The Possible Protective Role of the High Dose Atorvastatin on Urografin Induced Nephropathy in Adult Male Albino Rat. Histomorphometric study

Thesis

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Contents

List of Abbreviations

ADH	**:**	Anti diuretic hormone
BUN	**:**	Blood urea nitrogen
CARE	**:**	Committee of Animal research ethics
CIN	**:**	Contrast induced nephropathy
CKD	**:**	Chronic kidney disease
CVD	**:**	Cardiovascular disease
DCT	**:**	Distal convoluted tubule
GBM	**:**	Glomerular basement membrane
HDL	**:**	High density lipoprotein
HMG-CoA	**:**	3-hydroxyl-3-methylglutaryl coenzyme
HOCM	**:**	High osmolar contrast media
Ig A	**:**	Immunoglobulin A.
PCT	**:**	Proximal convoluted tubule.
LDL	**:**	Low density lipoprotein
LOCM)	**:**	Low osmolar contrast media
NAC	**:**	N-acetylcysteine
NIH	**:**	National Institute of Health.

Introduction

Contrast medium induced nephropathy (CIN) is the third leading cause of hospital acquired acute renal failure. Till today, there is no universally accepted method for preventing contrast induced nephropathy, except for extracellular fluid expansion ***(Pannu et al., 2006; Zhang et al., 2017)***.

Contrast induced nephropathy (CIN) was defined as an acute deterioration of the renal function after contrast media administration in the absence of other causes. It involves an increase in serum creatinine concentration of 0.3-0.5 mg/dL, 25-50% or 44μmol/L above baseline, or oliguria < 0.5 mL/kg/h for more than six hours within 48 h after contrast administration without other reasons ***(Stacul et al., 2011; Zhang et al., 2017).***

The pathophysiology of CIN is not well known. Some studies have suggested a toxic effect of the contrast medium on the renal tubules ***(Seeliger et al., 2012; Zhang et al., 2017).*** In addition to its direct injury to renal tubular epithelial cells, contrast medium can be taken up into the cells and impair mitochondrial function resulting in increased generation of reactive oxygen species with

resultant cell apoptosis ***(Tumlin et al., 2006; Sendeski, 2011; Zhang et al., 2017).***

Contrast medium-induced nephropathy in animal models is thought to be due to the effects of contrast media on the action of many substances, including dopamine-1, adenosine, angiotensin II (Ang. II), nitric oxide, and endothelin ***(Rosenstock et al., 2008)***.

Statins are widely used drugs due to their cholesterol-lowering effect and cholesterol-independent effects, such as improving endothelial function as well as decreasing oxidative stress and inflammation ***(Taylor et al., 2013).*** Statins were reported to protect the kidney against experimental nephritis and IgA nephropathy in clinical practice through restoring the balance between proliferation and apoptosis in different types of renal cells ***(Buemi et al., 2002)***.

Blum and Shamburek (2009) and Babelova et al. (2013) mentioned that statins have also a pleotropic effect which include:

1- Increases in endothelial nitric oxide formation.
2- Vasodilatation.
3- Suppression of inflammation.

4- Reduction of inflammatory biomarkers (such as C-reactive protein).
5- Reduction in T-cell activation and reduction of cytokines.
6- Neovascularization induction in ischemic tissue.
7- Thrombosis and coagulation improvement.

On the basis of the chemical and pharmacologic properties, radiographic contrast agents can be classified into ionic or nonionic. These can have either a high osmolality or low osmolality. Urografin dye (Diatrizoate) is considered a high-osmolality contrast agent and is widely used in Egypt due to its low cost compared with ultravist (iopromide) which is expensive and not popular in Egypt. The osmolarity of the contrast media plays an important role concerning kidney damage. The use of low osmolarity contrast media substantially reduces the risk of nephropathy in high-risk patients compared with the use of high osmolarity contrast media ***(Mruk, 2016).***

Some researches focused on the protective role of many substances like beta-blockers and others against contrast induced kidney damage. However, reviewing the literature there have been few studies investigating the possible protective effect of high dose atorvastatin on high osmolality contrast media (urografin) induced nephropathy.

Aim of the work

The aim of the present work was to study the possible protective role of high dose atorvastatin on urografin induced nephropathy in male albino rats.

Specific objectives:

1-Detection of histopathological characteristic findings related to nephropathy before and after treatment.

2-Biochemical study for kidney function before and after treatment.

3-Serum inflammatory marker measurement before and after treatment.

4-Histomrphometric measurements of renal structures before and after treatment.

Anatomy of the Kidney

The kidneys are paired bean shaped retroperitoneal organs situated on the posterior abdominal wall on each side of the vertebral column. In humans, they extend from the twelfth thoracic vertebra to the third lumbar vertebra. The right kidney is usually slightly more caudal in position. The weight of each kidney ranges from 125 - 170 gm in the adult male. The human kidney is approximately 11 - 12 cm in length, 5 - 7 cm in width, and 2.5 -3 cm in thickness ***(Verland, 1998; Standring, 2015).***

In rat, the mean weight of the kidneys ranges from 0.96-1.1 gm. Their average dimensions are; 1.23-1.28 cm in length, 0.85-0.88 cm in width, and 0.79-0.81 cm in thickness ***(El Gammal et al., 2010).***

In both human and rat, through the hilum, the renal pelvis, renal artery, vein, lymphatics, and nerve plexus pass into the sinus of the kidney. The kidney is surrounded by a tough fibrous capsule, peri-renal fat, renal fascia and para-renal fat ***(Wein et al., 2007; Standring, 2015; Skorecki et al., 2016)***.

On the cut surface of a bisected rat kidney two regions can be identified: a pale outer region, the cortex, and a darker inner region, the medulla. The same histology was in human ***(Al Samawy, 2012).***

In humans, the medulla is divided into 8 to 18 renal pyramids. The base of each pyramid is positioned at the cortico-medullary boundary, and the apex extends toward the renal pelvis to form a papilla. On the tip of each papilla are 10 to 25 small openings that represent the distal ends of the collecting ducts (of Bellini) ***(Standring, 2015).***

The rat kidney resembles human kidney in gross appearance but, the rat kidney has a single renal pyramid (uni-papillate) with only one calyx and specializied fornices which are long evaginations of the renal pelvis ***(Pannabecker et al., 2004; Kiss and Hamar, 2016*** **(Fig. 1)*; Skorecki et al., 2016)***.

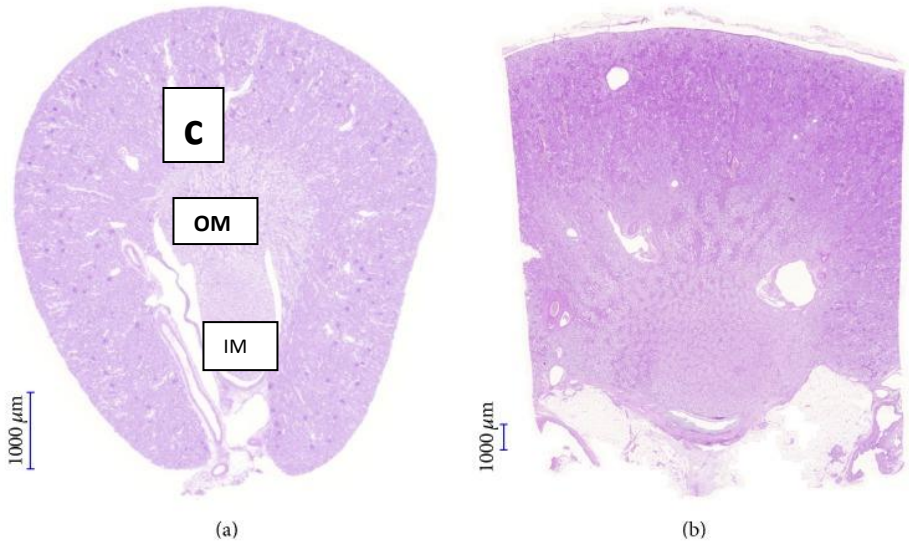

Fig. (1): (a) Unipapillate rat kidney showing cortex **(C),** outer medulla (OM) and inner medulla (IM) versus **(b)** the multi-papillate human kidney ***(Kiss and Hamar, 2016)***.

The renal pelvis is lined by transitional epithelium and represents the expanded portion of the upper urinary tract. In humans, two or three major calyces, extend outward from the upper dilated end of the renal pelvis. From each major calyx, several minor calyces extend toward the papillae of the pyramids to drain the urine formed by each pyramidal unit ***(Standring, 2015)***.

In rat, the papilla is surrounded by the renal pelvis. At the uretero-pelvic junction, the ureters originate from the lower portion of the renal pelvis ***(Skorecki et al., 2016).***

Blood supply

In humans, the blood supply to the kidneys arises from the paired renal arteries at the level of L2. They enter into the renal hilum. The renal artery divides into an anterior and a posterior division, and these divide into 4-5 segmental arteries. Three segmental or lobar arteries arise from the anterior branch and supply the upper, middle, and lower thirds of the anterior surface of the kidney. The posterior branch supplies more than half of the posterior surface and occasionally gives rise to a small apical segmental branch. The segmental arteries branch into interlobar arteries, which travel in a parallel way between the major calyces and then branch into arcuate arteries that run within the cortex across the bases of the renal pyramids. They then radiate into interlobular arteries, which extend into the cortex of the kidney to finally become afferent arterioles, then peritubular capillaries then efferent arterioles ***(Standring, 2015).***

In rats, the right and left renal arteries emerge from the abdominal aorta. They divide into dorsal and ventral primary divisions. The dorsal and ventral branches are divided into two branches, the cranial and caudal secondary branches (segmental arteries). Segmental arteries give off

5-7 inter lobar arteries which give off arcuate arteries. The interlobular arteries arise from arcuate arteries. No significant anastomosis exists between any of the sub branches of the renal arteries ***(Yoldas and Dayan, 2014).***