Research Article

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Study the Histopathological Effects of Sildenafil Treatment on the Kidney of Adult Male Rats

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Abstract

The present study was aimed to detection the histopathological changes on the kidney of male rats treated with sildenafil drug. In this study, 40 adult male rats were used. These rats divided into four equal groups, each group involved ten rats, group I receive normal saline (1ml/Kg) as control group (N= 10). Group II, III and group IIII was received sildenafil orally at a with following concentration of (1.25,2.5 and 5mg/kg) body weight for 3 months respectively. At the end of experiments. All animals are euthanized and both kidney samples are collected for histopathology assessment. The result demonstrate deferent lesion in kidney structures in treated groups involved degeneration and necrosis of cortical renal tubules, Area of cystic dilation in glomeruli. Cystic dilation in renal tubules also the result recorded dilation glomeruli with dilation of bowman space, finally dilation glomeruli's with degenerate cellularity and calcification of tubules in compared to control group including normal glomeruli and normal renal tubules.

Keywards: **Sildenafil, Histopathological, Kidney, Male Rat.**

دراسة التاثيرات المرضيه النسيجيه لعقار السلدنافيل على كلى ذكور الجرذان البالغة

الخلاصة

الدراسة تهدف الى تشخيص التغيرات المرضية النسيجية لكلى ذكور الجرذان المعالجة بعقار السلدنافيل ، اجريت التجربة على اربعين ذكر جرذ بالغ قسمت الى اربع مجاميع لكل مجموعه عشرة جرذان . المجموعة الاولى جرعت فمويا (1) مل من المحلول الملحي كمجموعة سيطرة.والمجموعة الثانية والثالثة والرابعة جرعت بالتراكيز 1.25 و 2.5 و 5 ملغم لكل كلغم على التوالي يوميا لمدة ثلاثة اشهر وفي نهاية التجربة قتلت جميع الحيوانات وبعدها اخذت عينات الكلى لغرض الفحص النسيجي. اضهرت النتائج لكل المجاميع المعالجة بالعقار تغيرات مرضية نسيجية في تراكيب نسيج الكلية تمثلت بتنكس وتنخر بالنبيبات الكلوية، توسع كيسي في النبيبات وتوسع كيسي بالكبيبة وتمدد بمحفظة بومان. بالإضافة الى التنكس الخلوي وتكلس في النبيبات الكلوية بالمقارنة الى مجموعة السيطرة.

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Introduction

Sildenafil is a prescription drug. It is comes in two forms, those are a suspension (liquid) and a tablet, by mouth, both are taken. Other form used in IV Route, but is only given by a doctor. This oral tablet drug is available in the brand-name drugs ((Viagra)) and ((Revatio)). As well as available in a generic drug. (1).

Approved drug to treat pulmonary hypertension and erectile dysfunction, it's a phosphodiesterase type 5 inhibitor. Sildenafil in general, is safe but it has some side effects like headaches, heartburn, and flushed skin. Rare but serious side effects include sudden-onset hearing loss and prolonged erections, which can lead to damage to the penis (2). When used overdose of sildenafil for long time may cause acute kidney injury, this report in old man (67 year), he was took sildenafil in over dose (400 mg) for erectile dysfunction, this patient affected by acute tubular necrosis in acute kidney injury during hospitalization, as well as the peak of serum creatinine was 5.07 mg/dL during his renal function repair with encouragement care (2,3). Erectile dysfunction (ED) case associated with cardiovascular diseases, including hypertension, diabetes mellitus and atherosclerosis (4). In healthy volunteers, sildenafil is larger scale absorbed; while, the metabolism of rapid first-pass permit the bioavailability absolute to 40% in approximately, Cmax in 30 to 120 minutes is reached in administration orally in the fast test, with half-life 4h. (4). Detoxification in the liver by the hepatic CYP2C9 and P450 enzymes CYP3A4 converted the sildenafil to a number of metabolites. (5).

The sildenafil is eliminated and excreted in the feces by predominantly metabolites (80% of the oral dose approximately by this way), while only excreted a small amount by urine (13% of the oral dose approximately by this way) (6).

Kidney function improved in PAH patients was associated with sildenafil treatment, which associated switch with exercise capacity improved and class function, a risk reduced of worsening of clinical, then mortality reduced. (7). Sildenafil, PDE-5 inhibitor, is widely used to treat ED. Its pharmacological action is due to its ability to prolong the signaling actions of NO in penile smooth muscle through raising the available cGMP pool by preventing its hydrolysis. Therefore, diabetic males suffered from ED are now treated routinely with Sildenafil (8)

Materials and methods

1. Experimental animals:

Forty male rats were brought from animals house of veterinary medicine collage, Basra University.

The rats were equally divided into four groups(group1 , group2 ,group3 and group 4), 10 rat in each group , one of these are untreated as control group, and others three treated groups. (Treated with sildenafil)

All group receive normal diets, animals were housed cages in standard home with adequate temperature, ventilation and the experiment was done for three months.

Group I served as a control group (N=10) was given normal saline 1 ml daily, group II given sildenafil drug at dose level 1.25 mg/kg, group III sildenafil drug at dose level 2.5 mg/kg and the(group IIII) was given sildenafil drug at a dose level 5 mg /kg of body weight orally (a gavage needle) at day. The administration given only one time for three months respectively.

2. Histological examination

Animals were killed under diethyl ether anesthesia after three months of treatment, the kidney rapidly was collected For slides

preparations, kidneys was cut into short slices fixed in 10% formalin, after that, dehydrated in a ethanol graded series, paraffin wax embedded and sectioned at 5um thickness. By hematoxylin and eosin stain, the slides were stained for examination of histology (9).

Results and discussion

Kidney histological sections of control group, reveal section of kidney with normal glomerulus and normal renal tubules, this represented in figure (1).

In group II. with sildenafil treatment (1.25mg/kg), the result was reveal the histopathological changes in kidney section include cystic dilatation of cortical tubules, also glomeruli with dilated bowman space (4x) figure (2) and some section shown area of degenerate, necrotic in cortical tubules (10x) figure (3).

In group III treated with (2.5 mg/kg) of sildenafil, the result appeared kidney sections reveal cystic dilation glomeruli's with degenerate cellularity and calcification (4x) figure (4) and cystic dilation of tubules (4x) figure (5).

Group IIII treated with (5 mg/kg) of sildenafil, the kidney section appeared lesion as (4x) . Kidney area of degenerate necrotic cortical tubules(10x) figure (6), necrotic tubules with infiltration inflammatory cells and glomeruli with dilation of bowman space figure (7).

The kidney is an organ concerned in body detoxification filtering and elimination in animal and human bodies, and it's also objective though their metabolism to many xenobiotics. Sildenafil drug (SILD) is phosphodiesterase-5 (PDE5) inhibitor selective, in the cyclic guanosine monophosphate (cGMP) which degradation participates and relaxation of smooth muscle cells of the arterioles (10). Moreover, to reduce oxidative stress (11) and spend anti-inflammatory effect through pathway of NO/cGMP (12).

The present study uncover in all treated groups by sildenafil 1.25, 2.5 and 5 mg/kg body weight for three month induced various histopathological changes in kidney architecture.

In the current study, microscopic examination appears mild to various alterations in the structure of kidney involve degeneration, necrosis and dilatation in renal tubules (medullary tubules, proximal convoluted tubules and cortical tubules). These modulations could be due to cytotoxic effects of sildenafil drug involve cytoplasmic vacuolations and nuclei pyknosis. or could be due to increase fluid uptake as a result of changes permeability of membrane of the cell. Damage of the cell membrane could be referred to oxidative stress. Another explanation demonstrate vacuolations of cytoplasm due to lactate accumulation in the kidney tubules. This results evaluation in osmotic pressure with water influx subsequently. Tubular cells degeneration and necrosis was the prominent features in rat and mice kidneys were administrated sildenafil (Viagra). The result agreed with researcher like Sherlock and Dooley; Zhang and Wang the recorded similar lesion in renal tissue by sildenafil treatment. Cytoplasmic vacuolization or degeneration has been conveyed the one of the responses of paramount primary to all types of injury cell and to occur due to permeability increased of cell membranes which increase resulting of intracellular water (13,14). The accumulates of sufficiently water within the cell, it output vacuolization of cytoplasmic. Zhang and Wang explain the relationship of the changes of vacuolar degenerative to the marked disturbances which come from the inclusions of the lipid as a result of treatments of the injurious (14) .While, diverge with the same authors in glumruli, the authors recorded shrinking of glumeruli but our study record dilation may be due to edama.

Our study dis agreement with Yousry et al there reported study of histological on the potential has

sildenafil effect on the testosterone level and kidney (15), these authors proposed that this primarily preservation due to necrosis inhibition and apoptosis, as exposed by iNOS /eNOS increased, as well as activation reduced of TUNEL-positive cells, caspase-3 and the ratio of Bax/Bcl-2. (15,16,17)

Our study represent cystic dilation of glomeruli, and increase bowman space that's may be due to odema was agreement with Cadirci et al those authers reported segmental degeneration and dilatation of glomerular capillary were observed obstructed of the lumens of the medullar tubules, and nuclei was hyperchromatic and their cells had more eosinophilic cytoplasm, as well as the vacuolization showed in the cytoplasm of these cells (18).

Our study noted some sections of calcification in glomeruli this result may be due disturbances in kidney function lead to calcium deposition in glomeruli. Adam et al were no recognized changes in glumruli, these compounds shown to decrease kidney ischemic injury and progress flow of local blood renal, this result dis agreement to our study (19,20,21,22)

As well, this therapeutic category, clinically using for above two decades for pulmonary hypertension and erectile dysfunction treatment, know have definite approach to be secure and invalid of many side effects (22). As well as, this experiment disagreement with Ali et al were elucidate the non-nephrotoxic prospect of SILD (23).

Conclusion

Depend on the outcome of the present histological analyses, it is concluded that, when Sildenafil administered for a long- term, will produce deferent and varying effect in the tissue structure of kidney in rats, especially degeneration and necrosis of cortical renal tubules and area of cystic dilation in glomeruli.

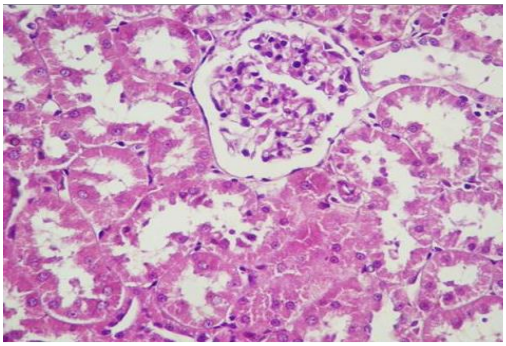

Figure 1. Section of kidney group 1 show Normal renal tubules and normal glumeruli

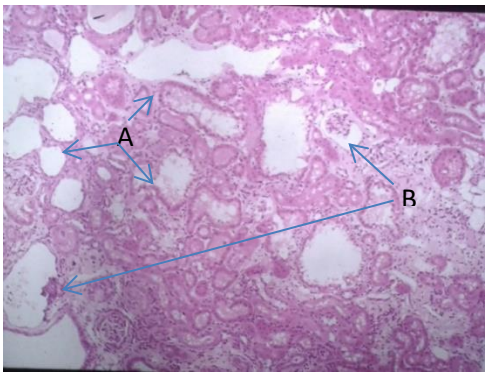

Figure 3. Section of renal cortex group2 show: Cystic dilatation of cortical tubules **A.** And glomeruli with dilated bowman space **B.** (4x)

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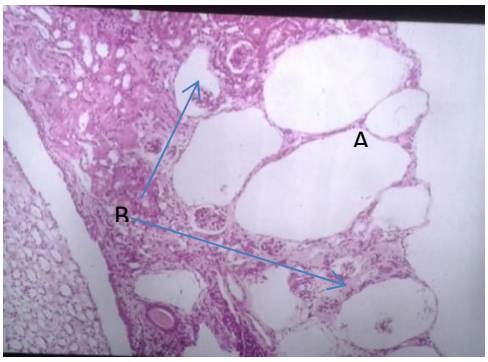

Figure 2. Section in renal cortex group2 show: Cystic dilatation of cortical tubules **A.** And glomeruli with dilated bowman space **B.** (4x)

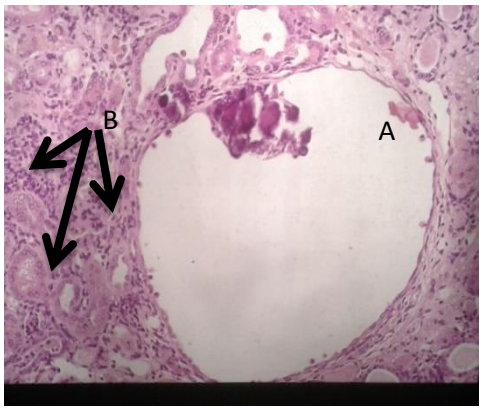

Figure 4. Section in renal cortex group3 show: Cystic dilation glomeruli's **A.** Degenerate cellularity and calcification of renal tubules **B.** (4x)

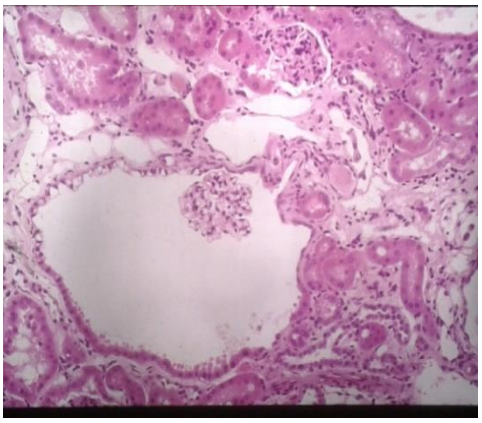

Figure 5. Section in renal cortex group3 show cystic dilation of tubules (4x)

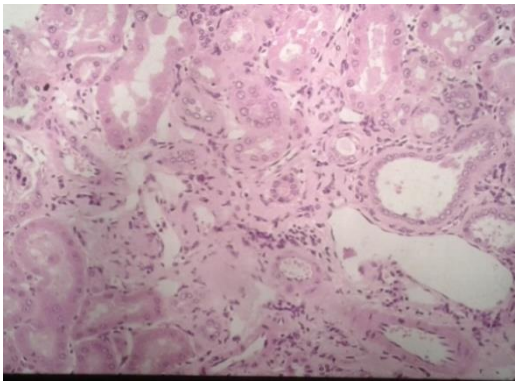

Figure 6. Section of kidney show. Kidney area of degenerate necrotic cortical tubules and infiltration inflammatory cells (10x)

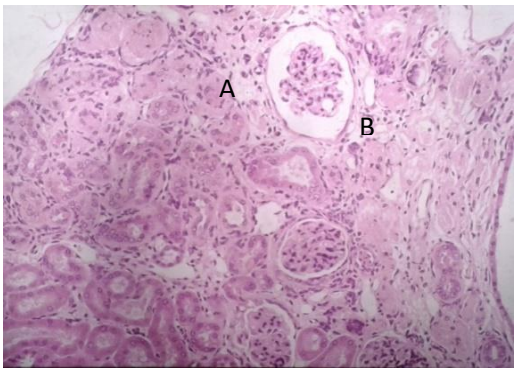

Figure 7. Section of kidney show: Necrotic tubules and infiltration inflammatory cells **A.** Glomeruli with dilation of bowman space **B**.

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