شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

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HANAA ALY

A Study of the Protective Role versus the Curative Role of Pentoxifylline on Experimentally Induced Diabetic Nephropathy in a Rat Model

Thesis

Submitted for Partial Fulfillment of

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By

Hanan Mohammed El Sayed Tarabeh

Assistant lecturer of Anatomy and Embryology

Faculty of Medicine, Helwan University

Supervisors

Prof. Dr. Shahira Youssef Mikhail

Professor of Anatomy and Embryology

Faculty of Medicine, Ain Shams University

Prof. Dr. Soheir Ibrahim Saleh

Professor of Anatomy and Embryology

Faculty of Medicine, Ain Shams University

Prof. Dr. Eman Kamal Mohammed Habib

Professor of Anatomy and Embryology

Faculty of Medicine, Ain Shams University

Prof. Dr. Amany Helmy Mohamed

Professor of Pharmacology

Faculty of Medicine, Ain Shams University

Assist. Prof. Dr. Marwa Matboly Sayed

Assist. Professor of Biochemistry

Faculty of Medicine, Ain Shams University

Faculty of Medicine, Ain Shams University

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Hanan Mohammed El Sayed Tarabeh

Dedication

To the Memory of My Father I give thanks to my family my Mother who I can never do it without her support and caring every single moment, my Husband Abd Allah who I can't forget his effort and wishes for me to do it, my Daughter Farida, My son Fahd and my Sisters Om Zyad and Om Salma for all they have shared Every time they've cared all the love they gave and support they continually give.

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List of Abbreviations

Abb.	Full term
ACR	Albumin creatinine ratio
AGEs	Advanced Glycation End Products
DCT	Distal convoluted tubules
DKD	Diabetic kidney disease
DM	Diabetes Mellitus
DN	Diabetic nephropathy
EGF	epidermal growth factor
eGFR	Estimated glomerular filtration rate
ESKD	End stage kidney disease
FBG	Fasting blood glucose
GFB	Glomerular filtration barrier
Hb A1c	Haemoglobin A1c (glycated haemoglobin)
HIF-1α	Hypoxia-inducible factor 1-alpha
Hx&E	Hematoxylin And Eosin.
IGF-1	Insulin-like growth factor 1
IL1	Interleukin 1
IL6	Interleukin 6
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear Factor Kappa B
PCT	Proximal convoluted tubules
PDGF	Platelet Derived Growth Factor
PTX	Pentoxifylline
RAGE	Receptor advanced glycation endproducts.
RAS	Renin angiotensin system
RNS	Reactive nitrogen species
ROS	Reactive Oxygen Species
STZ	Streptozotocin
TGF-b	Transforming growth factor beta
TNF-α	Tumor Necrosis Factor Alpha
VEGF	Vascular endothelial growth factor

INTRODUCTION

Diabetes Mellitus (DM) is known to be one of the most serious diseases threatening the human health in the world. Unfortunately, according to the World Health Organization forecasts, the number of diabetic patients all over the world will reach up to 366 million in 2030 ***(Roessner et al., 2012).***

A high glucose level is responsible for the diabetes induced multisystem damages. As a result, long-lasting hyperglycemia causes cell damage via increased glucose oxidation, glycolysis, polyol pathway formation, glycation end product activation and alteration of nitric oxide (NO) production ***(Turgut and Bolton, 2010).***

Diabetic nephropathy (DN) in type 1 diabetic patients is the largest cause of chronic kidney disease in the working age group ***(Eboh and Chowdhury, 2015).*** It is defined as the chronic loss of kidney function occurring in those with diabetes mellitus. Protein loss in urine due to damage of the glomeruli may become massive, and causes a low serum albumin with resulting generalized body swelling (edema) that might leads to end-stage kidney disease ***(Longo et al., 2011).***

In DN, histopathological changes such as thickening in the glomerular and tubular basal membranes, glomerular and tubular hypertrophy, vacoulation, mesangial cell proliferation and increase of the mesangial matrix ***(Donder et al., 2013).***

Moreover, hyperglycemia can lead to endothelial dysfunction, which may result from decreased production of nitric oxide (NO) ***(Honing et al., 1998).*** Nitric oxide has been implicated in the pathogenesis of diabetic nephropathy ***(Sonmez et al., 2012).*** Nitric oxide plays numerous physiological functions including control of renal and glomerular hemodynamics by interfering at multiple and physiologically critical steps of nephron function and maintenance of medullary perfusion ***(Mount and Power, 2006; Zoccali, 2007).***

On the other hand, it is well known that inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumer necrosis factor- α (TNF- α) are involved in the development of diabetic nephropathy. Previous studies have demonstrated that mRNA expression for TNF- alpha increased significantly in kidneys from diabetic rats, as compared to those from normal animals ***(Navarro and Mora 2008).*** This cytokine is cytotoxic to the glomerular, mesangial and epithelial cells and may induce significant renal damage ***(Ortiz et al., 1995).***

Pentoxifylline (PTX), a nonspecific phosphodiesterase inhibitor, was first considered for use in the treatment of peripheral vascular diseases. It exerts several pharmacological effects, including improvement of microcirculation, reduction in blood viscosity, inhibition of platelets aggregation, endothelium-dependent vascular relaxation, immunomodulatory, anti-inflammatory, and anti-proliferative effects ***(Nasiri et al.,***

2013). In addition, it has been used as an antioxidant in order to heal damage in several tissues ***(Stojiljkovic et al., 2009).***

Pentoxifylline therapy reduced proteinuria and improved glucose control and insulin resistance ***(An et al., 2015).*** It competitively inhibits phosphodiesterase (PDE), resulting in increased intracellular cyclic AMP (cAMP), activation of protein kinase A (PKA), inhibition of interleukin (IL) and tumor necrosis factor (TNF) synthesis and reduced inflammation ***(Bhanot and Leehey, 2016).***

AIM OF THE WORK

The present study was designed to:

- Demonstrate the histopathological changes of the kidney following induction of diabetes mellitus.
- Demonstrate the possible protective effect of pentoxifylline on diabetic nephropathy.
- Demonstrate the possible curative effect of pentoxifylline on diabetic nephropathy.
- Compare the possible protective effect of pentoxifylline with its curative effect on diabetic nephropathy.
- Discuss the mechanism of action of Pentoxifylline.