ROLE OF MACROPHAGES IN DIABETIC NEPHROPATHY HISTOPATHOLOGIAL AND IMMUNOCHEMICAL
Study

Thesis
Submitted for partial fulfillment of master deree (M.Se.)
In pathology

By
Dalia nabil abdel hafez mostafa
M.B.B.CH.

Supervised by

Prof. dr. sawsan abdel moneim fadda
Professor of pathology
Faculty of medicine
Cairo university

Dr. mostafa Mohamed samy salem
Ass. Professor of pathology
Faculty of medicine
Cairo university

Dr. hana hassan Mohamed
Lecturer of pathology
Faculty of medicine
Cairo university

2009

Acknowledgement

First of all, I would like to thank ***GOD*** who helped me to accomplish this work and all my family for their great support.

Then, I sincerely thank Prof.Dr. Sawsan Fadda, professor of Pathology, faculty of medicine, Cairo University for giving me the chance to work honourably under her effective supervision and for her continuous support.

I am profoundly grateful to Prof. Dr. Mostafa Salem, assistentent

Abstract

Key words : diabetic nephropathy, role, macrophage, proteinuria

Background: Diabetic nephropathy is one of major causes of end stage renal disease. Although it is associated with interstitial and glomerular macrophage infiltrates, the actual role of macrophages in pathogenesis of diabetic nephropathy is still unclear.

Methods: This study analyzed the clinical, laboratory data and renal biopsies of diabetic patients. According to the biopsy findings, patients were categorized as, diabetic nephropathy group and other renal lesions in diabetic patients. Relations between macrophage numbers in renal tissue biopsies (detected by CD68 antibodies) and the predictors of disease progression (proteinuria, tubular atrophy and interstitial fibrosis) was estimated.

Results: Accumulation of macrophages was apparent in the glomeruli (3.3±1.5/gcs) and in the interstitium (262.3±67.5/mm^2) in 30 diabetic nephropathy patients. The number of macrophages was significantly related to both tubular atrophy and interstitial fibrosis with p=0.005 and 0.006 respectively.

Conclusion: In diabetic nephropathy, macrophages recruit within glomeruli and interstitium and the intensity of macrophage infiltrate is proportional to the degree of nephropathy. These human data support the animal studies that suggest a pathogenic role for macrophages in diabetic nephropathy.

CONTENTS

LIST Of TABLES

LIST OF FIGURES

INTRODUCTION

Diabetic nephropathy is one of the most frequent and clinically important complications of diabetes, it affects approximately 40% of patients who have diabetes mellitus for more than 20 years ***(Gross et al., 2005).***

The global epidemic and the prevalence of diabetic nephropathy and end- stage renal failure due to diabetes is increasing at a disturbing rate. From 25% to 50% of patients with diabetes will develop nephropathy and of these significant proportion will progress to renal failure. ***(Ritz et al., 1999) .***

In Egypt the estimated prevalence of end stage renal disease (ESRD) was increased from 225 per million population in 1996 to 375 per million in 2001 ***(Afifi, 2003).***

Despite several advances, pathogenesis of diabetic nephropathy remains far from clear ***(Raptis, 2001)***. In experimental diabetic nephropathy, macrophages accumulate within renal tissue at an early stage ***(Prigent et al, 2000)***. Also, both metabolic and hemodynamic events are interwoven together in the pathogenesis of diabetic nephropathy ***(Kanwar et al., 2008)***.

Macrophages-depletion studies in rodent models have demonstrated a causal role for macrophages in development of diabetic complications. In diabetes, the high glucose, advanced glycation end–products and oxidized low-density lipoproteins promote macrophage accumulation via induction of chemokines, adhesion molecules, and macrophage activation. Macrophages mediate diabetic injury through a variety of mechanisms including production of reactive oxygen species, cytokines and proteases, which result in tissue damage leading to sclerosis ***(Tesch , 2007).***

AIM OF THE WORK

This study was designed to investigate the relationship between the number of glomerular and interstitial macrophages, and progression of diabetic nephropathy.

It also aim to correlate the macrophage number with different renal histopathological changes and with known clinical predictors of disease progression.

HISTOLOGY OF THE KIDNEY

The human kidney consists of about million elongated structural & functional units, known as nephrons. Each nephrons consists of a glomerulus or a renal corpuscle and the uriniferous tubules ***(Kaissling & Kriz , 1998).***

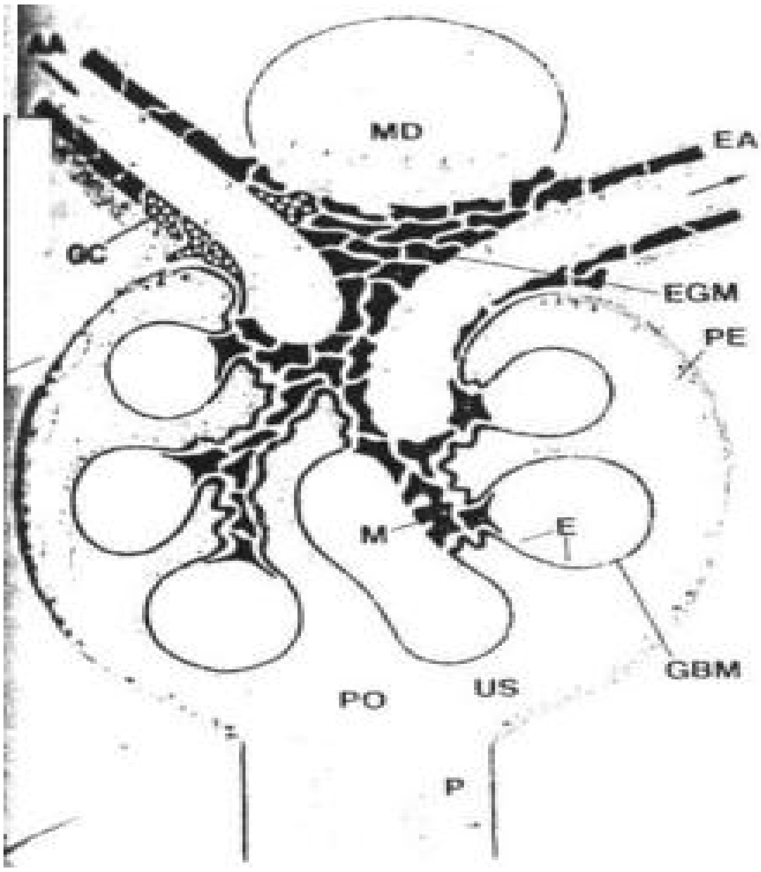
There are two types of nephrons according to the level of the cortex at which they orginate , that is, the cortical level, where the parent glomeruli are situated. These types are : *superficial;* when they are located within few millimeters deep to the cortical surface & *juxtamedullary;* when they are situated immediately above the corticomedullary junction (***Kriz & Kassling ,1992).***

Structure of the glomerulus:

The renal corpuscle (Fig.1) is formed of capillary network lined by a thin layer of endothelial cells, a central region of mesangial cells with surrounding mesangial matrix material, the visceral and the parietal layer of Bowman's capsule (which forms a pouchlike structure within which glomerular capillary tuft is located) and its associated basement membrane ***(Tisher and Brenner, 1994).***

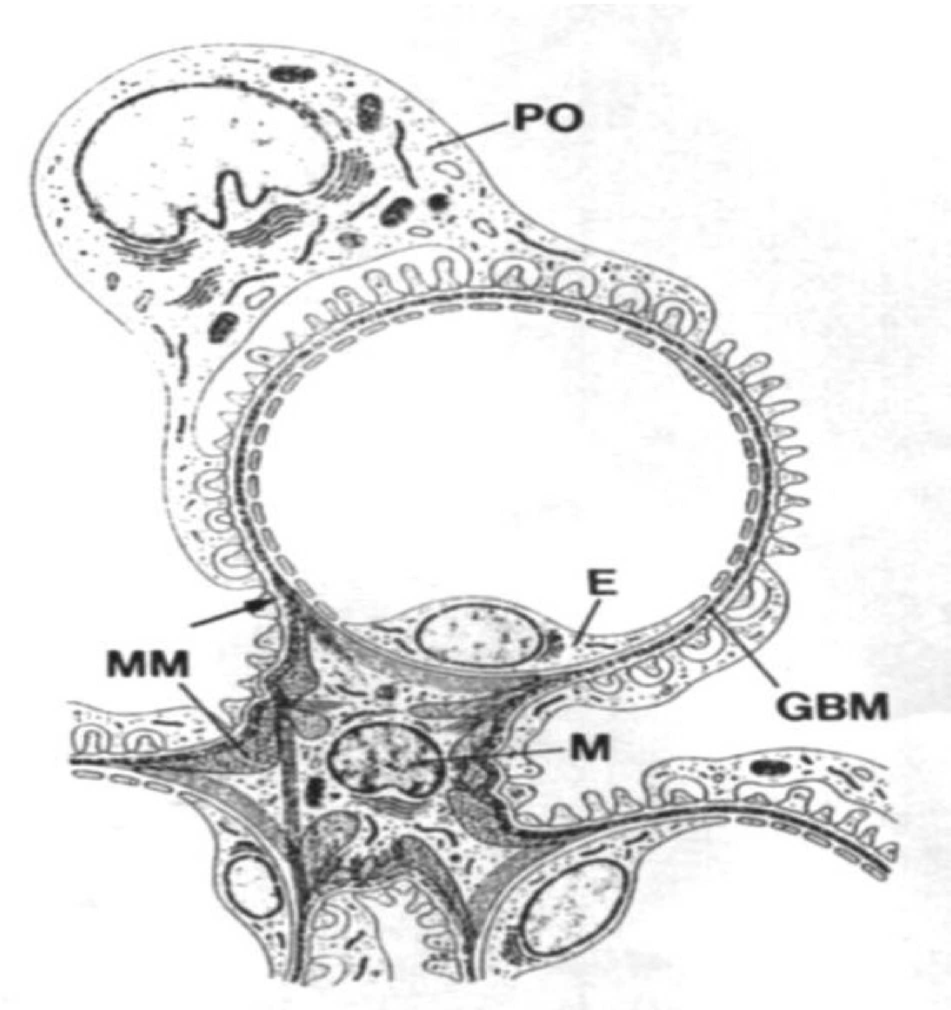
The filtration barrier between the blood and urinary space is composed of a fenestrated endothelium, the peripheral glomerular basement membrane and the slit pores between the foot processes of the visceral epithelial cells ***(osterby, 1980).***

***Fig. (1):**



Schematic diagram of a longitudinal section , through a glomerulus and the juxtaglomerular apparatus. At the vascular pole, an afferent arleriole (AA) enters and an efferent arteriole (EA) leaves the tuft. The glomerular capillary tuft is surrounded by Bowman's capsule. There are different epithelia. One is the visceral epithelium (podocyles; PO), which, at the vascular pole reflects onto Bowman's capsule at the parietal epithelium (PE). Between both epithelia lies the urinary space (US), which is continuous with the lumen of proximal tubule (P). The endothelium (E) of glomerular capillaries is fenestrated. Between the endothelial cells and the podocytes, the glomerular basement membrane (GBM) is found. At the vascular pole, the GBM continues as the basement membrane of Bowman's capsule. Mesangial cells (MC) situated in the axis of glomerular lobules. At the vascular pole, mesangial cells are continuous with extraglomerular mesangial cells (EGM); together with the granular cells (GC) and the macula densa (MD), they make up the JGA. (***Modified from Kriz W, et al: Morphological aspects of glomemlar function, In Davison MA, ed. Nephrology. London' Baillere Tindall, |D(6. p. 2. With permission***)

***Fig. (2):**



Schematic diagram shows the arrangement of structures in the glomerular tuft. Part of a glomerular lobule is shown, with three glomerular capillaries (two are incomplete) attached to a mesangtal center. The glomerular capillary endothelium (E) is fenestraled. The peripheral part of the endothelial tube is surrounded by the GBM, which deviates from a pericapillary course and covers the mesangium. Interdigitating foot processes of Ihe podocyte (PO) form the external layer of the filtration barrier. Podocyte foot processes are also found covering the para mesangial GBM. In Ihe center, a mesangial cell (M) is shown. US many processes contain microfilamental bundles and run toward the GBM, to which the processes are connected. The mesangial matrix (MM) contains an interwoven network of microfilaments***. (Modified from Kriz W: Die Harn-abfeilenden Organe. In FleischhauerK, ed. Benninghoff-Mak-roskopische und Mikroskopische Artatomie des Menschen, Bd 2: Kreislauf und Eingeweide. Miinchen: Urban S Schwa-rzenberg, 1985, p. 413. Wilh permission.)***