شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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التأثير العلاجي المحتمل لحامض اورسوديوكسيكوليك مقارنة بالراميبريل في نموذج للجرذان المصابة باعتلال الكلى السكري

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٢٠٢١

Potential Therapeutic Effects of Ursodeoxycholic Acid in Comparison to Ramipril in a Rat model of Diabetic Nephropathy

Thesis

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List of Abbreviations

ACEIs	angiotensin converting enzyme inhibitors
AGEs	advanced glycation end products
ALP	Alkaline phosphatase
AMDCC	Animal Models of Diabetes Complications Consortium
ARBs	angiotensin receptor blockers
ATF6	activating transcription factor 6
ATP	Adenosine tri phosphate
CA	Cholic acid
CDCA	chenodeoxycholic acid
DCA	deoxycholic acid
DM	Diabetes millitus
DN	Diabetic nephropathy
ECM	Extra cellular matrix
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic Reticulum
ERAD	endoplasmic reticulum kinase - associated degradation
ESRD	End stage renal disease
FDA	Food and drug administration
FXR	farnesoid x receptor
GBM	Glomerular basement membrane
GFR	glomerular filtration rate
GLP-1	Glucagon like peptide-1
HbA1c	Hemoglobin A1C
HFD	High fat diet
IL-1b	interleukin 1b
IRE1	inositol requiring protein-1
LCA	lithocholic acid
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLD	Nonalcoholic fatty liver disease

List of Abbreviations (Cont.)

NASH	Non-alcoholic steato-hepatitis
OLETF	Otsuka Long-Evans Tokushima fatty
PBC	Primary biliary cholangitis
PERK	PKR-like endoplasmic reticulum kinase
RAAS	renin–angiotensin–aldosterone system
ROS	Reactive oxygen species
SHR	spontaneously hypertensive rats
STZ	Streptozotocin
TGF-B	transforming growth factor beta
TGR5	G protein coupled receptor 5
TNF	tumor necrosis factor
UDCA	Ursodeoxycholic acid
UPR	unfolded protein response
VEGF	vascular endothelial growth factor

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REVIEW OF LITERATURE

Diabetic nephropathy (DN) is a chronic progressive disorder that complicates a long standing diabetes mellitus (DM). DN is characterized clinically by microalbuminuria, followed by macroalbuminuria, increased blood pressure, and a decline in renal function, which ultimately leads to end-stage renal disease (ESRD). DN is the leading cause of chronic kidney disease and its prevalence has increased dramatically in the past few decades. This increase is primarily the result of a pandemic increase in DM **(Rossing and Frimodt-Moller. 2019)**

Diabetic nephropathy can occur in patients with type 1 DM or type 2 DM. In both forms of the disease, the common feature is chronic hyperglycaemia, leading to microvascular complications. In the pathophysiological relationship between diabetes and its complications, type 1 diabetes mainly involves glucose injury and the presence of diabetic nephropathy is associated with increased mortality risk, while non-nephropathic individuals have a more favorable life expectancy. Renal disease in type 2 diabetes is generally considered more heterogeneous, including factors other than glucose such as lipids, inflammation or blood pressure and is associated with increased cardiovascular mortality and morbidity **(Hadjadj et al, 2016).**

The clinical diagnosis of DN depends on the detection of microalbuminuria (urinary albumin > 30 mg/ day in 2 out of 3 urine samples collected within a six months period) that usually occurs after five years from the onset of the disease in type 2 DM. The development of microalbuminuria or macroalbuminuria is a hallmark of disease progression. Annually, about 3% of patients of type 2 DM with microalbuminuria progress to macroalbuminuria **(American Diabetes Association, 2011).**

The progression of diabetic nephropathy can be divided clinically into five stages; **the first stage** starts prior to any renal damage and is characterized by renal vasodilation and hyperfiltration that occur early in the onset of diabetes. It has also been associated with increased urinary albumin excretion related to physical activity. **In the second stage**, morphologic lesions develop without signs of clinical disease; the kidney with early diabetes starts to suffer significant hypertrophy and to show histological changes like glomerular basement membrane thickening and mesangial expansion. **The third stage** is named incipient nephropathy and is characterized by small amounts of albumin in the urine, microalbuminuria is considered to be predictive of progression to nephropathy in Type 2 DM. Overt nephropathy with macroalbuminuria (urinary albumin > 300 mg/day) characterizes **the fourth stage** that usually accompanies a decrease in glomerular filtration rate (GFR). Macroalbuminuria has been associated with

the presence of proliferative retinopathy, coronary heart disease, and foot ulcers. The prevalence of hypertension increases with higher levels of albuminuria. **The fifth and last stage** is the end-stage renal disease (ESRD) and defined by the presence of signs and symptoms of kidney failure requiring replacement therapy, regardless of the GFR level **(Suarez et al, 2013)**

Pathologically, the renal pathology society proposed a histologic classification system for diabetic nephropathy in 2010 that is used for both type 1 and type 2 DM and based on the severity of glomerular lesions, four classes were proposed: Class I, glomerular basement membrane thickening: isolated and only mild, Class II, mesangial matrix expansion, mild (IIa) or severe (IIb): glomeruli classified as mild or severe mesangial expansion in more than 50% of glomeruli. Class III, nodular sclerosis (Kimmelstiel–Wilson lesions): at least in one glomerulus. Class IV, advanced diabetic glomerulosclerosis: more than 50% global glomerulosclerosis **(Tavaert et al, 2010)**

In Type 2 DM, the severity of glomerular lesions, interstitial fibrosis and tubular damage are significantly associated with renal outcomes, independent of clinical features. Thus, usage of the pathologic classification as a predictive indicator for renal outcome in patients of type 2 DM with DN might be of value **(An et al, 2015).**

Dysregulation of the renin–angiotensin–aldosterone system (RAAS) has a critical role in the pathogenesis of diabetic nephropathy. Under physiological conditions, the prorenin is secreted by renal juxtaglomerular cells in response to decreases in circulating blood volume triggering the production of angiotensin II in the circulation and in the tissues **(Ruggenenti et al, 2010).** Angiotensin II is a pleiotropic hormone with several targets, including the kidneys, blood vessels, and nervous system. Pathological production of renin with continued RAAS activation constricts renal arterioles leading to increased peripheral and renal resistance, increases glomerular capillary pressure, augments oxidative stress via the NADPH oxidase pathways leading to glomerular endothelial dysfunction and stimulates profibrotic processes. The effects of RAAS activation on blood pressure seem to be mainly driven by systemically generated angiotensin II, whereas the specific effects on renal tissue seem to be caused by locally generated angiotensin II (**Siragy and Carey, 2010).**

Hemodynamic changes, associated with blood pressure changes both systemically and within the kidney, have been reported to occur early in type 2 diabetes giving rise to glomerular hyperfiltration, the major contributor to the damage of the glomerulus **(Gurley and Coffman. 2007**). These hemodynamic changes are considered to occur as a result of the metabolic milieu of diabetes that enhances up-regulation of both pro fibrotic growth