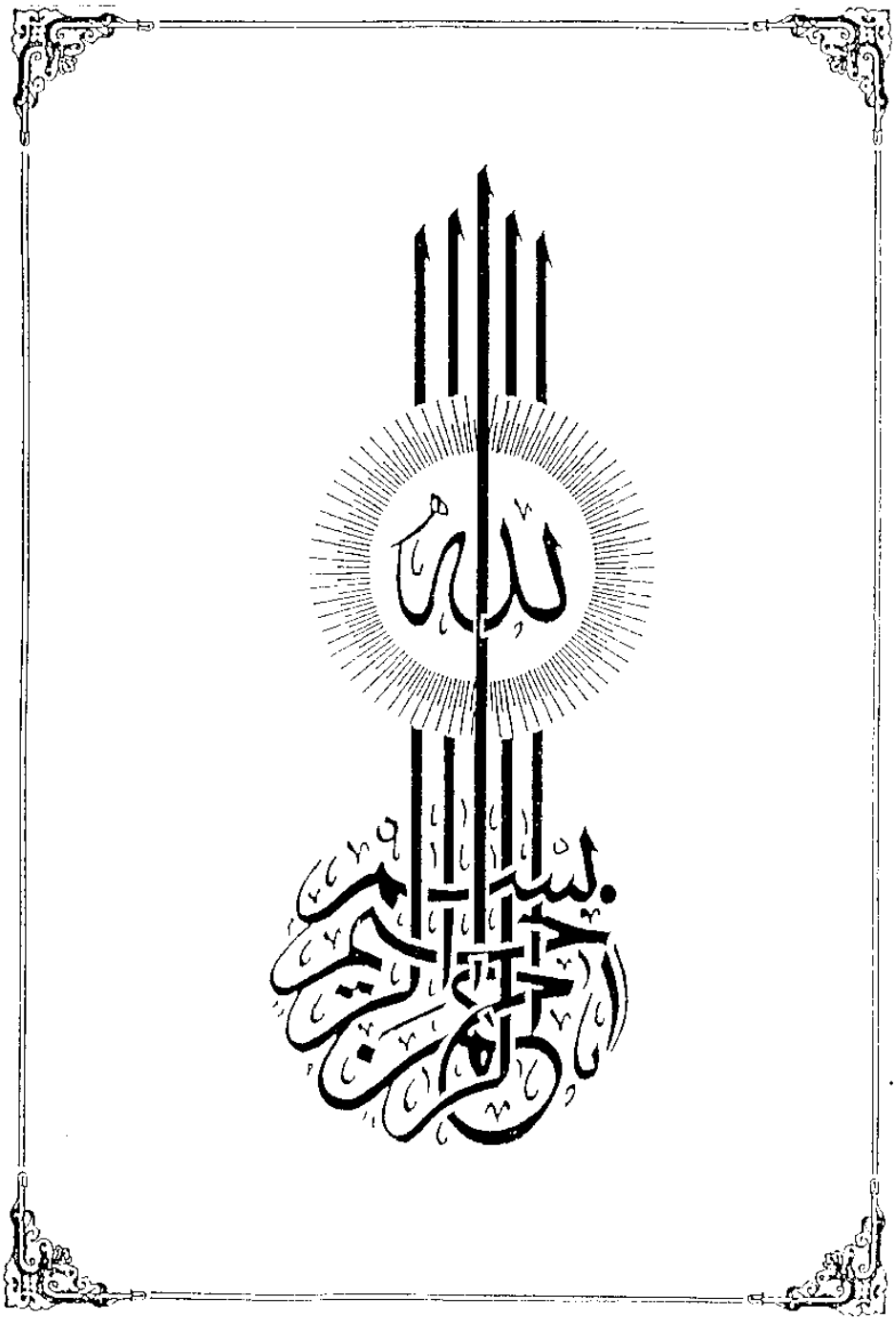

ACKNOWLEDGMENT

Thanks to **GOD** who have lightened my path to become a homble student of a nobel profession and granted me the ability to accomplish this work.

Words can never express my hearty thanks and indebtedness to **Prof. Dr. Laila Mohamed Abou El Magd, Prof. of Clinical and Chemical Pathology, Ain Shams University** for her generous advice, continuous encouragement and faithfully motherly guidance.

My deepest appreciation and sincerest gratitude to **Ass. Prof. Dr. Nasser Sadek Rez, Ass. Prof. of Clinical and Chemical Pathology, Ain Shams University**. His wise supervision gave me invaluable opportunity to benefit from his faithful guidance and constant support.

My sincere gratitude goes to **Dr. Aziza Ahmed El Sebai, Lecturer of Clinical and Chemical Pathology, Ain Shams University** for her great help, continuous guidance and for offering me much of her time and effort. Her extreme patience, careful supervision and precise advice are more than I can express.

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LIST OF ABBREVIATIONS

α1-M:	Alpha 1 microglobulin
ALP:	Alkaline phosphatase
DKA:	Diabetic ketoacidosis
DOPA:	DL-3,4-dihydroxyphenyl alanine
EAIA:	Enzyme antigen immunoassay
EIA:	Enzyme immunoassay
ELISA:	Enzyme linked immunosorbent assay
FIA:	Fluorescent immunoassay
HPLC:	High performance liquid chromatography
IAP:	Intestinal alkaline phosphatase
IDDM:	Insulin dependent diabetes mellitus
IGT:	Impaired glucose tolerance
LMW:	Low molecular weight
NAG:	N-acetyl ß-glucosaminidase
NIDDM:	Non-insulin dependent diabetes mellitus
RBP:	Retinol binding protein
RIA:	Radioimmunoassay
RID:	Radial immunodiffusion
ß2-M:	Beta 2 microglobulin
SRID:	Single radial immunodiffusion
ZIA:	Zone immunoelectrophoresis assay

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Introduction

The early detection and prediction of diabetic nephropathy is important not only from a scientific point of view but also in light of possibility of retarding the devlopment of overt diabetic nephropathy through adaptation of insulin treatment, low protein diet, antihypertensive treatment and modulation of intraglomerular pressure ***(Mogensen, 1987 and Bakris, 1993)***.

Microalbuminuria has been proposed as a predictive marker of diabetic nephropathy. However, the methodology is complicated and several other clinical conditions such as congestive heart failure urinary tract infections may influence microalbuminuria ***(Breyer, 1992)***.

Thus, prerequisties for an ideal marker proposed by ***Verpooten et al. (1992)*** should include renal cellular localization, tubular segment specificity and an easy, precise and stable assay system.

Recently, it was demonstrated morphologically, biochemically with the use of monoclonal anibody technology that human intestinal alkaline phosphatase IAP is exclusively present in brush border of cells lining of S3 segment pars recta of human proximal tubule. Accordingly, IAP will form an ideal and promising marker ***(Nuyts et al., 1994)***.

Aim of he work:

In the present work, we aim to study the value of urinary intestinal alkaline phosphatase as a unique early renal tubular marker, specific for certain anatomic site of the nephron S3 segment.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus is a heterogenous primary disorder of carbohydrate metabolism with multiple etiological factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. All causes of diabetes ultimately lead to hyperglycemia which is the hallmark of this disease syndrome ***(Olefsky, 1993)***.

A. Classification and clinical presentation:

Diabetes mellitus is classified into the following types:

1. Insulin dependent or type I diabetes (IDDM), formerly called juvenile onset or ketosis prone diabetes. Patients with IDDM have little or no endogenous insulin and usually present with relatively abrupt clinical symptoms of polyuria, polydipsia and polyphagia. Weight loss, fatigue and infection can often accompany the initial presentation ***(Ziegler et al., 1990)***.

In some cases, detection of this preclinical state may be possible by assessing the presence of circulating antibodies to islets cells or insulin ***(Rawley et al., 1992)***.

2. Non-Insulin dependent or type II diabetes (NIDDM), formerly called adult onset, maturity onset or non-ketotic diabetes. Patients with NIDDM typically present with polyuria and polydipsia of several weeks to months duration. Polyphagia can occur but is less common whereas weight loss, weakness and fatigue are frequent. Dizziness, headache and blurry vision are common accompanying complaints. In many patients, no symptoms are apparent and the disease is diagnosed by routine blood or urine testing ***(Molina and Olefsky, 1990)***.

3. Secondary diseases:

Any disease process that limit insulin secretion or impairs insulin action can cause secondary diabetes ***(Ziegler et al., 1990)***. The following are common causes in this group:

a. Pancreatic disease such as pancreatectomy, pancreatic insufficiency and hemochromatosis.

b. Excess counter insulin-hormones as in Cushing syndrome, acromegaly and pheochromocytoma.

c. Drug-induced hyperglycemia such as thiazide diuretics and steroids.

d. Hyperglycemia associated with genetic syndromes such as lipodystrophy, myotonic dystrophy and ataxia-telangiectasia ***(Olefsky, 1993)***.

4. Impaired glucose tolerance (IGT):

This presentation was formerly called chemical, latent, borderline, or subclinical diabetes. Persons with IGT are also at greater risk of developing early cardiovascular diseases ***(Zimmet and Kelly, 1992)***.

5. Gestational diabetes:

This group include glucose intolerance with onset during pregnancy ***(Zimmet and Kelly, 1992)***.

B. Metabolic complications:

1. Diabetic ketoacidosis (DKA):

DKA can be life threatening situation, and the clinical presentation is often dramatic. An antecedent history of polyuria and polydipsia for one to several days is typically and nausea, vomiting and anorexia are frequent accompanying symptoms. Clinical findings include tachypnea, dehydration and disorientation, or even coma. Precipitating causes of DKA include failure of the patient to take

insulin, infection, intercurrent illness, trauma or emotional stress. Although the diagnosis can be strongly suspected on a clinical basis, confirmation is based on laboratory analysis. The diagnosis is made by demonstrating hyperglycemia (350-700 mg/dl) and ketonemia in the presence of acidosis ***(Kreisberg, 1990)***.

2. Non-ketotic hyperosmolal syndrome:

This syndrome comprises a spectrum ranging from mild dogree of hyperosmolality with minimal CNS symptoms to severe hyperosmolality with accompanying coma ***(McGarry and Foster, 1980)***. The biochemical hallmarks are extreme hyperglycemia (600-2400 mg/dl) in the absence of overt ketoacidosis. Dehydration, and disorientation are accompanying features ***(McGarry and Foster, 1980)***.

3. Hypoglycemia:

Hypoglycemia may follow accidental insulin overdosage or may be due to changing requirements or to failure to eat after insulin has been given. The level of plasma glucose is usually less than 45 mg/dl. The patient manifested by faintness, dizziness or lethargy may progress rapidly to coma. If untreated, permanent cerebral damage or death may result ***(Raskin et al., 1987)***.

Vascular complications:

The epidemiology and risk factors for microvascular and macrovascular complications in diabetes are quite different ***(Zimmet and Kelly, 1992)***. Duration and degree of hyperglycemia have been consistently shown to be the major risk factors for microvascular complications ***(Zimmet and Kelly, 1992)***. On the other hand, several metabolic abnormalities including hyperinsulinemia and other risk factors such as excessive alcohol consumption, cigarette smoking and physical inactivity contribute to the risk of

macrovascular complications. It was found that the commonest cause of mortality in NIDDM is cardiovascular disease ***(Zimmet, 1989 and Zimmet and Kelly, 1992)***.

I. Macrovascular complications:

Arteriosclerosis of the type seen in non-diabetic occurs more extensively in the diabetic patients than in the general population ***(Brownlee et al., 1988)***. Atherosclerosis may produce symptoms in a variety of sites, such as intermittent claudication, gangrene and coronary artery disease ***(Brownlee et al., 1988)***.

II. Microvascular complications:

A. Hematological abnormalities:

It was been suggested that relative tissue hypoxia may play a role in the pathogenesis of certain diabetic complications ***(Ditzel and Standl, 1985)***.

Several haematological abnormalities are associated with diabetes ***(Brownlee, 1985)***. White blood cell changes include decreased chemotaxis, diapedesis, phagocytosis and bactericidal activity. Red cell abnormalities include increased aggregation and decreased oxygen hemoglobin dissociation curve. Platelets were reported to have increased aggregation, adhesion and prostaglandin (PGE2).

B. Microangiopathy:

Microangiopathy occurs due to metabolic derangement of diabetes mellitus. It could affect the vessels of the kidneys, eyes and nervous system ***(Drury, 1986)***.

The poorer glycemic control and the longer the diabetic duration, the more complication the diabetic patients had such as retinopathy, neuropathy and nephropathy ***(Tai-Ty et al., 1991)***.